THE TREATMENT OF HERPES SIMPLEX GENITAL INFECTION

A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF MEDICINE OF THE UNIVERSITY OF LONDON

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ABSTRACT

The introduction reviews the virology, epidemiology, clinical features and previous treatments for genital herpes. The studies described here involve 6 randomised controlled trials for the treatment of genital herpes.

The first was a double blind placebo controlled study of intravenous acyclovir in 30 patients with first attack genital herpes. Patients treated with acyclovir had a statistically significant reduction in the duration of viral shedding, symptoms and the time to healing, but the drug had no effect on the development of recurrences.

The second study was designed to determine whether prolonged treatment of primary herpes could prevent recurrences. Sixty patients were treated with either 42 days of acyclovir or 5 days of acyclovir followed by 37 days of placebo. Prolonged treatment delayed the onset of recurrences but did not decrease their subsequent frequency.

Two studies were conducted to assess the efficacy of suppressive oral acyclovir in patients with frequent recurrences. The first was a 12 week double blind placebo controlled trial in 56 patients which showed a statistically significant decrease in the frequency of recurrences in acyclovir recipients. The second assessed the safety and dosage of suppressive oral acyclovir in 134 patients over a year and showed that the likelihood of recurrences was related to dosage and the frequency of tablet taking. No important side effects were noted.

The final 2 trials compared the efficacy of acyclovir and inosine pranobex. Eighty-eight patients with primary and 32 with recurrent herpes were treated. Patients with primary herpes treated with acyclovir healed more quickly and had a shorter duration of symptoms and viral shedding than those treated with inosine pranobex. Suppression with oral acyclovir was shown to be vastly superior to inosine pranobex.

These studies have established that acyclovir is the drug of choice for the treatment of primary and the suppression of recurrent genital herpes.

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Abstracts of the above papers have also been presented at the following international meetings.

International Society for Sexually Transmitted Disease Research, Heidelberg - 1981, Brighton - 1985, Atlanta - 1987.

International Union Against Venereal Diseases and Treponematoses, Dublin - 1981, Montreal - 1984.

Second World Congress on Sexually Transmitted Diseases, Paris 1986.

First International Acyclovir Symposium, Washington - 1981

Second International Acyclovir Symposium, London - 1983.

Wellcome International Antiviral Symposium, Monte Carlo - 1987.

Anglo Scandinavian Conference on Sexually Transmitted Diseases, London - 1988.

Medical Society for the Study of Venereal Diseases, Bordeaux - 1989.

CHAPTER ONE

INTRODUCTION - HERPES SIMPLEX VIRUS, VIROLOGY, EPIDEMIOLOGY AND PREVIOUS TREATMENTS

INTRODUCTION

The clinical syndromes associated with the herpes viruses have been recognised for centuries, however interest in this group of viruses has recently been reawakened due to a number of factors.

1. Infection with Herpes simplex virus is now a major and increasing cause of sexually transmitted infections.
2. Infections with several herpes viruses may cause devastating disease in the newborn and the immunologically compromised host.
3. One of the herpes viruses (Epstein Barr virus) is currently among the best viral candidates as a possible causal agent in human cancers.
4. After primary infections, these viruses can become latent in the body for the life of the individual. Reactivation and subsequent recurrent infection particularly with genital herpes is a major cause of psychological distress and sexual dysfunction.
5. Technology is now available to study the molecular biology of these viruses.
6. The recent introduction of potentially effective and apparently safe antiherpes drugs has raised hopes for control of these infections.

This thesis will review the virology, epidemiology and clinical features of genital herpes as well as previous therapies. The study itself will assess the efficacy of a new antiviral drug acyclovir and an immune modulatory drug inosine pranobex for the treatment of genital herpes.

VIROLOGY

The Structure of Herpes Simplex Virus (HSV) (Figure 1)

The herpes virion consists of a DNA core, an icosahedral capsid containing 162 capsomers and an envelope. Between the capsid and the envelope is a structure

consisting of fibrous proteins called the tegument. The total diameter of the enveloped virion measures 250nm and that of the nucleocapsid 100nm.

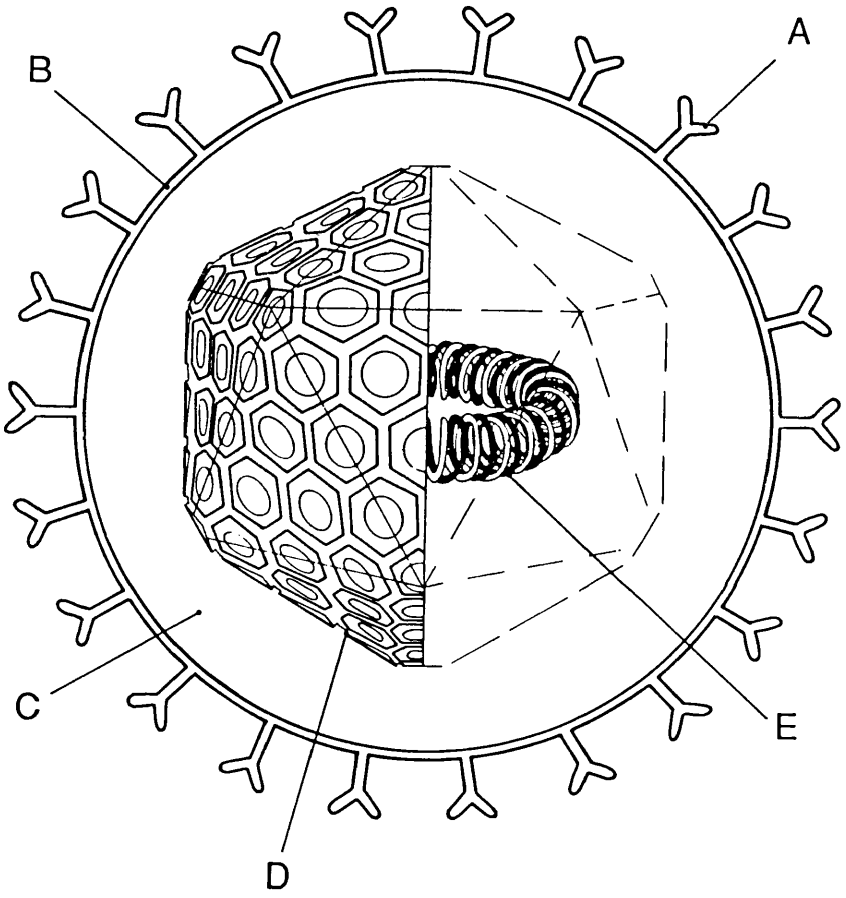
The Envelope

The envelope is the outer covering of the virus derived from modified cell membrane as the DNA containing capsid breaks through the nuclear membrane of the host cell (Roizman and Furlong. 1974). The envelope consists of a lipid bilayer with the glycoproteins embedded in it (Spear 1984). The glycoproteins thus far identified are designated gB, gC, gD, gE gG, gH, gI, and gJ. Glycoproteins C and D appear to be the most important ones in binding the virus to the cell surface and gB is involved in penetration (Little et al. 1981). Glycoprotein C also binds to the C3b component of complement (Friedman et al. 1984) and gD is a potent inducer of neutralising antibodies. One of the roles of gE is to bind to the Fc portion of IgG. (Bauke and Spear 1979). The functions of gG are yet to be determined. This glycoprotein is however type specific and has already been utilised in a type specific serological assay. (Lee et al. 1985, 1986; Ashley et al. 1988). gI stabilisse the membrane, and gH and gJ are essential for infectivity (Desai et al. 1988).

The Capsid

The capsid consists of 162 capsomers arranged in an icosahedral symmetry. It is a highly rigid structure with 20 triangular facets and 12 corners or apices. The laws of crystal structure determine the number of capsomers. Each apex consists of a single capsomer surrounded by 5 others (pentons). The non apical capsomers are surrounded by 6 others (hexons). Thus the virus has 150 hexons and 12 pentons (Wildy et al. 1960). Other viruses with icosahedral symmetry have different numbers of capsomers (eg. adenoviruses contain 252 capsomers and papovaviruses 72). The capsomers are made up of several polypeptides. They have the shape of hexagonal prisms with a hollow tube running the length of the long axis (Wildy et al. 1960).

FIGURE 1



THE STRUCTURE OF HERPES SIMPLEX VIRUS

A. Viral glycoproteins
B. Envelope
C. Tegument
D. Capsid
E. DNA

The Core

The core contains the viral DNA. The HSV genome is an extremely complex double stranded linear DNA with a molecular weight of 100 X 10^6 (Frenkel and Roizman 1971). HSV DNA consists of two covalently linked sequences designated l (long) and s (short), comprising 82% and 18% of the DNA respectively. Each component consists of unique sequences Ul (unique long) and Us (unique short) bracketed by smaller inverted sequences. The two unique sequences can invert in relation to each other; so that the DNA extracted from HSV has been observed to occur in 4 different isomeric configurations, depending upon the relative orientation of the Ul and Us sequences (Roizman 1979).

Most of the genetic capacity of the virus is involved in coding of the large number of HSV polypeptides. Fifty polypeptides are readily identifiable, however it is likely that the genome enicodes for over 70 (McGeoch et al 1988). Three classes of polypeptides have been identified and designated alpha, beta and gamma (the production and role of these proteins is discussed in detail below). However, the exact number and function of all the viral genes and their products is yet to be determined.

The 2 Herpes simplex viruses (HSV 1 and HSV 2) have a considerable degree of genetic similarity with approximately 50% of the sequences highly conserved. These sequences are found throughout the genomic map. In addition, many of the polypeptides specified by HSV 1 are antigenically related to those produced by HSV 2.

Viral Replication (figure 2)

In order for viral replication to occur the genome needs to be transported through the cell surface and cytoplasm to the nucleus. This occurs as a result of 3 steps; adsorption of the virion to the cell surface; penetration across the plasma membrane to the nuclear pore and finally uncoating of the capsid to release the viral DNA.

Adsorption occurs when HSV attaches to the cell membrane probably by means of 1 or more specific cellular receptors. There is some evidence that HSV 1 and 2 attach to different receptors (Vahlne et al. 1979, 1980). Initial binding events involve molecules that are heparin sulphate proteoglycans (Wodunn et al 1989). When the virus has attached to the cell surface, the viral envelope fuses with the cell membrane and the nucleocapsid is released into the cytoplasm (Morgan et al. 1968; DeLuca et al. 1981). Glycoprotein B may have a function in this process (Sarmiento et al. 1979). The nucleocapsid is transported to the nuclear pore where the capsid is disassembled and the viral DNA released into the nucleus. (Dales 1973).

Transcription of mRNA's occur in the nucleus; HSV is believed not to have a virion transcriptase and viral RNA synthesis is probably catalysed by cellular RNA polymerase II. The mRNA's are then transported to the cytoplasm where translation into viral proteins occurs. The protein synthesising capacity of the cell is slowly taken over. The majority of the proteins produced are returned to the nucleus which is also the site of DNA replication and reassembly of capsids.

Biosynthesis occurs in 3 phases in a highly regulated fashion (Honess and Roizman 1974). The mRNA's produced during each of these phases correspond to 3 grades of polypeptide named alpha (α) beta (β) and gamma (γ). mRNA is translated during each of these phases from non-contiguous areas of the viral DNA. Initially only α gene products are synthesised. They represent 10% of the genome and amongst their functions are the production of β proteins (Kozak and Roizman 1974; Honess and Roizman 1974).

The β proteins terminate α polypeptide production (in the cytoplasm) and start the production of γ polypeptides (Honess and Roizman 1974; Fenwick and Roizman 1977). The β proteins include several regulatory proteins and enzymes (including thymidine kinase and DNA polymerase) that are essential for DNA replication. The final phase (the expression of γ genes and the production of γ proteins) follows the replication of viral DNA. The majority of the structural proteins of the virus are γ proteins. At the onset of viral DNA synthesis β protein production ceases. In addition cellular DNA and protein synthesis are

also terminated.

Assembly of viral capsids occurs in the nucleus when a critical concentration of viral structural proteins is reached. The capsids spontaneously assume their icosahedral shape (Vilcek and Sreevalson 1984).

Complete virions are probably transported to the cell membrane via the endoplasmic reticulum and the Golgi apparatus (Spear 1984). The glycosylation of the viral proteins that are inserted into the envelope probably also occurs in the Golgi apparatus. As a consequence identical glycoproteins are found on the viral envelope and the surface of the infected cells. These glycoproteins carry specific antigenic determinants that may be important in the immune destruction of infected cells (Norrild et al 1980).

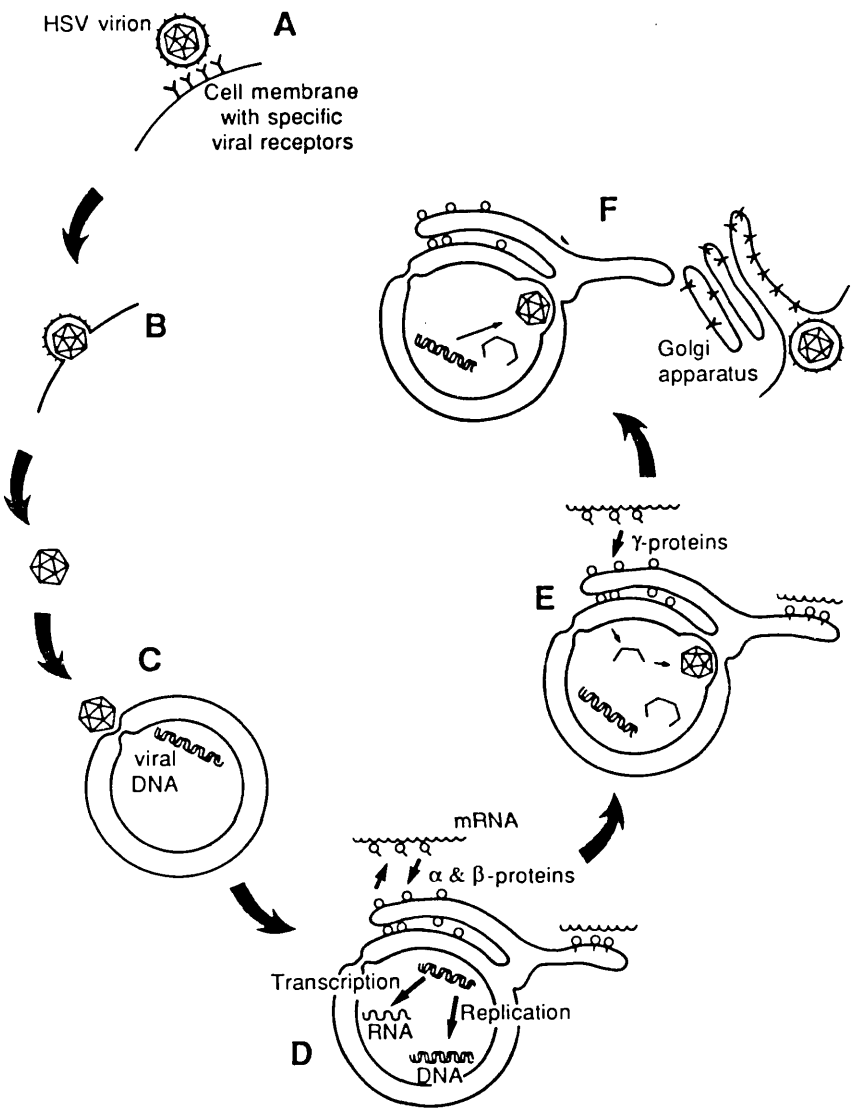
It is presumed that the final egress of complete infectious viral particles into the extracelluar spaces and fluids occurs by a process of inverted endocytosis (Johnson and Spear; 1982).

EPIDEMIOLOGY

Introduction

Infections with HSV 1 and HSV 2 are amongst the commonest human viral infections. However the majority of individuals exposed to these viruses remain asymptomatic which makes epidemiological studies difficult. One of the fundamental, biological properties of HSV (and other human viruses of the herpes group including Varicella zoster, Cytomegalovirus and Epstein Barr Virus) is the ability to establish latency following the initial infection. This ability has an important bearing on the epidemiology of herpes infections in that latent virus may periodically reactivate giving rise to clinical illness or asymptomatic but none the less infectious viral excretion.

FIGURE 2



HERPES SIMPLEX VIRUS REPLICATION

A. HSV attaches to specific viral glycoprotein receptors
B. Viral envelope merges with cell membrane and the capsid enters the cytoplasm and is transported to the nucleus
C. Disassembly of the capsid and release of the DNA into the nucleus
D. Expression of α and β proteins
E. Expression of γ proteins. Formation of new viral genome and capsid. Envelopment of virion as it buds through the inner nuclear membrane into the perinuclear space
F. Transport to the Golgi apparatus where glycosylation occurs. Release into the extracelluar space

Dowdle et al (1967) first discovered that there were two distinct HSV viruses. It was initially believed that HSV 1 caused disease above the waist, and HSV 2 below. However this is now known to be an over simplification and both viral types can cause all the clinical syndromes. An additional problem in trying to unravel the complex epidemiology of HSV infection, is that although patients exposed to HSV (both clinical and subclinical) develop HSV antibodies there is considerable antigenic cross reactivity between HSV 1 and HSV 2 and differentiation of the two viral types on serological tests has proved difficult. Seroepidemiological surveys need to be viewed with these problems in mind.

Transmission

Infection occurs when a susceptible individual comes into contact with infectious virus during close personal contact, including mouth to mouth, genital to genital, mouth to genital, genital to anal, or mouth to anal contact. The incubation period is two to 14 days. Human beings are the sole reservoirs of HSV infections.

Studies have shown that early lesions namely, vesicles and ulcers are more likely to be shedding high titres of virus, then crusted lesions (Spruance et al. 1977; Guinan et al. 1981; Corey et al. 1983a; Mindel et al. 1988), and transmission occurring from individuals with obvious clinical herpes is well documented. However, infection can also come from patients with no apparent herpetic lesions. Asymptomatic or inapparent viral excretion can occur in 2 situations. Firstly patients with clinical herpes can shed virus asymptomatically from time to time. Studies in women with recurrent genital herpes have shown that HSV can be isolated from 4-14% of them during periods when they were asymptomatic (Rattray et al. 1978; Adam et al. 1980; Guinan et al. 1981). The second group of patients are those who have never had clinical herpes and are yet found to shed virus asymptomatically. Viral shedding of this type has been documented from the saliva of 1-5% of adults (Herrmann 1967; Lindren et al. 1968) and 18-20% of young children (Buddingh et al. 1953; Cesario et al. 1969) and the genital tract of 1-15% of women (Centifanto et al. 1971; Rawls et al. 1971; Vesterinen et al. 1977; Baker and Plotkin 1979; Adam et al.

1980) and occasionally from men (Deardourff et al. 1974). All of these studies almost certainly underestimate the true incidence of asymptomatic viral excretion and in most only a single specimen was taken.

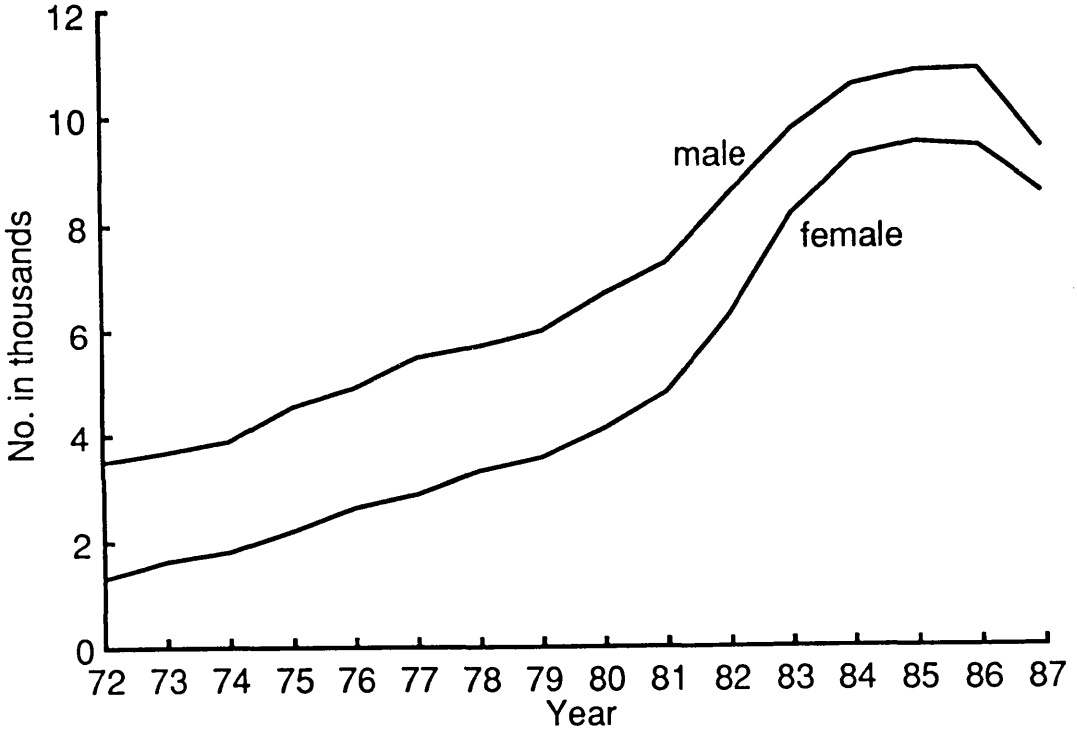
In an attempt to answer how often patients acquired infection from individuals who were unaware that they were infected, a study evaluated 66 source contacts of patients with first-episode genital herpes. Only 17 (26%) were aware that they had herpes at the time of transmission (Mertz et al. 1985). In addition to the patients who knew they had herpes, the authors identified three groups who were able to transmit herpes unknowingly. Firstly, there are truly asymptomatic patients; secondly, there are those with complaints which they were unaware were herpes; and finally there were patients with asymptomatic but none the less clinically apparent genital lesions.

Further studies confirm that transmission of herpes often occurs from individuals who are unaware that they themselves are infected (Mertz et al. 1988a; Langeberg et al. 1989; Koutsky et al. 1990).

Incidence

Genital herpes was first reported from Sexually Transmitted Disease (STD) clinics in the United Kingdom in 1972, when 4,500 cases were reported. The number of cases has increased each year and by 1985 the number reported was 20347. Just under half the cases have occurred in females (CDSC 1988) (Figure 3). Since 1985 there has been a decrease in the number of reported cases, perhaps reflecting increased condom use since the advent of the Human immunodeficiency virus epidemic. Although the sexual orientation of males is not reported on clinic returns, a study from London showed that 20% of patients were homosexual (Hindley and Adler 1985). Genital herpes is now the fifth commonest diagnosis from STD clinics. The apparent increase in herpes infection in the 1970's and early 1980's may have partly be due to increase publicity about the disease and current antiviral treatments, the inclusion of both primary and recurrent cases in clinic returns (Hindley and Adler 1985) and the increase use of viral culture for diagnosis. The size of the increase

FIGURE 3



REPORTED CASES OF GENITAL HERPES FROM SEXUALLY TRANSMITTED DISEASE CLINICS IN THE UNITED KINGDOM 1972-1987 (Communicable Disease Surveillance Centre 1989 - unpublished data)

however, suggests that a considerable part of it was real.

The size of the problem in other countries is less clear. In the United States of America (USA) no accurate national data are available. However, herpes is said to be one of the most common sexually transmitted diseases. The Centres for Disease Control (CDC) have estimated that there are between 300,000 and 500,000 new cases of herpes each year in the USA based on a survey of ten STD clinics (Centres for Disease Control 1982). However, the validity of this figure is questionable as these clinics only serve a small and very selected population. A review of patients attending private physicians in the USA showed that attendances increased 7 and a half fold between 1966 and 1981 (Becker et al. 1985). This study suggests that the increases seen in the USA have been similar to those in the UK.

A seroprevalence study from the USA using a type specific HSV2 assay showed that 16.4% of a randomly selected population between the ages of 15-74 had antibodies to HSV2. This would be equivalent to 25 million Americans (Johnson et al. 1988).

Information from other Western countries is scarce. However, herpes appears to be a common infection. In the third world very little information is available, although, in many of these countries chancroid, appears to be the commonest cause of genital ulceration.

THE CLINICAL FEATURES OF GENITAL HERPES

Introduction

The clinical manifestation of genital herpes are influenced by several factors including past exposure (usually to HSV1) previous episodes of genital herpes, gender and viral type (Corey et al. 1983a). In common with many other viral infections HSV infections are often asymptomatic (Nahmias and Roizman 1973; Mertz et al. 1985, 1988a; Langenberg et al. 1989; Koutsky et al. 1990).

The disease has three phases - the first occurs when the patient is exposed to the virus for the first time, the second when the disease becomes latent, and the third when and if the patient suffers a relapse.

First attack of genital herpes

Symptoms occur 2-20 days after exposure. (Kaufman et al. 1973a; Nahmias & Roizman 1973). The contact may be sexual or orogenital and either HSV type 1 or type 2 can cause the illness (Corey et al. 1983a). Both viral types cause a clinically similar illness, although in persons with evidence of prior HSV infection (either clinical or serological) the illness is often less severe and of shorter duration (Corey et al. 1983a). Infection occurring in individuals with previous HSV infection has been termed "non primary first episode" genital herpes to differentiate them from the true "primary" episode occurring in individual with no clinical or serological evidence of previous HSV infections.

First attack of genital herpes in females

The presenting symptoms in women include vulval pain, groin pain, dysuria and vaginal discharge (Kaufman et al. 1973a; Davis and Keeney 1981; Corey et al. 1983a). Systemic symptoms occur in a considerable percentage of patients. These include a flu like illness, fever, myalgia, headache and abdominal pain. Some or all of these symptoms were seen in 73% of female patients studied by Brown et al. in 1979. Local symptoms usually increase in the first 6-7 days with a maximum intensity around 7-10 days gradually receding during the second week of illness. Systemic symptoms are of shorter duration (Figure 4) (Corey et al. 1983a). Lesions commonly occur on the labia minora and majora, clitoris, perineum and perianal area (Ng et al. 1970). The cervix is involved in up to 80% of patients (Corey et al. 1983a). Bilateral tender inguinal lymphadenopathy occurs in 80% of patients (Corey et al. 1983a). Other sites which maybe infected include the vagina, and mons pubis as well as numerous extragenital sites including the rectum, pharynx, lip, breast, finger, eye, buttocks, and groin (Corey et al. 1983a; Mindel et al. 1990).

The lesions commence as erythematous papules which vesiculate, the vesicles burst to leave ulcers with an erythematous halo and a greyish white exudate in the base (Poste et al. 1972). Lesions in the moist areas e.g. labia minora heal without crusting, although lesions in dry areas e.g. the mons or buttocks heal with crusts (Brown et al. 1979). Herpetic vulvitis is often widespread with diffuse, bilateral confluent ulceration whereas other external genital or extra genital lesions are often localised (Corey et al. 1983a).

Josey and colleagues (1966) described four types of herpetic cervicitis:-

1. Diffuse cervicitis - where the entire ectocervix is diffusely inflamed, often exuding muco-pus and bleeding profusely to touch.

2. Multiple discreet ulcers - each with a greyish white base and an erythematous halo.

3. Necrotic cervicitis - in this condition the entire ectocervix is greyish and necrotic looking and is sometimes mistaken for carcinoma of the cervix.

4. Single or multiple deep ulcers - ulcers approximately 1 cm in length and 1 cm in depth.

One of the features of first attack genital herpes is the production of crops new lesions in up to 70% of patients, usually around the eighth day (Corey et al. 1983a).

Corey and co-workers (1983a) studied 126 females with first attack genital herpes and found the mean duration of lesions was 19.7 days and the mean duration of viral shedding was 11 days for cervical lesions and 12 days for external genital lesions.

<u>First attack genital herpes in males</u>

Two very different types of 'genital' herpes occur in men. Penile herpes is a

relatively mild infection whereas perianal and anal herpes is often a severe and prolonged disease.

Penile herpes

The symptoms of penile herpes include pain either in the genital area or the groin (associated with inguinal lymphadenopathy) and dysuria (if the lesions are near the urethra). Systemic symptoms occur less commonly in males (39%) than in females (73%) (Brown et al. 1979; Corey et al. 1983a).

Lesions can occur anywhere on the penis, however the glans, coronal sulcus and foreskin are the commonest sites. As in female patients, extragenital lesions are not uncommon (Crane and Lerner 1978; Sumers et al. 1980; Corey et al. 1983a; Mindel et al. 1990). Lesions progress through the same vesicular, ulcerative, crusting phases as in females, however, lesions on moist sites (eg the glans in uncircumcised men) heal without crusting (Davis and Keeney 1981). Tender inguinal lymphadenopathy occurs in over 80% of cases (Corey et al. 1983a). The mean duration of lesions in men is 16.5 days compared with 19.7 days in women (Corey et al. 1983a).

Perianal and anal herpes

The first attack of anal herpes is usually a severe disease characterised by fever, inguinal lymphadenopathy, anal discharge, pain, and tenesmus (Goodell et al. 1983). Goodell and co-workers (1983) studied the clinical features of 23 patients with herpes proctitis and compared them to 79 patients with non herpes proctitis (Table 1). Significantly more patients with HSV proctitis had anorectal pain, tenesmus, constipation, pruritus, perianal lesions, inguinal lymphadenopathy and fever than those with non HSV proctitis.

There are few reports on the natural history of first attack HSV proctitis. The average reported duration of symptoms is 17-21 days (Samarasinghe et al. 1979; Quinn et al. 1981; Goodell et al. 1983) and the duration of lesions 2-32

days (Waugh 1976). However all of these studies involved small numbers of patients.

Complications of first attack genital herpes

A number of complications have been described during or following the first attack of genital herpes. These include dissemination to sites distant from the genitalia, meningitis, sacral radiculomyelopathy and autonomic nervous system dysfunction, urinary difficulties or retention, necrotising balanitis, synechia vulva (fusion of labia minora), urethral stricture, suppurative lymphangitis, salpingitis and secondary bacterial or fungal infection.

1. Extragenital involvement

Extragenital involvement may occur from primary inoculation at sites such as fingers, throat or breasts, from haematogenous spread during the viraemic phase of the illness or from autoinoculation to any mucocutaneous site (Corey et al. 1983a; Mindel et al. 1990). Corey and co-workers (1983a) reported that the commonest sites of extragenital involvement were the fingers, and areas adjacent to the genitalia suggesting that lesions arose from autinoculation rather than viraemia.

2. Meningitis

Meningitis occurs in up to 36% of women and 13% of men with primary genital herpes (Corey et al. 1983a). The clinical features include fever, headache, malaise, photophobia, neck stiffness and a positive Kernigs sign. The CSF shows a slight increase in both protein and lymphocytes. The condition, in common with most viral meningitides resolves within a few days without residual neurological sequelae (Meyer et al. 1960; Skoldenberg et al. 1975; Corey et al. 1983a).

TABLE 1

COMPARISON BETWEEN HERPETIC AND NON-HERPETIC PROCTITIS

	HSV PROCTITIS	NON HSV PROCTITIS
	n = 23	n = 79
	n (%)	n (%)
Anorectal pain	23 (100)	61 (77)
Tenesmus	23 (100)	61 (77)
Constipation	18 (78)	32 (41)
Pruritus ani	17 (74)	36 (46)
Neurological symptoms	12 (52)	10 (13)
Urinary difficulties	11 (48)	8 (10)
Sacral paresthesias	3 (13)	0
Posterior thigh pain	6 (26)	0
Perianal lesions	16 (70)	6 (8)
Inguinal lymphadenopathy	13 (57)	9 (11)
Fever	11 (48)	13 (16)

All were significantly more frequent in the HSV Group
$p < 0.01$

Anal discharge	21 (91)	65 (82)
Bleeding (anal)	14 (61)	32 (41)
Abdominal pain	2 (9)	17 (22)

No significant differences.

Based on Goodell et al 1983

3. Sacral radiculomyelopathy and autonomic nervous system dysfunction

Both of these conditions have been described as occurring in genital herpes (Klastersky et al. 1972; Craig and Nahmias 1973; Caplan et al. 1977) and appear to be particularly common in homosexual men with herpetic proctitis (Oates and Greenhouse 1978; Samarsinghe et al. 1979). Signs and symptoms of the autonomic nervous system dysfunction include hyperaesthesia or anaesthesia in the perineum, thighs or buttocks with decreased sensation over the sacral dermatomes, difficulty with urination and defecation, poor rectal and perianal sphincter tone, an enlarged bladder and an absent bulbocavernosus reflex (Goldmeier et al. 1975; Oates and Greenhouse 1978; Riehle and Williams 1979; Samarsinghe et al. 1979; Jacome and Yanez 1980). This resolves without residual neurological problems usually in 2-3 weeks.

4. Urinary difficulties or retention

Urinary problems commonly occur in patients with first attack genital herpes either because of severe pain associated with urethral or peri urethral lesions (Nahmias and Roizman 1973) or because of the sacral radiculomyelopathy or autonomic nervous system dysfunction described above. The problem is self limiting although in severe cases catheterisation may be necessary (Corey et al. 1983a).

5. Rare complications

A number of rare complications have been attributed to herpes. Ortells in 1921 described a man with a urethral stricture following repeated attacks of urethral herpes. Necrotising balanitis following herpes infection has been described by several workers (Peutherer et al. 1979; Powers et al. 1982). The condition appears to have a good prognosis. Other rare complications include a suppurative lymphangitis of the dorsum of the penis (Tottie 1942) and synechia vulvae - fusion of labia minora (Brain 1956, De Marco et al. 1987, Walzman and Wade 1989).

HSV may occasionally be isolated from the endometrium, Fallopian tubes and pouch of Douglas in women with pelvic inflammatory disease (Heinonen et al. 1985). The significance of this finding is unclear.

Recurrent genital infections

The major differences between first attack and recurrent infections are shown in Table 2 and Figure 4. Recurrences are usually shorter and less severe and viral shedding only lasts a few days (Guinan et al. 1981; Corey et al. 1983a; Mindel et al. 1988). For example Corey found that the mean duration of lesions in women with recurrent infection was 9.3 days compared with 19.7 in those with primary infections and the mean duration of viral shedding 3.9 days in recurrent infection compared with 11.8 in primary.

Recurrent infections usually consist of a single or a small group of vesicles or ulcers at a one anatomical site (usually on the external genitals or buttocks). Local symptoms are mild and systemic symptoms uncommon. The lesions last longer in men than in women, but pain and dysuria are more common and more severe in women (Mindel et al. 1988).

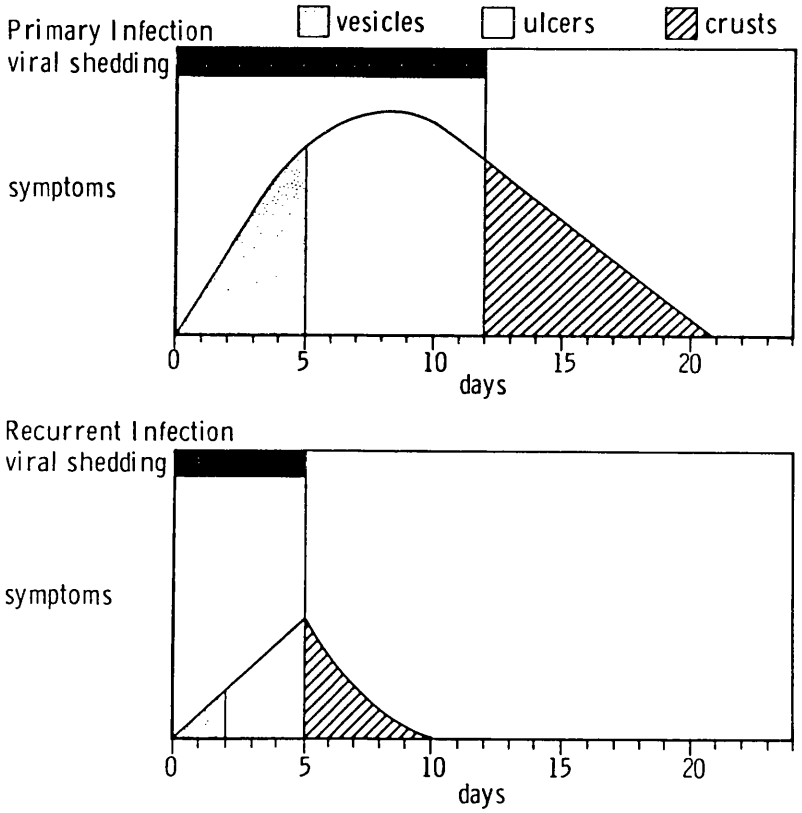
Although each recurrence usually lasts only a few days, there are 2 aspects of recurrent herpes that cause considerable distress, pain and anxiety. Firstly each recurrence may be preceded by a prodrome (Corey et al. 1983a). This prodrome takes many forms, the most common being a "neuralgia like pain", occurring 24-48 hours prior to the onset of lesions in the dermatomal distribution where the lesions occur. Other prodromal symptoms include malaise, fever, irritability, and painful inguinal lymphadenopathy. Many patients find the prodrome more distressing than the lesions themselves. The frequency of recurrences is the second factor causing considerable distress. The frequency of recurrences varies enormously with some patients having 15 or more recurrences a year (Mindel et al. 1988).

TABLE 2

DIFFERENCES BETWEEN PRIMARY AND RECURRENT GENITAL HERPES

	PRIMARY	RECURRENT
Duration	10-21 days	5-10 days
Pain/Dysuria	Severe	Mild
Systemic Symptoms	Common	Uncommon
Anatomical sites	Many	Usually one
Number of lesions	Many	One or a small group
Prodromal symptoms	-	Common
Neuralgia	-	Common
Involvement of cervix	Common	Uncommon
Viral type	Both	Mostly HSV 2

FIGURE 4



A COMPARISON BETWEEN PRIMARY AND RECURRENT GENITAL HERPES

There are two major potential long term consequences of genital herpes. The first is the possible association with cervical cancer and the second is the risk of transmission to the neonate at the time of delivery. Neither of these have any relevance to the clinical trials and will not be discussed any further.

PREVIOUS TREATMENT FOR GENITAL HERPES

Introduction

Numerous and diverse therapies have been tried for the treatment of genital herpes. Belsey and Adler (1978) found that sixteen different therapies were routinely being used for the treatment of genital herpes in S.T.D. clinics in the United Kingdom. Corey et al. (1981) from the other side of the Atlantic listed 23 treatments commonly used for mucocutaneous HSV infection. This chapter will review all treatments available up and till the introduction of acyclovir.

Antivirals (Table 3)

Several antiviral drugs have an antiherpetic effect, however, at the time of the introduction of acyclovir only vidarabine (ara-a), idoxuridine, 2-deoxy-d-glucose and ribavarin had been tested in clinical trials in patients with genital herpes. Of the remaining agents vidarabine monophosphate, cytosine arabinoside and lysine had been tested in orolabial HSV and phosphonoformate was being evaluated in genital herpes.

Considering first the drugs which had been evaluated for the treatment of orolabial herpes. Intramuscular vidarabine monophosphate was said to have some efficacy, however this was an open study and therefore difficult to evaluate (Sklar and Buimovici-Klein 1979). A double blind placebo controlled study with topical vidarabine monophosphate showed no effect (Spruance et al. 1979). Both topical cytosine arabinoside (ARA-C) and oral lysine have been tested in double blind trials and both showed no benefit (Marks and Koutts

TABLE 3

ANTIVIRAL DRUGS FOR THE TREATMENT OF GENITAL HERPES

ANTIVIRAL DRUGS WITH ACTIVITY AGAINST HSV

Idoxuridine (IDU)
Triflourothymidine
Vidarabine
Vidarabine monophosphate
Cytosine arabinoside
Ribavarin
Bromovinyl deoxyuridine (BVDU)
Phosphonoformate

DRUGS WITH NON-SPECIFIC ANTIVIRAL EFFECTS

2-Deoxy-d-glucose
Lysine

Only drugs available at the time of the introduction of acyclovir are reviewed.

1975; Milman et al. 1978). Toxicity with parenteral cytosine arabinoside probably precludes its use except in severely immunocompromised patients.

Topical adenine arabinoside (ARA-A) (3%) has been tested in three randomised double blind placebo controlled studies in patients with genital herpes. All three trials showed the drug to be no better than placebo (Goodman et al. 1975; Adams et al. 1976; Hilton et al. 1978).

Two antiviral drugs which warrant further consideration are 2-Deoxy-D-Glucose and Idoxuridine. At first glance the trial conducted by Blough and Giuntoli (1979) using topical 2-Deoxy-D-Glucose in patients with both recurrent and first attack genital herpes appears to have excellent results. The trial was said to be randomised double blind and placebo controlled, and the authors showed that the duration of lesions and of viral shedding in both first attack and recurrent disease were significantly shorter in patients receiving the therapy compared with the placebo group. However closer inspection of these data reveal a number of discrepancies which call into question the validity of this study. The first problem arises when considering the number of patients receiving the drug and those receiving placebo. In patients with primary genital herpes, 18 received the drug and 8 the placebo, and in the recurrent group 18 received the active agent and 7 the placebo. The authors comment that 'because of ethical and moral considerations, the number of placebo-treated patients was limited.' They unfortunately did not state what their moral or ethical objections were to using a placebo. The main concern however, relates to the data on the duration of lesions and viral shedding. Previous studies have shown that the mean duration of lesions in untreated patients with primary genital herpes is approximately 19 days (Vontver et al. 1979; Corey et al. 1981, 1983a). In the Blough and Giuntoli study the mean duration of lesions in the placebo group was 27 days and in those receiving the drug 24.6 days; considerably longer than in untreated patients in other studies. A similar discrepancy is noted in relation to viral shedding. The mean duration of viral shedding in untreated patients from previous studies is around 10 days (Vontver et al. 1979; Corey et al. 1981). In the Blough and Giuntoli study, placebo treated patients shed virus for 24 days whilst those receiving 2-Deoxy-

D-Glucose shed virus for 13.3 days. When recurrent disease is considered the lengths of viral shedding were found to be 3.6 and 4.5 times longer than in earlier studies (Corey et al. 1979a). In addition the mean length of viral shedding in the placebo treated patients exceeded the duration of lesions by several days - a phenomenon which has not been noted by any other worker. There are no other published trials with 2-Deoxy-D-Glucose however, a laboratory study with guinea pigs and mice showed no benefit (Kern et al. 1982).

5-iodo-2-deoxyuridine (IDU) has been used in the treatment of Herpes simplex virus infections for over 20 years (Hall-Smith et al. 1962) and still the information regarding its use in genital HSV is contradictory. Several 'open' studies in the early 60's reported favourable results with IDU therapy in genital and orolabial HSV (Hall- Smith et al. 1962; Schofield 1964). Schofields study included 50 patients however no attempt was made to differentiate primary from recurrent disease, and over a quarter of patients were lost to follow after one week!

Two controlled trials (Hutfield 1964; Taylor and Doherty 1975) both used 0.5% IDU and had 3 treatment arms (IDU, placebo and in one trial, penotrane jelly and, in the other, photodynamic inactivation). In both studies patients with primary and recurrent genital HSV were combined, patients were not randomised and statistical analysis was inadequate. The only parameter assessed was time to healing. One of the trials showed marginal decrease in healing time, the other did not.

The trial by Parker (1977) compared three treatment groups in a double blind trial in patients with recurrent herpes. The groups were 20% IDU in DMSO, 5% IDU in DMSO and DMSO alone. The trial showed that the healing time and virological shedding times were both significantly reduced when 20% IDU and DMSO were compared with DMSO alone. This trial too, has a number of fundamental flaws. Although 108 patients were recruited only 53 were available for analyses, with the largest drop out rate amongst the control group. Of the 36 'control' patients entered only 12 were available for analysis,

compared with 20 out of 36 in the treatment group. The second problem was that very little information was presented to show that the 3 groups were in fact comparable. The final criticism relates to the definition of healing. The author of this study stated that 'healing was assumed when the sores had dried whether scabbed or not.' This definition fails to recognise that sores on the moist mucosal surfaces do not dry up or scab they simply epithelialise.

The balance of evidence suggests that the idoxuridine preparation is of little value for the treatment of genital herpes.

Miscellaneous therapies (Table 4)

The majority of the miscellaneous treatments have not been the subject of clinical trials and do not warrant any further consideration.

Cotrimoxazole (Trimethoprim and Sulphamethoxazole) is frequently prescribed to patients (Belsey and Adler 1978) in order to decrease bacterial superinfection. An open trial with the drug showed no benefit in HSV infections (Laird and Roy 1975). Bacterial suprainfection is probably a rare occurrence in any event (Corey et al. 1983a).

Topical surfactants

Topical surfactants have some antiviral activity. There have been four randomised double blind placebo controlled studies with topical surfactants in patients with herpes. Two in genital disease and two in orolabial. The orolabial studies were with ether and chloroform, the genital with ether and nonoxynol-9 (Taylor et al. 1977; Corey et al. 1978; Vontver et al. 1979; Guinan et al. 1980). The two orolabial studies showed ether and chloroform to be ineffective. Corey's study with ether in genital herpes showed the preparation to be both toxic and ineffective. Nonoxynol-9 was also of no benefit. Thymol, another agent with similar activity has not been the subject of clinical trials.

Photodynamic inactivation

The observation that HSV loses its infectivity when exposed to a variety of photosensitive dyes and then to light, prompted numerous trials with this form of therapy in the early seventies. Despite promising claims following early use (Kaufman et al. 1973b; Felber et al. 1973; Frederich 1973) several subsequent studies have shown photodynamic inactivation to be ineffective (Taylor and Doherty 1975; Meyers et al. 1975; Roome et al. 1975). It has also been suggested that this form of therapy may enhance the oncogenic potential of the herpes viruses (Cusumano and Monif 1975).

Immune modulators (Table 5)

A variety of non specific immunostimulation therapies have been used to treat herpes infections.

Two trials using interferon in patients with oro-labial HSV have been reported. Both trials used prophylactic human leucocyte interferon in an attempt to prevent HSV reactivation. The two trials had conflicting results. The first trial in 41 renal transplant recipients showed no benefit (Cheesman et al. 1979). The other trial considered 27 patients following recent trigeminal root surgery and showed a significant reduction in the severity of subsequent HSV infections (Pazin et al. 1979). It is impossible to compare these two studies as the patient population and dosage regimens were completely different.

Levamisole a phenyl thiazolidine with anthelminthic and antianergic properties has been used for the treatment of genital herpes. Several open studies suggested some benefit (Kent and Verlinden 1974; Symoens and Brugmans 1974; O'Reilly et al. 1977) however, a double blind placebo controlled study on 109 patients with recurrent herpes showed that levamisole was no better than the placebo in regard to the severity of each attack and the frequency of recurrences. In addition severe side effects limited to use. These included dysgeusia (change of taste), hyperosmia (abnormal sense of smell), nausea, urticaria and neutropenia (Chang and Fiumara 1978).

TABLE 4

MISCELLANEOUS THERAPIES FOR GENITAL HERPES

Topical Surfactants

- Ether
- Chloroform
- Nonoxynol-9
- Thymol

Photodynamic Inactivation - Neutral Red
- Proflavine

Zinc

Lithium

Dimethyl sulphoxide (DMSO)

Povidone iodine

Oral or topical antibiotics

Topical steroids

Analgesic creams

Saline washes

Methyl alcohol

Gentian violet

Copper sulphate

Potassium permangernate

Vitamins E, C, B12

Ginseng

Aloe vera extracts

Red algae

Laser therapy

Urea

Tannic Acid Ointment

TABLE 5

IMMUNE MODULATING DRUGS FOR GENITAL HERPES

Interferons

Levamisole

Isoprinosine (Inosine pranobex)

TP5 (Thymopentin)

Vaccines

Vaccines

In an attempt to boost cell mediated immunity in patients with herpes a number of non specific vaccination techniques have been attempted. A controlled trial with smallpox vaccine in patients with orolabial disease (Kern and Schiff 1959) and a double blind trials with BCG vaccination in recurrent genital herpes, showed no benefit (Bierman 1976; Corey et al. 1976). Influenza and yellow fever vaccines are said to reduce the frequency of HSV infections (Neumann 1977; Miller 1979) however, neither have been tested in controlled trials. Tager in 1974 reported that patients treated in an uncontrolled study with Sabin poliomyelitis oral vaccine had a decreased frequency of recurrences, however, this finding is in direct contradiction to a subsequent placebo controlled study (Morel et al. 1980).

Two types of Herpes simplex virus vaccine have been produced, a whole virus vaccine and 2 subunit vaccines. The whole virus vaccine, a heat inactivated HSV antigen, has been available commercially in Germany for many years and despite claims that the vaccine decreases frequency and severity of HSV infections (Nasemann and Wassilew 1979), there are no controlled clinical trials to support this view. Two subunit vaccines were under evaluation. at the time when acyclovir was introduced. The one was a purified glycoprotein subunit type 2, said to contain no viral DNA (Hilleman et al. 1981), the other is a polypeptide subunit of HSV 1 (Skinner et al. 1982a,b). Neither of the 2 vaccines had yet been tested in controlled trials, and some concern had been expressed regarding the safety of vaccines possibly containing HSV genetic material (Wise et al. 1977).

PROBLEMS WITH PREVIOUS STUDIES

One of the major problems with many of the earlier studies was the inappropriate combination of oro-labial with genital disease. The natural history of these two infections is totally different and these two diseases should be studied separately.

Earlier I outlined the difference in natural history between primary and recurrent genital herpes. Many studies have not stratified patients into these two separate and distinct syndromes (Schofield 1964; Hutfield 1964; Kaufman et al. 1973b). Viral type and previous antibody status are also important parameters and the relevance of these factors has only recently been recognised (Reeves et al. 1981; Corey et al. 1981). Other common flaws in previous studies include high drop out rate, inappropriate patient assessment and lack of statistical analysis. (Schofields study with idoxuridine in 1964 had a drop-out rate of 25% after one week and the study by Parker (1977) with the same drug had a drop out rate of over 50%).

In several studies the assessment of therapeutic benefit was through self assessment by the patient (Friedrich 1973; Chang and Fiumara 1978) whereas the majority of studies relied on the investigators assessment of lesion severity and duration (Schofield 1964; Hutfield 1964; Felber et al. 1973; Kaufman et al. 1973b; Friedrich 1973; Laird and Roy 1975; Meyers et al. 1975; Hilton et al. 1978). Only a handful of previous studies have relied on the length of virus excretion as a measure of therapeutic benefit (Kaufman et al. 1973b; Taylor and Doherty 1975; Roome et al. 1975; Adams et al. 1976; Parker 1977; Corey et al. 1978; Vontver et al. 1979; Blough and Giuntoli 1979).

There are several reasons why the validity of open studies is questionable. The first and most important reason is the variability of the clinical features between one patient and another and also between one attack and another in the same patient. Similar variability is noted in the duration and severity of the first attack which may last anything from a few days to several weeks. Lack of appreciation of this variability explains why open studies with preparations such as idoxuridine, levamisole and photodynamic inactivation all showed clinical benefit whereas subsequent randomised double blind placebo controlled studies did not. The second reason why the findings of many of the open studies were at variance with double blind placebo controlled studies was the marked placebo effect. This effect was evident in the open studies of idoxuridine where patients on placebo assessed their own response to therapy as "excellent" (Hall-Smith et al. 1962; Schofield 1964).

THE IDEAL STUDY

Considering the problems with previous studies, the ideal drug trial in genital herpes should be designed as follows:

1. Patients with primary or recurrent genital herpes should be studied separately
2. In a study of first attack genital herpes - patients should be stratified into primary (no previous exposure to HSV) or initial (previous HSV) infections
3. Patients should be stratified into HSV 1 and HSV 2
4. The study should be randomised and double blind
5. As there is no accepted therapy for genital herpes the trial should be placebo controlled
6. Patient assessments should be objective (eg healing time, and the length of viral shedding) as well as subjective (pain, dysuria etc)
7. Follow up should be long enough to assess the effect of treatment on subsequent recurrences
8. In first attack genital herpes topical therapy should not be used as the disease is systemic.

THE AIMS OF TREATMENT

If one considers the problems of previous trials and the design of the ideal trial outlined above it is possible to formulate the major aims of treatment in genital herpes.

In primary genital herpes they are:

1. To reduce the duration and severity of symptoms
2. To reduce the time to healing
3. To reduce the duration of 'viral shedding'
4. To prevent the development of subsequent recurrences (or reduce their frequency)

5. To prevent or treat the complication associated with primary herpes (eg meningitis and radiculomyelopathy)

In recurrent herpes the aims of treatment are:

1. To decrease the severity and duration of each recurrence
2. To decrease the duration of viral shedding
3. To prolong the interval between recurrences or to prevent recurrences developing

THE DEVELOPMENT OF ANTIHERPETIC DRUGS

In 1959 Prusoff synthesised a halogenated pyrimidine analogue 5-iodo-2'-deoxyuridine (idoxuridine). The drug had marked antiviral activity against several DNA viruses including Herpes simplex virus (Herrmann 1961; Bauer 1977). The synthesis of idoxuridine opened the way to modern antiviral chemotherapy and in the years that followed several drugs were produced which had activity against Herpes simplex viruses.

The first generation of antiviral drugs were discovered as an offshoot of the production and subsequent testing of anticancer drugs. By and large these drugs are non-selective inhibitors of both viral and host cell replication, and as a consequence many are extremely toxic. Drugs synthesised during this phase include idoxuridine, cytosine arabinoside (cytarabine) and adenine arabinoside (vidarabine).

Over recent years scientific effort has been directed towards specific alteration in the structure of the drugs to create new preparations which inhibit virus specific process. Amongst the drugs produced in this way are the following, acyclovir, bromovinyldeoxyuridine (BVDU) and phosphonoformic acid. The structure of the various nucleoside analogues active against HSV is shown in Figure 5.

ACYCLOVIR

Acyclovir is a nucleoside analogue with a high potency and a selectivity for Herpes simplex viruses based on differences between cellular and Herpes simplex virus specified enzymes (Figure 6). First the herpes virus specified thymidine kinase phosphorylates acyclovir, whereas cellular thymidine kinase does not (Elion et al. 1977; Fyfe et al. 1978) into a monophosphate derivative which is subsequently converted into diphosphate and triphosphate derivatives, by cellular enzymes.

The acyclovir triphosphate inhibits viral DNA polymerase resulting in chain termination of the DNA template. In addition acyclovir monophosphate inactivates viral DNA polymerase by binding to the polymerase fifty times better than does the active template (Derse et al. 1981).

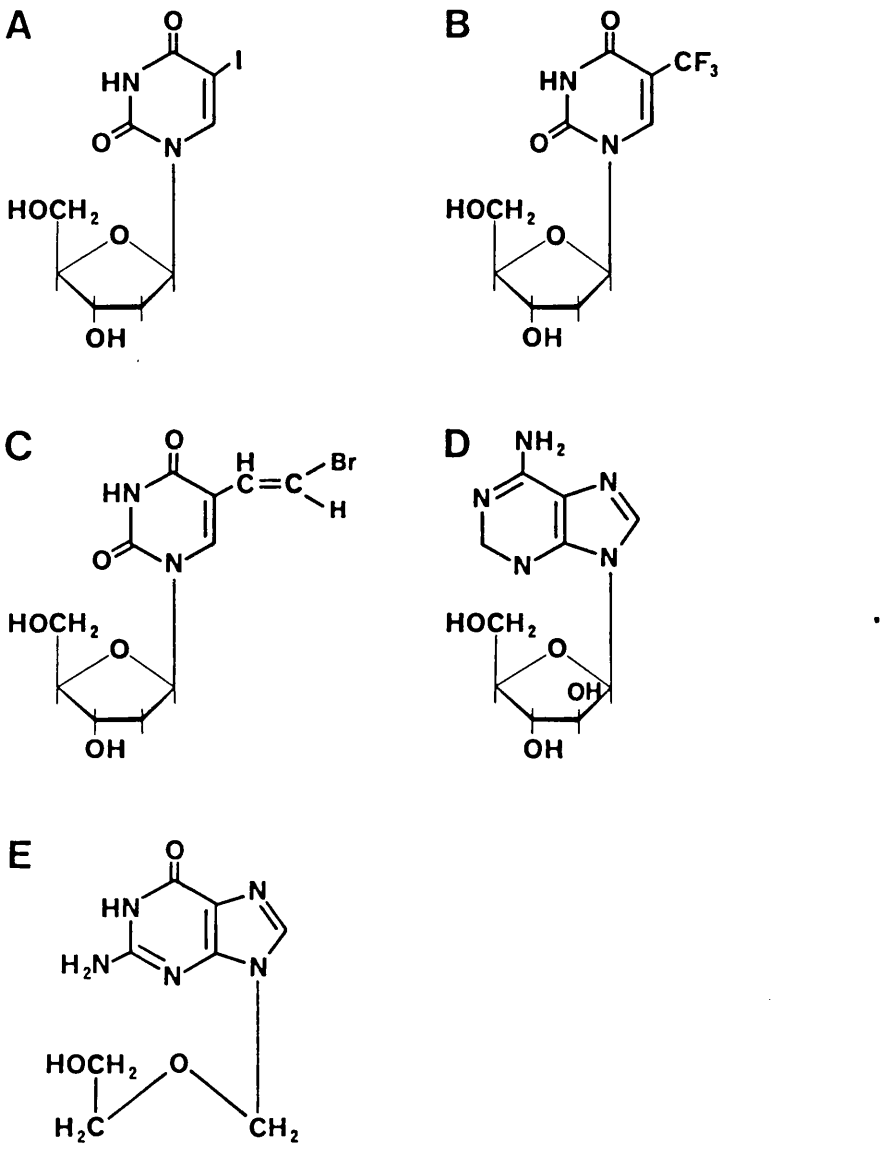
Range of antiviral activity

Acyclovir inhibits Herpes simplex virus in vitro and in vivo (Schaeffer et al. 1978). Varicella zoster which also has the thymidine kinase enzyme appears to be less sensitive to the drug (Biron and Elion 1980). Acyclovir has less effect on Cytomegalovirus and the Epstein Barr virus in vitro even with higher drug concentrations (Tyms et al. 1981); both of these viruses lack the virus specific thymidine kinase. The drug also has some effect on the Hepatitis B virus (which has no virus specific thymidine kinase) possibly by inhibiting the production of complete hepatitis B virus particles (Weller et al. 1983).

Clinical trials and safety (Up till the time we completed the first study with acyclovir)

Double blind controlled trials have shown acyclovir to be useful in ophthalmic herpes simplex infections when used topically (Jones et al. 1979; Collum et al. 1980). Intravenous and oral acyclovir has been used in immunocompromised patients (Mitchell et al. 1981; Straus et al. 1982), heart transplant patients (Chou et al. 1981) and patients with bone marrow transplants (Wade et al.

FIGURE 5



CHEMICAL STRUCTURE OF NUCLEOSIDE ANALOGS WITH ANTIHERPETIC ACTIVITY

A. Idoxuridine
B. Triflourothymidine
C. Bromovinyldeoxyuridine
D. Vidarabine
E. Acyclovir

1982) with disseminated mucocutaneous herpes to excellent effect, and to prevent herpes simplex infection in bone-marrow recipients (Saral et al. 1981). The results of intravenous therapy in herpes zoster have been less impressive (Peterslund et al. 1981).

The drug appeared to have minimal toxicity especially in normal patients (Anon 1981) and with its novel mode of action, offered considerable hope for the treatment of genital herpes.

INOSINE PRANOBEX (Inosiplex, Isoprinosine and Methiosprinal)

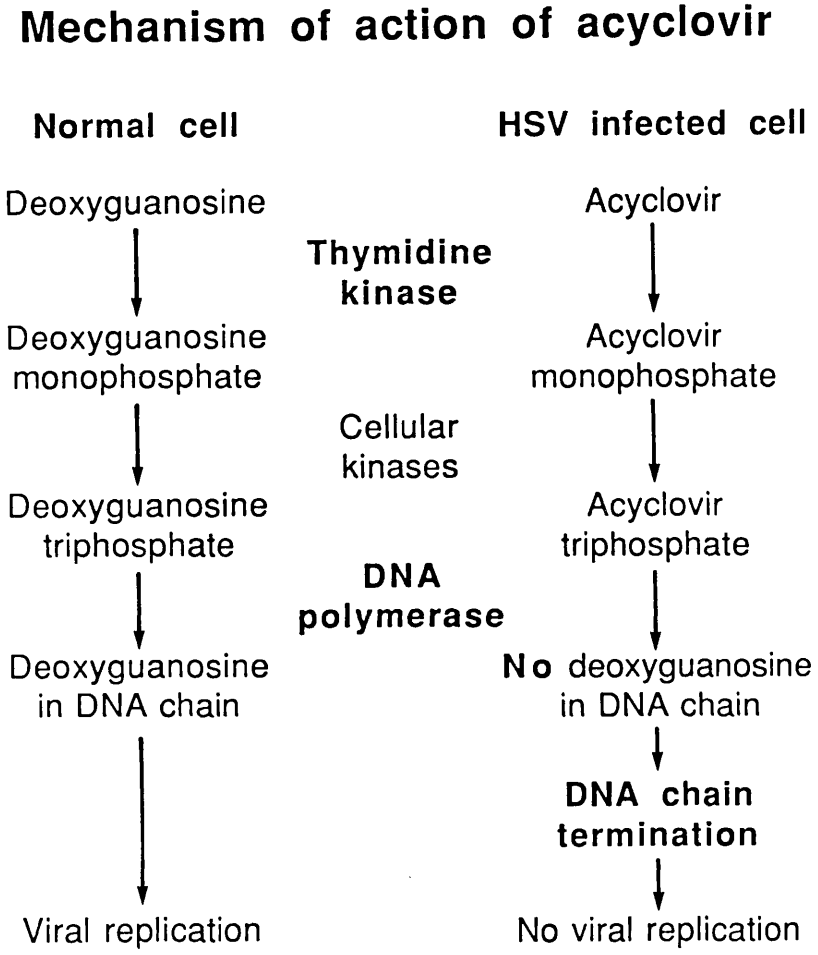
Inosine pranobex is a unique drug bearing no resemblance to any existing agent. It is formed from the p-acetamidobenzoate salt of N,N diethylamino-2 propanol and inosine in a 3:1 molar ratio (Figure 7).

The drug is said to have both immunopotentiating and antiviral activity although the detailed mechanisms involved in the latter have not been fully elucidated. The drug enhances T cell proliferation to mitogens and antigens, and encourages interleukin production (Hadden et al. 1976; Wybran et al. 1978).

Previous clinical trials (up till the time we commenced the first study with inosine pranobex)

Several trials have been reported in patients with mucocutaneous herpes (Wickett et al. 1976; Corey et al. 1979; Bradshaw et al. 1980; Bouffat and Sourat 1980; Galli et al. 1982; Salo and Lassus 1983; Kalimo et al. 1983). The results of these studies are difficult to interpret as several have only been reported in abstract form, many were poorly designed and different doses and durations of treatment were used. Finally, several combined both oral and genital infection and did not separate first attacks from recurrences. Despite these reservations there was some suggestion that the drug may be beneficial for the treatment of first attack and recurrent genital herpes. There were no studies looking at the long term suppressive effects of inosine pranobex.

FIGURE 6

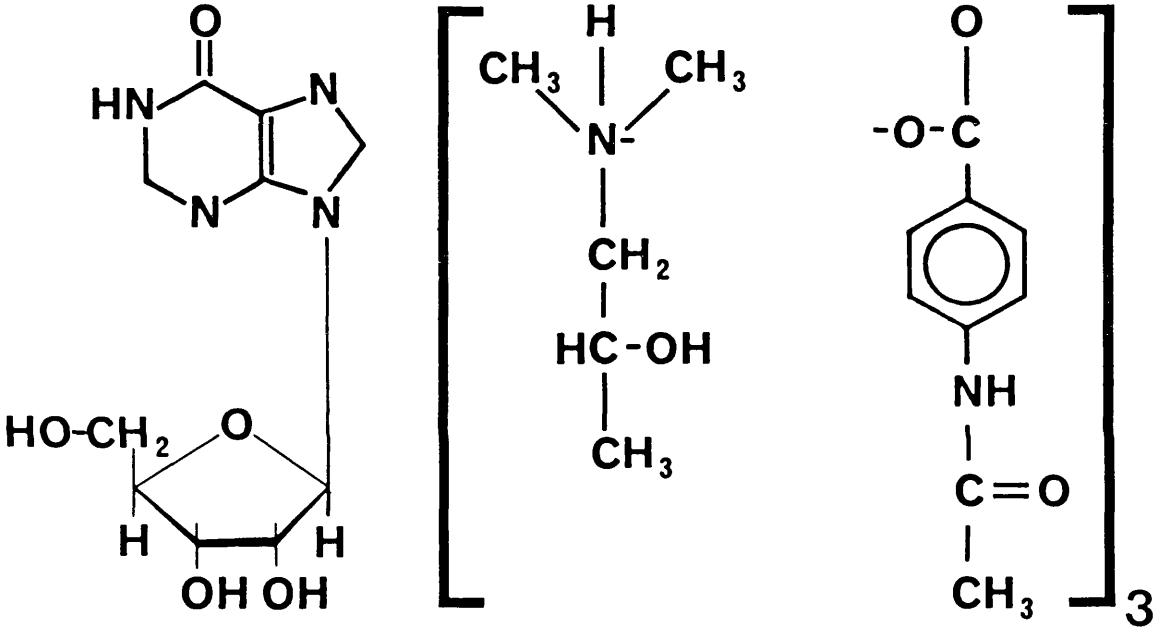


MECHANISM OF ACTION OF ACYCLOVIR

The drug acts at three points:

1. Competition with deoxyguanine for thymidine kinase
2. Competition with DNA POLYMERASE
3. DNA chain termination

FIGURE 7



CHEMICAL STRUCTURE OF INOSINE PRANOBEX

CHAPTER TWO

GENERAL METHODS

INTRODUCTION

This section will consider the methods applicable to all the trials. This will include the design of the clinical trials, the staffing of the studies, the virological methods and the statistical tests used. Detailed information about the methodology of each individual trial will be given in the appropriate section.

DESIGN OF THE TRIALS

Six studies have been conducted, 4 using acyclovir alone and 2 comparing acyclovir with inosine pranobex. The details and rationale of each study are presented in the appropriate sections. All 6 studies were randomised and 5 were double blind (the remaining study was an open study designed to assess the safety and efficacy of long term acyclovir). Three of the studies with acyclovir alone were placebo controlled. The 2 studies comparing acyclovir with inosine pranobex used a double dummy technique; this involved half the patients taking active acyclovir and dummy inosine pranobex and the remainder active inosine pranobex and dummy acyclovir. In the 5 controlled studies active drug and placebo were packaged in identical containers, and appeared to be indistinguishable.

Local "Ethical Committee" approval was obtained for all the studies. Written consent was obtained from all participating patients.

STAFFING

The author was responsible for the overall design, co-ordination and running of 5 of the trials. The remaining study, "Treatment of First Attack Genital Herpes: Acyclovir versus Inosine Pranobex" was jointly co-ordinated by the author and Dr Kinghorn in Sheffield. In addition all the clinical observations, data recording and specimen collection in the first study and approximately 50% the remaining studies were performed by the author. The remainder of the clinical work was carried out by a research fellow and a research nurse. All

viral isolation, typing and serology was performed in the department of Virology at the Middlesex Hospital or University College London by Dr S. Sutherland or Dr G. Patou.

Biochemical and haematological tests were carried out in the routine laboratories at the Middlesex Hospital.

VIROLOGY

Swabs were sent to the laboratory in Viral Transport Medium and inoculated into Human Lung Embryo Fibroblasts which were incubated at 37°C and examined daily for cytopathic effect (Hsiung et al. 1984). The first isolate from each patient was confirmed by neutralisation tests (Zheng et al. 1983).

Viral isolates were typed using either restriction enzyme technology (Londsdale 1979) with 3 restriction endonucleases, EcoRI, HindIII, and Hpa1, or an immunofloresence test using monoclonal antibodies (Grist 1974).

Complement fixing antibody to HSV was analysed in microtitre plates using the method of Bradstreet and Taylor (1962).

STATISTICAL ANALYSIS

Comparison of demographic characteristics and the frequency of recurrences was carried out by either the Chi-squared or Mann Whitney test.

Differences between groups in healing time, duration of symptoms and duration of viral shedding was assessed using a Log Rank Test (Peto and Pike 1973). Medians were used because many of the variables had a skewed distribution.

Differences in the time to the first recurrence were again assessed using a Log Rank Test (Peto and Pike 1973).

Other tests used included a paired T test to compare the duration of recurrences and a test of "homogeneity for ordered alternatives" (Bartholomew 1955a,b) to compare the frequency of change of drug dosage. The latter 2 tests were only used in the study to assess the long term safety of acyclovir.

All the statistical analysis was done by Mr D Hindley and Mr P Williams, Academic Department of Genitourinary Medicine, Middlesex Hospital.

CHAPTER THREE

INTRAVENOUS ACYCLOVIR IN PRIMARY GENITAL HERPES

INTRODUCTION

As mentioned earlier the first attack of genital herpes is often a severe illness lasting 2-3 weeks, characterised by pain and dysuria and often accompanied by systemic symptoms including headache and malaise. Acyclovir appeared to offer a realistic hope for treating the condition.

The aims of the study were to find out whether acyclovir decreased the length and severity of the illness, the duration of viral excretion and frequency of subsequent recurrences.

Intravenous therapy was decided upon for several reasons. The first was that in addition to the genital symptoms the first attack is usually a systemic illness with fever and malaise. The second was that some complications are also systemic (namely meningitis and sacral radiculopathy). The third and most important reason was the question of drug absorption and serum levels which may have varied with oral therapy. Finally, at the time when the trial was initiated the majority of human studies (both pharmacological and toxicological) had been performed with the intravenous preparation.

METHODS

Patient selection

All patients with a first attack of genital herpes presenting to the Department of Genito Urinary Medicine at the Middlesex Hospital were interviewed by the author and considered for inclusion. Patients with genital herpes of 6 days duration or less, who were considered to be severe enough to warrant hospital admission were offered the opportunity of participating in the trial. Written informed consent was obtained from all patients.

Patient exclusions

a. Patients under 16 years of age
b. Patients known to be pregnant
c. Female patients not using adequate contraception (usually the pill or I.U.C.D.)
d. Patients unwilling or unable to be hospitalised for one week.
e. Patients not remaining in London for at least 6 months after therapy
f. Patients with clinical evidence of renal impairment
g. Patients with a previous history of genital herpes
h. Patients who had used specific antiviral therapy in the previous 14 days

Initial interview and examination

A full medical and sexual history was obtained and a complete examination performed on each patient. Particular note was made of genital and systemic symptoms, and the site, nature and number of genital lesions. The details were recorded on a standardised recording schedule (Appendix 1).

Clinical assessments

All patients were admitted to the Middlesex Hospital for seven days (or longer when this was considered necessary). Patients were examined daily whilst in hospital. After discharge they were assessed twice weekly until complete healing occurred. Symptoms including pain, dysuria, discharge, numbness, itching, headache and malaise, and the appearance of the lesions (vesicle, ulcers or crusts) were assessed and recorded at each visit.

In order to compare the effect of acyclovir and placebo a number of clinical assessments were used.

1. Healing time
2. Duration of new lesions formation
3. Duration of vesicles
4. Duration of symptoms

Treatment

The trial was randomised, double blind and placebo controlled. Both acyclovir and placebo were packaged in indistinguishable vials with individual code numbers. The placebo was mannitol. The dosage of acyclovir was 5mgm/Kg 8 hourly for 15 doses.

The first 4 patients received the drug or placebo as a bolus injection. One of the 4 had a transient rise in urea and creatinine. Consequently the rest were given treatment by slow infusion over 45-60 minutes through an indwelling intravenous canula.

In addition patients were prescribed:-

1. Saline bathing using 2 tablespoons of salt per quarter filled bath at least four times daily
2. Analgesics - usually soluble aspirin ii 4 hourly if required
3. Night sedation if required

Virology

Swabs were taken from all lesions on admission, and then daily during hospitalisation and then twice weekly until complete healing occurred. Serum was obtained on admission and on days 12 and 28 for estimation of complement fixing herpes antibodies. The method of handling of swabs and serum in the laboratory is outlined in Chapter 2.

Viral isolates from the first episode and any recurrences were typed using restriction enzyme technology (Chapter 2).

Laboratory investigations and safety testing

On admission tests were taken to exclude gonorrhoea, trichomoniasis candidiasis, and syphilis. All female patients had cervical cytology performed. Additional blood tests taken on admission included a full and differential blood count and ESR, urea, electrolytes and creatinine and liver function tests. The blood tests were repeated on days 4 and 7. Any unusual occurrences or events which might be attributable to the drug were recorded.

Long term follow up

After complete healing patients were asked to return monthly for 6 months and also the first time they suffered a recurrence. At each visit the number and duration of recurrence was recorded, and genital examination performed. Swabs for viral culture were taken in females from the vulva and cervix and in males the penis, perianal area or rectum, whether lesions were present or not.

RESULTS

Patient characteristics (Table 6)

Fifteen patients received the drug and 15 placebo. Patients were stratified into those with primary infection (those with no previous exposure to Herpes simplex virus) and non primary first episode genital infection (those whose serum antibody levels indicated a previous exposure to Herpes simplex virus).

Twenty patients had primary infections and their reciprocal complement fixing antibody titres rose from <2 in the first serum to 32-256 in the second sample tested. The six male patients all had primary infections. Ten patients were classified as non primary first episode genital infections. Three of these had no antibody rise from titres of 1/32 or 1/64 and seven showed antibody rise of 4 fold or greater. Two in this group with starting titres of <1 in 8 may have had primary infections. All but one of the isolates were typed. In the remaining

TABLE 6

PATIENT DEMOGRAPHY COMPARING ACYCLOVIR AND PLACEBO TREATED PATIENTS

	Acyclovir	Placebo
	n = 15	n = 15
Age in years*	22 (18-43)	21 (16-31)
Number of Females/Males	12/3	12/3
Median duration of symptoms+	4	4
External genital lesions	14	15
Internal genital lesions	14	15
Systemic symptoms or signs	10	8
HSV 2/1	10/5	8/6
Primary/Initial	12/3	8/7

* Median (range)

+ Days before entry

patient HSV failed to grow on tissue culture. Ten of the acyclovir treated patients had HSV type II and 5 type I, compared with 8 type II's and 6 type I's in the placebo group. There were 6 males, 3 in each group. Five of them were homosexual with herpetic proctitis. Nine of the 12 female patients who received the drug had primary infection and 3 non primary first episode, compared with 5 primary and 7 non primary in the placebo group. At presentation no statistically significant differences existed between patients and controls in relation to age, duration of lesions and the mean number of severity of symptoms.

Healing time (Table 7)

The median healing time in the four patient groups (females, primary infection, HSV2 and all patients) comparing acyclovir and placebo treated patients is shown in Table 7. There were too few male patients, patients with non-primary first episode and HSV1 infection to analyse separately. Acyclovir treated patients in all the groups healed more quickly than those who received the placebo. The median healing time in all acyclovir treated patients was half that of the placebo treated group (7.75 days vs. 14 days $p < 0.01$). This difference is represented graphically in figure 8 where it can be seen that over half the acyclovir treated patients were healed by day 7 compared with none of the control group. All the patients treated with the drug were healed by day 16, whereas some placebo treated patients continued to have lesions for up to 30 days.

Internal lesions seemed to heal more swiftly in response to acyclovir than those externally. In all the groups acyclovir treated patients had median healing times significantly shorter than placebo treated patients.

New lesion formation and duration of vesicles (Table 8)

Five of the 15 acyclovir treated patients (33%) continued to form new lesions after the onset of therapy compared with 10 out of the 15 in the control group ($p<0.05$). Figure 8 shows the duration of new lesion formation in all patients.

TABLE 7

HEALING TIME COMPARING ACYCLOVIR AND PLACEBO TREATED PATIENTS

	Acyclovir	Placebo	P Value
A) ALL LESIONS			
Female	7 (5-16)	12.5 (7->21)	< 0.05
Primary	9 (5-16)	15 (8-30)	< 0.05
HSV 2	8 (5-15)	13.5 (8->21)	< 0.05
All patients	7 (5-16)	14 (7-29)	< 0.001
B) EXTERNAL LESIONS (vulva, penis, scrotum, perineum, perianal area)			
Female	7 (4-16)	10.5 (5-17)	ns
Primary	7 (5-17)	11 (6-29)	ns
HSV 2	8 (5-17)	11 (5-17)	ns
All patients	7 (4-16)	11 (5-29)	ns
C) INTERNAL LESIONS (cervix, vagina, anal canal and rectum)			
Female	5 (4-7)	8 (2->21)	< 0.05
Primary	6 (4-7)	13.5 (2-22)	< 0.05
HSV 2	5 (4-7)	12.5 (2->22)	< 0.05
All patients	5.5 (4-8)	10 (2->22)	< 0.01

All values given a median (range) in days

No acyclovir treated patient formed new lesions beyond the third day whereas in the control group new lesion formation continued up to 16 days. The median duration of vesicles in all acyclovir treated patients was 3 days compared with 5 in placebo recipients ($p<0.05$). Figure 8 shows that vesicles persisted in the placebo group for up to 17 days compared to 9 days in the acyclovir treated group.

Symptoms (Table 9)

Improvement in symptoms was less impressive. There were no significant differences in the duration of pain, dysuria or discharge between the 2 groups, however, when all symptoms were combined the median duration was shorter in the acyclovir treated patients than controls (6.5 days vs 9 days ($p<0.05$). Figure 8 shows the duration of any symptoms comparing acyclovir treated patients with controls. By the 10th day all the acyclovir treated patients were symptom free, compared with half the placebo group.

Viral shedding (Table 10)

The most dramatic effect of the drug was seen in regard to the duration of viral shedding.

Table 10 shows the median duration of viral shedding from all lesions, internal lesions and external lesions comparing acyclovir treated patients with placebo treated patients. In all the groups except from females with internal lesions patients treated with the drug were found to shed virus for a significantly shorter period than those who did not. No patient who received the drug was found to shed virus after the fifth day of treatment whereas viral excretion continued for up to 21 days in those who did not (Figure 8).

Safety

All the patients in the trial had normal haemoglobin, red cell count and indices throughout. One patient on placebo had an elevated white blood count (WBC)

TABLE 8

DURATION OF NEW LESION FORMATION AND VESICLES COMPARING ACYCLOVIR AND PLACEBO TREATED PATIENTS

A. NEW LESION FORMATION

	ACYCLOVIR		PLACEBO		P VALUE
All	0	(0-3)	3	(0-16)	< 0.001
Female	0	(0-3)	2	(0-16)	< 0.05
Primary	0	(1-3)	3	(0-16)	< 0.01
HSV 2	0	(0-3)	3	(1-16)	ns

B. VESICLES

All	3	(0-8)	5	(0-17)	< 0.05
Female	2.5	(0-8)	5	(0-17)	ns
Primary	2.5	(0-6)	5	(0-17)	ns
HSV 2	3	(0-8)	7	(3-17)	ns

All values given as a median (range) in days

TABLE 9

SYMPTOMS COMPARING ACYCLOVIR AND PLACEBO TREATED PATIENTS

	ACYCLOVIR	PLACEBO	P VALUE
A) PAIN			
All patients	4 (0-9)	4 (1-17)	ns
Female	4 (0-9)	4 (1-15)	ns
Primary	3.5 (0-7)	5 (1-17)	ns
HSV 2	4 (0-8)	6 (0-15)	ns
B) ALL SYMPTOMS			
All patients	6.5 (2-10)	8.5 (2-21)	< 0.05
Female	6.8 (2-10)	7.3 (2-21)	ns
Primary	6.3 (3-8)	8.8 (5-21)	ns
HSV 2	6 (3-10)	13 (3-21)	< 0.05

All values given as a median (range) in days

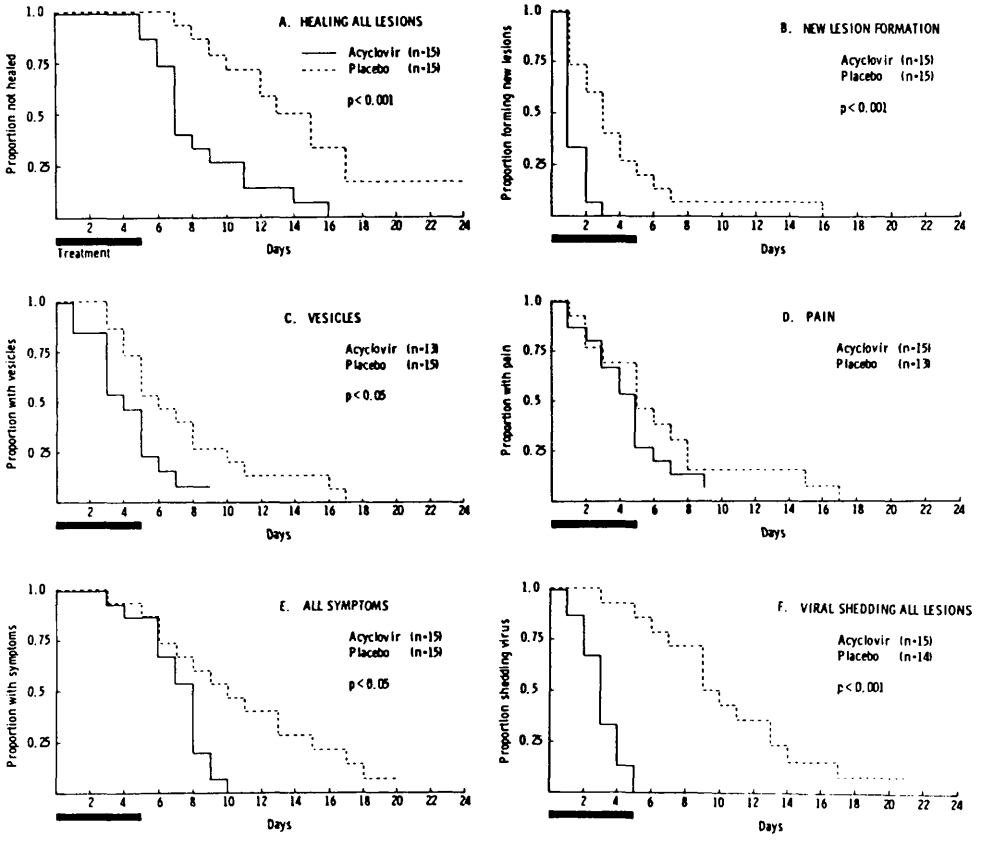
TABLE 10

DURATION OF VIRAL SHEDDING COMPARING ACYCLOVIR AND PLACEBO TREATED PATIENTS

	ACYCLOVIR	PLACEBO	P VALUE
A) ALL LESIONS			
All patients	2 (0-5)	8.5 (2->20)	< 0.001
Female	2 (0-5)	7.5 (2->20)	< 0.001
Primary	2 (0-5)	8.8 (2->20)	< 0.001
HSV 2	2 (0-5)	10 (3->21)	< 0.01
B) EXTERNAL LESIONS			
All patients	1.5 (0-5)	7.8 (2->20)	< 0.001
Female	1.0 (0-5)	5.5 (2->20)	< 0.001
Primary	2.6 (0-5)	8.5 (4->20)	< 0.01
HSV 2	2.7 (0-5)	8 (2->21)	< 0.05
C) INTERNAL LESIONS			
All patients	2 (0-5)	6 (2->21)	< 0.01
Female	2 (0-5)	3 (2->21)	ns
Primary	2 (0-5)	8.5 (2->21)	< 0.05
HSV 2	1.8 (0-5)	9 (2->21)	< 0.05

All values given as median (range) in days

FIGURE 8



TIME TO HEALING AND DURATION OF NEW LESIONS, VESICLES, PAIN, ALL SYMPTOMS AND VIRAL SHEDDING COMPARING ACYCLOVIR AND PLACEBO TREATED PATIENTS

prior to commencing therapy, and this remained elevated during the course of the treatment. Two other patients, one in each group, had elevated WBC during the course of therapy. Elevations were in all cases moderate. The highest WBC was 15 x 10^9 /l. Abnormal differential counts were recorded in 10 patients, five in each group. The abnormalities were in all cases minimally above the upper limits of normal and were almost certainly a reflection of the illness rather than the treatment.

Seven patients had abnormal LFT's during the study period (4 acyclovir and 3 placebo). These abnormalities were all mild and short lived and did not differ between the two groups.

One of the patients who received acyclovir in a bolus had a transient rise in urea (7.1 mmol/l) and creatinine (137 umol/L) on day three. Both tests returned to normal in 48 hours. Table 11 shows the mean creatinine levels comparing acyclovir and placebo treated patients on day three. Patients treated with acyclovir had a significantly higher creatinine level than placebo treated patients. However, when the four patients who received the drug or placebo by bolus injection were excluded this difference was no longer apparent.

Two patients had nausea, vomiting and dizziness. Both received acyclovir and dihydrocodeine. We believe the symptoms were due to dihydrocodeine.

Long term follow up

Twenty nine of the 30 patients were followed for a minimum of six months, the remaining patient was lost to follow up 30 days after commencing therapy. Eleven patients were followed for one year and eight for over one year. The mean length of follow up in all patients (excluding the patient lost after 30 days) was 344 days (range 180 - 697 days).

TABLE 11

MEAN SERUM CREATININE (in μmol/litre) ON DAY 3 COMPARING ACYCLOVIR AND PLACEBO TREATED PATIENTS

PATIENT GROUP	ACYCLOVIR	PLACEBO	P VALUE
All patients	80.56	73.12	< 0.05
Slow I.V. infusion[+]	76.6	76.3	ns

[+] Excluding the 4 patients who received bolus injections

Normal creatinine value: 45-110 μmol/l

Time to first clinical recurrence

1. Acyclovir treated patients compared with placebo

Figure 9 shows the time to first clinical recurrence comparing patients who received the drug and those who received the placebo. The percentage of patients whose illness had recurred at various points in time was similar in the two groups. For example, at the end of six months 67% of the acyclovir patients and 57% of the placebo patients had recurred and at the end of a year 83% of the acyclovir treated patients and all of the placebo treated patients had recurred.

2. HSV2 infection compared with HSV1

There was a significant difference in the time to first recurrence comparing HSV 1 and HSV 2 infections irrespective of treatment. At the end of six months 45% of patients with HSV type 1 and 82% of those with HSV type 2 had recurred and by the end of a year 59% of the type 1 and all the type 2 patients had recurred ($p<0.02$) (Figure 10).

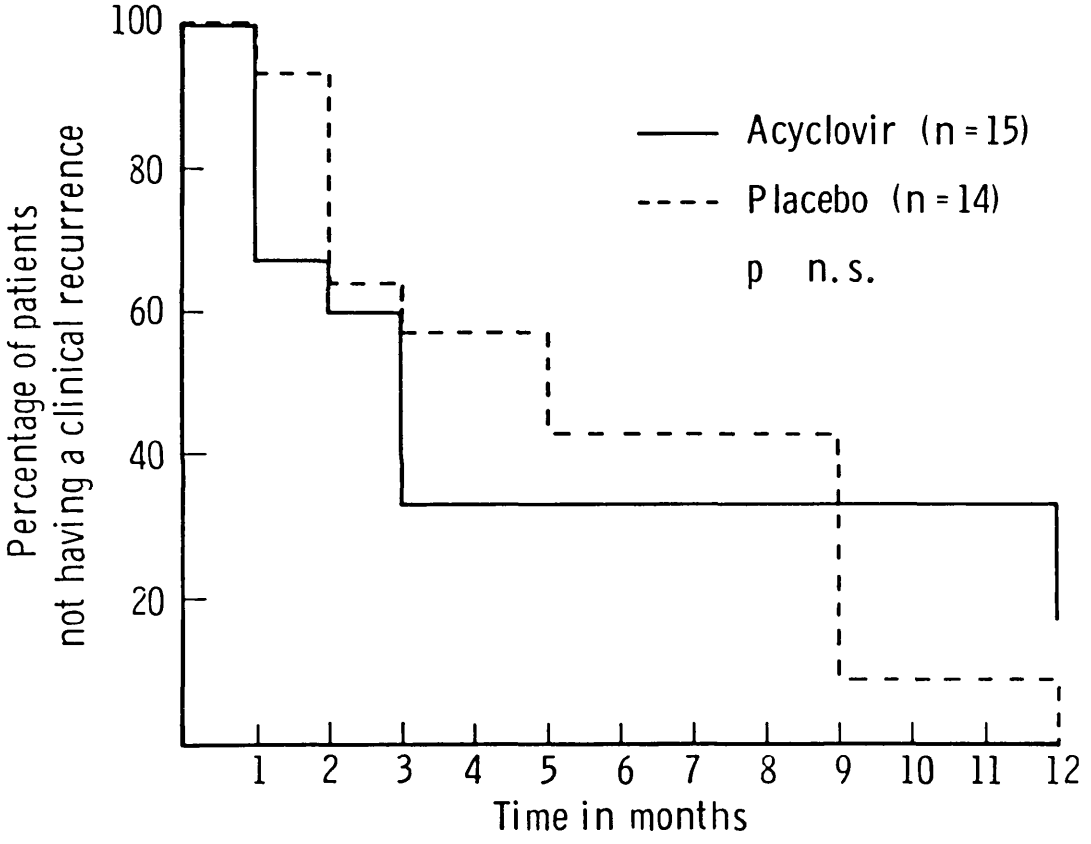
The frequency of recurrences

Table 12 shows the frequency of recurrences comparing acyclovir and placebo treated patients at the end of three and six months. There were no significant differences. In contrast at the end of three months the median number of recurrences in patients with HSV 1 infection was 0.27 and in those with HSV 2 it was 1.47 ($p<0.01$). At six months the values were 0.73 and 2.53 ($p<0.05$).

Viral isolation and typing of recurrences

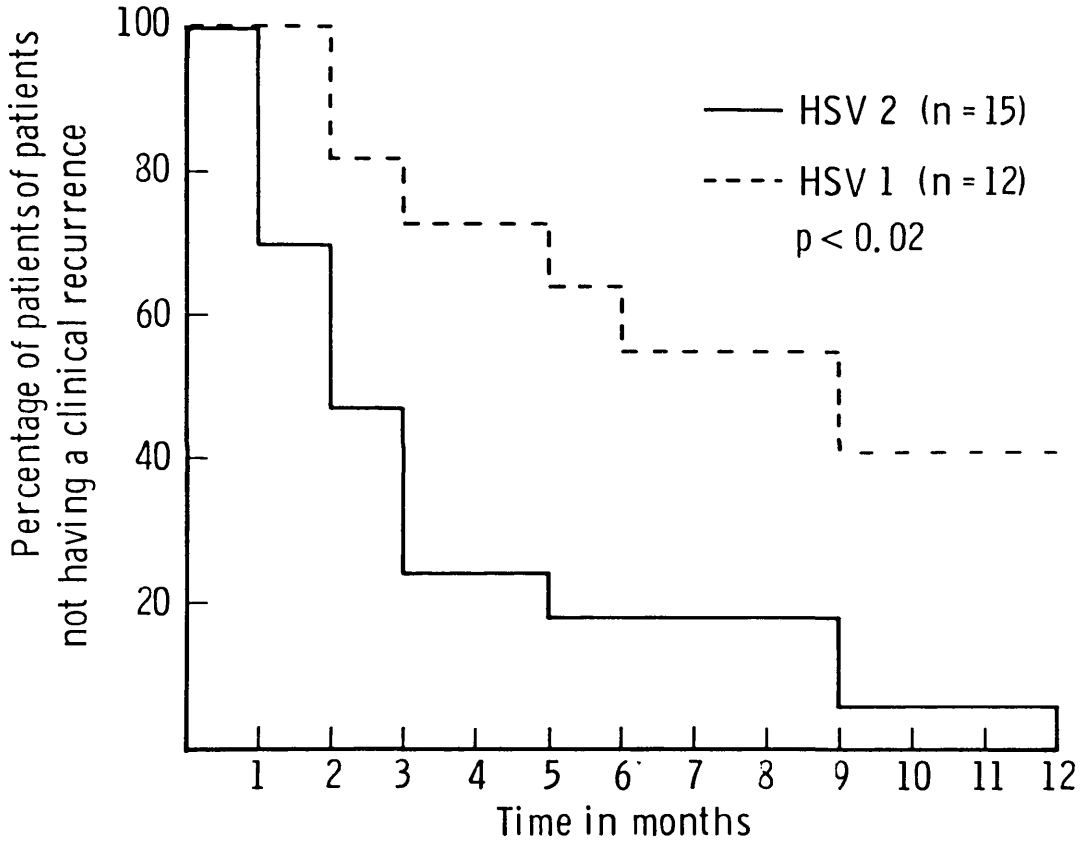
Herpes simplex virus was isolated from 28 recurrences in 16 patients. In addition HSV was isolated from six patients during a time when the patients had neither symptoms nor signs of a recurrence. In all instances except one, the virus isolated during the recurrences was identical to the first attack.

FIGURE 9



TIME TO FIRST RECURRENCE COMPARING ACYCLOVIR AND PLACEBO RECIPIENTS

FIGURE 10



TIME OF FIRST RECURRENCE COMPARING PATIENTS WITH HSV 1 AND HSV 2 INFECTIONS

TABLE 12

THE MEAN NUMBER OF RECURRENCES BY 3 AND 6 MONTHS

ACYCLOVIR VS PLACEBO

TIME (MONTHS)	ACYCLOVIR	PLACEBO	P V A L U E
0-3	1.33	0.64	ns
0-6	2.67	1.64	ns

HSV 1 VS HSV 2

	HSV 1	HSV 2	
0-3	0.27	1.47	< 0.01
0-6	0.73	2.53	< 0.05

One patient who had a HSV 1 isolated during the primary attack returned at six months with a severe 'recurrence' which was identified as type 2. This 'recurrence' lasted almost two weeks and was almost as severe as the first attack, and was probably a new infection.

Asymptomatic viral isolation

HSV was isolated from six patients who had no symptoms or signs of a recurrence at the time. In three patients the asymptomatic recurrences occurred soon after the end of therapy. All had received acyclovir and had type 2 primary infection.

The first was a 25 year old female with severe vulval ulceration and necrotic cervicitis. HSV 2 was originally isolated from the cervix, vulva and the axilla. Virus shedding ceased after day five. Complete healing was noted at day 10. On day 15 when the patient re-attended for routine follow up, she was asymptomatic and no lesions were noted however HSV type 2 was isolated from the vulva.

The second patient was a 25 year old female also with extensive vulval ulceration and necrotic cervicitis. HSV 2 was isolated from cervix, vulva and perineum and ceased after day 4. Complete healing was noted on day 12. On day 36 at routine follow up HSV was isolated from the vulva.

The final patient was a 21 year old homosexual man with an extensive proctitis who shed virus from the rectum and throat for 2 days. Healing was complete by day 8. On day 22 at routine follow up HSV was isolated from the rectum. In the remaining 3 patients asymptomatic viral shedding was noted many months after the first attack.

CONCLUSIONS

1. Intravenous acyclovir significantly reduces the duration of viral shedding, the time to healing, the duration of vesicles, and the duration of new lesions in patients with severe first attack genital herpes.

2. The effect of the drug on symptoms is less dramatic. The duration of all symptoms was significantly reduced however, there was no significant effect on pain, dysuria and discharge.

3. Intravenous acyclovir does not prevent the development of subsequent recurrences.

4. Infection with HSV type 2 is more likely to recur than infection with HSV type 1.

5. Asymptomatic viral excretion may occur after first attack of genital herpes irrespective of whether the patient has been treated with acyclovir or not.

CHAPTER FOUR

ACYCLOVIR AND THE PREVENTION OF RECURRENCES IN PRIMARY GENITAL HERPES: THE EFFECT OF PROLONGED ACYCLOVIR TREATMENT

INTRODUCTION

Short courses of acyclovir (intravenous, oral and topical) have been shown to hasten healing and reduce the duration of symptoms and viral shedding in patients experiencing a first attack of genital herpes. The drug does not however appear to reduce the frequency of subsequent recurrences (See previous chapter and Corey et al 1982, 1983b; Nilsen et al. 1982; Bryson et al. 1983; Thin et al. 1983; Fiddian et al. 1983; Kinghorn et al. 1983; Mertz et al. 1984). For a full discussion see chapter 8. For many patients recurrences are the most troublesome aspect of genital herpes and constitute a reservoir of infection in the community. In the previous study we showed that 30% of patients with HSV type 2 had had a recurrence within 6 weeks of the primary attack. We therefore decided to compare a 5 day course of acyclovir with a prolonged course in patients experiencing a first attack of genital herpes, to see if the prolonged course could reduce the likelihood of subsequent recurrences.

METHODS

Patient selection

Female patients attending our department within five days of a first attack of genital herpes were offered the opportunity of participating in the study. The study was limited to female patients since they usually have more severe infections. Exclusion criteria were identical to those used in the previous study. Written informed consent was obtained from all patients.

Clinical evaluation and viral isolation

The clinical status was assessed at entry, daily for the first seven days (excluding weekends) and twice weekly for the following six weeks. At the end of six weeks patients attended monthly, for a minimum of six months and were also asked to attend if they suffered a recurrence. At each visit a history was taken and an examination performed. The results were recorded on a standardised recording schedule. (Appendix 2)

Swabs for viral culture were taken at each visit and handled as previously described. Isolates were typed using either restriction endonuclease analysis or an immunofluorescence test using monoclonal antibodies (see chapter 2).

Treatment

Patients were randomised into two treatment groups. Patients in treatment Group A received the prolonged course of acyclovir; 200mg five times daily for five days followed by acyclovir 200mg four times daily for 37 days; and those in group B received the short course of acyclovir 200 mg, 5 times daily for 5 days followed by placebo four times daily for 37 days. The total duration of therapy in both groups was therefore 42 days.

Safety testing

Blood for a full and differential blood count, urea, creatinine, electrolytes and liver function tests were taken prior to the onset of treatment and on days 5, 20 and 40.

RESULTS

Patient characteristics (Table 13)

Sixty patients were entered into the study. Half received treatment A and half treatment B. At presentation there were no significant differences between the two treatment groups in relation to age, or duration and severity of signs and symptoms. Viral isolates were typed in 55 of the 60 patients. Forty-one of the 55 (75%) were HSV type II and 14 (25%) HSV type I. The distribution of viral types between the two treatment groups was similar. All but one of the patients were followed for a minimum period of six months. One group B patient was lost to follow up after 37 days. The median duration of follow-up in Group A patients was 317 days and in Group B patients 297 days. This difference was not statistically significant.

TABLE 13

PATIENT DEMOGRAPHY COMPARING PATIENTS IN THE TWO TREATMENT GROUPS

TREATMENT GROUP	A	B
	N = 30	N = 30
Age (Years)+	24.3 (5.7)	25.2 (7.0)
Duration of symptoms (days)+	4.0 (1.6)	4.1 (1.6)
Duration of signs (days)+	2.7 (1.2)	3.0 (1.4)
No. with previous oral HSV	6	7
No. with systemic symptoms	20	25
No. with lymphadenopathy	27	29
No. with Type I virus	9	5
No. with Type II virus	18	23
No. not typed	3	2

+ Mean (+/- SD)

Treatment A: Acyclovir 200 mg 5 X daily X 5days, followed by Acyclovir 200 mg 4 X daily for 37 days.
Treatment B: Acyclovir 200 mg 5 X daily X 5 days, followed by Placebo 1 tablet qds X 37 days

First attack healing time, duration of viral shedding and symptoms (Table 14)

There were no significant differences in healing times, the duration of viral shedding or the duration of local or systemic symptoms comparing patients in the two treatment groups. Individual symptoms including pain, itching, dysuria, discharge, fever, headache and malaise were also compared and showed no significant differences between the two groups.

Time to first recurrence and frequency of recurrences

The median time to the first recurrence in Group A patients was 66.5 days compared to 24 days in Group B. This difference was statistically significant ($p < 0.0001$) for the 42 day treatment period but not for the full duration of follow up (Figure 11). During the first 42 days (the duration of therapy) patients in treatment group A had significantly fewer recurrences than those in group B (0.12 recurrences/month compared to 0.76 recurrences/month p 0.0004). However, during subsequent follow up there was no significant differences in the frequency of recurrences between the two treatment groups (Table 15).

In contrast the median time to the first recurrence was significantly longer and the frequency of recurrences significantly less in patients with HSV type 1 than in those with HSV type II, irrespective of the treatment. The median time to the first recurrence in HSV I patients was 193 days compared with 44 days in patients with HSV II (Figure 12). Table 16 shows the frequency of recurrences comparing patients by viral type. At each follow up period patients with HSV 1 infection had significantly fewer recurrences than those with HSV II. For example, looking at the period 0-180 days there were 0.07 recurrences/month in HSV I patients compared to 0.6/month in those with HSV II ($p < 0.0001$).

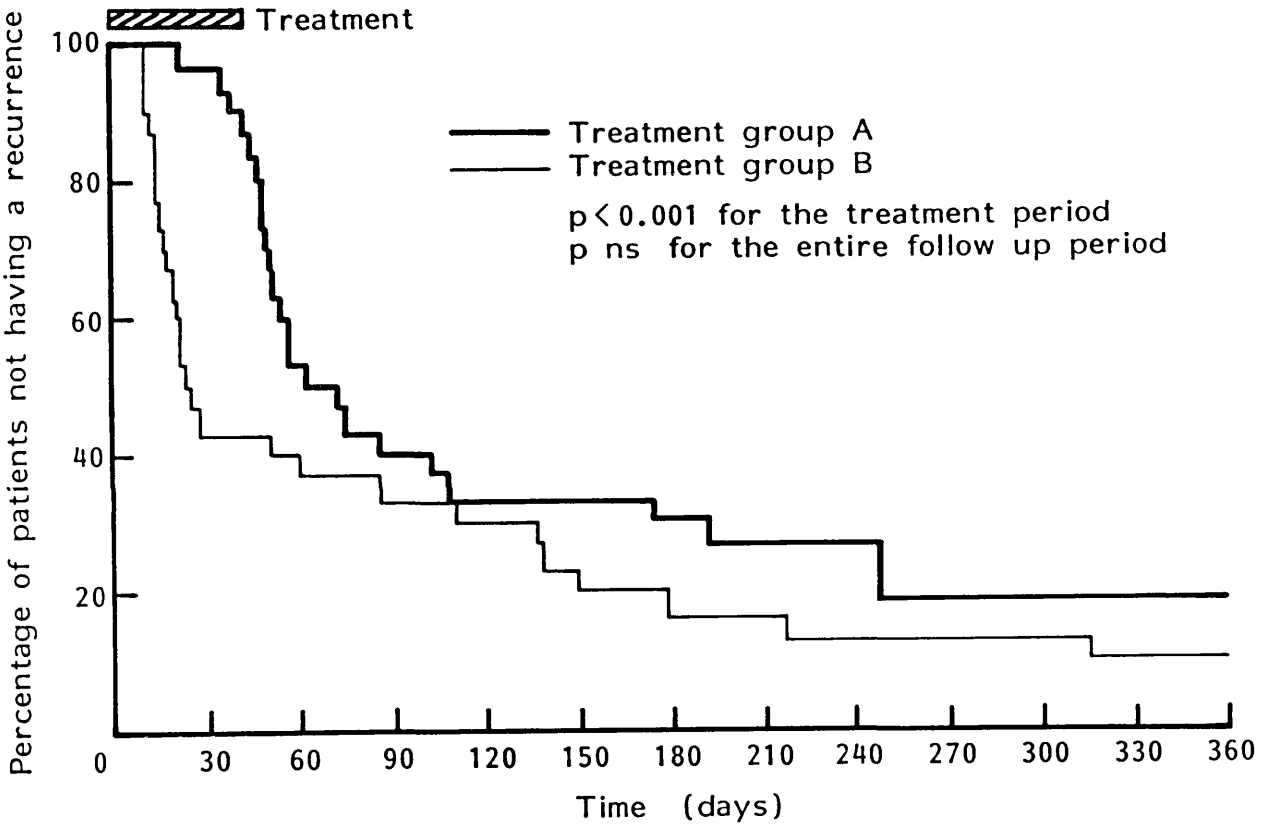
TABLE 14

THE DURATION OF SYMPTOMS, THE TIME TO HEALING AND THE DURATION OF VIRAL SHEDDING COMPARING PATIENTS IN THE TWO TREATMENT GROUPS

	TREATMENT A		TREATMENT B		
	n	Time+	n	Time+	P Value
Local symptoms	30	11 (1 - 31)	30	11 (2 - 28)	N.S.
Systemic symptoms	21	4 (2 - 24)	25	5 (1 - 31)	N.S.
Healing	30	11 (5 - 34)	30	11 (5 - 32)	N.S.
Viral shedding	29	11 (1 - 8)	29	4 (1 - 10)	N.S.

+ Median Time in days (range)

FIGURE 11



TIME TO FIRST RECURRENCE COMPARING PATIENTS IN THE TWO TREATMENT GROUPS

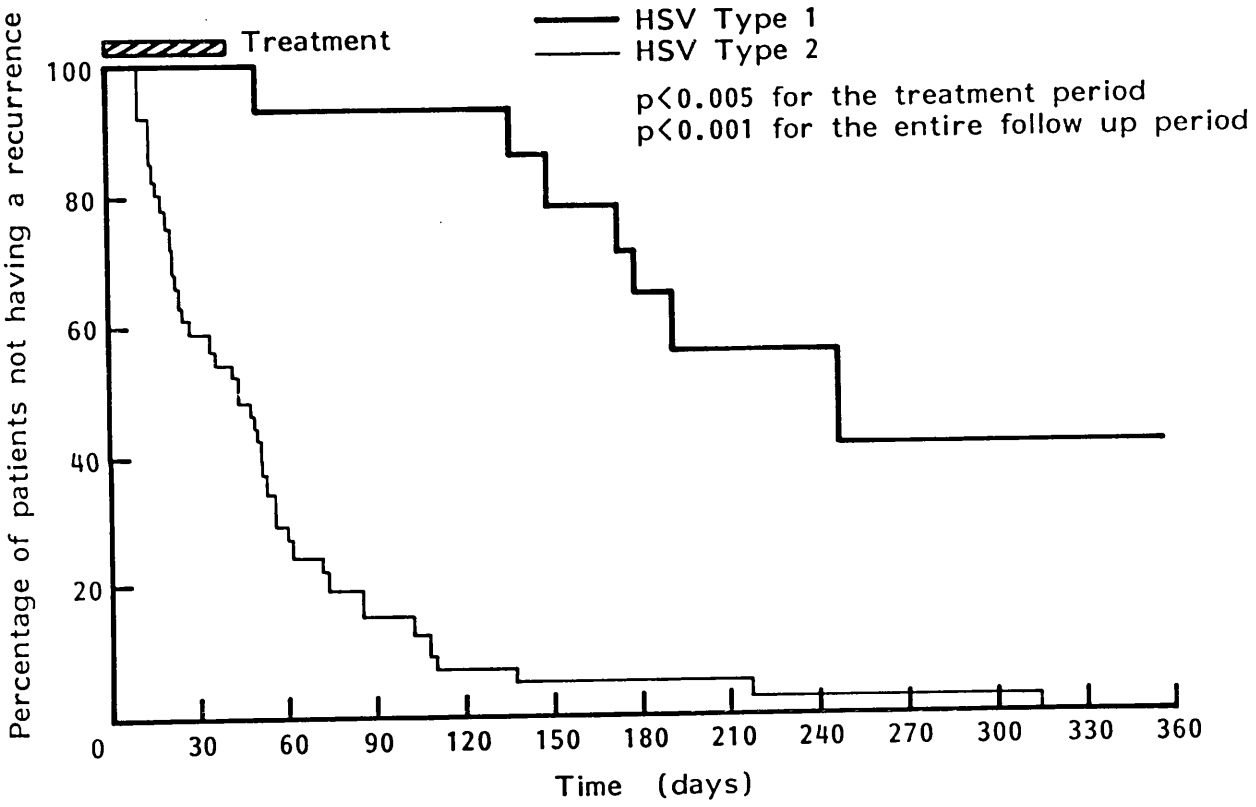
Group A = 42 days of acyclovir
Group B = 5 days of acyclovir followed by 37 days of placebo.

TABLE 15

FREQUENCY OF RECURRENCES COMPARING PATIENTS RECEIVING ACYCLOVIR FOR 42 DAYS (GROUP A) OR THOSE WHO RECEIVED THE DRUG FOR 5 DAYS (GROUP B)

	Treatment Group A		Treatment Group B		
Follow-up Period (Days)	No with recurrences/ No followed up	Mean (SD) recurrences/ month	No with recurrences/ No followed up	Mean (SD) recurrences/ month	Difference
0 - 42	4/30	0.12 (0.4)	16/29	0.76 (1.2)	p = 0.0004
0 - 90	18/30	0.43 (0.6)	19/29	0.60 (0.9)	NS
0 - 180	21/30	0.42 (0.6)	24/29	0.46 (0.6)	NS
0 - 270	18/20	0.45 (0.6)	13/17	0.30 (0.4)	NS
0 - 360	12/12	0.42 (0.5)	7/9	0.22 (0.3)	NS

FIGURE 12



TIME TO FIRST RECURRENCE COMPARING PATIENTS WITH HSV 1 WITH THOSE WITH HSV 2 GENITAL INFECTIONS

TABLE 16

FREQUENCY OF RECURRENCE COMPARING PATIENTS INFECTED WITH HSV TYPE I WITH THOSE INFECTED WITH HSV2

	Patients Infected with HSV 1		Patients Infected with HSV 2		
Follow-up Period (Days)	No with recurrences/ No followed up	Mean (+/- SD) recurrences/ month	No with recurrences/ No followed up	Mean (+/- SD) recurrences/ month	Difference
0 - 42	0/14	0 (0)	19/40	0.61 (1.0)	p = 0.002
0 - 90	1/14	0.02 (0.1)	34/40	0.72 (0.9)	p = 0.0001
0 - 180	5/14	0.07 (0.1)	38/40	0.60 (0.7)	p = 0.0001
0 - 270	6/9	0.10 (0.1)	25/26	0.51 (0.6)	p = 0.0001
0 - 360	3/4	0.10 (0.2)	16/16	0.41 (0.5)	p = 0.013

Compliance with therapy and side effects

Compliance with therapy was similar between the two groups. In group A patients the mean number of missed tablets was 4.2 compared with 4.3 in group B patients (p = N.S.).

Several patients had complaints that they thought might be associated with treatment. In group A patients these included two with slight constipation and one with transient nausea and in group B patients three with transient diarrhoea, one with nausea, one with an increase in appetite and one who developed a Bells palsy. A small number of patients were noted to have biochemical or haematological abnormalities. One group A patient had a marginal and transient decrease in the total white cell count. One group B patient had an elevated AST and one an elevated urea, but in both the elevation was slight and short lived. Seven patients had elevated bilirubin levels. In two patients (one in each group) this elevation was persistent (before, during and after treatment) and in the remaining five (two in group A and three in group B) the elevation was slight and only noted on a single occasion. None of the symptoms or biochemical or haematological abnormalities were thought to be due to treatment.

CONCLUSIONS

1. Prolonged oral acyclovir treatment in first attack genital herpes does not prevent the establishment of latency or subsequent recurrences.

2. Prolonged acyclovir treatment delays the development of recurrences but after stopping therapy relapses occur with the same frequency as in those patients who received a short course of acyclovir.

3. Patients with HSV 2 infection recur earlier and more frequently than those with HSV 1 irrespective of treatment.

CHAPTER FIVE

PROPHYLACTIC ORAL ACYCLOVIR IN RECURRENT GENITAL HERPES

INTRODUCTION

Recurrent genital herpes causes pain and discomfort, disrupts sexual relations and results in considerable emotional disturbance (Adler and Mindel 1983). As mentioned in the previous chapters treating the first attack with acyclovir does not reduce the frequency of subsequent recurrences. Treating recurrences with acyclovir again has no effect on the natural history of the disease. (Corey et al. 1982; Reichman et al. 1984). The use of continuous prophylactic (suppressive) acyclovir treatment has proved to be highly effective in preventing HSV recurrences in severely immunocompromised patients including bone marrow transplant recipients and those receiving chemotherapy (Saral et al. 1981, 1983; Wade et al. 1982; Hann et al. 1983). A similar approach appeared to offer a realistic hope for suppressing recurrences in patients with frequently recurring genital herpes.

METHODS

Patient selection and exclusions

Male and female patients attending the department of Genitourinary Medicine at the Middlesex Hospital with at least four recurrences per year were enroled into the study. Written informed consent was obtained from all patients. Patients were excluded if they did not have a culture positive recurrence during a three month observation period prior to the start of therapy. Other exclusion criteria included antiviral treatment in the preceding month, pregnancy, impaired renal function, females not on adequate contraception (Pill or IUCD), patients under 16, and those unable to attend at the required intervals.

Clinical assessment and follow up

All patients had a history taken and an examination performed at the time of enrolment and on each subsequent visit.

Particular note was made of the site, duration, date and frequency of recurrences. The details were recorded on a standardised recording schedule (Appendix 3). After the initial interview there was a three month observation period during which patients were required to attend with each recurrence. The purpose of the observation period was firstly, to have an objective assessment of the frequency of recurrences and secondly, to obtain a pre-treatment viral isolate.

Patients attended at two weekly intervals during the 12 week treatment period and monthly for six months after this period. Patients were also asked to attend outside these set times if they suffered a recurrence. Swabs for viral culture were taken at each visit and were handled as previously described.

Drug administration

Patients were randomised to receive either oral acyclovir 200mg or placebo four times daily for 12 weeks. Therapy was commenced one week after healing of an observed culture positive recurrence. The trial was double blind. Compliance with treatment was assessed by counting the number of missed tablets.

Safety testing

A full and differential blood count, serum urea, electrolytes and creatinine and liver function tests were taken at entry and every four weeks during therapy and four weeks after the end of treatment to assess possible toxicity.

RESULTS

Patient characteristics (Table 17)

Twenty-nine patients received acyclovir and 27 placebo. At presentation there were no statistically significant differences between acyclovir and placebo treated patients in relation to age, sex and the frequency, site, duration and

TABLE 17

DEMOGRAPHIC FEATURES OF PATIENTS RECEIVING ACYCLOVIR AND PLACEBO

	Acyclovir n = 29	Placebo n = 27
No of males	13	9
No of females	16	18
Age in years+	31.3 (1.5)	30.4 (1.4)
No of recurrences in previous 3 months+	2.9 (0.3)	3.0 (0.3)
Average duration of recurrences (days)+	8.4 (0.7)	7.4 (0.6)
Percentage with prodromal symptoms	68	57
Percentage with mild or moderate pain	76	81
Usual site of involvement:-		
Penis/vulva - percentage	90	93
Other sites* - percentage	41	52

+ Mean (+/- SE)

* Including perineum, perianal, scrotum, finger, oral

severity of previous recurrences. All but 2 of the isolates were HSV type 2.

Recurrences during treatment

Twenty-six (96%) of the placebo treated patients had a recurrence during the 12 week treatment period compared with only 4 (14%) in the acyclovir group ($p<0.0001$). The four patients who recurred while on acyclovir only had a single recurrence which were all short lived and adjudged to be minor. The mean recurrence rate per month of treatment was 1.4 in the placebo treated patients and only 0.05 in the acyclovir group ($p<0.0001$) (Table 18). Nineteen (70%) of the 27 placebo treated patients had at least one positive herpes culture during therapy. In contrast only one of the 29 acyclovir patients (5%) had a single positive culture during treatment ($p<0.001$).

Time to first recurrence

The median time to first recurrence after the start of therapy was 14 days in the placebo group compared to 100 days in the acyclovir group ($p<0.0001$ for the treatment period) (Figure 13).

The median time to the first culture proven recurrence after the onset of therapy was considerably longer than the time to the first clinical recurrence in both acyclovir and placebo treated patients. The median time in the acyclovir group was 49 days compared to 112 days in controls ($p<0.0001$ for the treatment period) (Figure 14).

Recurrences after the end of therapy

The median duration of follow-up after the end of 12 weeks therapy was similar in the two groups of patients; 168 days (range 0-259) in acyclovir treated patients, and 157 (range 4-239) in controls. There was no statistically significant difference in the recurrence rate per month of follow up between the two groups. In acyclovir treated patients the mean was 1.09 compared with 1.25 in controls (Table 18).

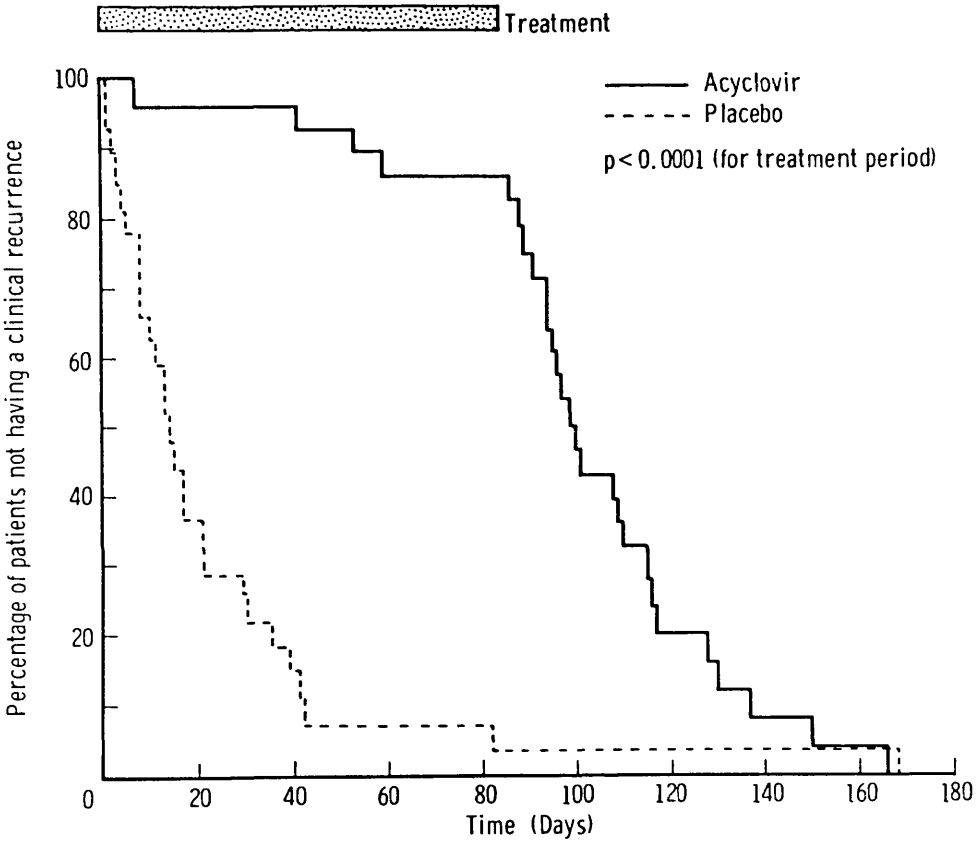
TABLE 18

MEAN NUMBER OF RECURRENCES PER MONTH (+/- SE)

COMPARING ACYCLOVIR WITH PLACEBO TREATED PATIENTS

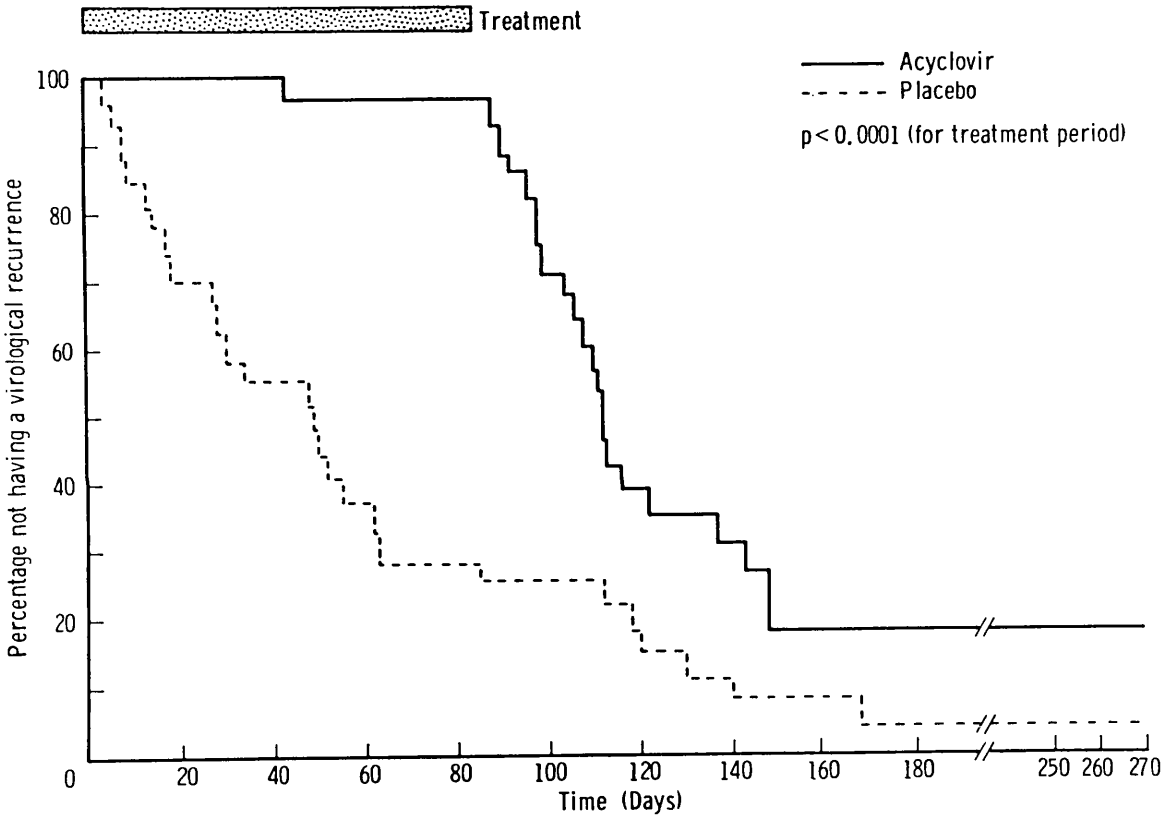
	Pre-Treatment	Treatment	Post-Treatment
Acyclovir	0.72 (0.07)	0.05 (0.02)	1.09 (0.13)
Placebo	0.92 (0.1)	1.4 (0.3)	1.25 (0.3)
P Value	NS	<0.001	NS

FIGURE 13



TIME TO FIRST CLINICAL RECURRENCE IN PATIENTS WITH FREQUENTLY RECURRING GENITAL HERPES COMPARING PATIENTS TREATED WITH SUPPRESSIVE ACYCLOVIR AND THOSE TREATED WITH PLACEBO

FIGURE 14



TIME TO FIRST VIROLOGICALLY PROVEN RECURRENCE IN PATIENTS WITH FREQUENTLY RECURRING GENITAL HERPES COMPARING PATIENTS TREATED WITH SUPPRESSIVE ACYCLOVIR AND THOSE TREATED WITH PLACEBO

Side effects

Six patients complained of side-effects which they felt might be attributable to therapy. These occurred with similar frequency amongst acyclovir and placebo treated patients and included dry vagina, alcohol intolerance, palpitations, dry lips, nausea and depression. These side effects were in all instances minor and transient, and no abnormalities were found on examination.

Nine patients (six acyclovir and three placebo) had abnormal urea, creatinine or liver function tests during the study period. In five patients these abnormalities were mild, short lived and did not differ between the two groups. The remaining four patients included three (two placebo and one acyclovir) with persistent hyperbilirubinaemia (before, during and after treatment) and one homosexual patient on acyclovir who developed acute hepatitis B.

Compliance with therapy

The compliance with therapy was similar in the two groups. The mean number of missed tablets over the 12 weeks treatment period in the acyclovir group was 6.5 compared with 7.4 in the placebo treated patients.

CONCLUSIONS

1. The time to first recurrence was statistically longer in patients on long term acyclovir compared with placebo.

2. The frequency of recurrences was also significantly reduced comparing acyclovir with placebo. Most patients on acyclovir had no recurrences. The few that did occur were mild, short lived and usually virus culture negative.

3. No significant side effects were noted.

4. Acyclovir prophylaxis appears to be highly effective method of controlling frequently recurring genital herpes.

5. Questions in regard to dose, duration of treated and safety of long term suppression remain to be answered.

CHAPTER SIX

LONG TERM SUPPRESSIVE ACYCLOVIR THERAPY IN PATIENTS WITH RECURRENT GENITAL HERPES - DOSAGE AND SAFETY

INTRODUCTION

Our previous study and work by others has shown that short courses of suppressive oral acyclovir are extremely effective in reducing both the frequency and severity of recurrences in patients with frequently recurring genital herpes (Douglas et al. 1984; Straus et al. 1984; Kinghorn et al. 1985; Thin et al 1985, Halsos et al. 1985, for a full discussion see chapter 8), but several questions about this form of treatment remain unanswered. How long should treatment continue, is the drug safe, what is the ideal dose, who should be treated and does acyclovir have any effect on the natural history of the illness?

This study was designed with the objectives of answering some of these questions. The aims were to determine the ideal dose of acyclovir required to control attacks in patients with frequently recurring herpes, to consider the drug's long term safety and to see if treatment had any effect on the natural history of infection.

METHODS

Male and female patients over the age of 16 with at least 8 recurrences per year were enroled in the study. Patients were excluded if they did not have a culture positive recurrence in a 2 month observation period prior to the onset of therapy, were known to be immunosuppressed or were unable to attend at the required intervals. Females were also excluded if they were either pregnant or not using adequate contraception.

After giving written informed consent patients were randomised to receive one of the two different treatment schedules. All patients received an initial therapeutic course of acyclovir 200 mg 5 times daily for 5 days. On Schedule A patients continued treatment with acyclovir 200 mg qds reducing to 200 mg tds, 200 mg bd and 200 mg od over four 12 week periods. On Schedule B treatment continued at a dosage of 400 mg bd, reducing to 800 mg od, 400 mg od and 200 mg od again over four 12 week periods. Patients who had a recurrence during treatment returned to the previous dose where they remained

until the end of the 48 week treatment period. Patients who recurred on the highest daily dose (either 200 mg qds or 400 mg bd) had their dose doubled. Compliance was assessed by counting the number of missed tablets.

All patients had a history taken and an examination performed at each visit. The date, duration and severity of recurrences was recorded. Patients attended monthly during the treatment period and for 6 months after. They were also asked to attend outside these fixed visits if they had a recurrence. The details were recorded on a standardised recording schedule (Appendix 4).

Swabs were taken for viral culture if there were any lesions suggestive of herpes present and were handled as previously described. Liver function tests, serum urea, creatinine, electrolytes and differential blood count were performed at entry and every 12 weeks during treatment and 12 weeks after completing treatment to assess possible toxicity.

RESULTS

Patient Demography (Table 19)

One hundred and thirty four patients were enroled. Three who failed to complete treatment were excluded. At presentation there were no significant differences between patients in the 2 treatment groups in relation to age or sex and the frequency, site, duration and severity of previous recurrences.

Time to First Recurrence (Figure 15)

The time to first recurrence was related both to the total daily dose of acyclovir and the frequency of tablet taking. Only 6% of patients who commenced therapy on 200 mg qds had recurred by the end of 84 days compared with 13% in those who commenced on 400 mg bd ($p<0.02$). As the total daily dose and the frequency of therapy were lowered so the time to first recurrence was shortened. For example at the end of the 60 days 19% of those on 200 mg bd had recurred compared with 31% of those on 800 mg od, 39%

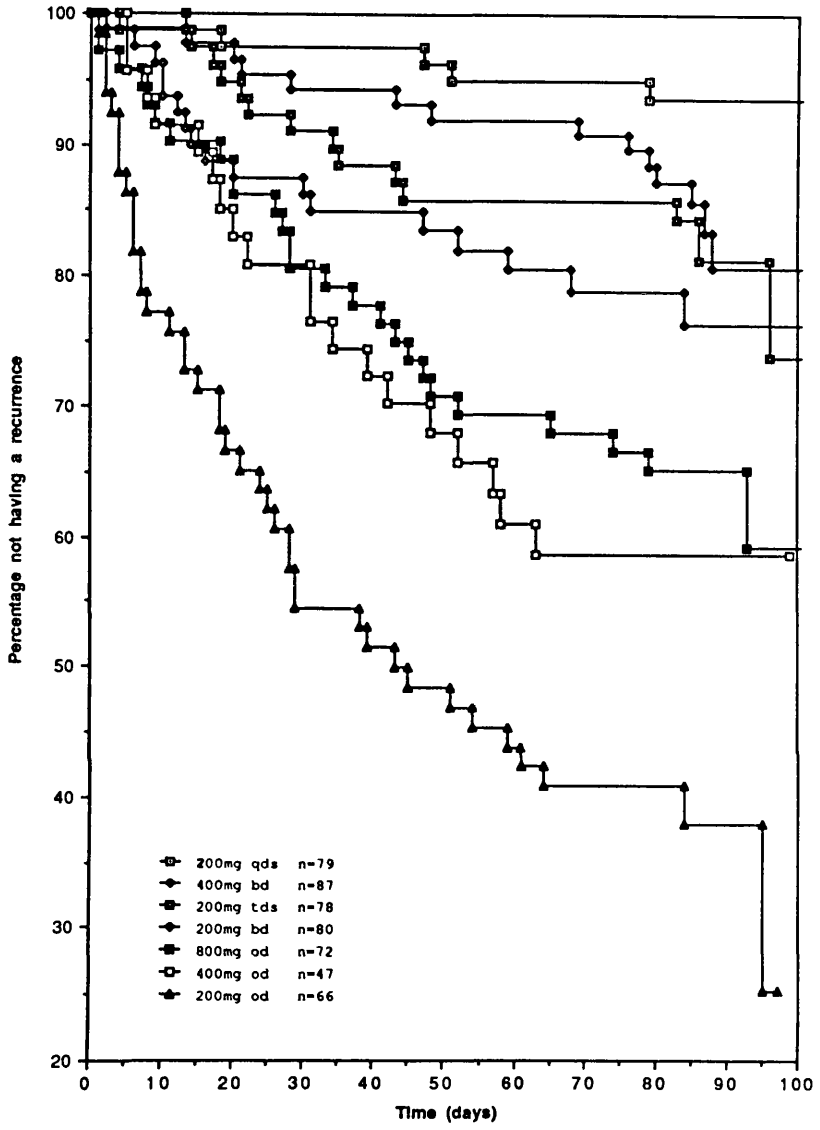
TABLE 19

LONG TERM TREATMENT WITH ACYCLOVIR: CHARACTERISTICS OF PATIENTS IN THE TWO TREATMENT GROUPS

	Schedule A n = 66	Schedule B n = 65
Age in years+	31.0 (7.12)	30.4 (6.82)
No of Males/Females	34/32	33/32
No of recurrences in last year+	14.9 (6.88)	14.2 (6.39)
No of recurrences in last 3 months+	4.2 (2.12)	3.4 (1.85)
Pain score+I	1.4 (0.89)	1.6 (0.79)
Usual site of lesions*		
Vulva/Penis	58 (88%)	56 (86%)
Perineum/Perianal	19 (29%)	20 (31%)
Buttock	9 (14%)	4 (6%)
Previous oral HSV	24 (36%)	13 (20%)

\+ Mean (+/- SD)
I Pain graded 0-3 (none, mild, moderate, severe)
* Some patients had lesions at several sites

FIGURE 15



TIME TO FIRST RECURRENCE WITH DIFFERENT DOSES OF ACYCLOVIR

od = once daily
bd = twice a day
tds = thrice a day
qds = four times a day

At the end of 60 days only 4% of patients commencing on acyclovir 200mg qds had recurred compared with 19% on 200 mg od, 31% on 800 mg od, 39% on 400 mg od and 56% or 200 mg od (all $p<0.05$)

on 400 mg od and 56% on 200 mg od. (All higher with $p<0.05$ compared with 200 mg qds).

Frequency of Change of Dose (Table 20)

One of the seventy nine (1%) patients who received a four times daily dose of acyclovir therapy required to change dose because of recurrence compared to 15% on 3 times 13% on twice and 35% on once a day therapy. ($p<0.005$)

Frequency and Duration of Recurrences (Table 21)

The mean number of recurrences per 28 days was 1.1 (+/- 0.5) in the two months prior to treatment compared to only 0.11 (+/- 0.08) during treatment ($P=0.0001$). After stopping treatment the mean number of recurrences was 0.7 (+/- 0.55) and this was a statistically significant difference from both the pre-treatment and treatment periods ($P=0.0001$ for both).

One hundred and eight recurrences were clinically confirmed during treatment. However, only 29 (27%) of these were culture positive. 24 (36%) of the 67 recurrences that occurred when patients were on once daily therapy were virus culture positive compared with only 5 (12%) of the 41 observed on the more frequent doses $p<0.01$.

The duration of recurrences during the treatment period (Mean 5.4 +/- 4.1 days) was shorter than those occurring in the pre-treatment (7.8 +/- 3.8) and post-treatment (7.8 +/- 6.6) periods. ($P<0.005$ for both).

Side Effects and Compliance With Therapy

Several patients reported problems that they thought were caused by the treatment (five with headaches, 3 each with weight gain, alcohol intolerance, itching and skin rash, 2 with constipation and 1 each of thinning of head hair, dry vagina, brittle nails, dizziness, nausea, dry mouth and tinnitus) in all instances these were short lived and not associated with any detectable clinical

TABLE 20

LONGTERM TREATMENT WITH ACYCLOVIR. FREQUENCY OF CHANGE OF DOSE

DOSE	QDS	TDS	BD	OD
No Treated	79	78	167	188
No changing dosage because of recurrence	1	12	22	66
% changing dose	1	15	13	35

$p < 0.005$

Qds includes only 200 mg qds
Tds " " only 200 mg tds
Bd " " 400 mg bd and 200 mg bd
Od " " 800 mg od, 400 mg od and 200 mg od

TABLE 21

FREQUENCY OF RECURRENCES COMPARING PATIENTS IN THE TWO TREATMENT GROUPS

	All Patients	Schedule A	Schedule B	P Value+
Before Treatment	1.11 (0.51)	1.14 (0.53)	1.09 (0.49)	ns
During Treatment	0.11 (0.08)	0.09 (0.07)	0.12 (0.1)	ns
After Treatment	0.71 (0.55)	0.71 (0.65)	0.68 (0.45)	ns

+comparing schedule A vs schedule B

p = 0.0001 comparing Before vs During}
Before vs After } In All three groups
During vs After }

All Values median (+/- SD)

abnormality. Twenty patients complained of depression. In 8 this had pre-dated treatment and in 4 this was attributable to specific life events. One patient had recently found out he was HIV antibody positive, one had recently been made redundant and the remaining 2 had relationship problems. In the remaining 8 there was no obvious cause for the depression.

Twenty four patients had elevated serum bilirubin levels. In 14 the abnormality was noted before treatment was started and it persisted during treatment; probably reflecting Gilberts' syndrome. In the remaining 10 the elevation was noted on a single occasion. All 10 were minimal and not associated with any clinical or other biochemical abnormalities. Nine patients had elevated serum aspartate transaminase (AST) levels. One was taking anabolic steroids, in the remainder there was no obvious cause. All deviations were minimal, only noted on 1 occasion, and unassociated with any other biochemical or clinical abnormality. One female who was taking phenytoin for epilepsy had a persistently elevated alkaline phosphatase, and one male patient who was later found to be HIV antibody positive and a Hepatitis B e antigen positive carrier had a persistent thrombocytopenia (platelet count 98-127 X 10^9/litre).

Nineteen (15%) of the 131 patients did not miss any tablets, 55 (42%) missed between 1 and 5, 36 (27%) missed between 6 and 20 and 21 (16%) missed more than 20 during the 48 weeks of treatment.

CONCLUSIONS

1. Long term suppressive acyclovir therapy significantly reduces the number and severity of recurrences.

2. Long term suppressive acyclovir therapy is safe.

3. Recurrences are less likely on higher doses.

4. The likelihood of relapses is related both to the total daily dose and the frequency of tablet taking.

5. Patients should be started on treatment with 200 mg qds and the dosage should be sequentially reduced over the coming months if the patient has no recurrences, to a level which is acceptable to both the patient and the doctor.

6. After 1 year, treatment should be stopped as in some patients the frequency of recurrences may well have reduced.

CHAPTER SEVEN

ACYCLOVIR VERSUS INOSINE PRANOBEX FOR THE TREATMENT OF GENITAL HERPES

INTRODUCTION

Both acyclovir and inosine pranobex have been reported to be effective in the management of genital herpes, (See Chapter 1) and it seemed appropriate to compare the efficacy of the 2 drugs. Two trials were therefore designed to do this. The first trial compared the efficacy of the 2 drugs in patients with first attack genital herpes and the second compared the suppressive action of acyclovir and inosine pranobex in patients with frequently recurring genital herpes.

ACYCLOVIR VERSUS INOSINE PRANOBEX FOR THE TREATMENT OF FIRST ATTACK GENITAL HERPES

METHODS

Patient Selection

Patients with a first attack of genital herpes presenting within five days of onset to the Departments of Genito Urinary Medicine, at The Middlesex Hospital, London or the Royal Hallamshire Hospital, Sheffield, were offered the opportunity of participating in the study. Written informed consent was obtained from all patients. Exclusion criteria were identical to those used in previous studies. However, we also excluded patients with a history of gout, or hyperuricaemia (inosine pranobex has been reported to increase uric acid, Chang and Heel 1981), or immune depression. As the majority of males attending the Middlesex Hospital were homosexual (with a high attendant prevalence of HIV infection) it was decided to exclude males from this centre.

Treatment

Patients were randomly allocated to one of three treatment groups: one group received active acyclovir and dummy inosine pranobex, one received active inosine pranobex and dummy acyclovir and the final group received active acyclovir and inosine pranobex. The final group was added to see if the two

treatments complimented each other in any way.

The dosage of acyclovir was 400 mg qds and of inosine pranobex 1 gram qds. Treatment was for 7 days.

Clinical evaluation, Virology and Safety Testing

Patients were assessed at entry and three times weekly until complete healing occurred. Thereafter patients reattended (or were contacted by telephone) monthly for the next six months and during the first recurrence. The clinical status of patients was recorded at each visit on a standardised recording schedule (Appendix 5).

At each visit if lesions were present swabs were taken for viral culture and handled as previously described. In London isolates were typed using an immunofluorescence test with monoclonal antibodies, whilst those from Sheffield were typed using a modified ELISA technique (Vestergaard and Jensen 1981). Acute and convalescent sera were tested for herpes antibodies. Patients with a titre of ≤ 2 on the acute serum were classified as primary infection whilst those with antibodies in the acute phase serum were classified as initial first episode genital infections.

At entry blood was taken for a full blood count, urea and electrolytes, creatinine, urate and liver function tests. These were repeated on day 8.

RESULTS

Patient Demography

Eighty-eight patients were recruited (39 in London and 49 in Sheffield), however, 11 were excluded (8 who were lost to follow up after the initial visit, one who lost her tablets, one who was found to have Varicella zoster and not HSV and one who was virus negative with no antibody response). The data from 77 patients was analyzed, 24 patients received acyclovir alone, 28 inosine

pranobex alone and 25 both drugs. At entry there were no significant differences in age, sex, viral type, antibody status or duration of signs and symptoms comparing patients in the three treatment groups or those from the two centres (Table 22).

Healing Time

The median time to healing in the acyclovir group and the group receiving acyclovir and inosine pranobex were both statistically shorter than in the inosine pranobex group ($p<0.05$ acyclovir vs. inosine pranobex; $p<0.001$ both vs. inosine pranobex). Indeed by the 11th day over 75% of patients treated with acyclovir or both drugs were healed compared with only 2% of those who received inosine pranobex alone (Figure 16).

Duration of Viral Shedding

The duration of viral shedding was significant longer in patients treated with inosine pranobex compared with those in the other two treatment groups ($p<0.0001$ for both). All patients treated with acyclovir or both drugs were culture negative by the 8th day whereas 45% of those treated with inosine pranobex were still shedding virus. Twenty percent of the inosine pranobex patients were still virus culture positive on the 18th day after entry (figure 17).

Symptoms

There were no significant differences in the duration of symptoms comparing all patients in the three treatment groups. However females treated with acyclovir had a shorter duration of dysuria and all symptoms compared with those treated with inosine pranobex. These differences were statistically significant ($p<0.02$ for dysuria, $p<0.05$ for all symptoms) (Figure 18).

Table 23 summarises the differences in healing time, duration of viral excretion and symptoms comparing patients in the three treatment groups.

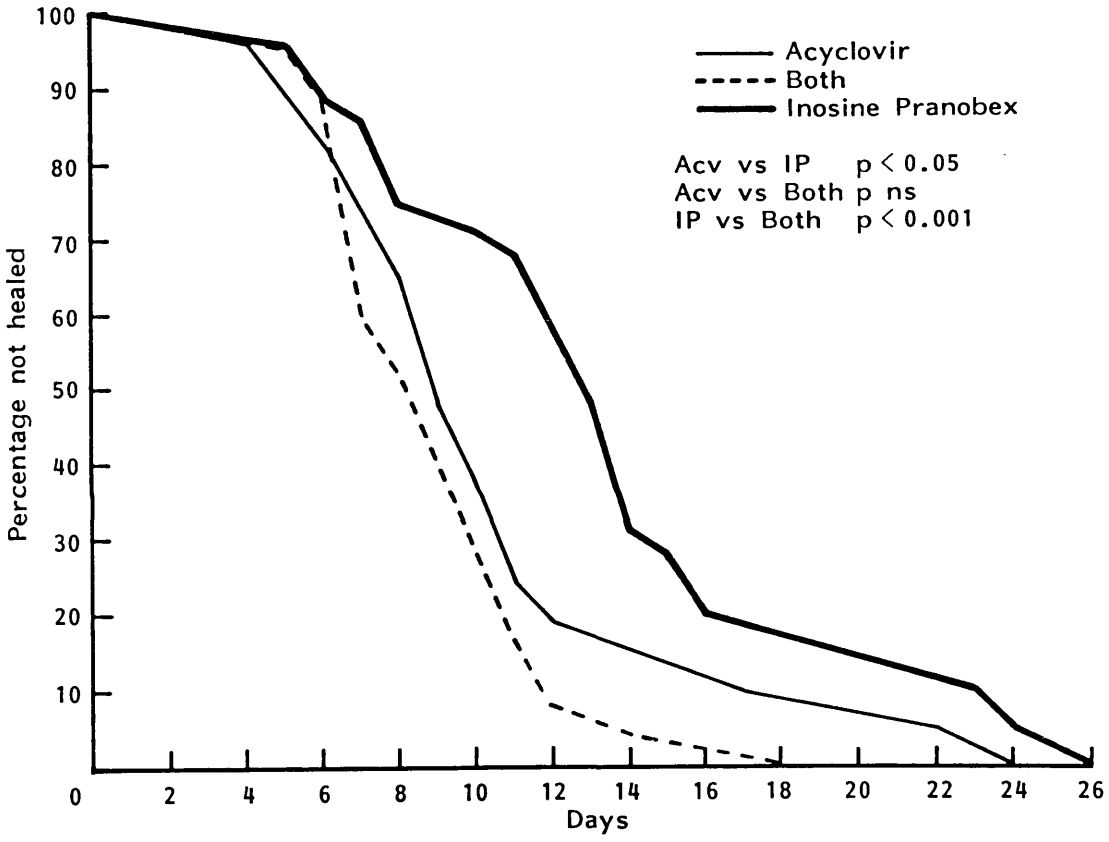
TABLE 22

DEMOGRAPHIC CHARACTERISTICS OF 77 PATIENTS WITH FIRST ATTACK GENITAL HERPES TREATED WITH ACYCLOVIR, INOSINE PRANOBEX, OR BOTH DRUGS

	Acyclovir n = 24	Inosine Pranobex n = 28	Both n = 25
Age (yr)+	25.5 (7.02)	23.3 (4.9)	24.3 (7.9)
Duration of symptoms at entry (days)+	4.3 (1.4)	3.9 (1.3)	4.6 (3.3)
Duration of signs at entry (days)+	3.4 (1.8)	3.2 (1.5)	2.9 (1.3)
Females/Males	21/3	24/4	21/4
London/Sheffield	11/13	12/16	13/12
External lesions (%)	24 (100)	28 (100)	25 (100)
Internal lesions (%)	15 (63)	14 (50)	11 (44)
Type I (%)	9 (37)	13 (46)	12 (48)
Type II (%)	11 (46)	12 (43)	10 (40)
Not typed (%)	4 (17)	3 (11)	3 (12)
Primary (%)	13 (54)	18 (67)	16 (64)

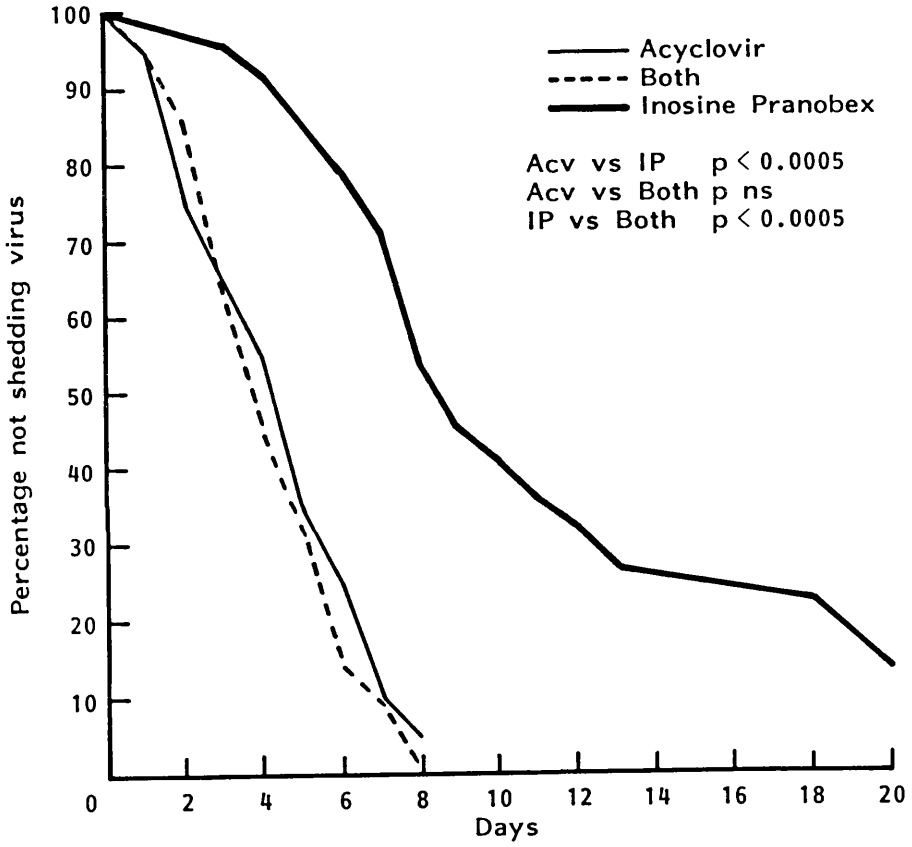
+ Mean (+/- SD)

FIGURE 16



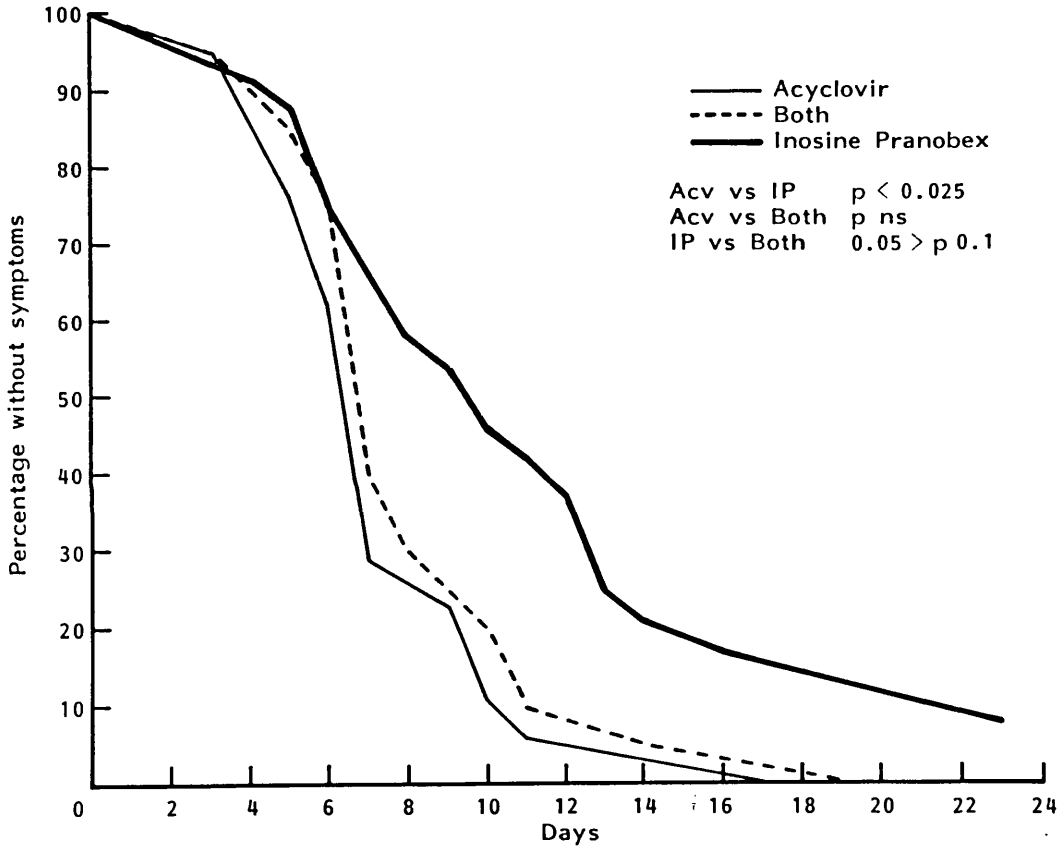
TIME TO HEALING OF LESIONS IN PATIENT RECEIVING ACYCLOVIR, INOSINE PRANOBEX OR BOTH DRUGS

FIGURE 17



DURATION OF VIRAL SHEDDING IN PATIENTS RECEIVING ACYCLOVIR, INOSINE PRANOBEX OR BOTH DRUGS

FIGURE 18



DURATION OF ALL SYMPTOMS IN FEMALE PATIENTS RECEIVING ACYCLOVIR, INOSINE PRANOBEX, OR BOTH DRUGS

TABLE 23

HEALING TIME, DURATION OF VIRAL SHEDDING AND SYMPTOMS IN THE 3 TREATMENT GROUPS

	Acyclovir (n=24)	Inosine pranobex (n=24)	Both (n=25)	Acyclovir vs inosine pranobex (p)	Acyclovir vs both (p)	Inosine pranobex vs both (p)
All patients						
Healing	9 (4-24)	13 (1-26)	9 (5-18)	<0.05	NS	<0.001
Viral shedding	5 (1-8)	8 (3-20)	4 (1-8)	<0.0005	NS	<0.0005
Dysuria	6 (3-18)	7 (1-21)	7 (1-21)	NS	NS	NS
All symptoms	7 (3-19)	8 (4-23)	7 (3-19)	0.05>p<0.1	NS	0.05>p<0.1
Women						
Healing	9.5 (4-24)	13 (1-26)	9 (5-18)	0.05>p<0.1	NS	<0.005
Viral shedding	5 (1-8)	8 (3-20)	4 (1-8)	<0.005	NS	<0.005
Dysuria	5.5 (3-11)	7.5 (1.21)	6 (3-19)	<0.02	NS	NS
All symptoms	7 (3-19)	9.5 (4-23)	7 (3-19)	<0.05	NS	0.05>p<0.1

All values Median (range). NS, not significant (p>0.05)

Side effects

No side effects were noted in any patient.

Recurrences

The median time to first recurrence (acyclovir 187.4 days, inosine pranobex 142.5 days, both 132.7 days) (Figure 19) and the frequency of recurrences was similar in the three treatment groups (Table 24). Patients with Type 2 infections recurred earlier (median 64 days) than those with Type 1 (median 238.2 days $p=0.0015$) and also had more frequent recurrences. These differences were irrespective of treatment given.

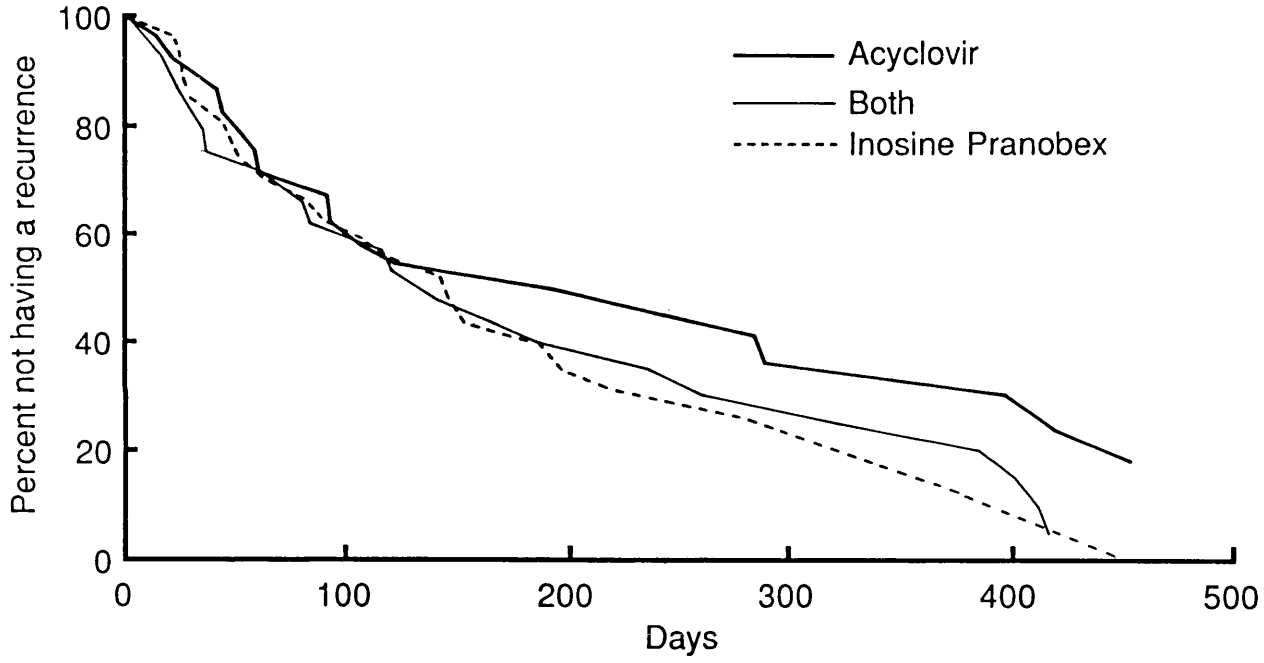
CONCLUSIONS

1. Patients treated with acyclovir (either alone or in combination with inosine pranobex) healed more quickly, and had a shorter duration of viral shedding and symptoms than those treated with inosine pranobex.

2. Neither preparation appeared to have any effect on the time to first recurrence or the frequency of subsequent recurrences.

3. Acyclovir is the drug of choice for treating patients with first attack genital herpes.

FIGURE 19



TIME TO FIRST RECURRENCE IN PATIENTS RECEIVING ACYCLOVIR, INOSINE PRANOBEX OR BOTH DRUGS

TABLE 24

FREQUENCY OF RECURRENCES (PER 28 DAYS OF FOLLOW UP) COMPARING PATIENTS IN THE 3 TREATMENT GROUPS BY VIRAL TYPE

VIRAL TYPE	TREATMENT GROUP			
	Acyclovir	Isoprinosine	Both	All Patients
Type I	0.11 (0.13)	0.14 (0.22)	0.21 (0.24)	0.16 (0.2)
Type II	0.49 (3.2)	0.38 (0.51)	0.48 (0.32)	0.45 (0.39)
P Value	0.004	0.138	0.044	< 0.0005

All values Mean (+/- SD)

SUPPRESSION OF FREQUENTLY RECURRING GENITAL HERPES ACYCLOVIR VS. INOSINE PRANOBEX

METHODS

Male and female patients with a minimum of 8 recurrences of genital herpes per year were recruited. Exclusion criteria were identical to those used in previous studies. In addition patients who did not have a culture positive recurrence in the 2 months prior to the onset of treatment were excluded, as were those with a history of gout, hyperuricaemia or severe atopic eczema. Informed consent was obtained from all the participants.

The treatment was randomised double blind and double dummy. Patients received either active acyclovir and dummy inosine pranobex or active inosine pranobex and dummy acyclovir. The dosage of acyclovir was 200 mg qds and of inosine pranobex 1 gm qds. Treatment was for 12 weeks. Compliance was assessed by counting the number of missed tablets.

Patients attended every 2 weeks during the treatment period and monthly for 6 months after stopping therapy. Additional visits were made during any recurrence. Liver function tests, serum uric acid, creatinine, urea and electrolytes and a full and differential blood count were done at entry and every 4 weeks during treatment. All information was recorded on a standardised recording schedule. (Appendix 6)

Statistical tests used included the Chi squared, Mann Whitney U and a Log Rank test.

RESULTS

Patient Characteristics

Initially the trial was designed to include 100 patients but after only 32 had

been treated it was obvious to the investigators that some patients were deriving no benefit from treatment whereas others were considerably improved. After careful assessment of our previous experience using suppressive acyclovir, it was considered unethical to continue, and the trial was prematurely halted.

One of the 32 patients was lost to follow-up after two weeks and was excluded from the analysis. The demographic characteristics of the remaining 31 patients is shown in Table 25. There were no statistically significant differences in respect of age, sex and the frequency, severity and duration of previous recurrences, comparing patients in the two treatment groups.

Recurrences During Treatment

All of the 17 inosine pranobex recipients recurred during treatment compared with five of the 14 (36%) acyclovir recipients ($p<0.001$). Each of the latter 5 patients recurred within the first 5 days. The time to first recurrence was significantly shorter in the inosine pranobex recipients $p<0.0001$ (Figure 20).

The mean number of recurrences per 28 days of treatment was 0.16 (+/- 0.28) in the acyclovir group compared with 1.22 (+/- 0.8) in the inosine pranobex group, $p=0.0001$ (Table 26).

Recurrences After Treatment

After stopping treatment the frequency of recurrences was similar in the 2 groups: 1.03 (+/- 0.53) in the acyclovir group compared with 1.0 (+/- 0.9) in the inosine pranobex group pns (Table 26).

Safety and Compliance

No side effects were noted and the mean number of missed tablets was similar in the 2 groups.

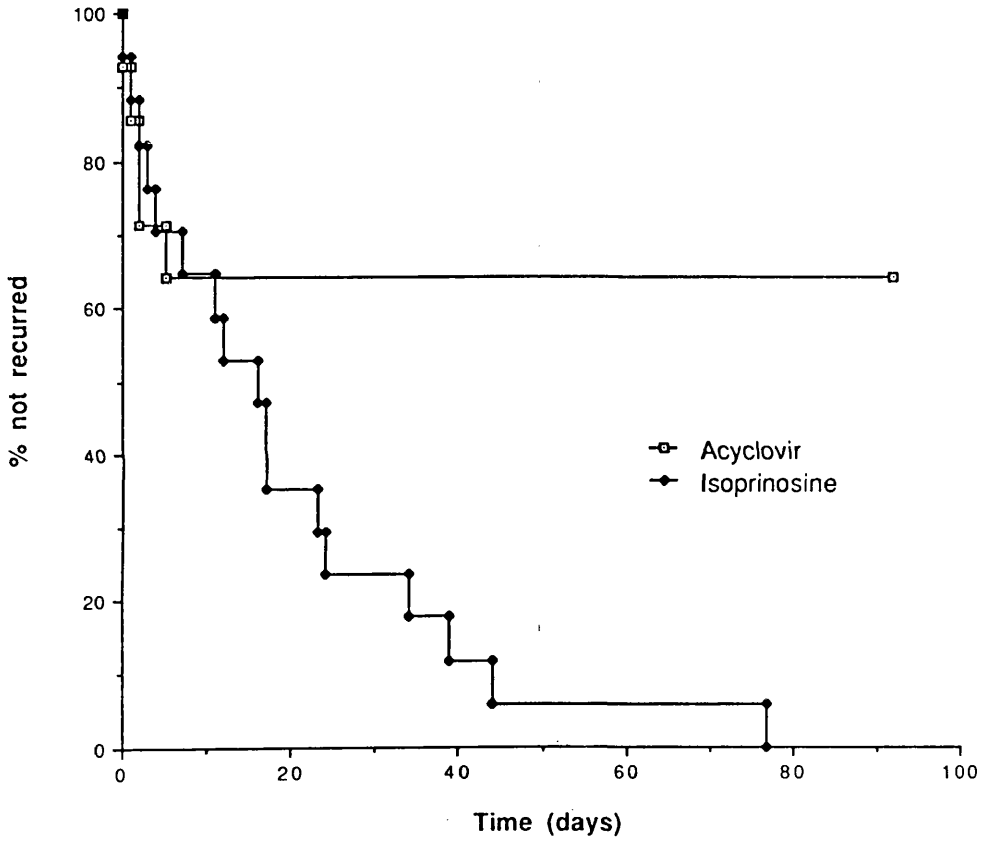
TABLE 25

DEMOGRAPHIC CHARACTERISTICS COMPARING PATIENTS IN THE TWO TREATMENT GROUPS

	Acyclovir n = 14	Inosine Pranobex n = 17
Age - Years+	34.2 (6.8)	32.3 (6.8)
Sex Male/Female	9/5	6/11
Years with HSV+	5.7 (4.7)	5.5 (4.2)
No of attacks		
- previous 12 months+	11.8 (3.4)	16.2 (10.6)
- previous 3 months+	3.6 (1.8)	4.9 (3.1)
Duration of attacks (Days) +	6.4 (1.4)	6.8 (4.2)
% with prodrome+	72.1 (34.7)	69.1 (39.1)
No with orolabial HSV	4 (28.6%)	4 (23.5%)

+ Mean (+/- SD)

FIGURE 20



THE TIME TO FIRST RECURRENCE COMPARING ACYCLOVIR AND INOSINE PRANOBEX RECIPIENTS

TABLE 26

FREQUENCY OF RECURRENCES COMPARING PATIENTS TREATED WITH ACYCLOVIR AND INOSINE PRANOBEX

	Acyclovir	Inosine Pranobex	P Value
Before Treatment (2/12 - observation)	1.3 (0.9)	1.99 (0.76)	ns
During Treatment	0.16 (0.28)	1.22 (0.8)	0.0001
After Treatment (6/12 - observation)	1.03 (0.53)	1.0 (0.9)	ns

Mean Number of Recurrences per 28 days (+/- SD)

CONCLUSIONS

1. Patients treated with acyclovir had a significant reduction in the frequency of recurrences during treatment.

2. Inosine pranobex has no apparent effect on the time to first recurrence or the frequency of recurrences.

3. Acyclovir is the drug of choice for the suppression of frequently recurring genital herpes.

CHAPTER EIGHT

DISCUSSION

INTRODUCTION

In this discussion I would like to review the way the studies presented in this thesis have contributed to current knowledge and practice for the management of genital herpes. I would also like to consider the safety of acyclovir and its possible future uses and the reasons why treatment sometimes fails.

THE EFFECT OF ACYCLOVIR ON FIRST ATTACK GENITAL HERPES

We have shown that intravenous acyclovir fulfils all the aims of therapy outlined in Chapter 1 (a reduction in the time to healing and a reduction in duration of symptoms and viral shedding) except that there was no apparent effect on the development of subsequent recurrences. The effect was most marked with viral shedding, less so with healing and least with symptoms. This suggests that the more subjective the assessment the less apparent the effect.

The dramatic effect of the drug on viral excretion shows that this is the most important assessment in evaluating the effect of antiviral therapy. Indeed no patient treated with acyclovir shed virus from any site after the 5th day whereas placebo recipients continued to shed virus for up to 21 days. The time to healing in acyclovir treated patients was however, considerably longer (up to 17 days) suggesting that the amount of tissue damage prior to the onset of treatment is important in determining the time to healing. The observation that acyclovir decreases the duration of vesicles and of new lesion formation supports this view. Early initiation of therapy before extensive tissue damage would seem desirable especially in women and men with perianal or anal herpes, where the initial episode is often severe and prolonged.

In addition to the amount of tissue damage prior to the onset of therapy, several other factors may be important in determining healing time. For example small discrete ulcers will heal more quickly than large areas of confluent ulceration, lesions subject to repeated trauma by clothing may take longer to heal and secondary infection although uncommon may delay healing (Corey et al. 1983a). An interesting finding in this study was that internal

lesions appeared to heal more quickly than external lesions, possibly because scabs which only occur on dry external areas take longer to disappear.

The results of the subjective assessments (pain, dysuria, discharge, numbness, itching etc.) were less impressive and indeed proved difficult to interpret. When all the symptoms were assessed together, acyclovir decreased the duration of such symptoms, however the drug appeared to have almost no effect on the duration of pain and dysuria. The individual patients response to, and interpretation of pain varies enormously, and is dependent upon numerous subjective and emotional variables, including previous exposure to pain, stress relating to the diagnosis and treatment, fear of hospitals and doctors, and the sexual implications of the diagnosis. Pain is also dependent on several other factors. The site of the lesion is important. In women lesions on the labia minora or clitoris are more painful than those on the perineum or labia majora. Cervical involvement is usually painless. In men lesions around the urinary meatus and on the glans penis or foreskin are more painful than those on the penile shaft. The number of sores is also relevant, the more sores the more pain.

Comparison with other clinical trials

Since completion of this study 8 additional trials in patients with first attack genital herpes have been published. One with intravenous acyclovir (Corey et al. 1983b), three with oral acyclovir (Nilsen et al. 1982; Bryson et al. 1983; Mertz et al. 1984), and four with a topical preparation (Corey et al. 1982; Thin et al. 1983; Fiddian et al. 1983; Kinghorn et al. 1983).

All these studies were randomised double blind and placebo controlled, and all were conducted in a similar manner. In all but two of the studies median values were used to assess healing, viral shedding and symptoms. In an attempt to compare our study with the other published trials the percentage reduction in median (or mean) values between acyclovir and placebo was assessed. The "P" value in all the trials relates to a log rank test.

Healing Time

The healing times comparing acyclovir and placebo in the 9 trials (the 8 published studies and our own) is shown in Table 27.

The percentage reductions in the time to healing was most marked in the intravenous studies (50% - 57%) less so in the oral studies (20 - 45%) and least with topical preparations (14 -43%).

Viral shedding

The median (or mean) duration of viral shedding in the 9 trials is shown in Table 28. All trials showed that acyclovir significantly reduced the duration of viral shedding with percentage reduction ranging from 30 - 92%

Symptoms

The effect on symptoms was less consistent. Some studies showed a significant reduction in the duration of pain whereas other did not (Table 29). However, the duration of all symptoms was shown to be significantly reduced in the 4 studies that looked at this parameter (Table 30).

The overall impression of the nine studies suggests that the effect of topical therapy is less consistent than that shown with the systemic preparations. Systemic therapy would appear to be better than topical and as oral treatment is almost as efficacious as intravenous, the best method of treatment for first attack genital herpes would appear to be with oral acyclovir.

TABLE 27

TRIALS WITH ACYCLOVIR IN FIRST ATTACK GENITAL HERPES 1 HEALING TIMES

ROUTE	ACYCLOVIR	PLACEBO	% REDUCTION	P VALUE+	AUTHOR
IV	7.0*	14.0*	50	< 0.0001	Mindel et al 1982
IV	9.0*	21.0*	57	0.002	Corey et al 1983b
O	6.0*	11.0*	45	< 0.01	Nilsen et al 1982
O F	9.5-	13.7-	31	0.05	} Bryson et al 1983
M	12.0-	15.0-	20	N.S.	}
O Primary	12.0*	16.0*	25	< 0.01	} Mertz et al 1984
O Non-Primary	9.0*	13.0*	31	N.S.	}
T	10.6	12.3	14	N.S.	Corey et al 1982
T	9.0*	13.5*	33	< 0.05	Thin et al 1983
T	8.0*	12.0*	33	< 0.001	Fiddian et al 1983
T F	8.0*	14.0*	43	< 0.001	} Kinghorn et al 1983
M	9.0*	14.0*	36	N.S.	}

+ Log rank test * Median in days - Mean in days

IV = Intravenous O = Oral T = Topical F = Female M = Male

TABLE 28

TRIALS WITH ACYCLOVIR IN FIRST ATTACK GENITAL HERPES 2 VIRAL SHEDDING

ROUTE	ACYCLOVIR	PLACEBO	% REDUCTION	P VALUE+	AUTHOR
IV	2.0*	8.5*	76	< 0.001	Mindel et al 1982
IV	2.0*	13.0*	85	0.001	Corey et al 1983b
O	1.0*	13.0*	92	< 0.001	Nilsen et al 1982
O F	8.5-	12.2-	30	0.05	} Bryson et al 1983
M	4.0-	8.4-	52	N.S.	}
O Primary	2.0*	9.0*	78	< 0.01	} Mertz et al 1984
O Non-Primary	0*	6.0*	-	< 0.01	}
T	3.1-	5.6	45	< 0.01	Corey et al 1982
T	2.0*	9.0*	78	< 0.05	Thin et al 1983
T	3.0*	9.0*	67	< 0.001	Fiddian et al 1983
T F	4.0*	11.0*	64	< 0.001	} Kinghorn et al 1983
M	6.0*	10.0*	40	N.S.	}

+ Log rank test * Median in days - Mean in days

IV = Intravenous O = Oral T = Topical F = Female M = Male

TABLE 29

TRIALS WITH ACYCLOVIR IN PRIMARY FIRST ATTACK GENITAL HERPES 3 PAIN

ROUTE	ACYCLOVIR	PLACEBO	% REDUCTION	P VALUE+	AUTHOR
IV	4.0*	4.0*	0	N.S.	Mindel et al 1982
IV	3.0*	7.0*	57	0.03	Corey et al 1983b
O	4.0*	8.0*	50	< 0.001	Nilsen et al 1982
O F	2.8-	3.4-	18	N.S.	}
M	2.0-	3.8-	47	0.015	} Bryson et al 1983
O Primary	5.0*	7.0*	29	< 0.05	}
O Non-Primary	2.0*	4.0*	50	N.S.	} Mertz et al 1984
T	6.2-	8.8	30	N.S.	Corey et al 1982
T	3.0*	5.0*	40	< 0.05	Thin et al 1983
T	4.0*	7.0*	43	< 0.05	Fiddian et al 1983
T F	4.0*	5.0*	50	< 0.01	}
M	4.0*	5.0*	20	N.S.	} Kinghorn et al 198

+ Log rank test * Median in days - Mean in days

IV = Intravenous O = Oral T = Topical F = Female M = Male

TABLE 30

TRIALS WITH ACYCLOVIR IN PRIMARY FIRST ATTACK GENITAL HERPES 4 ALL SYMPTOMS

ROUTE	ACYCLOVIR	PLACEBO	% REDUCTION	P VALUE+	AUTHOR
IV	6.5	8.5	24	< 0.05	Mindel et al 1982
O	4.0	9.0	56	< 0.05	Nilsen et al 1982
T	5.0	10.0	50	< 0.01	Thin et al 1983
T	5.0	8.0	38	< 0.01	Fiddian et al 1983

+ Log rank test

All values are given as median in days. Several studies did not look at this parameter.

IV = intravenous O = Oral T = topical

PROLONGED ORAL TREATMENT FOR FIRST ATTACK GENITAL HERPES

There were no apparent benefits (in terms of healing time, duration of symptoms and viral shedding) when patients were treated with prolonged oral therapy for their first attack genital herpes (see Chapter 4). This was not surprising as our intravenous study and studies from other centres showed that viral shedding ceased in all patients within a few days of commencing therapy (see table 27). No similar studies have been conducted.

THE EFFECT OF ACYCLOVIR ON RECURRENCES

The effect of intravenous acyclovir on the development of recurrences following therapy was disappointing. The drug did not appear to reduce the time to the first clinical recurrence or the frequency of recurrences. Prolonged oral acyclovir also did not prevent the development of recurrences it merely delayed their onset. This lack of effect on subsequent recurrences has been confirmed by several other workers (Corey et al. 1982, 1983b; Bryson et al. 1983; Mertz et al. 1984). There is one study which appears to be at variance with these findings (Bryson et al. 1985). This study suggested that for the first six months following therapy, the frequency of recurrences in patients with HSV2 was similar in acyclovir and placebo recipients. Thereafter patients with primary HSV2 (as opposed to those with non primary first episode) who were treated with acyclovir had a statistically significant reduction in the frequency of recurrences over the next 18 months. The reasons for the difference between this study and the others is unclear, but the long term follow up only involved a very small number of patients.

The reason why acyclovir does not appear to reduce the likelihood of recurrences probably relates to the delay in initiating therapy. In our study the median duration of lesions prior to first attendances was 4 days. In addition the incubation period is anything from 2 - 14 days making the total delay from the time of exposure to the start of the treatment 6 - 18 days. Animal experiments suggest that HSV establishes latency very soon after the initial exposure

(Simmons and Nash 1984; Blyth and Hill. 1984; Wildy 1985). As the drug only effects replicating virus it is unlikely to have any effect on latent viral particles and subsequent recurrences. Experimental studies in mice have confirmed that acyclovir has no effect on established latent infection (Field et al. 1979; Klein et al. 1981). However, if given very soon after inoculation (3 hours) the drug can prevent the establishment of latency (Klein et al. 1979; Park et al. 1980). It is extremely unlikely that therapy in humans could be started early enough to prevent latency and subsequent reactivation and recurrences.

DIFFERENCES IN THE TIME TO FIRST RECURRENCE AND THE FREQUENCY OF RECURRENCES COMPARING HSV 1 AND HSV 2

The two viral types show a marked difference in the time to first clinical recurrence and the frequency of recurrences. Almost all HSV 2 genital infections seem to recur and many recur within the first few months after the primary infection. Type 1 genital infection appears to recur later and less frequently.

The time to first recurrence comparing the two viral types was studied by Reeves et al (1981) who found that at 6 months after the first attack 90% of patients with Type 2 had recurred compared with only 40% of the Type 1 infections ($p<0.01$). These findings are very similar to those in our studies. In our intravenous acyclovir study 82% of the Type 2 infections and 45% of the Type 1 infections had recurred at 6 months ($p<0.05$), and at one year all the Type 2 infections compared with 59% of the Type 1's had recurred ($p<0.02$). Similar differences were noted in the longterm oral acyclovir study where 36% of type 1 infections and 95% of type 2 infections had recurred by 6 months ($p=0.0001$).

Further evidence that Type 2 infections recur more frequently than Type 1 comes from studies where viral isolates from recurrences have been typed. Guinan et al. (1981) found that all 18 isolates from females with recurrent disease were Type 2; Kawana et al. (1982) found that all 16 females with recurrences also had Type 2 infections whilst Smith et al. (1981) found that 27

of 31 (87%) females with recurrences had Type 2 infections. Lafferty et al. (1987) prospectively followed 39 adults with concurrent orolabial and genital HSV infection with the same viral type. Patients with HSV 2 infections recurred earlier and more frequently at the genital site than those with HSV1. Conversely patients with HSV1 recurred earlier and more frequently at the oral site than those with HSV2. The reason why Type 2 genital infections recur more frequently than Type 1 genital infections is unclear. It is possible that the ability of the two viral types to establish latency varies and that Type 1 infections have a predilection for the trigeminal ganglia, whereas Type 2 'prefers' the dorsal root ganglia in the sacral plexus. When the Type 1 virus finds itself in an 'abnormal' site it has difficulty in establishing latency. Another possible explanation is that the two viral types differ in their ability to be reactivate with the Type 2 virus possibly more able to reactivate than Type 1.

Recognition of the differences in recurrence rates between the two viral type may be important in counselling patients about the risk of subsequent recurrences.

SUPPRESSIVE ORAL ACYCLOVIR FOR FREQUENTLY RECURRING GENITAL HERPES

We have shown that continuous oral acyclovir for 3 months at a dosage of 200 mg qds is a highly effective form of therapy for patients with frequently recurring genital herpes. Most patients did not have any recurrences during therapy and the few recurrences that did occur were mild and transient. Disappointingly, but not surprisingly, after cessation of therapy the frequency of recurrences returned to the pretreatment level.

The virus was only cultured on a single occasion in one patient during acyclovir therapy. This suggests that even if the occasional breakthrough recurrence does occur it is unlikely that patients will be infectious during that time.

Several other studies have shown similar findings (Douglas et al. 1984; Straus et al. 1984; Kinghorn et al. 1985; Thin et al. 1985; Halsos et al. 1985; Mertz

et al. 1988b; Baker et al. 1989). Douglas and his group in Seattle (1984) treated 153 patients in a similar study to our own. Fifty-one patients received acyclovir 200mg 5 times daily ("acyclovir 5"), 52 acyclovir 400mg bd ("acyclovir 2") and 50 patients received placebo. Patients were treated for 4 months. Patients in both the acyclovir groups ("acyclovir 5" and "acyclovir 2") had a significant reduction in the frequency and severity of recurrences during treatment and as with our study recurrence returned to the pretreatment level after cessation of therapy. It is of interest that the patients who received acyclovir therapy twice daily appeared to recur with similar frequency to those who had medication 5 times daily.

The study by Straus et al. (1984) used a slightly different approach. Thirty-five patients with frequently recurring genital herpes were treated. Seventeen with acyclovir and 18 with placebo. The dosage was 200mg tds. Treatment was continued until a recurrence occurred or if no recurrence occurred for 125 days. The mean duration of treatment in the placebo group was 24.8 days compared with 114.9 days in acyclovir recipients ($p<0.001$). After stopping treatment all patients had recurrences.

Kinghorn et al. (1985) studied 40 patients in Sheffield. This study was of similar design to the previous one in that treatment continued with either acyclovir or placebo until a recurrence occurred. The mean time to the first recurrence in the placebo recipients was 24 days compared with more than 84 days in the acyclovir group ($p<0.001$). As in the previous studies after cessation of treatment the disease returned to its pretreatment pattern.

The study by Thin et al. (1985) used a double-blind crossover method. Eighty eight patients were treated with either acyclovir 200mg qds or placebo for 84 days or until the first recurrence (whichever was the shorter). Eighty eight percent of the patients had a recurrence whilst on placebo compared only 13% on acyclovir $p<0.001$. The time to first recurrence was 22 days in the placebo recipients compared with greater than 84 days in acyclovir recipients.

Halsos et al. (1985) conducted a trial in Oslo and Helsinki. Thirty-one patients were treated with either acyclovir 200mg qds or placebo for 12 weeks and then switched for a further 12 weeks to the alternative therapy. The median time to the first recurrence in placebo recipients (whether they received placebo first or second) was 14 days compared with <84 days in acyclovir recipients ($p<0.001$).

The final two studies (Mertz et al. 1988b; Baker et al. 1989) were both large multicentre North American studies. In both, patients were treated with acyclovir 400mg bd or placebo for 1 year. The first study (Mertz et al. 1988b) from 24 centres compared 575 suppressive acyclovir recipients with 571 patients who received placebo. The time to first recurrence in patients receiving placebo was 18 days compared with 246 in those receiving suppressive acyclovir ($p<0.0001$). The frequency of recurrences was also markedly reduced in the acyclovir recipients. The findings from the second North American study (Baker et al.1989) in 261 patients from 25 centres were very similar.

The frequency of medication varied in the 7 trials from twice to 5 times daily and the total dosage from 600mg - 1g, however, all the treatments showed a similar reduction in the frequency of recurrences, and confirmed the efficacy of suppressive oral acyclovir for patients with frequently recurring genital herpes.

PROLONGED SUPPRESSIVE ACYCLOVIR

Our study using suppressive oral acyclovir for 1 year established the efficacy of this form of treatment for a prolonged period. Indeed the frequency of recurrences was markedly reduced and the duration of the few remaining recurrences significantly shorter.

One of our primary aims was to determine the most efficacious dose for commencing and maintaining suppressive acyclovir therapy. Patients who started on treatment with 200 mg qds were significantly less likely to have a recurrence than those on 400 mg twice daily, and throughout the period of this study

patients on more frequent doses fared better than those on less. Whilst breakthrough recurrences occurred on all doses, virus positive episodes were more common on once daily treatment. Only one other dose titration study has been reported (Kroon et al. 1990) and although this was a rather small study involving only 20 patients, the results were very similar to ours, with an increasing likelihood of recurrences as the dose of acyclovir was reduced. On the basis of these studies we would recommend that all patients should commence therapy on 200 mg qds, and this should be reduced to 200 mg 3 times daily after 2-3 months if the patient is recurrence free. Further reductions to 200 mg bd and eventually once daily may be possible. However it is worth bearing in mind that over 40% of patients will have a recurrence on once daily therapy and suboptimal doses may be a factor in the development of drug resistance (see below).

Are there any alternatives to continuous suppressive therapy? Several double blind placebo controlled trials treating each recurrence with either oral or topical acyclovir have shown that the duration and severity of that particular episode may be statistically significantly reduced (Nilsen et al. 1982; Fiddian et al. 1983; Kinghorn et al. 1983; Salo et al. 1983; Reichman et al. 1984; Rubnek-Forsbeck et al. 1985). However the actual clinical benefit is questionable. Most of the studies showed that healing times were approximately one day shorter in the acyclovir recipients compared with controls, and taking tablets or using cream for 5 days to reduce the duration of the illness from 6 days to 5 is at best a marginal benefit. Using the treatment as early as possible in the attack does appear to be somewhat better (Reichman et al. 1984) and may be suitable management for patients with infrequent attacks. Treating individual recurrences has no effect on the development of subsequent recurrences.

Several recent studies have shown that treating each recurrence is less efficacious and less acceptable to the patient than suppressive therapy (Goldberg et al. 1986; Mattison et al. 1988b; Mertz et al. 1988c). Another approach treating patients only at weekends again showed little benefit (Straus et al. 1986). One is led to the conclusion that at present there is no acceptable

alternative to suppression for patients with frequent recurrences.

The thorny question of how long patients should be treated remains unresolved. Our study suggested that the frequency of recurrences declined after 1 year and a study by Straus et al. (1988) supports this view. Whether this is due to treatment or is the natural history of the infection is unclear. In any event this observation suggests that therapy should be stopped after a year to ascertain if the frequency of recurrences warrants further treatment.

Whilst the efficacy of the therapy is undisputed the question of who to treat remains controversial. Several factors should be taken into consideration when deciding who to treat, including the following:-

1. Frequency of recurrences
2. Duration of recurrences
3. Severity of symptoms
4. Associated psychological or psycho-sexual morbidity
5. Total duration of illness
6. Likelihood of transmission to sexual partner

Considering all of these factors, the easiest to assess are the frequency, duration and severity of recurrences. My own belief is that patients with 8 or more recurrences per year generally require suppression, whereas those with fewer than 6 probably do not. Between 6 and 8 it is important to assess the duration and severity of recurrences and the other factors mentioned above. We have found that the easiest way of doing this is to follow patients prospectively from the time of presentation until the observer is confident, firstly that the patient does indeed have herpes, and secondly that the recurrences are sufficiently frequent or severe to warrant therapy. Patients who present with primary herpes should not be given suppressive acyclovir until sufficient time passed to assess that the patient is having at least 6 recurrences per year. Our study also suggests treatment should be stopped after one year as in some patients the frequency of recurrences will have reduced to a level where suppression is no longer required. This finding is supported by recent

work from the U.S.A. (Mertz et al. 1988c). We would suggest that patients should be started on 200 mg qds and the dose sequentially reduced, first to 200 mg tds and then to 200 mg bd over the coming months to a level (determined by considering the frequency of breakthrough recurrences) acceptable to the patient.

Patients who are immunosuppressed (eg those with a malignancy, receiving chemotherapy or other immunosuppressive drugs, or those with HIV infection) should be handled differently, as more serious cutaneous consequences may occur. These include chronic progressive cutaneous lesions where localised sores fail to heal and may become larger, deeper and more painful (Logan et al. 1971; Muller et al. 1972; Schneidman et al. 1979; Siegal et al. 1981) or acute mucocutaneous dissemination where the lesions spread widely over the body (Solomon 1961; Smith & Melnick 1962; Lynfield et al. 1969). These patients should probably be offered suppressive oral acyclovir as soon as recurrences become either more frequent or more severe than they were previously (Mindel 1989). It has been suggested that higher doses of the drug (400 mg five times daily) are required in immunosuppressed patients (Saral et al. 1981, 1983; Hann et al. 1983; Wade et al. 1984); however, clinical trials comparing different doses have not been conducted.

SAFETY OF ACYCLOVIR

The studies presented in this thesis all demonstrate that acyclovir is an extremely safe drug, both in the short and medium term. The only notable side effect was transient renal toxicity in the patients who received intravenous acyclovir as a bolus injection. Transient renal toxicity is probably due to deposition of acyclovir crystals in the renal tubules (Brigden et al. 1982) and has been reported by other workers (Brigden et al. 1982; Weller et al. 1983). Administration of the drug by slow intravenous infusion, and ensuring that patients are adequately hydrated appears to overcome this problem.

The observation that a small number of patients complained of depression on long term therapy is of interest and needs further investigation. One possible

explanation is that over the period of the study the patients came to know the investigators so well they were willing to discuss personal matters which they had not previously mentioned.

The remarkable safety of acyclovir was recently reviewed by Tilson (1988) who looked at both published reports of adverse events and reports to Burroughs Wellcome in the USA and the Wellcome Research Laboratories in the UK. Although numerous side effects have been attributed to acyclovir the number of such reports is minuscule. For example, in the USA against a total exposed population denominator of over 5 million only 730 side effects involving 469 patients have been reported. In many instances the "side effect" could not be directly attributed to the drug and in most the problems were minor and transient. There were 31 deaths in the American experience. All the patients who died were otherwise severely ill and the physicians involved did not consider acyclovir as a cause of death in any of these patients. The commonest side effects were nervous system problems with the IV preparation (confusion, convulsions, coma, sleep disturbances and acute brain syndrome), gastrointestinal (diarrhoea nausea and vomiting) and skin problems (various types of rash) with the oral preparation. In each instance only a handful of patients was reported with each side effect (not forgetting the similar denominator).

FAILURE TO RESPOND TO ACYCLOVIR THERAPY

The majority of patients with genital herpes who are treated with acyclovir (either for the first attack or suppression of recurrences) respond to therapy, but a small number fail to do so. There are several reasons for failure of therapy including, patients not taking the drug in sufficient dose, malabsorption (Mindel and Carney 1988), the condition due to some other pathology and finally resistance to therapy.

Resistance can result from alteration in 2 loci on the HSV genome; the regions coding for thymidine kinase (TK) and DNA polymerase enzymes (Coen and Schaffer 1980; Schnipper and Crumpacker 1980; Field et al. 1980). Viruses with

reduced sensitivity to acyclovir (mostly TK negative strains) have been reported, although the number of reports is small and mostly in immunocompromised patients who have received long or repeated courses of therapy. (Burns et al. 1982; Crumpacker et al. 1982; Sibrack et al. 1982; Wade et al. 1983; Schinazi et al. 1986; Norris et al. 1988; Erlich et al. 1989; Chatis et al. 1989). A handful of reports suggest that resistance isolates may rarely be found in patients with normal immunity, even prior to the administration of acyclovir (McLaren et al. 1983; Straus et al. 1984). It is of interest that recovery of resistant virus may not correlate with the clinical response, and that virus isolated from patients who previously demonstrated resistant strains may be sensitive to subsequent treatment.

Although resistance remains uncommon vigilance will be required to see that it remains so. It is interesting to postulate "biological situations" that may be likely to give rise to resistant strains. Repeated courses of treatment using sub-optimal doses (eg repeated short courses of topical acyclovir for recurrent oral or genital herpes) may favour the emergence of such strains, whereas suppressive therapy (in sufficient dose) may prevent their emergence by stopping viral replication. On the other hand, it has been suggested that suppressions may increase the likelihood of the emergence of drug resistant strains (Hirsch & Schooley 1989). Viral lesions often contain mixtures of clonal types, the majority sensitive to acyclovir but some drug resistant (mostly TK negative) mutants, normally at a selective disadvantage, may in the presence of acyclovir, compete successfully with drug sensitive strains. TK negative strains occur spontaneously and are probably eliminated by the immune system, however, in immunosuppressed patients this may not occur. Making sure that immunosuppressed patients receive adequate acyclovir doses to prevent re-activation may be important.

OTHER POTENTIAL USES OF ACYCLOVIR

Prevention of Genital Herpes

Experiments on animals have shown that if acyclovir is administered within 48 hours of exposure to HSV, both clinical lesions and latency can be prevented (Klein et al. 1979, 1982; Landry et al. 1982; van Ekdom & Versteeg 1982). The potential use of acyclovir in humans for preventive therapy is therefore a possibility. The problem is that the majority of people who contract herpes do so from someone who is unaware that they are infected at the time. A controlled trial of acyclovir in this situation would be difficult. Nonetheless it would seem worthwhile to treat any individual presenting within 48 hours who had been inadvertently exposed to HSV.

Prevention of Neonatal Herpes

Neonatal herpes is a serious infection resulting in neurological damage or severe disseminated infection in many infants (Nahmias and Keyserling 1984). Without treatment 60% of infants die. The introduction of anti-viral chemotherapy (vidarabine and acyclovir) has reduced the mortality (Whitley et al. 1991). Nonetheless a considerable number of infants will either die or be left with severe neurological impairment.

The majority of infections are contracted from the mother's birth canal at the time of delivery. Caesarian section has been shown to be able to prevent neonatal herpes, presumably by allowing the baby to bypass the infected birth canal. In an attempt to identify the women at risk of infecting the baby during delivery screening procedures involving genital examinations and viral cultures have been adopted. However, these have recently come in for severe criticism (Kelley 1988; Welch et al. 1988). The grounds for these criticisms are firstly that the women at risk are not necessarily identified and that Caesarian sections themselves carry a mortality and morbidity.

It has been suggested that suppressive oral acyclovir given during the last 4 weeks of pregnancy could prevent both neonatal herpes and the need for Caesarian section by preventing reactivation of latent infection (Carney and Mindel 1988). Stray-Pederson (1990) has recently reported the results of a study where pregnant women with a history of recurrent genital herpes were either treated for the last week of pregnancy with oral acyclovir or received no treatment. There was a statistically significant reduction in the number of caesarian sections in the treated group. The results are unfortunately suspect as the study was open and unrandomised and there was little evidence that the two groups were comparable. Carefully controlled clinical trials will be needed to evaluate this therapy, both in terms of its efficacy and safety.

Preliminary analysis of inadvertent use of acyclovir in pregnancy has not shown any adverse events, although the number of patient reported in these studies has been small (Andrews et al. 1988).

INOSINE PRANOBEX FOR THE MANAGEMENT OF FIRST ATTACK AND RECURRENT GENITAL HERPES

As discussed above the efficacy of acyclovir for the treatment of first attack genital herpes has been confirmed in numerous randomised double blind placebo controlled trials. The use of inosine pranobex on the other hand has been surrounded by controversy (Viza 1985). Although several trials have been reported in patients with mucocutaneous herpes (Chang and Weinstein 1973; Wickett et al. 1976; Corey et al. 1979; Bouffat and Sourat 1980; Bradshaw et al. 1980; Galli et al. 1982; Kalimo et al. 1983; Salo and Lassus 1983), a recent review commented that the "results are difficult to assess because most of the trials are poorly designed or reported" (Drugs and Therapeutics Bulletin 1986). The only randomised double blind placebo controlled study looking exclusively at patients with first attack genital herpes (prior to our study) (Corey et al. 1979) has never been reported in full. A brief abstract of this trial suggested that inosine pranobex may be beneficial in patients with "primary infections." However our study showed no such benefit.

Indeed, our study showed that patients treated with acyclovir (either alone or in combination with inosine pranobex) healed more quickly, and had a shorter duration of symptoms and viral shedding than those treated with inosine pranobex alone.

The observation that neither drug had any impact on the time to first recurrence, or the frequency of recurrences, is of particular interest. As discussed previously it is well documented that acyclovir, when used to treat first attack genital herpes, does not reduce the frequency of subsequent recurrences, probably because the virus has already established latency by the time therapy is initiated. Inosine pranobex on the other hand is said to have both antiviral and immuno-potentiating properties. Despite this the drug has no apparent effect on the establishment of latency or subsequent reactivation. This suggests that in the context of genital herpes the immune enhancing properties of the drug are unimportant.

The results of our study comparing the efficacy of suppressive oral acyclovir and inosine pranobex in patients with frequently recurring genital herpes showed conclusively that acyclovir is vastly superior to inosine pranobex. Indeed, patients treated with acyclovir showed a significant reduction in the frequency of recurrences whilst those treated with inosine pranobex continued to have attacks without any apparent reduction.

We believe our studies end the controversy concerning the use of inosine pranobex for the treatment of first attack and the suppression of recurrent genital herpes and suggest that the drug no longer has a place in its treatment.

RECOMMENDATIONS FOR THE MANAGEMENT OF GENITAL HERPES

The results of studies presented in this thesis have established that acyclovir is the only drug currently available that has any consistent efficacy for the treatment of first attack and the suppression of recurrent genital herpes.

As a result of these studies (and the other studies discussed above) the following recommendations can be made.

1) Treatment of First Attack Genital Herpes

Acyclovir 200mg PO 5 times daily for 5 days

- Treatment should be started as early as possible
- There is no benefit in prolonging treatment
- Intravenous therapy should be reserved for the most severely ill patients
- Patients should be counselled that despite therapy recurrences may occur.

2) Treatment of Recurrent Genital Herpes

- Patients with frequently recurring herpes may benefit from long term suppressive oral acyclovir.
- Decision about who to treat will depend upon a consideration of the frequency, duration and severity of recurrences, any associated psychosexual morbidity and the likelihood of spread to a sexual partner
- Treatment should commence at a dose of 200 mg qds and reduced sequentially to the lowest dose at which the patient remains recurrence-free
- Treatment should be stopped after 1 year to reassess the necessity to treat.

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INITIAL ASSESSMENT SHEET 1

Patient's Surname ..... Hospital No. .....

Patient's Initials ..... Clinic No. .....

Address ..... N.H.S. No. .....

..... Sex .....

Date of Birth ..... Age .....

Weight .....kg. Height .....cm.

HISTORY

	(Please tick) Yes	No
1. Is this the initial genital herpes episode?	☐	☐
2. Has patient had Herpes simplex infections at other sites? If YES please specify:	☐	☐
3. Have any attacks occurred in her partner? If YES please specify details:	☐	☐
4. Is patient of child-bearing potential? If NO please give reason:	☐	☐
5. If YES is patient using an oral contraceptive? If NO please specify contraceptive used:	☐	☐
6. Has patient had L.M.P. in past 28 days? If NO give result of pregnancy test:	☐	☐
7. Is patient taking any other medication? If YES please specify on attached sheet.	☐	☐
8. Has patient given informed consent?	☐	☐

Associated Conditions (please tick)

None	☐	Rheumatoid arthritis	☐
Asthma	☐	Ulcerative Colitis	☐
Hayfever	☐	Others	☐
Eczema	☐	If others please specify:	

GENERAL

	Yes	No
Other antiviral therapy in last 14 days?	☐	☐
Any renal impairment?	☐	☐
Inguinal lymphadenopathy	☐	☐
Fever (temp. = ...^{o}C)	☐	☐
Signs of other infections/infestations	☐	☐
Other (specify):	☐	☐

FOLLOW-UP ASSESSMENTS

Date				
Day No. (counting initial assessment as Day 1)				
SYMPTOMS:		Please score	Please score	Please score
Key: 0 = None, 1 = Mild, 2 = Mod., 3 = Sev.	Itching	☐	☐	☐
	Pain/Burning	☐	☐	☐
	Vaginal Discharge	☐	☐	☐
	Dysuria	☐	☐	☐
	Numbness	☐	☐	☐
	Other (specify):	☐	☐	☐
EXAMINATION:	Vulva:-			
Key: Extent/Severity; 0 = None, 1 = Mild, 2 = Mod., 3 = Sev.	Erythema	☐	☐	☐
	Vesicles	☐	☐	☐
	Ulcers	☐	☐	☐
	Crusts	☐	☐	☐
	Extent	☐	☐	☐
	Vagina:-			
	Erythema	☐	☐	☐
	Vesicles	☐	☐	☐
	Erosions	☐	☐	☐
	Discharge	☐	☐	☐
	Cervix:-			
	Erythema	☐	☐	☐
	Vesicles	☐	☐	☐
	Erosions	☐	☐	☐
	Discharge	☐	☐	☐
	Perineum	☐	☐	☐
	Anus	☐	☐	☐
	New Lesions (site: .....)	☐	☐	☐

GENERAL:	Yes	No	Yes	No	Yes	No
Inguinal lymphadenopathy	☐	☐	☐	☐	☐	☐
Fever (temp. = ...^{o}C)	☐	☐	☐	☐	☐	☐
Signs of other infections/infestations	☐	☐	☐	☐	☐	☐
Complete healing occurred (all lesions)	☐	☐	☐	☐	☐	☐
Have any adverse effects occurred?	☐	☐	☐	☐	☐	☐
Any concomitant medication?	☐	☐	☐	☐	☐	☐

Name/Initials/Study No. .....

LABORATORY VIRAL DIAGNOSIS

Date							
Study Day No.	1	2	3	4	5	6	7
HSV culture*							
HSV C.F.T."							
Other:							
Other:							

Date							
Study Day No.							
HSV Culture*							
HSV C.F.T."							
Other:							
Other:							

* record as +, - or N.D. and indicate whether type 1 or 2.

"specify titre.

Name/Initials/Clinic No. .....

RECORD OF TREATMENT WITH ACYCLOVIR

Date	Day	Time	Dose (mg)	Time plasma sampled
	1	(1)		
		(2)		
		(3)		
	2	(1)		
		(2)		
		(3)		
	3	(1)		
		(2)		
		(3)		
	4	(1)		
		(2)		
		(3)		
	5	(1)		
		(2)		
		(3)		
	6	(1)		
		(2)		

Name/Initials/Clinic No. .....

SCREENING TESTS - SHEET 1

Date				
Study Day No.		1	4	7
Test	Normal Range			
Haematology				
RBC				
Hb				
Hct				
MCV				
MCH				
MCHC				
WBC				
Differential:				
Polys				
Lymph				
Eos				
Baso				
Mono				
Other (specify):				
Platelets				
ESR				
Biochemistry:				
Plasma Na				
Plasma K				
Plasma Urea				
Plasma Bicarbonate				
Plasma Alk. Phos.				
Plasma AST				
Plasma ALT				
Se Creatinine				
Se Bilirubin				

Urinalysis: Day No.	1	2	3	4	5	6	7	12	
Protein									
Sugar									
Other (specify):									

Name/Initials/Clinic No. .....

SCREENING TESTS - SHEET 2

EXCLUSION OF OTHER DISEASES/INFECTIONS

TEST*	DATE	RESULT	TREATMENT	OUTCOME

*should include wet film examination, gram smear, bacterial cultures, MSU, Pap smear, VDRL and any other tests performed.

REPEAT HAEMATOLOGY/BIOCHEMISTRY TESTS (if abnormal on day 7)+

TEST DATE RESULT OUTCOME					

+further results, if relevant, should be recorded on a separate sheet.

Name/Initials/Clinic No. .....

Record of Adverse Effects or Other Unusual Events

Date	Comments

Details of Concomitant Medication

Dates	Drug	Dose	Reason

Date ..... Trial No. .....

TRIAL OF ACYCLOVIR IN PRIMARY GENITAL HERPES

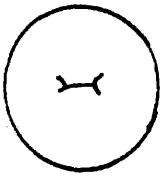
Patient's Initials .....:..... Hospital/Clinic No. .....

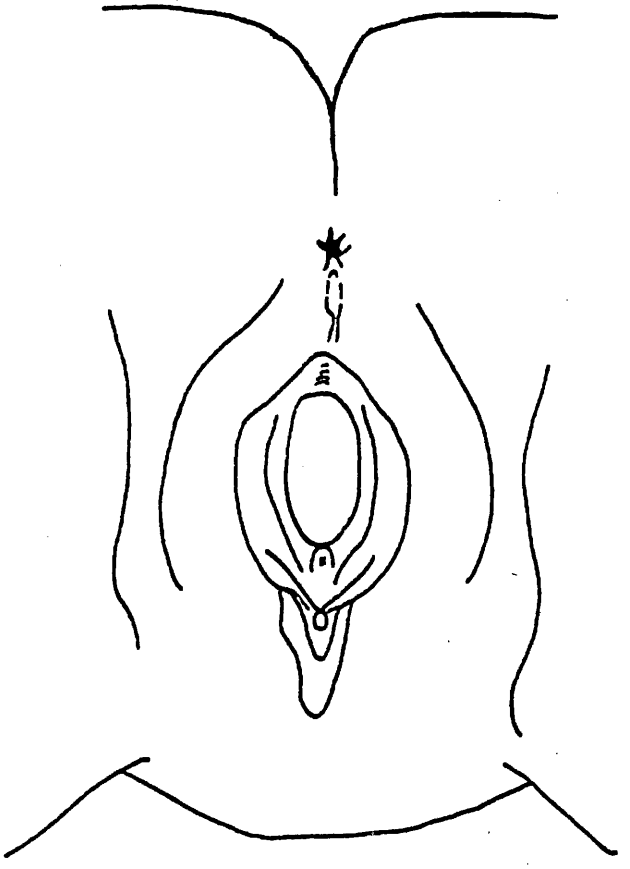
Date of Birth ..... Age ..... Sex .....

Ethnic group ..... Weight .....(kg) Height .....(cm)

HISTORY AT PRESENTATION

	YES	NO
1. Is this the first genital herpes episode?	☐	☐
Possible source of infection: ..... Date:		
Onset of symptoms (specify):		
..... Date:		
Onset of signs (specify):		
..... Date:		
2. Has patient had herpes simplex infections at other sites?	☐	☐
Site: ..... Date:		
Site: ..... Date:		
3. Has partner had herpes simplex infections at any site?	☐	☐
Site: ..... Date:		
Site: ..... Date:		
4. Has patient practised oro-genital sex recently?	☐	☐
Details:		
5. Has patient received any other antiviral in previous month?	☐	☐
If YES please specify:		
6. Is patient adequately protected from pregnancy?	☐	☐
Details:		
7. Does patient have any underlying diseases?	☐	☐
If YES please specify (e.g. eczema, diabetes, renal or liver impairment etc.)		
8. Has patient given informed consent?	☐	☐





Clinic No.: ..... Trial No.: .....

Date			
Study Day No.			
Symptoms	Please SCORE	Please SCORE	Please SCORE
LOCAL Pain - at rest	☐	☐	☐
- on movement	☐	☐	☐
- site (specify)	.....	.....	.....
Itching	☐	☐	☐
Dysuria	☐	☐	☐
Discharge	☐	☐	☐
Other:	☐	☐	☐
SYSTEMIC Fever	☐	☐	☐
Headache	☐	☐	☐
Malaise	☐	☐	☐
Other:	☐	☐	☐

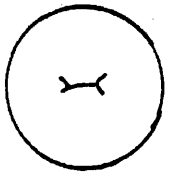
KEY
0=None
1=Mild
2=Mod.
3=Sev.

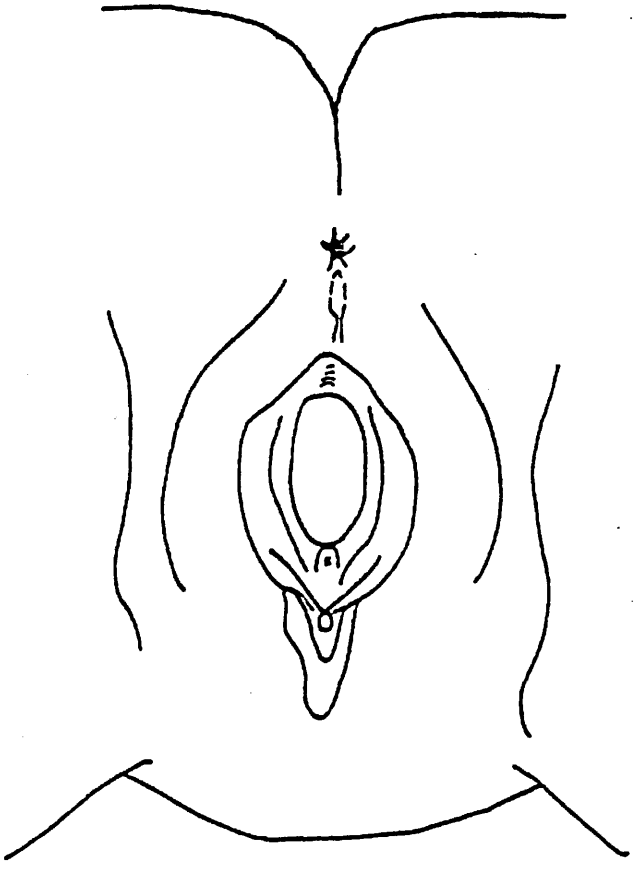
Site (code) **FEMALE / MALE / HOMOSEXUAL**	TICK	NO.OF LESIONS	TICK	NO. OF LESIONS	TICK	NO. OF LESIONS
Vulva/Penis/Rectum = A	☐	☐	☐	☐	☐	☐
Perineum/Scrotum/Anal Canal = B	☐	☐	☐	☐	☐	☐
Cervix/Perianal/Perianal = C	☐	☐	☐	☐	☐	☐
Other: ..... = D	☐	☐	☐	☐	☐	☐
Other: ..... = E	☐	☐	☐	☐	☐	☐

Appearance of cervix			
Signs	Please SCORE	Please SCORE	Please Score
Site code*			
Erythema/Macule			
Papules			
Vesicles/Pustules			
Ulcers/Erosions			
Crusts			
Healed (TICK)			
Inguinal lymphadenopathy (tender)	☐	☐	☐
New lesion formation	☐	☐	☐

KEY
0=None
1=Mild
2=Mod.
3=Sev.

*subcode for new lesions e.g. A2, C2.





Clinic No.: ..... Trial No.: .....

COMPLIANCE ASSESSMENT

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Week 2	Week 3	Week 4	Week 5	Week 6
No. tablets taken											

No. tablets returned at end of treatment period = (A): ..... (B): .....

CLINICAL RESPONSE TO TREATMENT

Estimate when complete healing occurred (if between visits) -

Original lesions - Site A: Date = ... Day No. = ...
B: Date = ... Day No. = ...
C: Date = ... Day No. = ...
E: Date = ... Day No. = ...

New lesions .....: Date = ... Day No. = ...

All lesions : Date = ... Day No. = ...

ADVERSE EVENTS

Date	Details	Association with acyclovir (1-4)*

*KEY
1=definite
2=probable
3=possible
4=unlikely

Clinic No.: ..... Trial No.: .....

DIAGNOSIS OF OTHER INFECTIONS

Date	Diagnosis	Treatment	Outcome

CONCOMITANT MEDICATION

Drug	Dose	Date Started	Date stopped	Indication

Clinic No.: ..... Trial No.: .....

VIRAL LABORATORY DIAGNOSIS

HSV CULTURE: VIRUS TYPE = ...

Date										
Study Day No.										
EXTERNAL GENITAL - original lesions: ..... - new lesions:										
INTERNAL GENITAL - cervix/rectum - urethra/other:										
OTHER SITES - throat -										

Date										
Study Day No.										
EXTERNAL GENITAL - original lesions: ..... - new lesions:										
INTERNAL GENITAL - cervix/rectum - urethra/other:										
OTHER SITES - throat -										

HSV SEROLOGY

Date							
Study Day No.						First recurrence	6 months
C.F.T. titre							

True primary/initial*
*delete as applicable

LABORATORY SCREENING TESTS

Date						
Week						
Haemoglobin g/dl						
Haematocrit						
RBC x 10^{12}/l						
WBC x 10^{3}/l						
Neutrophils %						
Lymphocytes %						
Platelets x 10^{9}/l						
ESR						
Urea mmol/l						
Creatinine µmol/l						
AST						
LDH						
Alkaline phosphatase						
Bilirubin						
Urine - protein						
- sugar						
- cells						
- other (specify:)						

Clinic No.: ..... Trial No.: .....

FOLLOW-UP ASSESSMENTS

Date				
Reason for attendance -				
Routine follow-up (Y/N)	☐	☐	☐	☐
Recurrent attack (Y/N)†	☐	☐	☐	☐
Other (specify) (Y/N)	☐	☐	☐	☐ .....
History since last visit -	☐	☐	☐	☐
No. further recurrences (dates)	....	....	....	....
Average duration attacks (days)	☐	☐	☐	☐
Usual severity pain (0-3)	☐	☐	☐	☐
Provoking factors (Y/N)+	.....	.....	.....	.....
Prodromal symptoms (Y/N)*	.....	.....	.....	.....
Treatment of recurrence (Y/N)*	.....	.....	.....	.....
HS at other sites (Y/N)*	.....	.....	.....	.....
Attacks in partner (Y/N)*	.....	.....	.....	.....
Adverse drug events - (Y/N)*	.....	.....	.....	.....
Other information				

* Specify relevant details

† If patient currently has a recurrence give details on CLINICAL ASSESSMENT SHEET

TIMETABLE/CHECKLIST

Date										
Study Day No.	0	1	2	3	4	5	6	7	10	14
Clinical assessment										
HSV cultures*										
HSV serology		X	X	X	X	X	X	X		X
Lab. screening tests		X	X	X	X		X	X	X	X
Tablets (bottle)	A	A	A	A	A	A/B	B	B	B	B

Date									
Study Day No.	17	21	24	28	31	35	38	42	Monthly
Clinical assessment									
HSV cultures*									
HSV serology	X		X	X		X	X		1st recurrence and 6 months
Lab. screening tests	X		X	X	X	X	X		X
Tablets (bottle)	B	B	B	B	B	B	B	B/-	-

* see VIRAL LABORATORY DIAGNOSIS sheet for details of sites previously tested (N.B. external lesions, cervix, new lesions and other sites e.g. throat)

Date ..... Trial No. .....

ACYCLOVIR PROPHYLAXIS IN RECURRENT GENITAL HERPES

Patient's Initials ..... Hospital/Clinic No .....

Date of Birth ..... Age ..... Sex .....

Ethnic group ..... Weight ..... (kg) Height ..... (cm)

HISTORY

1. First genital herpes episode, date: .....
2. Number of episodes since first episode .....
3. Number of episodes in page year: .....
4. Number of episodes in past 3 months: .....
5. Last episode, date: .....
6. Average duration of attacks (days): .....
7. Associated with (intercourse/other?): .....
8. Frequency of prodrome (0%, 25%, 50%, 75%, 100%): .....
9. Usual severity of pain (0, 1, 2, 3): .....
10. Usual site/extent of involvement: .....
11. Usual treatment used: .....
12. Herpes simplex at other sites? YES ☐ NO ☐

    Specify: .....
13. Herpes simplex in partner? ☐ ☐

    Specify: .....
14. Informed consent given? ☐ ☐

FOLLOW-UP ASSESSMENTS

Date				
Reason for attendance -				
Routine follow-up (Y/N)	☐	☐	☐	☐
Recurrent attack (Y/N)†	☐	☐	☐	☐
Other (specify) (Y/N)	☐	☐	☐	☐ .....
History since last visit -	☐	☐	☐	☐
No. further recurrences (dates)	....	....	....	....
Average duration attacks (days)	☐	☐	☐	☐
Usual severity pain (0-3)	☐	☐	☐	☐
Provoking factors (Y/N)+	.....	.....	.....	.....
Prodromal symptoms (Y/N)*	.....	.....	.....	.....
Treatment of recurrence (Y/N)*	.....	.....	.....	.....
HS at other sites (Y/N)*	.....	.....	.....	.....
Attacks in partner (Y/N)*	.....	.....	.....	.....
Adverse drug events - (Y/N)*	.....	.....	.....	.....
Other information				

* Specify relevant details

† If patient currently has a recurrence give details on CLINICAL ASSESSMENT SHEET

Clinic No.: ..... Trial No.: .....

COMPLIANCE ASSESSMENT*

End of Week No.	2	4	6	8	10	12
No. of tablets returned						
No. of missed doses						

*attach completed patient record forms to clinical proforma.

CONCOMITANT MEDICATION

Drug	Dose	Date Started	Date Stopped	Indication

ADVERSE EVENTS

Date	Details	Association with acyclovir (1-4)*

*KEY
1=definite
2=probable
3=possible
4=unlikely

VIRAL LABORATORY DIAGNOSIS

HSV CULTURE: VIRUS TYPE = ...

Date										
Study Day No.										
EXTERNAL GENITAL - original lesions:										
- new lesions:										
INTERNAL GENITAL - cervix/rectum										
- urethra/other:										
OTHER SITES - throat										
-										

Date										
Study Day No.										
EXTERNAL GENITAL - original lesions:										
- new lesions:										
INTERNAL GENITAL - cervix/rectum										
- urethra/other:										
OTHER SITES - throat										
-										

HSV SEROLOGY

Date							
Study Day No.						First recurrence	6 months
C.F.T. titre							

True primary/initial*
*delete as applicable

LABORATORY SCREENING TESTS

Date						
Week						
Haemoglobin g/dl						
Haematocrit						
RBC x 10^{12}/l						
WBC x 10^{3}/l						
Neutrophils %						
Lymphocytes %						
Platelets x 10^{9}/l						
ESR						
Urea mmol/l						
Creatinine µmol/l						
AST						
LDH						
Alkaline phosphatase						
Bilirubin						
Urine - protein						
- sugar						
- cells						
- other (specify:)						

Clinic No.: ..... Trial No.: .....

TIMETABLE/CHECKLIST

Date	-						
Week No.	0	2	4	6	8	10	12/0
History							
Clinical Assessment*							
HSV culture - lesion*							
- cervix/urethra							
HSV serology		X	X	X	X	X	
Lab. screening tests		X	X	X	X	X	
Exchange patient record form							

FIRST OBSERVATION PERIOD - ceases after the first recurrence.

Date							
Week No.	12/0	2	4	6	8	10	12/0
History							
Clinical Assessment*							
HSV culture - lesion*							
- cervix/urethra							
HSV serology		X		X		X	
Lab. screening tests		X		X		X	
Exchange patient record form/tablets							

TREATMENT PERIOD

*only required if a recurrence occurs

Clinic No.: ..... Trial No.: .....

TIMETABLE/CHECKLIST (continued)

Date							
Week No.	12/0	4	8	12	16	20	24
History							
Clinical Assessment*							
HSV culture - lesion*							
- cervix/urethra							
HSV serology		X	X	X	X	X	
Lab. screening tests†			X	X	X	X	
Exchange patient record form							

SECOND OBSERVATION PERIOD

*only required if a recurrence occurs
†if previous tests revealed any abnormalities

ACYCLOVIR SUPPRESSION OF RECURRENT GENITAL HERPES

Clinic No. .....

Date of Birth ..... Sex M .....

HISTORY

1. First genital herpes episode, date: .....
2. Number of episodes in past year: .....
3. Number of episodes in past 3 months: .....
4. Last episode, date: .....
5. Average duration of attacks (days): .....
6. Associated with (intercourse/other?): .....
7. Frequency of prodrome (%): .....
8. Usual severity of pain (0, 1, 2, 3): .....
9. Usual genital site of involvement: .....
10. Herpes simplex at other sites? YES / NO
    specify: .....
11. Previous antiviral used (specify): .....
12. Herpes simplex in present partner? YES / NO
    specify: .....
13. Sexual orientation: HETERO / HOMO / BISEX
14. Source of infection: KNOWN / UNKNOWN
    specify: .....
15. Have you infected any contacts? YES / NO
    specify: .....
16. Any time off work for herpes in last year YES / NO NO. DAYS .....
17. Previous STDs YES / NO
    specify: .....
18. Have you been given any advise about sexual intercourse during attacks? YES / NO
    specify: .....
    .....
19. Does your present partner know about your herpes? YES / NO

FOLLOW-UP ASSESSMENTS

Date			
PRESENT ATTACK - Recurrent attack at present (Y/N)			
Date started			
Date healed			
Recurrence confirmed: clinically (Y/N)			
Recurrence confirmed: virologically (Y/N)			
HISTORY - Date started / Date finished	/ / / /	/ / / /	/ / / /
Usual severity of pain (0-3)			
Provoking factors (Y/N)			
Prodromal symptoms (Y/N)*			
HS at other sites (Y/N)*			
Adverse Drug Events - (Y/N)*			
Other information			

*Specify relevant details

Trial No.: .....

Date				
Symptoms		Please SCORE	Please SCORE	Please SCORE
LOCAL	Pain - at rest	☐	☐	☐
	- on movement	☐	☐	☐
	Itching	☐	☐	☐
KEY 0=None 1=Mild 2=Mod. 3=Sev.	Dysuria	☐	☐	☐
	Discharge	☐	☐	☐
	Other:	☐	☐	☐
SYSTEMIC	Fever:.....	☐	☐	☐
	Headache	☐	☐	☐
	Malaise	☐	☐	☐
	Other:	☐	☐	☐

Site	(code)	TICK	NO. OF LESIONS	TICK	NO. OF LESIONS	TICK	NO. OF LESIONS
MALE							
Penis	= A	☐	☐	☐	☐	☐	☐
Perianal	= B	☐	☐	☐	☐	☐	☐
Anal Canal	= C	☐	☐	☐	☐	☐	☐
Other:	= D	☐	☐	☐	☐	☐	☐
Other:	= E	☐	☐	☐	☐	☐	☐

Signs		Please SCORE	Please SCORE	Please SCORE
	Site code*			
KEY 0=None 1=Mild 2=Mod. 3=Sev.	Erythema/Macule			
	Papules			
	Vesicles/Pustules			
	Ulcers/Erosions			
	Crusts			
	Healed (TICK)			
Inguinal lymphadenopathy		☐	☐	☐

Other Clinical Information

Trial No. .....

COMPLIANCE ASSESSMENT*

End of Month No.	1	2	3	4	5	6
Dose given (mg/tablet & no. tablets per day)						
No. of tablets returned						
No. of missed doses						

End of Month No.	7	8	9	10	11	12
Dose given (mg/tablet & no. tablets per day)						
No. of tablets returned						
No. of missed doses						

*attach completed patient record forms to clinical proforma.

Trial No.: .....

CONCOMITANT MEDICATION

Drug	Dose	Date Started	Indication

ADVERSE EVENTS

Date	Details	Association with acyclovir (1-4)
		KEY 1=definite 2=probable 3=possible 4=unlikely

Trial No. .....

VIRAL LABORATORY DIAGNOSIS

HISV CULTURE: VIRUS TYPE = ...

IDate										
-- penis										
-- perianal										
-- anal canal										
-- other										
-- other										
-- other										

Date										
- penis										
- perianal										
- anal canal										
- other										
- other										
- other										

Trial No.: .....

- LABORATORY SCREENING TESTS

	OBSERVATION			TREATMENT		
Date						
Week						
Haemoglobin g/dl						
Haematocrit						
RBC x 10^{12}/l						
WBC x 10^{3}/l						
Neutrophils %						
Lymphocytes %						
Platelets x 10^{9}/l						
ESR						
Urea mmol/l						
Creatinine µmol/l						
AST						
Albumin						
Alkaline phosphatase						
Bilirubin						

Trial No.: .....

TIMETABLE/CHECKLIST

Date				
Week No.	-8	-6	-4	-2
History				
Clinical Assessment*				
HSV culture(s)*				
Lab. screening tests				

*only required if a recurrence occurs.

FIRST OBSERVATION PERIOD - 2/12

Trial No.: .....

TIMETABLE/CHECKLIST (continued)

Date													
Week No.	0	4	8	12	16	20	24	28	32	36	40	44	48
History													
Clinical Assessment*													
HSV culture(s)*													
Lab. screening tests		X	X		X	X		X	X		X	X	

*only required if a recurrence occurs.

TREATMENT PERIOD - 12/12

Trial No.: .....

TIMETABLE/CHECKLIST (continued)

Date						
History						
Clinical Assessment						
HSV culture(s)						
Lab. screening tests						

Follow-up every 2 months for 6 months and for two recurrences.

POST TREATMENT PERIOD - 6/12

Hospital ..... Date ..... Trial No. .....

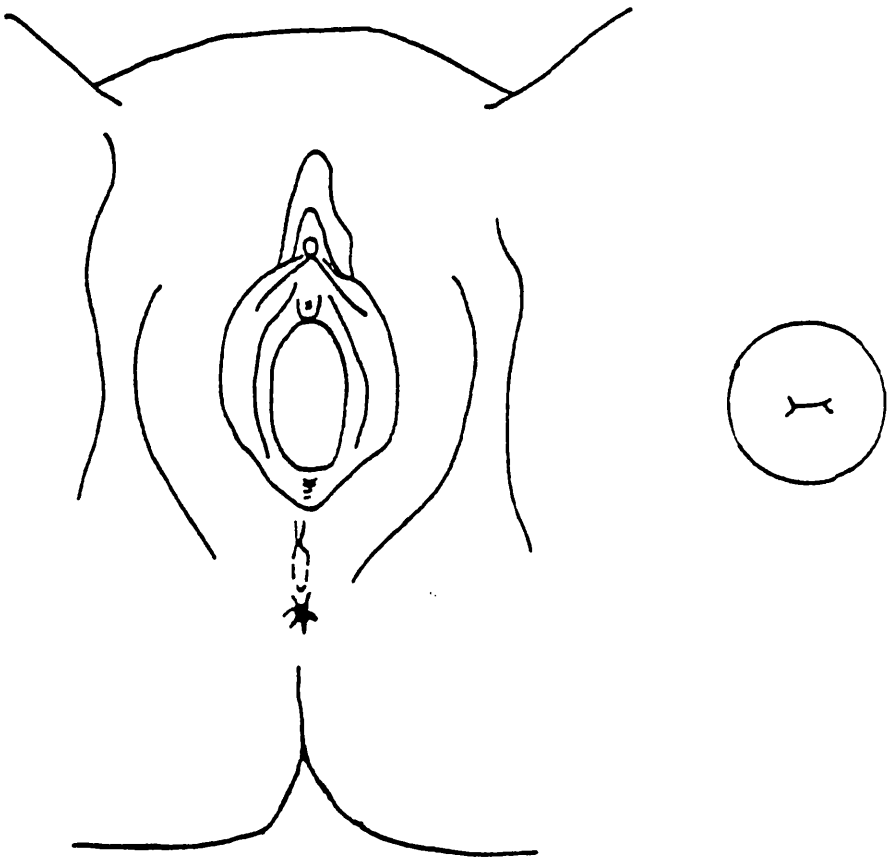
TRIAL OF ACYCLOVIR AND ISOPRINOSINE IN PRIMARY GENITAL HERPES

Hospital/Clinic No. ..... Sex F

Date of Birth ..... Age .....

HISTORY

		Yes	No
1.	Is this the initial genital herpes episode?	☐	☐
	Onset of symptoms (specify): ..... Date:		
	Onset of signs (specify): ..... Date:		
2.	Has patient had herpes simplex infections at other sites?	☐	☐
	Site: ..... Date:		
	Site: ..... Date:		
3.	Has partner had herpes simplex infections at any site?	☐	☐
	Site: ..... Date:		
	Site: ..... Date:		
4.	Does patient fulfill inclusion criteria of the study?	☐	☐



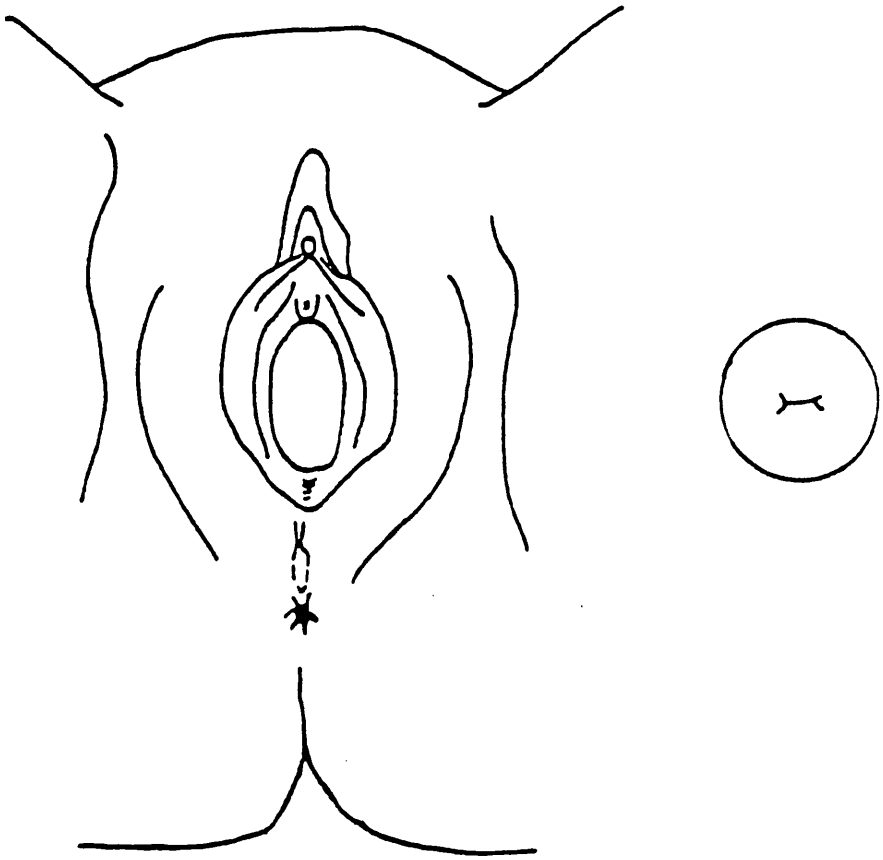
Hospital ..... Trial No. .....

CLINICAL ASSESSMENTS

Date			
Study Day No.			
Symptoms	Please SCORE	Please SCORE	Please SCORE
LOCAL Pain - at rest	☐	☐	☐
- on movement	☐	☐	☐
Itching	☐	☐	☐
Dysuria	☐	☐	☐
Discharge	☐	☐	☐
Other:	☐	☐	☐
SYSTEMIC Fever:	☐	☐	☐
Headache	☐	☐	☐
Malaise	☐	☐	☐
Other:	☐	☐	☐
Site (code)	TICK / NO. OF LESIONS	TICK / NO. OF LESIONS	TICK / NO. OF LESIONS
FEMALE			
Vulva = A	☐ ☐	☐ ☐	☐ ☐
Perineum = B	☐ ☐	☐ ☐	☐ ☐
Cervix = C	☐ ☐	☐ ☐	☐ ☐
Other: ..... = D	☐ ☐	☐ ☐	☐ ☐
Other: ..... = E	☐ ☐	☐ ☐	☐ ☐
Signs	Please SCORE	Please SCORE	Please SCORE
Site code			
Erythema/Macule			
Papules			
Vesicles/Pustules			
Ulcers/Erosions			
Crusts			
Healed (TICK)			
Inguinal lymphadenopathy	☐	☐	☐
New lesion formation (TICK)	☐	☐	☐
Other comments			

KEY
0=None
1=Mild
2=Mod.
3=Sev.

KEY
0=None
1=Mild
2.Mod.
3=Severe



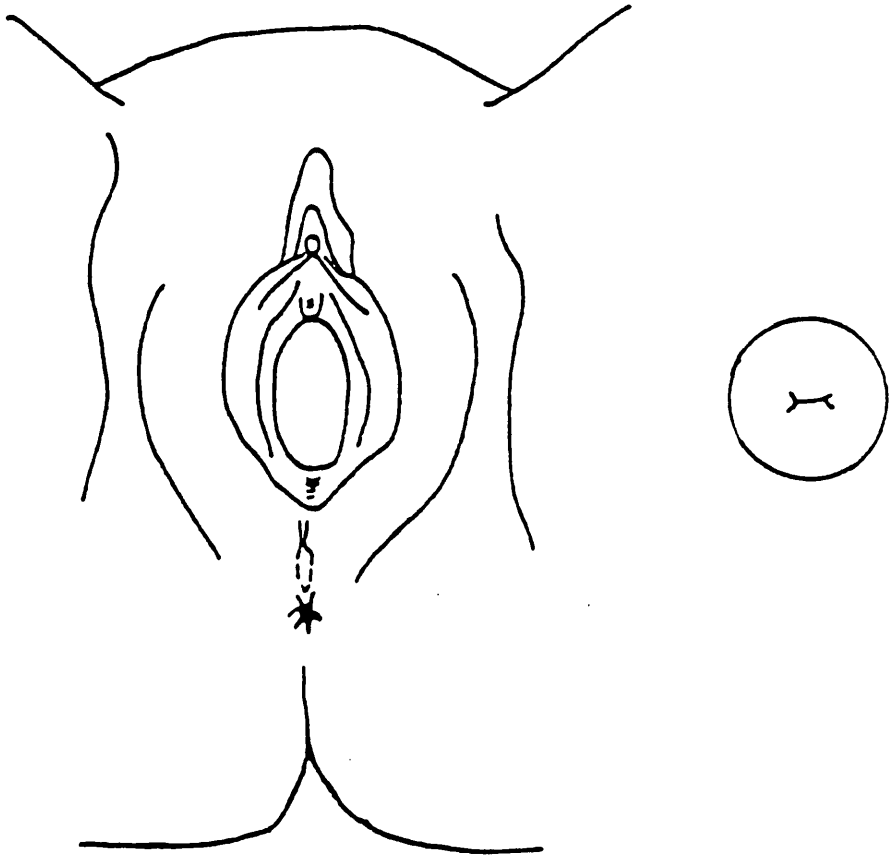
Hospital ..... Trial No. .....

VIRAL LABORATORY DIAGNOSIS

Date										
Study Day No.										
HSV culture - external genital										
- Internal lesions										
- extra genital lesions										
HSV C.F.T.										

LABORATORY SCREENING TESTS

Date			
Study Day No.			
Haematology (Normal range) RBC			
Haemoglobin			
Haematocrit			
WBC - Total			
- Neutrophils			
- Lymphocytes			
Platelets			
Biochemistry Serum creatinine			
Plasma urea			
Plasma alkaline phosphatase			
Plasma AST			
Plasma Uric Acid			
Bilirubin			
Albumin			



Hospital ..... Trial No. .....

VIRAL LABORATORY DIAGNOSIS

Date									
Study Day No.									
HSV culture - external genital									
- Internal lesions									
- extra genital lesions									
HSV C.F.T.									

LABORATORY SCREENING TESTS

Date			
Study Day No.			
Haematology (Normal range) RBC			
Haemoglobin			
Haematocrit			
WBC - Total			
- Neutrophils			
- Lymphocytes			
Platelets			
Biochemistry Serum creatinine			
Plasma urea			
Plasma alkaline phosphatase			
Plasma AST			
Plasma Uric Acid			
Bilirubin			
Albumin			

Hospital ..... Trial No. .....

CLINICAL RESPONSE TO TREATMENT

1. Estimate when complete healing occurred (if between visits) -

   Original lesions: Date = ... Study Day No. = ...

   All lesions: Date = ... Study Day No. = ...

DIAGNOSIS OF OTHER INFECTIONS

Date	Diagnosis	Treatment	Outcome

CONCOMITANT MEDICATION

Drug	Dose	Date Started	Duration	Indication

ADVERSE EVENTS

Date	Details	Association with acyclovir or isoprinosine (1-4)
		1=definite 2=probable 3=possible 4=unlikely

LONG TERM FOLLOW-UP ASSESSMENTS

Date			
Reason for attendance N month follow-up (specify which)			
Recurrent attack*			
History since last visit - No. recurrent episodes (dates)			
Usual severity pain (0-3)			
Provoking factors (specify:)			
Prodromal symptoms (Y/N)			
Treatment of recurrence (specify)			
HSV at other sites (specify)			
Assessment at this visit - Recurrent attack at present (Y/N)			
Date started			
Date healed			
Treatment given (specify)			
Recurrence confirmed clinically (Y/N)			
Recurrence confirmed virologically (Y/N)			
Adverse drug events - (Y/N)			
If YES specify:			
Other Information			

*For first recurrence, complete relevant page ahead

ASSESSMENTS OF FIRST RECURRENCE

Date			
Symptoms	Please SCORE	Please SCORE	Please SCORE
LOCAL Pain - at rest			
- on movement			
Itching			
KEY 0=None 1=Mild 2=Mod. 3=Sev — Dysuria			
Discharge			
Other:			
SYSTEMIC Fever:			
Headache			
Malaise			
Other:			
Site (code)	TICK / NO. OF LESIONS	TICK / NO. OF LESIONS	TICK / NO. OF LESIONS
FEMALE Vulva = A			
Perineum = B			
Cervix = C			
Other: ..... = D			
Other: ..... = E			
Signs	Please SCORE	Please SCORE	Please SCORE
Site code			
KEY 0=None 1=Mild 2=Mod. 3=Sev. — Erythema/Macule			
Papules			
Vesicles/Pustules			
Ulcers/Erosions			
Crusts			
Healed (TICK)			
Inguinal lymphadenopathy			
New lesion formation (TICK)			
Other infections (TICK) specify			
Medication given (TICK) specify			
Other comments			

Summary Flow Chart

Men and women with primary or initial genital herpes will be entered into the study → Seven day course of oral acyclovir → oral isoprinosine or both drugs will commence. → Patient will be followed up 3 times weekly until lesions are healed → Patients will be followed up for 1 year

Resume of investigations to be undertaken

Acute Phase	Day of study:									
e.g.	1 (Entry)	3	5	8	10	12	16	19	23	26 etc.
Blood for measurement of herpes antibiodies	✓	-	-	✓	-	-		✓		-
Blood for haematology/ biochemistry	✓	-	-	✓	-	-	-	(✓)	-	-
Swabs for HSV culture	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Complete clinical proforma	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Follow up phase	Month of study:						
	1	2	3	6	9	12	Recurrence
Swabs for HSV culture	✓	✓	✓	(✓)	(✓)	(✓)	✓
Complete clinical proforma	✓	✓	✓	(✓)	(✓)	(✓)	✓
Assess severity of 1st recurrence	-	-	-	-	-	-	✓
Check & replace patient diary cards	✓	✓	✓	✓	✓	✓	(✓)

Trial of Acyclovir and Isoprinosine in the Suppression of Recurrent Genital Herpes

Clinic No. .....

Date of Birth ..... Sex ..... F .....

HISTORY

1.	First genital herpes episode, date:	.....
2.	Number of episodes in past year:	.....
3.	Number of episodes in past 3 months:	.....
4.	Last episode, date:	.....
5.	Average duration of attacks (days):	.....
6.	Associated with (intercourse/other?):	.....
7.	Frequency of prodrome (%):	.....
8.	Usual severity of pain (0, 1, 2, 3):	.....
9.	Usual genital site of involvement:	.....
10.	Herpes simplex at other sites? specify:	YES / NO
11.	Previous antiviral used: specify:	YES / NO
12.	Herpes simplex in present partner? specify:	YES / NO
13.	Form of contraception specify:	PILL / IUD / OTHER
14.	Source of infection: specify:	KNOWN / UNKNOWN
15.	Have you infected any contacts? specify:	YES / NO
16.	Any time off work for herpes in last year	YES / NO NO. DAYS .....
17.	Previous STDs specify:	YES / NO

Date ..... Trial No. .....

18. Previous cytology done? YES / NO

If YES, date of most recent cytology: .....

abnormalities: .....

19. Have you previously been given any advise about cervical cytology? YES / NO

If YES, how frequently were smears recommended? .....

20. Have you been given any advise about sexual intercourse during attacks? YES / NO

specify: .....

.....

.....

21. Does your present partner know about your herpes? YES / NO

Trial Number: .....

FOLLOW UP ASSESSMENTS (OBSERVATION PERIOD)

Date			
Visit number*			
PRESENT ATTACK Current attack at present (Y/N)			
date started			
date healed			
Recurrence confirmed clinically (Y/N)			
Recurrence confirmed virologically (Y/N)			
HISTORY SINCE LAST VISIT Number of recurrences (including aborted episodes)			
dates started			
dates healed			
Severity of pain (0-3)#			
Provoking factors (Y/N)			
Prodromal symptoms (Y/N)			
HSV at other sites (specify)			
HSV in partner (specify)			
Other information eg, other drugs			
Diary card returned and checked			

* every 4 weeks, plus at the onset of any recurrence

0=none, 1=mild, 2=moderate, 3=severe

Trial Number: .....

FOLLOW UP ASSESSMENTS (DURING TREATMENT)

Date			
Visit number*			
PRESENT ATTACK Current attack at present (Y/N)			
date started			
date healed			
Recurrence confirmed clinically (Y/N)			
Recurrence confirmed virologically (Y/N)			
HISTORY SINCE LAST VISIT Number of recurrences (including aborted episodes)			
dates started			
dates healed			
Severity of pain (0-3)#			
Provoking factors (Y/N)			
Prodromal symptoms (Y/N)			
HSV at other sites (specify)			
HSV in partner (specify)			
Adverse Drug Events (YES/NO, specify on separate sheet)			
Other information eg, other drugs			
Diary card returned and checked			

* every 4 weeks, plus at the onset of any recurrence

0=none, 1=mild, 2=moderate, 3=severe

Trial Number: .....

FOLLOW UP ASSESSMENTS (SUBSEQUENT TO TREATMENT)

Date			
Visit number*			
PRESENT ATTACK Current attack at present (Y/N)			
date started			
date healed			
Recurrence confirmed clinically (Y/N)			
Recurrence confirmed virologically (Y/N)			
HISTORY SINCE LAST VISIT Number of recurrences (including aborted episodes)			
dates started			
dates healed			
Severity of pain (0-3)#			
Provoking factors (Y/N)			
Prodromal symptoms (Y/N)			
HSV at other sites (specify)			
HSV in partner (specify)			
Other information eg, other drugs			
Diary card returned and checked			

* every 4 weeks, plus at the onset of any recurrence

0=none, 1=mild, 2=moderate, 3=severe

Trial No.: .....

Date				
Symptoms		Please SCORE	Please SCORE	Please SCORE
LOCAL	Pain - at rest	☐	☐	☐
	- on movement	☐	☐	☐
	Itching	☐	☐	☐
KEY 0=None 1=Mild 2=Mod. 3=Sev.	Dysuria	☐	☐	☐
	Discharge	☐	☐	☐
	Other:	☐	☐	☐
SYSTEMIC	Fever:.....	☐	☐	☐
	Headache	☐	☐	☐
	Malaise	☐	☐	☐
	Other:	☐	☐	☐

Site	(code)	TICK	NO. OF LESIONS	TICK	NO. OF LESIONS	TICK	NO. OF LESIONS
FEMALE							
Vulva	= A	☐	☐	☐	☐	☐	☐
Perineum	= B	☐	☐	☐	☐	☐	☐
Cervix	= C	☐	☐	☐	☐	☐	☐
Other:	= D	☐	☐	☐	☐	☐	☐
Other:	= E	☐	☐	☐	☐	☐	☐

Signs		Please SCORE	Please SCORE	Please SCORE
	Site code*			
KEY 0=None 1=Mild 2=Mod. 3=Sev.	Erythema/Macule			
	Papules			
	Vesicles/Pustules			
	Ulcers/Erosions			
	Crusts			
	Healed (TICK)			
nguinal lymphadenopathy		☐	☐	☐

ther Clinical Information			

Trial Number: .....

COMPLIANCE ASSESSMENT

End of Month No.	1	2	3
No. of acyclovir tablets returned			
No. of missed doses			
No. of isoprinosine tablets returned			
No. of missed doses			

CONCOMITANT MEDICATION

Drug	Dose	Date Started	Indication

Trial Number: .....

ADVERSE EVENTS

Date	Details	Association with acyclovir or isoprinosine (1-4)*
		* Key 1=definite 2=probable 3=possible 4=unlikely

VIRAL LABORATORY DIAGNOSIS

HSV CULTURE:

Date									
- vulva									
- cervix									
- perineum									
- other									
- other									
- other									

Date									
- vulva									
- cervix									
- perineum									
- other									
- other									
- other									

Trial Number: .....

LABORATORY SCREENING TESTS

Date			
Visit number			
HAEMATOLOGY (normal range) Haemoglobin g/dl			
Haematocrit			
RBC $x10^{12}/l$			
WBC - total $x10^{3}/l$			
- neutrophils %			
- lymphocytes %			
Platelets $x10^{9}/l$			
ESR			
BIOCHEMISTRY Plasma urea µmol/l			
Serum creatinine µmol/l			
Plasma AST			
Plasma uric acid (urate)			
Albumin			
Alkaline phosphatase			
Bilirubin			

Trial no: .....

TIMETABLE

	Observation		Treatment				Follow-up					
Week no	-8	-4	0	4	8	12	16	20	24	28	32	36
History	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Diary cards	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tablets			✓	✓	✓							
Clinical assessment*	✓											
HSV culture*	✓											
Lab screening tests			✓		✓		✓					

* Otherwise only required if a recurrence occurs

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INTRAVENOUS ACYCLOVIR TREATMENT FOR PRIMARY GENITAL HERPES

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Summary 30 patients with a severe first attack of genital herpes were treated with intravenous acyclovir in a randomised, double-blind, placebo-controlled trial. The medians for healing time, duration of vesicles, new lesion formation, viral shedding, and all symptoms were significantly shorter in patients treated with acyclovir than in the controls. No important side-effects were noted. Intravenous acyclovir seems to be a safe and effective therapy for patients having their first attack of genital herpes.

Introduction

GENITAL infection with herpes simplex virus (HSV) is a major and increasing cause of morbidity in many countries. 10 800 such cases were reported from sexually transmitted disease clinics in the U.K. in 1980, a rise of 60% over the previous five years.[1] The primary infection may be severe enough to warrant hospital admission, and recurrences may be frequent and may create profound morbidity and sexual dysfunction.[2,3] There is also the possible association with carcinoma of the cervix[4] and with neonatal infection, which can be fatal.[5] Inability to treat genital herpes is reflected in the diversity and number of remedies that have been used.[6] The recent introduction of acyclovir, an antiviral agent of low toxicity with high specificity against herpesviruses, has raised hopes for an effective therapy against genital HSV.[7,8] The parenteral form of acyclovir has been effective in the treatment of disseminated herpetic infections in immunocompromised patients[9] and in immunocompetent patients with varicella zoster.[8]

The aim of the present study was to find out whether acyclovir decreased the length and severity of the primary attack of genital herpes. We decided to use an intravenous preparation since the infection is often accompanied by marked systemic reaction. In addition, we considered that such a preparation was the most appropriate for establishing baseline information about the drug, because its use circumvents problems associated with gastrointestinal tract absorption. We conducted a randomised, double-blind, placebo-controlled trial of intravenous acyclovir in 30 patients having their first attack of genital HSV. This report is concerned only with the first attack. The information on recurrences will be presented in a future paper.

Patients and Methods

Study Population

Patients with a first attack of genital herpes infection severe enough to warrant hospital admission, who presented to the department of genito-urinary-medicine, Middlesex Hospital, within 6 days of the first appearance of genital sores were invited to participate in the trial. Informed consent was obtained from all patients. Criteria for exclusion were a history of previous genital herpes, age less than 16 years, renal impairment, or specific antiviral therapy in the previous 14 days. Females were excluded if they were pregnant or were not using adequate contraceptive measures (oral contraception or intrauterine device).

Patient Management

All patients were admitted for 7 days or longer if clinically indicated. On admission blood was taken for full and differential blood count, erythrocyte sedimentation rate, urea and electrolytes, creatinine, and liver function tests (LFTs). These tests were repeated on the 4th and 7th days of the hospital stay. Specimens were taken for *Neisseria gonorrhoeae, Trichomonas vaginalis,* and *Candida albicans,* and serological tests for syphilis were done.

Patients' clinical status was assessed by the use of a standardised recording schedule on admission and daily for 7 days, and then twice weekly until healing occurred. All the clinical assessments were done by one person (A. M.). Patients were prescribed frequent saline baths and analgesia as required. Fluid balance was monitored continuously.

After complete healing had occurred patients were requested to return to the clinic if they had recurrences and, in any event, 6 months after the initial episode. On each follow-up visit a full history was taken and an examination performed.

Drug Administration

Except for the first 4 patients who received the drug or placebo as a bolus injection, the rest were given slow (45–60 min) infusions through an indwelling intravenous cannula every 8 h for 15 doses, each dose being 5 mg/kg body weight. The placebo used was mannitol. The drug and placebo were packaged in indistinguishable vials with individual code numbers, so that the trial was double blind.

TABLE I—PATIENT DEMOGRAPHY

	Acyclovir	Placebo
No. of females	12	12
No. of males	3	3
No. with primary infections	12	8
No. with initial infections	3	7
Median age (years); range in parentheses	22 (18–43)	21 (16–31)
Median duration of symptoms before entry (days)	4	4
No. with systemic symptoms and signs	10	8
External genital lesions	14	15
Internal genital lesions	14	15

Virology

Serum was obtained on admission and on days 12 and 28 for herpes antibody estimation. Complement fixing antibody to HSV was assayed in microtitre plates by the use of the method of Bradstreet and Taylor.[10] Patients whose first serum specimen had antibody titres of <1/2 were classified as having primary infections; all others were considered to have initial infections of the genital tract.

Swabs for viral culture were taken from all lesions and, in females, from the cervix even if no infection was evident. These were repeated daily for the first 7 days and then twice weekly until complete healing occurred. Swabs were sent to the laboratory in transport medium and inoculated into cultures of human embryo lung fibroblasts which were incubated at 37°C and examined daily for 5 days. The first isolate from each patient was submitted to neutralisation tests for the identification of herpes simplex virus. Further isolates were identified by their cytopathic effects.

Analysis of Results

A one-tailed log rank test was used for all variables to compare the acyclovir group with the placebo group.[11] Medians were used because many of the variables had a skewed distribution.

Results

Patient Characteristics (Table I)

15 Patients received the drug and 15 placebo. Their infections were classified as primary or initial. 20 patients had primary infections and their reciprocal complement fixing antibody titres rose from <2 in the first serum to 32–256 in the second serum sample tested. The initial infection group comprised 3 patients showing no antibody rise from titres of 1/32 or 1/64, and 7 patients showing rises in antibody of four fold or greater. 2 in this group who had starting titres of <1/8 might have had primary infections. There were 6 male patients, 3 in each group. All the male patients had primary infections. Of the 12 female patients who received the drug 9 had primary infections and 3 initial, compared with 5 primary infections and 7 initial in the placebo group. At presentation no statistically significant differences existed between patients and controls in relation to age, duration of lesions, and mean number and severity of symptoms.

Side-effects

2 patients had nausea, vomiting, and dizziness. Both received acyclovir and dihydrocodeine. We believe the symptoms were due to dihydrocodeine. 7 patients (4 acyclovir and 3 placebo) had abnormal LFTs during the study period. These abnormalities were mild and short-lived and did not differ between the two groups.

1 of the patients who received acyclovir in a bolus had a transient rise in urea and creatinine which returned to normal in 48 h. All subsequent patients received acyclovir or placebo by slow intravenous infusion.

Healing Time (Table II)

The times taken for healing in different anatomical sites (external lesions, internal lesions, and all lesions combined) were compared for the acyclovir and placebo group. The median healing time for all lesions was significantly shorter in the acyclovir group (7 days) than in the placebo group (14 days). In half of the patients treated with acyclovir all lesions had healed by the 7th day compared with less than 10% who received placebo (fig. A).

The median healing times for internal lesions was 5·5 days in the treated group, compared with 10 days in the control group. However, there was no significant difference in the duration of external lesions between the two groups.

In females acyclovir was associated with a shorter healing time for internal lesions and all lesions combined, but not for external ones.

New Lesion Formation, Duration of Vesicles, and Symptoms

The median duration of new lesion formation was 0 days in the acyclovir group, compared with 2 days in the placebo group. No new lesions appeared in the acyclovir group after the second day (fig. B), but they continued to appear for up to 15 days in the controls. In females the duration of new lesion formation was also shorter in the acyclovir-treated patients than in the controls.

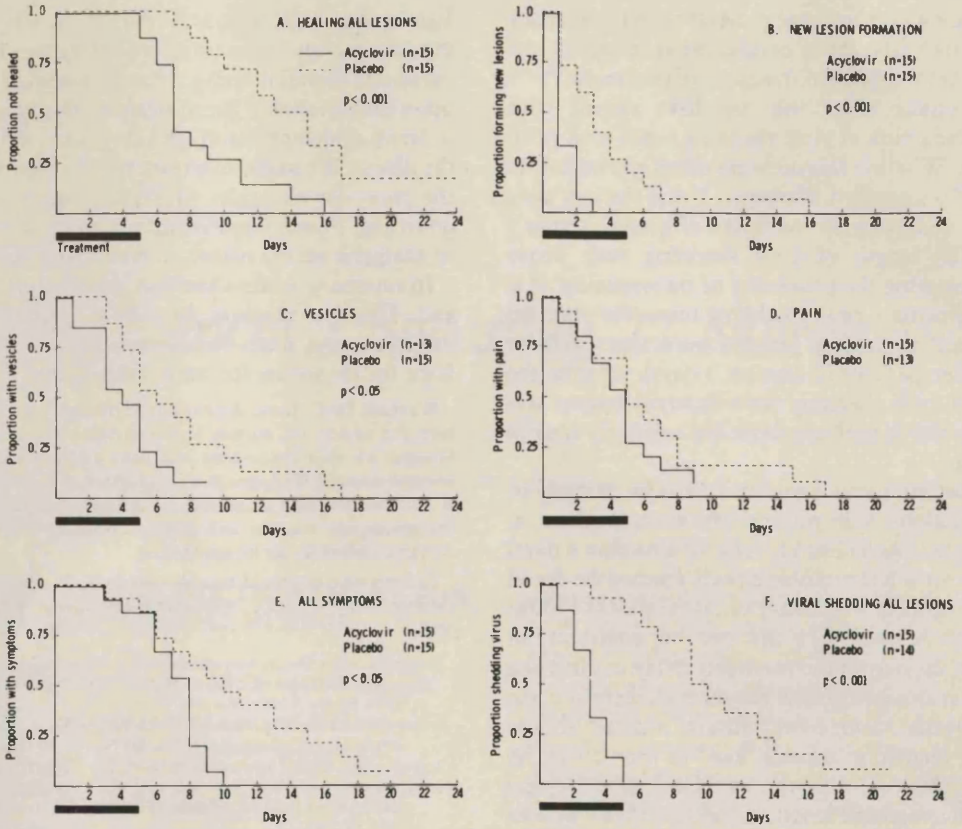
Vesicles lasted a median of 3 days in patients treated with acyclovir compared with 5 days in the placebo group. Vesicles persisted for up to 8 days in patients treated with acyclovir, and up to 16 days in placebo-treated patients (fig. C). Among females there was no significant difference in the duration of vesicles between the two groups.

Improvement in symptoms was less impressive. The median duration of pain in the treated and control groups was identical, whether all patients or females alone were considered; however, pain lasted longer in placebo-treated patients than in those receiving acyclovir (fig. D). Among females alone there was little difference between the acyclovir and control groups in the duration of all symptoms, but when all patients were considered the median duration of all symptoms in the acyclovir-treated patients was 6·5 days compared with 8·5 days in the placebo group. In addition all acyclovir-treated patients were symptom-free by the 10th day and this contrasts with placebo-treated patients, whose symptoms persisted for up to 20 days (fig. E).

TABLE II—MEDIAN HEALING TIMES (DAYS)

	All patients			Females		
Type of lesion	Acyclovir	Placebo	p value	Acyclovir	Placebo	p value
All lesions combined (range)	7·0 (5–16)	14·0 (7–29)	<0·001	7·0 (5–16)	12·5 (7–21+)	<0·05
Internal genital lesions* (range)	5·5 (4–7)	10·0 (2–22)	<0·01	5·0 (4–7)	8·0 (2–21+)	<0·05
External genital lesions† (range)	7·0 (4–16)	11·0 (5–29)	NS	7·0 (4–16)	10·5 5–17)	NS

*Cervix, vagina, anal canal, and/or rectum.
†Vulva, penis, scrotum, perineum, and perianal area.



Duration of various events for the two treatment groups.

The exact day on which certain events occurred was not determined because patients only attended the clinic twice weekly after hospital discharge.

Viral Shedding (Table III)

Whether all patients or female patients alone were considered, the median duration of viral shedding from all lesions, internal lesions, and external lesions was strikingly reduced when acyclovir-treated patients were compared with controls. All patients treated with acyclovir had ceased viral shedding by day 5, whereas placebo-treated patients continued viral shedding for up to 20 days (fig. F).

Primary Infections

Primary infections were analysed separately with regard to healing time, new lesion formation, duration of vesicles, symptoms, and viral shedding time. The differences between acyclovir and placebo-treated primary patients were similar to those seen among all female patients.

Overall Findings

Table IV summarises the main variables considered in this study. Acyclovir treated patients fared better throughout and particularly notable differences were evident with regard to viral shedding time, healing time, and duration of new lesion formation. In addition when all patients were considered acyclovir treatment was associated with a shorter duration of vesicles and of all symptoms.

Discussion

This trial has established baseline data on the use and efficacy of acyclovir in genital herpes. Intravenous acyclovir will seldom be the most appropriate form of treatment for a first attack of genital HSV, except in severely ill patients who require hospital admission. Oral outpatient treatment will

TABLE III—MEDIAN DURATION OF VIRAL SHEDDING (DAYS)

Type of lesion	All patients			Females		
	Acyclovir	Placebo	p value	Acyclovir	Placebo	p value
All lesions combined (range)	2·0 (0–4)	8·5 (2–20+)	<0·001	2·0 (0–4)	7·5 (2–20+)	<0·001
Internal genital lesions (range)	2·0 (0–4)	6·0	<0·01	2·0 (0–4)	3·0<0·05	NS
External genital lesions (range)	1·5 (0–4)	7·8 (2–20+)	<0·001	1·0 (0–4)	5·5 (2–20+)	<0·001

TABLE IV—MAIN DIFFERENCES BETWEEN PATIENTS TREATED WITH ACYCLOVIR AND PLACEBO

	Primary patients			Female patients			All patients		
	Acyclovir (n=12)	Placebo (n=8)	p	Acyclovir (n=12)	Placebo (n=12)	p	Acyclovir (n=15)	Placebo (n=15)	p
Viral shedding time (all lesions)	2·0	8·8	<0·001	2·0	7·5	<0·001	2·0	8·5	<0·001
Healing time (all lesions)	9·0	15·0	<0·05	7·0	12·5	<0·05	7·0	14·0	<0·001
Duration of new lesion formation	0·0	2·0	<0·01	0·0	1·5	<0·05	0·0	2·0	<0·001
Duration of vesicles	2·5	5·0	NS	2·5	4·5	NS	3·0	5·0	<0·05
Duration pain	3·5	5·0	NS	4·0	4·0	NS	4·0	4·0	NS
Duration all symptoms	6·3	8·8	NS	6·8	7·3	NS	6·5	8·5	<0·05

Results are given as median time in days.

probably be more suitable for most patients with a first attack of herpes, and trials have been conducted to ascertain the efficacy and optimum dosage of this form of treatment.[12]

The most dramatic effect that we have shown with acyclovir is the reduction in viral shedding times seen in all groups of patient. Whether this decrease offers any benefit to the patient remains unknown. However, if oral therapy were to be used more widely in the treatment of genital herpes a shortening in the length of viral shedding may prove important in decreasing the possibility of transmission. It is interesting that median viral shedding times for internal lesions (cervix and vagina) in females were short in both treated and placebo patients (2 days vs. 3 days), whereas the median length of viral shedding from external lesions was short in patients treated with acyclovir but relatively long in the control group.

It is unlikely that intravenous acyclovir used for primary or initial HSV infections will prevent recurrences since at presentation our patients had had lesions for a median 4 days, by which time the virus had probably already reached the dorsal root ganglion. Treatment of primary or initial attacks should be started as soon as possible to decrease the possibility of recurrent disease. In view of the inevitable delay in initiating treatment in a first attack of genital herpes and, therefore, the inability to prevent recurrences, future studies should concentrate on recurrent disease and in particular on modifying the rate of recurrences. Oral and topical preparations do decrease the length of recurrent HSV attacks but do not alter the recurrence rate,[12,13] and we are planning studies to ascertain whether other treatment regimens with acyclovir—for example, low-dose continuous therapy or repeated treatment of each recurrent attack in the prodromal phase—will decrease the frequency of recurrences.

Even though acyclovir did not alter the duration of pain, the accurate assessment of such a subjective feature is difficult and dependent on several factors. Firstly, the number and site of the lesions will have an important effect. Lesions near the urethra and around the introitus are more painful than those on the perineum or labia majora. Perianal, anal, and rectal herpes is very painful, whereas sores in the vagina or on the cervix often do not produce symptoms. An interesting point in our study is that neither the difference in duration of pain nor the duration of external (and therefore usually painful) lesions was significantly different between acyclovir and placebo groups. Secondly, the individual response to pain varies and therefore subjective assessment of pain will depend upon the stoicism of the individual, the patient's expectation in terms of management, and the emotional upset caused by the illness. We made no attempt to ascertain the type or site of the pain—for example, whether it was painful to touch or on sitting. Finally, no attempt was made to evaluate the effect of analgesia on the nature, severity, and duration of pain.

In summary, it is evident that intravenous acyclovir is a safe and effective therapy in severe primary genital HSV infection, and other forms of acyclovir offer considerable hope for the future for those with genital herpes infections.

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Intravenous Acyclovir in Genital Herpes

An Interim Report

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Twenty-five patients with primary genital herpes were treated in a double-blind placebo-controlled randomized trial of intravenous acyclovir. Thirteen patients received the drug and 12 a placebo. Three in each group were male. In the acyclovir group 10 patients had true primary herpes compared with six in the control group. The median time to healing of all lesions was significantly decreased from 11 to seven days ($p < 0.05$), and the median duration of viral shedding from all lesions was decreased from eight to two days ($p < 0.001$). The time to cessation of new lesions was decreased from a median of two days to zero days ($p < 0.001$). Intravenous acyclovir is an effective treatment in decreasing the length and severity of primary genital herpes.

Herpes genitalis is now a major and increasing problem in both the United Kingdom and the United States. In 1979, 9,576 cases were seen in clinics treating patients with sexually transmitted diseases in the United Kingdom, an increase in the last four years of 42 percent [1].

There is no known effective therapy for genital herpes simplex virus (HSV) infection. The recent introduction of acyclovir (acycloguanosine), an agent with high specificity against HSV has raised hopes for an effective treatment for primary infections. To date the drug has been used effectively in immunocompromised patients with disseminated herpetic infections [2]. In view of this finding it was decided to perform a double-blind placebo-controlled randomized trial of intravenous acyclovir in primary genital herpes. The aims of the study were to ascertain whether the intravenous administration of acyclovir is effective in decreasing the length and severity of the primary attack and in reducing the recurrence rate.

PATIENTS AND METHODS

Patients with severe primary genital herpes infection who presented to the Department of Genitourinary Medicine, Middlesex Hospital, within six days of the initial development of genital sores participated in the trial. Informed consent was obtained from all patients. Subjects were excluded if they had a history of previous genital herpes, were under 16 years of age, had renal impairment, or had received specific antiviral therapy in the previous 14 days. Women were excluded if they were pregnant or were not using either oral contraception or an intrauterine device. All patients were admitted to the Middlesex Hospital for seven days or longer, when clinically indicated. On admission, blood was taken for full blood count (FBC) and differential, erythrocyte sedimentation rate (ESR), urea and electrolytes (U&E), creatinine liver function tests (LFTs), and herpes antibodies. These were all repeated on the fourth and seventh days of hospitalization. Additional specimens for

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TABLE I **Healing Times (Median Days) in Acyclovir- and Placebo-Treated Patients**

Lesions	Patients	Acyclovir	Placebo	p Value
External genital	True primary	6.5	9.0	NS
	Women	6.5	11.0	<0.01
	All	7.0	11.0	<0.05
Cervical or rectal	True primary	5.5	13.0	<0.05
	Women	5.0	6.5	NS
	All	5.5	8.0	<0.05
All	True primary	7.5	15.0	<0.01
	Women	7.5	13.0	<0.001
	All	7.0	15.0	<0.001

TABLE II **New Lesion Formation and Duration of Vesicles in Acyclovir- and Placebo-Treated Patients (Median Days)**

Lesions	Patients	Acyclovir	Placebo	p Value
Time to cessation of new lesions	True primary	0.0	2.0	<0.01
	Women	0.5	2.0	NS
	All	0.0	2.0	<0.01
Duration of vesicles	True primary	2.5	5.0	NS
	Women	2.5	5.0	NS
	All	3.0	6.0	NS

herpes antibodies were taken on days 12 and 28. Sera were tested for herpes simplex antibody by complement fixation test. Patients with antibody titers of <1:2 in the first serum were classified as having primary infections. Swabs for viral culture were taken from all lesions and from the cervix, even if no pathology was evident. These were repeated daily for the first seven days and then twice weekly until healing was complete. Herpes simplex virus was isolated and identified in human embryo lung cells. Cultures for *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and *Candida albicans*, and serologic tests for syphilis were taken from all patients.

Patients' clinical status was assessed using a standard recording schedule on admission, daily for seven days, and then twice weekly until healing occurred. Patients were prescribed frequent saline baths and analgesia as required.

The drug or placebo was administered through an indwelling intravenous canula every eight hours by slow infusion over 45 to 60 minutes for 15 doses. The dosage was calculated on the basis of 5 mg/kg body weight. The placebo used was mannitol. The drug and placebo were packaged in indistinguishable vials with individual code numbers.

Patients were asked to return if they experienced any further episodes and/or six months after the initial episode.

RESULTS

Thirteen patients received the drug and 12 the placebo. Six men were treated, three in each group, and all had true primary infections. Of the 10 women who received the drug, seven had true primary infection compared with three out of nine in the placebo group. At presentation no statistically significant differences were found between patients and controls in age, duration of lesions, and mean number and severity of symptoms. The patients were asked to assess symptoms on presentation as none, mild, moderate, or severe using a scale of 0 to 3.

The time to healing was compared in different anatomic sites, external genital lesions, cervical or rectal lesions, and all lesions combined (**Table I**). The median healing time from all lesions in all patients was 15 days in the placebo group compared with 7 days in the acyclovir group; this difference was statistically significant ($p < 0.001$). The healing times for cervical or rectal lesions in all patients was a median of eight days in the control group and 5.5 days in the treated group and all external lesions were healed in a median of 11 days in the placebo group compared with 7 days in those who received acyclovir. Both of these differences were statistically significant ($p < 0.05$).

In women treated with acyclovir the median healing time for the external genital lesions was 6.5 days and 11 days in the control group ($p < 0.01$). When all lesions were considered in these women, the treated group healed in a median of 7.5 days compared with 13 days in the placebo group ($p < 0.001$); however there was no difference for cervical lesions between the two groups.

The differences between the median healing times for the treated and control groups in true primary patients were significantly decreased from both the cervical and rectal lesions and all lesions combined, but not for the external genital lesions.

New lesion formation (**Table II**) continued in the untreated true primary and all patients for a median of two days and in the acyclovir-treated patients for a median of zero days ($p < 0.01$). There was no significant effect on the duration of vesicles in any of the treated patient groups compared with the placebo patients.

The time to termination of viral shedding for external genital and all lesions was reduced in acyclovir-treated patients compared with controls in the three patient groups (true primary, women, and all) (**Table III**). All these differences were statistically significant. However, viral shedding from the cervix was only decreased from a median of three to two days, which was not significant.

Patients treated with acyclovir had all ceased shedding virus by the fifth day, whereas 90 percent of the placebo group were still shedding virus at this time. All patients in the placebo group had ceased shedding virus by 17 days after treatment.

Symptomatic improvement was less impressive (**Table IV**). The median duration of pain in the treated and control patients was virtually identical in all three patient groups. The differences between the acyclovir

and control groups, in duration of all symptoms in the true primary and female patients, were not significant. The median duration of symptoms in all patients treated with acyclovir was 9.3 days compared with seven days in the placebo group ($p < 0.05$). All acyclovir-treated patients were symptom free by the 10th day. It took a further nine days for the entire placebo group to be symptomless.

The main variables we have considered are summarized in **Table V**. There was a statistically significant difference between acyclovir-treated patients and controls in all three patient groups in healing time and termination of viral shedding. In the true primary and 'all' patient groups the time to cessation of new lesion formation was significantly reduced in the treated groups compared with controls. There was no statistically significant effect on the duration of vesicles or pain but the duration of symptoms was significantly less in the patients receiving acyclovir.

TABLE III Viral Shedding Times (Median Days) in Acyclovir- and Placebo-Treated Patients

Lesions	Patients	Acyclovir	Placebo	p Value
External genital	True primary	2.5	5.0	<0.01
	Women	1.5	6.0	<0.001
	All	2.0	6.3	<0.001
Cervical or rectal	True primary	2.5	7.3	<0.01
	Women	2.0	3.0	NS
	All	1.5	5.0	<0.01
All	True primary	2.0	8.8	<0.001
	Women	2.0	7.5	<0.001
	All	2.0	8.0	<0.001

TABLE IV Duration of Symptoms (Median Days) in Acyclovir- and Placebo-Treated Patients

	Patients	Acyclovir	Placebo	p Value
Pain	True primary	4.0	5.0	NS
	Women	4.0	4.0	NS
	All	4.0	4.0	NS
Other symptoms	True primary	7.0	8.8	NS
	Women	7.0	7.5	NS
	All	7.0	9.3	<0.05

CONCLUSIONS

We have analyzed the results of a double-blind placebo-controlled study of intravenous acyclovir in 25 patients with a first attack of genital herpes. This is an interim analysis, and since the study is still in progress, we will not comment extensively on the results.

It is evident, however, that intravenous acyclovir has a significant effect on the course of initial genital herpes infections. The most profound effect is on length of viral shedding which was significantly decreased in the acyclovir-treated patients whether the patients were all considered together or separated into groups of women alone or patients with true primary infections only. The effect on healing time of all lesions was also impressive in the acyclovir-treated group. Median healing times were approximately halved in all groups of patients who received the drug. There was also a significant decrease in the length of all symptoms in all patients treated with acyclovir compared with controls.

Initial genital herpes infection usually produces new lesions for up to one week after onset of genital sores. The mean duration of illness at presentation for all patients in the acyclovir group was 4.3 days and in the placebo group 4.7 days. One would therefore have expected new lesion formation to continue for two to three days after entry into the trial. This was true for the placebo-treated group in whom new lesion formation continued for a median of two days. However, in the acyclovir-treated group the median time for new lesion formation was zero days and the difference between the two groups was statistically significant.

It is concluded that the administration of intravenous acyclovir in patients with initial genital herpes shortens healing time, time of viral shedding, and duration of all symptoms.

TABLE V Major Differences Between Patients Treated with Acyclovir (ACV) and Placebo (PCB) (Median Days)

	All True Primaries		All Women		All Patients	
	ACV (N = 10)	PCB (N = 6)	ACV (N = 10)	PCB (N = 9)	ACV (N = 13)	PCB (N = 12)
Viral shedding—All lesions	2.0*	8.8*	2.0*	7.5*	2.0*	8.0*
Healing time—All lesions	7.5†	15.0†	7.5*	13.0*	7.0*	15.0*
Time to cessation new lesions (no.)	0.0 (3)†	2.0 (5)†	0.5 (5)	2.0 (5)	0.0 (5)†	2.0 (8)†
Duration vesicles	2.5	5.0	2.5	5.0	3.0	6.0
Duration pain	4.0	5.0	4.0	4.0	4.0	4.0
Duration all symptoms	7.0	8.8	7.0	7.5	7.0‡	9.3‡

* $p < 0.001$.
† $p < 0.01$.
‡ $p < 0.05$.

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PROPHYLACTIC ORAL ACYCLOVIR IN RECURRENT GENITAL HERPES

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Summary 56 patients with frequently recurring genital herpes were treated in a randomised double-blind trial with either oral acyclovir 200 mg four times a day or placebo for 12 weeks. 29 patients received the drug and 27 the placebo. The mean recurrence rate per month of treatment was 1·4 in the placebo-treated patients and 0·05 in the acyclovir group. Median time to the first recurrence after the start of therapy was 14 days in the placebo group compared with 100 days in the acyclovir group. After the end of treatment the recurrence rate was similar in the two groups. Prophylactic oral acyclovir seems to be an effective treatment for patients with frequently recurring genital herpes.

Introduction

RECURRENT genital herpes causes pain and discomfort, disrupts sexual relations, and can result in considerable emotional disturbance.[1] Until recently little could be done to help patients. However, the introduction of acyclovir may have considerable impact on the treatment of genital herpes. Acyclovir is the only antiviral drug that has been shown in a series of clinical trials to have any efficacy in the treatment of genital herpes.[2–11] The drug has fulfilled most of the major goals of therapy—namely, it speeds the rate of healing, shortens the duration and lessens the severity of symptoms, and decreases the duration of viral shedding. However, acyclovir does not seem to decrease the likelihood of subsequent recurrences when used to treat patients during a first or a recurrent attack.[3,5,7,12] We have evaluated the effect of prophylactic oral acyclovir in patients with frequent recurrent genital herpes, to see whether a prolonged course of therapy has any effect on the frequency, duration, and severity of recurrences both during treatment and subsequently. We report the interim results of this study.

Methods

Patient Selection, Treatment, and Clinical Evaluation

Male and female patients attending the department of genitourinary medicine at this hospital with at least four recurrences per year were enrolled into the study. Patients were excluded if they did not have a culture-positive recurrence during a three month observation period before the start of therapy. Other exclusion criteria included antiviral treatment in the preceding month, pregnancy, impaired renal function, females not on adequate contraception (oral contraceptive or intrauterine contraceptive device), patients under 16, and those unable to attend at the required intervals. After the patients had given informed consent they were randomised to receive either oral acyclovir 200 mg or placebo four times daily for 12 weeks. Therapy was started one week after healing of an observed culture-positive recurrence. The trial was double blind.

All patients had a history taken and an examination performed at enrolment and on each subsequent visit. Patients attended every 2 weeks during the 12-week treatment period and monthly for 6 months after this period. Patients were also asked to attend outside these set times if they had a recurrence. Swabs for viral culture were taken at each visit and were handled as previously described.[2] The date, duration, and severity of each recurrence was recorded. Compliance with treatment was assessed by counting the number of missed tablets. A full and differential blood count; serum urea, electrolytes, and creatinine; and liver function tests were done at entry and every 4 weeks during therapy and 4 weeks after the end of treatment to assess possible toxicity.

Analysis of Results

Differences between acyclovir and placebo groups in the time to first recurrence were assessed by the log rank test. Comparison of demographic characteristics between the two groups was carried out by either the χ^2 or the Mann Whitney test.

Results

Patient Characteristics (table I)

29 patients received acyclovir and 27 received placebo. At presentation there was no statistically significant difference between acyclovir and placebo treated patients in relation to age, sex, and the frequency, site, duration, and severity of previous recurrences.

Recurrences during Treatment

26 (96%) of the placebo-treated patients had a recurrence during the 12-week treatment period compared with only 4 (14%) in the acyclovir group ($p<0\cdot0001$). 4 patients on

TABLE I—DATA ON PATIENTS RECEIVING ACYCLOVIR AND PLACEBO

—	Acyclovir	Placebo
Males	13	9
Females	16	18
Age (yr)*	31·3 (1·5)	30·4 (1·4)
Recurrences in previous 3 months *	2·9 (0·3)	3·0 (0·3)
Average duration of recurrences (days)*	8·4 (0·7)	7·4 (0·6)
Percentage with prodromal symptoms	68	57
Percentage with mild or moderate pain	76	81
Usual site of involvement:		
Penis/vulva (%)	90	93
Other sites† (%)	41	52

*Mean (SE).
†Including perineum, perianal, scrotum, finger, oral.

TABLE II—MEAN NUMBER OF RECURRENCES PER MONTH IN ACYCLOVIR AND PLACEBO TREATED PATIENTS

—	Pre-treatment	Treatment	Post-treatment
Acyclovir	0·72 (0·07)	0·05 (0·02)	1·09 (0·13)
Placebo	0·92 (0·1)	1·4 (0·3)	1·25 (0·3)
p value	NS	<0·001	NS

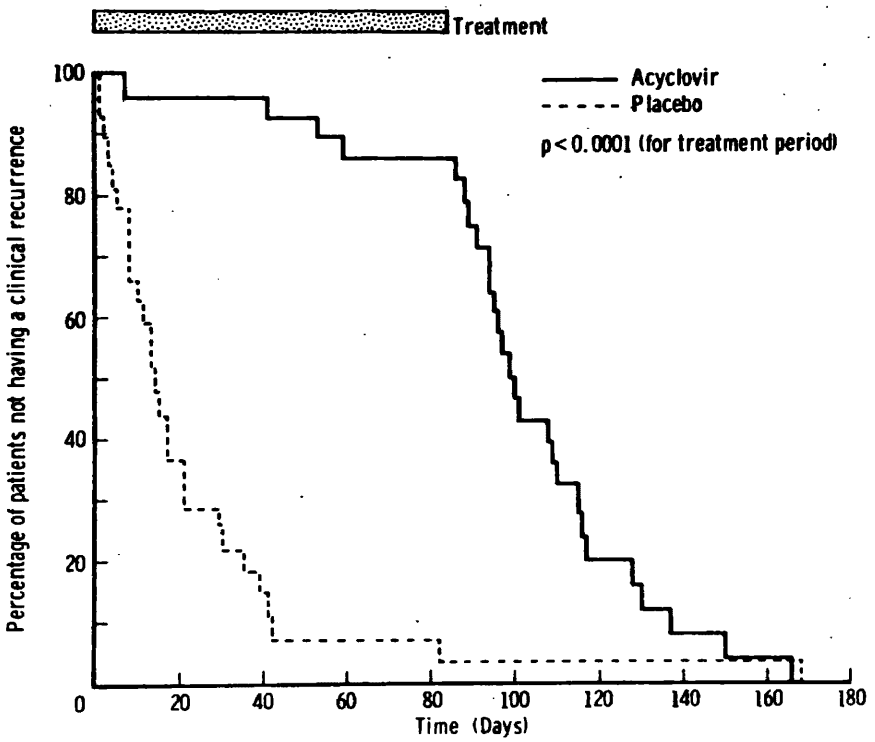
acyclovir had a short-lived minor single recurrence. The mean recurrence rate per month of treatment was 1·4 in the placebo-treated patients and only 0·05 in the acyclovir group ($p<0·00001$) (table II). 19 (70%) of the 27 placebo-treated patients had at least one positive herpes culture during therapy. In contrast only 1 of the 29 acyclovir patients (3%) had a single positive culture during treatment ($p<0·001$).

Time to First Recurrence

Median time to first recurrence after the start of therapy was 14 days in the placebo group and 100 days in the acyclovir group ($p<0·0001$) (see figure).

Recurrences after End of Therapy

The median duration of follow-up after the end of 12 weeks' therapy was similar in the two groups of patients (168 days [range 0–259] in acyclovir treated patients and 157 [range 4–239] in controls). There was no statistically significant difference in the recurrence rate per month of follow-up between the two groups. In acyclovir-treated patients the mean was 1·09 compared with 1·25 in controls (table II).



Time to first recurrence in acyclovir and placebo treated patients.

Side-effects and Compliance

6 patients complained of side-effects which they felt might be attributable to therapy. These occurred with similar frequency amongst acyclovir and placebo treated patients, were in all instances minor and transient, and no abnormalities were found on examination. 9 patients (6 acyclovir and 3 placebo) had abnormal urea, creatinine, or liver function tests during the study period. In 5 patients these abnormalities were mild and short-lived. The remaining 4 patients included 3 (2 placebo and 1 acyclovir) with persistent hyperbilirubinaemia (before, during, and after treatment) and 1 homosexual patient on acyclovir in whom acute hepatitis B developed.

Compliance with therapy was similar in the two groups. The mean number of missed tablets over the 12 weeks treatment period in the acyclovir group was 6·5 compared with 7·4 in the placebo-treated patients.

Discussion

This trial has shown that prophylactic oral acyclovir is a highly effective form of therapy for patients with frequently recurring genital herpes. Most patients did not have any recurrences during therapy and the few recurrences that did

occur were mild and transient. The virus was only cultured on a single occasion in one patient during therapy. This suggests that even if the occasional breakthrough recurrence does occur it is unlikely that patients will be infectious during that time. Breakthrough recurrences may occur for several reasons. Firstly, the dosage may be inadequate; secondly, the patient may have missed or delayed therapy, or drug-resistant strains may emerge. (Acyclovir-resistant strains of HSV have been seen in immunocompromised patients given repeated courses of acyclovir.[13,14])

The dosage used in this study (200 mg four times a day) was adequate to prevent most recurrences. A few patients may require a higher maintenance dose. The results of this study have raised several questions. Who should receive the drug and for how long, is the drug safe in the long term, and finally is treatment cost-effective? A patient with ten recurrences per year lasting 14 days on each occasion would clearly benefit from therapy, whereas a patient with one recurrence per year lasting only 6 days would not. It is difficult to know where to draw the line between these two extremes and this becomes a matter of clinical judgment. There is no clear answer as to how long therapy should continue. The only published studies with prophylactic oral acyclovir have been in immunocompromised or bone-marrow transplant patients[15–18] where the period of greatest risk of developing herpes infection can be determined. In recurrent genital herpes the at-risk period may be many years or even lifelong.

No important side-effects were demonstrated in this study. Long-term use of acyclovir in immunocompromised patients has also shown a similar lack of toxicity.[11–13] Studies with larger numbers of patients are being planned to assess whether the drug is safe in the long term. The final question concerns cost effectiveness. At present oral acyclovir costs £1 per tablet.[19] A year's supply for a single patient at the dosage used in this trial would be £1460. The possibility, however, that a lower dosage would prevent recurrences should not be ruled out.

We thank the Medical Laboratory Scientific Officers in the Virology Department for the virus isolation work.

Addendum

Two recently published trials in USA have shown very similar results to the present study (Douglas JM, Critchlow C, Benedetti J, et al. A double blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus

infection. *N Engl J Med* 1984; **310:** 1551–56; and Strauss SE, Takiff HE, Seidlin M, et al. Suppression of frequently recurring genital herpes. A placebo controlled double blind trial of oral acyclovir. *N Engl J Med* 1984; **310:** 1545–50).

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Treatment and prevention of herpes genital infection

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The recent introduction of acyclovir for the treatment of genital herpes offers new hope for sufferers of this troublesome and recurrent condition. The results of the published trials with acyclovir in both primary and recurrent genital herpes are reviewed. The results show that acyclovir is a useful drug for the treatment of primary infections, but has a limited role in treating recurrences. Preliminary results with prophylactic oral acyclovir suggest that this form of therapy may be useful in patients with frequent severe recurrences.

Introduction

Genital herpes is the sixth commonest disorder diagnosed in clinics for sexually transmitted diseases in the United Kingdom (P.H.L.S., 1983) (Figure 1). Primary infections are often severe with extensive genital ulceration, fever and malaise. Symptoms may persist for 3 to 4 weeks (Corey *et al.*, 1983*a*). Following the first attack patients may suffer recurrences. The recurrences although usually less severe than the first attack, may cause profound sexual and psychological dysfunction (Adler & Mindel, 1983). Until recently little could be done to help sufferers, either with first attack or with recurrences. However the introduction of acyclovir, an efficacious and apparently safe anti-herpes drug has the potential to revolutionize the therapy of genital herpes.

This paper will review the clinical trials with acyclovir in genital herpes and consider its present role and future potential. Other anti-viral therapies will also be assessed.

Acyclovir

Acyclovir is a nucleoside analogue that is a substrate for viral thymidine kinase (TK) (Elion *et al.*, 1977). The drug is selectively phosphorylated by cells infected with herpes simplex virus. Viral specified thymidine kinase converts acyclovir to acyclovir monophosphate which in turn is phosphorylated by guanydylate synthetase to acyclovir triphosphate (Miller & Miller, 1980). Acyclovir triphosphate is the active form of the drug, inhibiting viral DNA polymerase and also acting as a DNA chain terminator by competing with guanosine triphosphate (Furman *et al.*, 1979).

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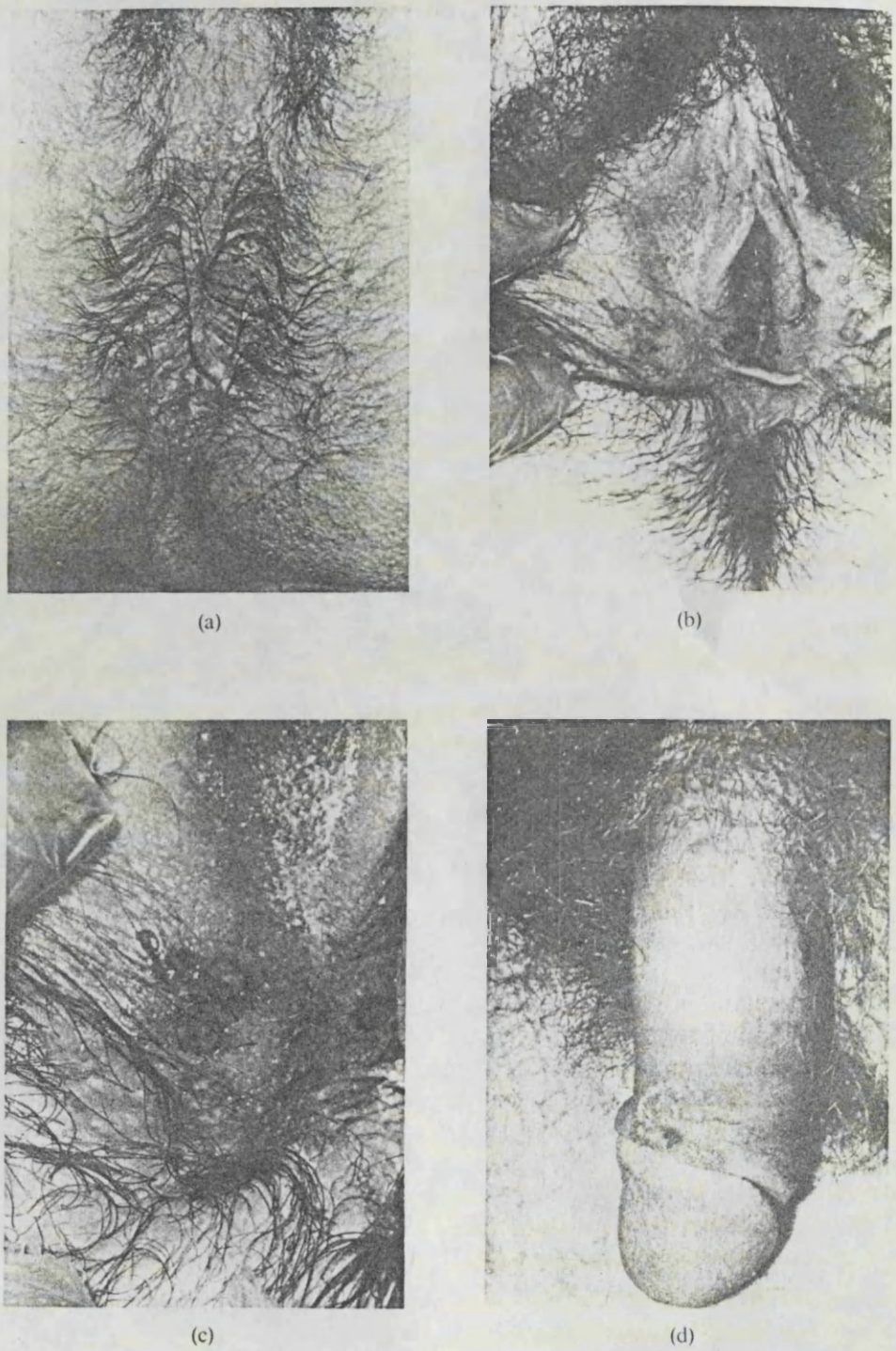

Figure 1. The clinical range of genital lesions caused by herpes virus. (a) Perianal herpes; (b) bilateral vulval ulceration; (c) herpetic ulcers on the vulva; (d) penile vesicles; (e) herpetic cervicitis.

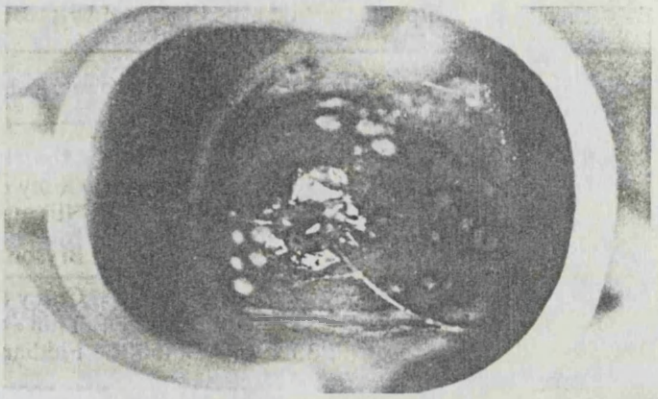

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Figure 1. Continued.

Acyclovir is the only drug which has been shown in a series of controlled clinical trials to have any significant effect on the clinical course of genital herpes. To date seven trials in patients with primary (first attack) herpes and four trials in patients with recurrent herpes have been published. All the trials have been randomised, double blind and placebo controlled. Four different formulations of the drug have been evaluated, an intravenous preparation, an oral preparation and two topical preparations (one containing 5% acyclovir ointment in polyethylene glycol and the other 5% acyclovir cream in a propylene glycol base).

Acyclovir in primary (first attack) genital herpes

Seven trials with acyclovir in patients with primary herpes have been published (Mindel *et al.*, 1982; Corey *et al.*, 1983*b*; Nilsen *et al.*, 1982; Bryson *et al.*, 1983; Corey *et al.*, 1982; Thin *et al.*, 1983; Fiddian *et al.*, 1983). Two of the trials used intravenous drug, two used oral drug, one used topical ointment and two used topical cream.

The seven trials were all conducted in a similar manner and the results are broadly comparable, except that patient selection in the two intravenous trials only included patients who were sufficiently ill to be admitted to hospital. In all but two of the trials median values were used to assess healing, viral shedding and symptoms. In an attempt to compare trials the percentage reduction in median (or mean) values between acyclovir and placebo was assessed. The *P* value in all cases relates to a log rank test and *not* to the mean or median values.

Healing time. Table I shows the healing times comparing acyclovir and placebo treated patients in the seven trials. The percentage reduction was most marked in the two intravenous acyclovir trials (50% or more), less so in the oral studies (20 to 45%) and least with the topical preparations (14 to 33%).

Viral shedding. The median (or mean) duration of viral shedding in the primary trials is shown in Table II. All the trials showed that acyclovir significantly reduced the duration of viral shedding, with percentage reductions ranging from 30 to 92%.

Symptoms. The effect of acyclovir on symptoms is less marked than the effect on healing or viral shedding. The duration of pain was shown to be significantly reduced in five of the seven trials with percentage reductions ranging from 0 to 57% (Table III). Only four trials reported the duration of all symptoms with percentage reduc-

Table I. Trials with acyclovir in primary (first attack) genital herpes: healing time

Route	Acyclovir	Placebo	% Reduction	*P* value‡	References
iv	7·0*	14·0*	50	<0·001	Mindel *et al.*, 1982
iv	9·0*	21·0*	57	0·002	Corey *et al.*, 1983*b*
O	6·0*	11·0*	45	<0·01	Nilsen *et al.*, 1982
O Females	9·5†	13·7†	31	0·05	Bryson *et al.*, 1983
Males	12·0†	15·0†	20	N.S.	
T	10·6†	12·3†	14	N.S.	Corey *et al.*, 1982
T	9·0*	13·5*	33	<0·05	Thin *et al.*, 1983
T	8·0*	12·0*	33	<0·001	Fiddian *et al.*, 198

*Median in days; †mean in days; ‡log rank test (author's original values).

Table II. Trials with acyclovir in primary (first attack) genital herpes: viral sheddi

Route	Acyclovir	Placebo	% Reduction	*P* value‡	References
iv	2·0*	8·5*	76	<0·001	Mindel *et al.*, 198
iv	2·0*	13·0*	85	<0·001	Corey *et al.*, 1983
O	1·0*	13·0*	92	<0·001	Nilsen *et al.*, 1982
O (a) F	8·5†	12·2†	30	0·05	Bryson *et al.*, 198
(b) M	4·0†	8·4†	52	N.S.	
T	3·1†	5·6†	45	<0·01	Corey *et al.*, 1982
T	2·0*	9·0*	78	<0·05	Thin *et al.*, 1983
T	3·0*	9·0*	67	<0·001	Fiddian *et al.*, 198

*Median in days; †mean in days; ‡log rank test (author's original values).

Table III. Trials with acyclovir in primary (first attack) genital herpes: pain

Route	Acyclovir	Placebo	% Reduction	*P* value‡	References
iv	4·0*	4·0*	0	N.S.	Mindel *et al.*, 198
iv	3·0*	7·0*	57	0·03	Corey *et al.*, 1983
O	4·0*	8·0*	50	<0·001	Nilsen *et al.*, 198
O Males	2·0†	3·8†	47	0·015	Bryson *et al.*, 198
Females	2·8†	3·4†	18	N.S.	
T	6·2†	8·8†	30	N.S.	Corey *et al.*, 1982
T	3·0*	5·0*	40	<0·05	Thin *et al.*, 1983
T	4·0*	7·0*	43	<0·01	Fiddian *et al.*, 198

*Median in days; †mean in days; ‡log rank test (author's original values).

tions ranging from 24 to 56% (Table IV). It is interesting to note that the median duration of symptoms amongst placebo recipients (10 days) was s one of the topical trials (Thin *et al.*, 1983) whereas in one of the intravenou (Mindel *et al.*, 1982), where only severely ill patients were included, the

Table IV. Trials with acyclovir in primary (first attack) genital herpes all symptoms

Route	Acyclovir	Placebo	% Reduction	*P* value†	References
iv	6·5*	8·5*	24	<0·05	Mindel *et al.*, 1982
O	4·0*	9·0*	56	<0·05	Nilsen *et al.*, 1982
T	5·0*	10·0*	50	<0·01	Thin *et al.*, 1983
T	5·0*	8·0*	38	<0·01	Fiddian *et al.*, 1983

*Median values in days; †log rank test (author's original values).

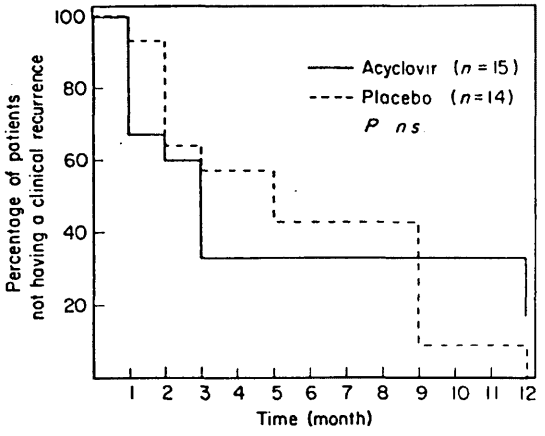

Figure 2. Time to first recurrence comparing acyclovir- and placebo-treated patients.

duration of symptoms in the placebo group was only 8·5 days, suggesting that topical applications may in fact prolong symptoms.

Subsequent recurrences. Treatment of first attack genital herpes with acyclovir does not appear to prolong the time to the first clinical recurrences nor to effect the frequency of subsequent recurrences (Mindel & Sutherland, 1983).

Figure 2 shows the time to first clinical recurrence comparing acyclovir and placebo treated patients given intravenous preparation (Mindel & Sutherland, 1983). There were no significant differences between the two groups. Three other trials have had similar findings (Corey *et al.*, 1982, 1983; Bryson *et al.*, 1983).

In summary, it is evident that acyclovir is a useful drug in the treatment of primary herpes. Parenteral therapy would appear to be more efficacious than topical. There is little to choose between oral and intravenous treatment and in most circumstances oral drug would seem to be the most appropriate form of therapy. The recommended oral dosage, 200 mg, 5 times daily, is probably sufficient to treat most primary infections. Only patients with severe or moderately severe infections should be treated, and the drug should be started as early as possible before the virus has caused extensive tissue damage.

Table V. Trials with acyclovir in recurrent genital herpes: healing

Route	Acyclovir	Placebo	% Reduction	*P* value‡	References
O_1 All	5·0†	6·0†	17	<0·01	Nilsen *et al.*, 1982
Males	5·0†	6·0†	17	<0·01	
O_2 All	6·0†	6·0†	0	<0·05	Salo *et al.*, 1983
Males	5·0†	6·0†	17	<0·05	
T_1 Females	7·4*	7·6*	3	N.S.	Corey *et al.*, 1982
Males	6·9*	8·4*	18	N.S.	
T_2 Females	3·5†	5·0†	30	<0·05	Fiddian *et al.*, 1983
Males	6·0†	6·0†	0	0·05	

*Median in days; †mean in days; ‡log rank test.

Table VI. Trials with acyclovir in recurrent genital herpes: pain

Route	Acyclovir	Placebo	% Reduction	*P* value‡	References
O_1 All	3·0*	2·5*	−16	N.S.	Nilsen *et al.*, 1982
Males	3·0*	2·0*	−33	N.S.	
O_2 All	2·0*	3·0*	33	N.S.	Salo *et al.*, 1983
Males	2·0*	3·0*	33	N.S.	
T_1 Females	2·7†	4·0†	33	N.S.	Corey *et al.*, 1982
Males	2·1†	3·1†	32	N.S.	
T_2 Females	2·0*	4·0*	50	<0·05	Fiddian *et al.*, 1983
Males	3·0*	5·0*	40	N.S.	

*Median in days; †mean in days; ‡log rank test (authors original values).

Table VII. Trials with acyclovir in recurrent genital herpes: all symptoms

Route	Acyclovir	Placebo	% Reduction	*P* value†	References
O_1 All	3·0*	3·0*	0	N.S.	Nilsen *et al.*, 1982
Males	3·0*	2·5*	−17	N.S.	
O_2 All	2·0*	4·0*	50	N.S.	Salo *et al.*, 1983
Males	2·0*	5·0*	60	N.S.	
T_2 Females	3·0*	5·0*	40	<0·05	Fiddian *et al.*, 1983
Males	3·0*	6·0*	50	<0·01.	

*Median in days; †log rank test (authors original values).

Acyclovir in recurrent genital herpes

The effect of acyclovir on recurrent genital infection is less impressive than primary disease. Four clinical trials in patients with recurrent disease have been published, two with oral therapy, one with topical ointment and one with topical cream (Nilsen *et al.*, 1982; Salo *et al.*, 1983; Corey *et al.*, 1982; Fiddian *et al.*, 19

Table VIII. Additional antivirals at present being evaluated for genital herpes

(1) Clinical trials in progress
ara-AMP
Phosphonoformic Acid
(2) Human studies
BVDU (bromovinyldeoxyuridine)
(3) *Animal studies*
dihydroxypropoxymethyl guanosine (DHPG) or Biolf 62
9-[[2 hydroxy-1-(hydroxymethyl)ethoxyl] methyl]—guanine
Glycylacyclovir
Arildone
Cyclaradine (carbocyclic arabinofuranosyladenine)
Cyclaradine 5′ methoxyacetate
ABPP
2-amino-5-bromo-6-phenyl-4-pyrimidinone (ABPP)

As with the trials in primary herpes the percentage reduction in the median (or mean) values between acyclovir and placebo treated patients has been assessed.

The median (or mean) healing times in the four recurrent trials are shown in Table V. Three of the four trials show a statistically significant difference between acyclovir and placebo treated patients, however, the actual median (or mean) healing times are very similar between treated and untreated patients. It is evident that the clinical benefit is minimal.

The duration of viral shedding was significantly shorter in acyclovir treated patients in the three trials that assessed the parameter.

The effect of the drug on symptoms, as with primary infections, was less apparent than the effect on healing and viral shedding. Only one of the four trials showed a significant reduction in the duration of pain (Table VI) and median duration of all symptoms was significantly less in only one of the three trials that considered this parameter (Table VII).

The clinical effect of acyclovir on recurrent herpes would appear to be minimal and the drug should probably not be used to treat recurrent genital herpes.

Therapeutic hopes for acyclovir in the future

Clinical trials with acyclovir at the present time have two main objectives. The first objective is to see if a prolonged course of oral acyclovir in patients with primary infection can decrease the likelihood of subsequent recurrences.

The second objective is to assess whether prophylactic acyclovir can prevent recurrences in patients with established recurrent disease. Anecdotal reports (Mindel, 1984) and preliminary reports of controlled trials (Halsos, Gavreilsen & Fiddian, 1983; Kinghorn *et al.*, 1983) suggest that prophylactic therapy will 'suppress' recurrences whilst the drug is being taken, but that the disease relapses when the treatment is stopped. This method of treatment poses a number of questions and dilemmas for the clinician. Firstly is prolonged therapy safe? Secondly, how long should treatment continue? Thirdly, will prophylactic therapy increase the likely development of drug resistant strains of herpes simplex virus?

The clinician will also need to decide which patients, on the basis of frequency of recurrences, warrant therapy. Clearly a person with a recurrence every month lasting two weeks on each occasion would seem a suitable candidate, whereas a patient with only one recurrence every 6 to 12 months would not warrant therapy. Where one draws the line between the two extremes is difficult to determine.

Two final problems with prophylactic therapy remain. Firstly, the drug is expensive. At present oral acyclovir costs £1 per tablet, with patients requiring two to four tablets daily for prophylactic treatment. Secondly, with a drug that is able to 'switchoff' recurrences, psychological dependence on the therapy may become extremely important in patient management.

Other possible uses for acyclovir include—prodromal therapy to attempt to abort recurrences; prophylactic therapy for an 'at risk' period (for example a college examination); and finally to treat pregnant women at term to prevent neonatal infections. This final form of therapy poses several ethical epidemiological and clinical problems.

Additional antivirals at present being evaluated for genital herpes

Several additional drugs show some potential for the treatment of genital herpes (Table VIII). ara-AMP, phosphonoformate, and arildone may have a limited role as systemic toxicity precludes parenteral use (De Clercq, 1983). BVDU being more active against HSV-1 will also probably be of limited use.

The two derivatives of acyclovir (DHPG and Glycylacyclovir) are potentially very useful. DHPG shows a very high potency in animal models and is equally effective against HSV-1 and HSV-2. Glycylacyclovir has a far greater solubility than acyclovir and can be considered as a prodrug of acyclovir. This preparation achieves very high blood levels following oral administration (De Clercq, 1983).

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Risk of Recurrence after Treatment of First-episode Genital Herpes with Intravenous Acyclovir

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To determine whether intravenous acyclovir treatment for a first episode of genital herpes could prevent or reduce subsequent recurrences, we combined and analyzed the results of two independently conducted, randomized, double-blind, placebo-controlled studies. Sixty-one patients were enrolled in the two trials; 30 received the drug, and 31 received placebo. At entry the demographic, epidemiologic, and clinical features of acyclovir- and placebo-treated patients from the two centers showed no significant differences. The median time to the first recurrence and the frequency of recurrences showed no significant differences when acyclovir and placebo recipients infected with either herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2) were compared. However, irrespective of treatment, the median time to the first recurrence was significantly longer (293 days vs. 69 days; $P < .02$) and the frequency of recurrence significantly less (0.11 recurrences per month vs. 0.43 recurrences per month; $P < .01$) among patients with HSV-1 infection as compared with those who had HSV-2. It is concluded that in patients with first-attack genital herpes, the type of HSV is the most important determinant of subsequent recurrences and that intravenous acyclovir has little effect on subsequent recurrences.

TWO INDEPENDENTLY CONDUCTED TRIALS of intravenous acyclovir for the treatment of first-episode genital herpes have shown that therapy markedly accelerates the rate of healing.[1,2] While this observation is an important new development in the management of herpes, another major consideration is the effect of the medication on the rate of subsequent recurrences. In animals, acyclovir therapy administered within 24–96 hr after inoculation with herpes simplex virus (HSV) can prevent the establishment of ganglionic latency.[3–5] However, clinical trials of both topical and oral acylovir in first episodes of genital herpes have shown that these preparations of acyclovir, when given within the first seven days of onset of disease, do not reduce the subsequent rate of recurrences of genital herpes.[6–8] The antiviral effects of intravenous acyclovir are more marked than those of either oral or topical therapy.[9] To evaluate whether this more potent antiviral effect might influence the natural history of disease, we analyzed the rate of subsequent recurrences of genital herpes in patients enrolled in two separate clinical trials of intravenous acyclovir in severe first episodes of genital herpes. Both of these trials, which were conducted in Seattle and London, had similar admission criteria, dosages, and clinical follow-up.

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Materials and Methods

Patient Selection and Management

Patients were eligible for the study if they presented within seven days of onset of genital lesions. Patients were randomly assigned to treatment with intravenous acyclovir (5 mg/kg) or placebo at 8-hr intervals by slow intravenous infusion. Therapy was administered in hospital for five days (15 doses).

Further details of the methods of patient selection, clinical management, and treatment have been outlined previously.[1,2] After resolution of the acute episode, patients were followed monthly by either clinic visits or telephone contact. Patients were also asked to return to the clinic during subsequent episodes of the disease. Details of each recurrence were recorded.

Viral Isolation and Serology

Viral isolation was performed at the respective institutions as previously described.[1,2] Viral isolates from the

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TABLE 1. Characteristics of Patients in Seattle and London Who Were Infected with Herpes Simplex Virus Type 1 (HSV-1) or Herpes Simplex Virus Type 2 (HSV-2)

	No. of Patients with Indicated Treatment					
	Seattle		London		Combined	
Group	Acyclovir	Placebo	Acyclovir	Placebo	Acyclovir	Placebo
Total	15	16	15	15	30	31
Females	14	13	12	12	26	25
Males	1	3	3	3	4	6
HSV-2, total	13	15	10	8	23	23
HSV-2, primary	12	12	9	3	21	15
HSV-1, total	2	1	5	6	7	7
HSV-1, primary	2	1	4	5	6	6

first genital lesion exhibiting the cytopathic effect typical of HSV was used for viral typing by either the indirect immunoperoxidase assay and/or restriction endonuclease analysis.

Serum was obtained on admission and on day 21 (Seattle) or day 25 (London) for determination of antibodies to HSV. In Seattle, antibody to HSV was measured by a microneutralization procedure; in London a CF assay was performed. Primary genital herpes was defined as the presence of titers of antibody of ≤1:8 (Seattle) or ≤1:2 (London) to either HSV type 1 (HSV-1) or HSV type 2 (HSV-2) in the microneutralization and/or CF test of the acute (day zero) serum. Nonprimary first-episode genital herpes was defined as the first episode of a clinical genital HSV infection plus the presence of antibody to HSV (titer, ≥1:8) in the acute-phase (day zero) sample of serum.

Statistical Analysis

A log rank test was used for evaluation of the effect of treatment on subsequent time to first clinical recurrence of disease. The recurrence rate of infections was derived by determination the number of recurrences over the duration of follow-up. Pretreatment, demographic, epidemiologic, and clinical data were compared by analysis of variance.

Results

Demographic and Virologic Characteristics of Study Population

Sixty-one patients were enrolled in the two trials: 31 in Seattle and 30 in London. Fifty-one of the patients were female, and ten were male (table 1). The mean age of patients was 24.8 years; all but one were Caucasian. The median time from onset of lesions to the start of treatment was four days for patients enrolled in both centers. The pretreatment, demographic, and epidemiologic characteristics were similar for the acyclovir- and placebo-treated groups of patients and for the two study centers. Of the 61 patients, 47 had primary HSV infection and 14 had nonprimary first-episode disease. HSV-2 was isolated from 46 patients (75%), and HSV-1 from 14 (23%). HSV was not isolated from a single patient in London. HSV-1 infection was more common among patients enrolled in London (11 of 29; 38%) than in Seattle (three of 31; 10%) ($.05 < P < 0.1$). Twelve of the 14 patients with first-episode genital HSV-1 infection lacked antibody to either HSV-1 or HSV-2 in their acute-phase sera, i.e., they had primary first-episode genital herpes. The remaining two patients had CF titers of 1:8 on day zero, with a fourfold rise in titer by day 21.

Recurrences in Patients with Genital HSV-2 Infection

The mean duration of follow-up for patients infected with HSV-2 after resolution of the first episode of illness was 10.7 months in the acyclovir-treated group and 10.8 months in the placebo group. This interval was similar for the two study centers (table 2). Thirty-seven (79%) of the 46 patients with genital HSV-2 infection relapsed during the follow-up period. Recurrences of genital herpes occurred in 17 (74%) of 23 acyclovir-treated vs. 20 (87%) of 23 placebo-treated patients. The difference was not significant. The mean rate of recurrences over the duration of follow-up was 0.34 recurrences per month in the acyclovir-treated group as compared with 0.47 in the placebo-treated group (table 3). Again, the difference was not significant.

The median time to the first clinical recurrence was 64 days for acyclovir-treated patients with genital HSV-2 infection as compared with 74 days for placebo recipients ($P = .40$).

Among patients with genital HSV-2 infection, the presence of antibody to HSV in acute-phase sera had no effect on the subsequent recurrence rate of disease. The mean rates of recurrences were similar among those with primary first-episode genital HSV-2 infection (0.43) and those with nonprimary first-episode genital HSV-2 disease (0.44 recurrences per month).

TABLE 2. Median Times to First Clinical Recurrence of Genital Herpes: Comparison of Patients Infected with Different Types of Herpes Simplex Virus (HSV) and Receiving Different Treatments

	Median Time (Days)			Median Time (Days)		
Patients	HSV-2	HSV-1	*P*	Acyclovir	Placebo	*P*
HSV-2 infections	...	...	...	64	74	NS*
HSV-1 infections	...	...	...	279	184	NS
All	69	239	<.02	...	...	

*NS = not significant.

Recurrences in Patients with Genital HSV-1 Infection

The median time to the first clinical recurrence was 279 days in acyclovir-treated patients with genital HSV-1 infections as compared with 184 days in the control group ($P = .40$) (table 2). The mean rates of recurrence during the follow-up period were also similar for acyclovir- and placebo-treated patients with genital HSV-1 infection; the former had 0.08 recurrences per month, and the latter had 0.14 recurrences per month. One patient who experienced primary genital HSV-1 infection in August 1981 had a recurrence in February 1982. The clinical recurrence was prolonged, and HSV-2 was isolated from genital lesions at the time of the recurrence.

The effect of antibody to HSV was not considered in this group because all but two of the patients with HSV-1 had primary infections.

Comparison of Recurrences: HSV-1 vs. HSV-2

The mean time to the first clinical recurrence was 239 days in the 14 patients with genital infection due to HSV-1 as compared with 69 days in the 46 patients with genital infection due to HSV-2 ($P < .02$). In addition, the mean rate of recurrence of genital HSV-1 infection (0.11 recurrences per month) was significantly lower than the mean rate of recurrences among patients with genital HSV-2 infections (0.43 recurrences per month) ($P < .01$) (table 3).

Discussion

This study indicates that viral type appears to be the most important determinant of the subsequent rate of recurrence of genital infections with HSV. Our results confirm those published previously.[10,11] Neither immune status toward HSV nor treatment with acyclovir appeared to influence the time to first recurrence or the subsequent rate of recurrence of disease. Although a previous analysis of the patients in Seattle suggested that acyclovir-treated patients with primary genital HSV-2 infection had a longer interval to their first clinical recurrences,[1] when study patients in both Seattle and London were analyzed, the median time to first clinical recurrence and the mean rate of recurrence over the duration of follow-up were similar for groups treated with intravenous acyclovir and those given placebo. Intravenous acyclovir appears to decrease markedly the duration of viral shedding and to accelerate the clinical course of first-episode genital herpes, but it does not appear to have a significant effect on subsequent recurrences.

These observations are of interest because in animal models it was observed that intraperitonal and topical application of acyclovir within 96 hr of viral inoculation significantly reduced the subsequent frequency and number of latently infected ganglia.[3] However, the median time from last sexual exposure to onset of symptoms with first-episode primary genital herpes is six to seven days.[1] In addition, the median time from onset of symptoms to appearance in the clinic was approximately three to four days. Thus, most patients enrolled in these studies were not being treated until about ten days after exposure to the virus, a time probably too late to prevent the establishment of latent infection of the sacral nerve. Whether early initiation of therapy with either intravenous or oral

TABLE 3. Number of Monthly Recurrences of Genital Herpes in Patients Infected with Different Types of Herpes Simplex Virus (HSV) and Receiving Different Treatments

	No. of Recurrences/Month			No. of Recurrences/Month		
Patients	HSV-2	HSV-1	*P*	Acyclovir	Placebo	*P*
HSV-2 infection	...	...	...	0.34 (0.33)*	0.47 (0.42)	NS†
HSV-1 infection	...	...	...	0.08 (0.08)	0.14 (0.15)	NS
All	0.44 (0.55)	0.10 (0.13)	<.01	...	...	...

*Mean (± Standard Deviation).
†NS = not significant.

acyclovir, i.e., within days 4–7 days after sexual exposure, and/or use of acyclovir during the incubation period of first-episode genital herpes will successfully alleviate disease and prevent latency remains to be determined.

Intravenous acyclovir is certainly of major benefit in the management of patients with severe first-episode genital HSV infection; however, patients who receive acyclovir should still be counselled as to the clinical manifestations of recurrences, the potential infectivity to future sexual partners during these recurrences, and the possible risks and hazards of transmitting neonatal HSV infection during subsequent deliveries.

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Acyclovir in first attacks of genital herpes and prevention of recurrences

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Acyclovir in first attacks of genital herpes and prevention of recurrences

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SUMMARY Sixty women patients experiencing a first attack of genital herpes were randomly treated with either oral acyclovir for 42 days or oral acyclovir for five days followed by placebo for 37 days. The median time to the first recurrence in patients receiving acyclovir for 42 days was 66·5 days compared with 24 days in those who received acyclovir for only five days ($p < 0·0001$). This significant difference, however, was only observed for the treatment period. The frequency of recurrences was also reduced during the period of treatment in those who received prolonged treatment. During the subsequent follow up period, however, patients in both groups had a similar frequency of recurrences. Patients with infections due to herpes simplex virus type I (HSV I) had a significantly longer time to the first recurrence ($p < 0·001$) and fewer recurrences ($p < 0·001$) than those infected with HSV II, irrespective of treatment.

Introduction

Short courses of acyclovir have been shown to hasten healing and reduce the duration of symptoms and viral shedding in patients experiencing a first attack of genital herpes.[1-9] The drug does not, however, appear to decrease the likelihood of recurrences,[2 4-6 10] and in one study over half the patients suffered at least one recurrence within three months after the first episode.[10] Recurrences are the most troublesome aspect of genital herpes and constitute a reservoir of infection in the community.[11]

It has been suggested that prolonged treatment of the first attack with acyclovir may decrease the frequency of recurrences.[3] We therefore decided to compare the recommended five day course with a prolonged course of acyclovir in patients experiencing a first attack of genital herpes to see if a prolonged course could reduce the likelihood of recurrences and confer any additional benefit during the first attack.

Patients and methods

SELECTION, TREATMENT, AND CLINICAL EVALUATION OF PATIENTS

Women patients attending the genitourinary clinic of this hospital within five days of a first attack of genital herpes were offered the opportunity of participating in the study. We limited the study to women patients as they usually have more severe infections.[12] Exclusion criteria were identical to those used in a previous study.[1] Informed consent was obtained from all patients.

We randomised patients into two treatment groups. Those in treatment group 1 received a prolonged course of acyclovir (200 mg five times a day for five days followed by acyclovir 200 mg four times a day for 37 days) and those in group 2 received a short course of acyclovir (200 mg five times a day for five days followed by placebo 200 mg four times a day for 37 days). The total duration of treatment in both groups was therefore 42 days.

The clinical status of each patient was assessed at entry, daily during the first seven days (excluding weekends), and twice weekly during the following six weeks. Thereafter patients attended monthly for at least six months and were also asked to attend if they suffered a recurrence. We examined and took a history of patients at each visit, and recorded the results on a standardised recording schedule.

At each visit we took swabs for viral culture, which were handled as described previously. Isolates were typed using either restriction endonuclease analysis[13] or an immunofluorescence test using monoclonal antibodies.[14]

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ANALYSIS OF RESULTS

We compared demographic characteristics and the frequency of recurrences either by the χ^2 or the Mann-Whitney test and assessed differences between groups in healing time, duration of symptoms, duration of viral shedding, and the time to first recurrence using a log rank test.

Results

PATIENT CHARACTERISTICS

Table I shows the demographic details of the 60 patients in the study. Half (group 1) received long term, and half (group 2) a short course of treatment with acyclovir. At presentation there were no appreciable differences between the two treatment groups in age or duration and severity of signs and symptoms. Viral isolates were typed in 55 of the 60 patients. Of the 55, 41 (75%) were infected with HSV II and 14 (25%) HSV I. The distribution of viral types was similar in the two treatment groups. All but one of the patients were followed up for at least six months; the exception was a patient receiving a short course of treatment, who was lost to follow up after 37 days. The median duration of follow up was 317 days in patients in group 1 and 297 days in patients in group 2. This difference was not significant.

HEALING TIME OF FIRST ATTACK, DURATION OF VIRAL SHEDDING, AND SYMPTOMS

Table II shows that the patients in the two treatment groups did not differ significantly in healing times, duration of viral shedding, or duration of local or systemic symptoms. Individual symptoms, which included pain, itching, dysuria, discharge, fever, headache, and malaise, were also compared and differences between the two groups were not significant.

TIME TO FIRST RECURRENCE AND FREQUENCY OF RECURRENCES

Figure 1 shows that the median time to the first recurrence in group 1 patients was 66·5 days compared with 24 days in group 2 patients. The difference was significant ($p < 0{\cdot}001$) for the 42 day treatment period but not for the full duration of follow up.

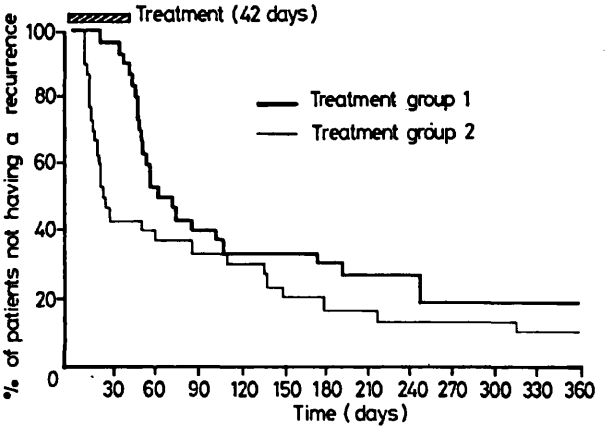

FIG 1 *Time to first recurrence comparing patients receiving acyclovir for 42 days (group 1) or five days (group 2).*

TABLE I *Demographic details of 60 women experiencing first attacks of genital herpes and receiving acyclovir for 42 days (group 1) or 5 days (group 2)*

	Treatment groups:	
	1 (n = 30)	2 (n = 30)
Mean (SD) age (years)	24·3(5·7)	25·2(7·0)
Means (SD) duration of symptoms before entry (days)	4·0(1·6)	4·1(1·6)
Mean (SD) duration of signs before entry (days)	2·7(1·2)	3·0(1·4)
No with history of oral herpes simplex virus	6	7
No with systemic symptoms at presentation	6	7
No with lymphadenopathy at presentation	8	9
No with herpes simplex virus type I	9	5
No with herpes simplex virus type II	18	23
No not typed	3	2

TABLE II *Duration of symptoms, time to healing, and duration of viral shedding in patients receiving acyclovir for 42 days (group 1) or 5 days (group 2)*

	Treatment group 1		*Treatment group 2*		
	n	*Median (range) time (days)*	*n*	*Median (range) time (days)*	*Difference*
Local symptoms	30	11 (1 - 31)	30	11 (2 - 28)	NS
Systemic symptoms	21	4 (2 - 24)	25	5 (1 - 31)	NS
Healing	30	11 (5 - 34)	30	11 (5 - 32)	NS
Viral shedding	29	3 (1 - 8)	29	4 (1 - 10)	NS

TABLE III *Frequency of recurrence a month comparing patients receiving acyclovir for 42 days (group 1) or 5 days (group 2)*

Follow up period (days)	Treatment group 1		Treatment group 2		Difference
	No with recurrences/ No followed up	Mean (SD) recurrences/ a month	No with recurrences/ No followed up	Mean (SD) recurrences/ a month	
0 - 42	4/30	0·12 (0·4)	16/29	0·76 (1·2)	p=0·0004
0 - 90	18/30	0·43 (0·6)	19/29	0·60 (0·9)	NS
0 - 180	21/30	0·42 (0·6)	24/29	0·46 (0·6)	NS
0 - 270	18/20	0·45 (0·6)	13/17	0·30 (0·4)	NS
0 - 360	12/12	0·42 (0·5)	7/9	0·22 (0·3)	NS

TABLE IV *Frequency of recurrence comparing patients infected with herpes simplex virus type I or II*

Follow up period (days)	Patients infected with HSV I			Patients infected with HSV II		Difference
	No with recurrences/ No followed up	Mean (SD) recurrences/ a month		No with recurrences/ No followed up	Mean SD recurrences/ a month	
0 - 42	0/14	0	(0)	19/40	0·61 (1·0)	p=0·002
0 - 90	1/14	0·02	(0·1)	34/40	0·72 (0·9)	p 0·0001
0 - 180	5/14	0·07	(0·1)	38/40	0·60 (0·7)	p 0·0001
0 - 270	6/9	0·10	(0·1)	25/26	0·51 (0·6)	p=0·0001
0 - 360	3/4	0·10	(0·2)	16/16	0·41 (0·5)	p=0·013

Table III shows that during the first 42 days (the duration of treatment) patients in treatment group 1 had significantly fewer recurrences (0·12 a month) than those in group 2 (0·76 a month) (p=0·0004). During subsequent follow up, however, the frequency of recurrences was not significantly different between the two treatment groups.

In contrast, the median time to the first recurrence was significantly longer and recurrences significantly less frequent in patients infected with HSV type I than in those infected with HSV type II, irrespective of their treatment. Figure 2 shows that the median time to the first recurrence in patients with HSV 1 was 193 days compared with 44 days in patients with HSV II (p< 0·001). Table IV shows the frequency of recurrences comparing patients by type of infection.

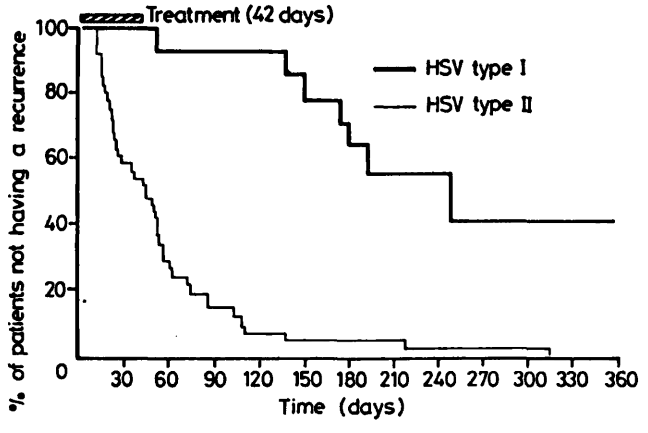

FIG 2 *Time to the first recurrence comparing patients infected with herpes simplex virus (HSV) types I or II.*

At each follow up visit patients with HSV I infection had significantly fewer recurrences than those with HSV II. For example, by day 180 patients infected with HSV I had had 0·07 recurrences a month compared with 0·6 a month in those with HSV II (p< 0·0001).

COMPLIANCE WITH TREATMENT AND SIDE EFFECTS

The two groups were similar in compliance with treatment. In group 1 patients the mean number of missed tablets was 4·2 compared with 4·3 in group 2 patients, which was not a significant difference.

Several patients had complaints that they thought might be associated with treatment. In group 1 patients these included slight constipation (experienced by two) and transient nausea (one), and in group 2 patients transient diarrhoea (three), nausea (one), increase in appetite (one), Bell's palsy (one). A few patients were noted to have biochemical or haematological abnormalities. One group 1 patient had a marginal and transient decrease in the total white cell count. One group 2 patient had an increase serum aspartate transaminase activity and one raised serum urea concentration, but in both the increases were slight and short lived. Seven patients had raised plasma bilirubin concentrations. In two patients (one in each group) this rise was persistent (before, during, and after treatment), whereas in the remaining five (two in group 1 and three in group 2) the rise was slight and only noted on a single occasion.

None of the symptoms or biochemical or haematological abnormalities were thought to be due to treatment.

Discussion

This study shows that prolonged treatment with oral acyclovir of patients experiencing a first attack of genital herpes confers little benefit over the recommended five day treatment. Indeed the duration of symptoms, the time to healing, and the duration of viral shedding were virtually identical in patients who received five days of active treatment and those who received 42 days. Several other trials with short courses of oral acyclovir in first attacks of genital herpes have shown similar durations of these variables.[3-5]

The time to the first recurrence was, however, significantly longer in patients who received the 42 day course of acyclovir compared with those who received five days of active treatment. While patients take acyclovir there seem to be no recurrences, but as soon as treatment stops the recurrences begin, and the frequency of recurrences in the two groups then becomes virtually identical. This is not surprising and is similar to results after treating prophylactically with acyclovir patients who had recurrent genital herpes; recurrences ceased, but started again after the drug was stopped.[15-17]

One of the most interesting points to emerge from this study is the observation that patients with HSV I infection have a significantly longer time to their first recurrence and far less frequent recurrences than those with HSV II infections. Some patients infected with HSV I will probably never have a recurrence. This difference in recurrence rates between the two viral types has been shown in several previous studies.[10 18] The fact that the two viral types differ so enormously in their natural history will have an impact not only on the conduct of future clinical trials but also on the management and counselling of patients. Some patients infected with HSV II who have frequent recurrences may require prophylactic treatment with oral acyclovir.[15-17] It is not clear why these two similar viruses show such a difference in their ability to produce recurrences. There are several possible explanations. Perhaps this difference reflects a relative inability of HSV I to become latent. The two viruses do differ in their interaction with neuronal tissue. For example, experiments in mice have shown that HSV II is more neurovirulent than HSV I, and HSV I is usually isolated from patients with herpes encephalitis, whereas HSV II is the commonest cause of herpes meningitis.[19 20] Receptor sites for HSV I and HSV II may differ with different neuronal tissue, and the sacral ganglia may have a relative lack of HSV I receptor sites. Another possible explanation is that, having become latent in the sacral ganglia, the HSV I virus has "difficulty" in reactivating. This may reflect an intrinsic property of the virus itself or may be the result of specific immune defence mechanisms of the host.

This trial has shown that the first attack of genital herpes can be successfully treated with a short course of oral acyclovir, that the only benefit in continuing treatment after five days is to delay the onset of recurrences, and that prolonged treatment does not appear to affect the subsequent recurrence rate. Finally, we have highlighted the difference in recurrence rate between patients with HSV I and those with HSV II infections.

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TREATMENT OF FIRST-ATTACK GENITAL HERPES—ACYCLOVIR VERSUS INOSINE PRANOBEX

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Summary 77 patients with a first attack of genital herpes were entered into a double-blind trial to compare the efficacy of acyclovir with that of inosine pranobex. 24 patients received acyclovir alone, 25 inosine pranobex, and 28 both drugs. Patients treated with acyclovir or both drugs healed more quickly and had a shorter duration of viral shedding than those treated with inosine pranobex. The time to first recurrence and frequency of subsequent recurrences were similar in the three treatment groups. Acyclovir is the treatment of choice for patients with a first attack of genital herpes.

Introduction

FIRST-ATTACK genital herpes is a severe illness lasting two to three weeks, characterised by genital pain and dysuria and often accompanied by systemic symptoms including malaise, fever, and headaches.[1] Until lately little could be done to treat such patients, but two drugs, acyclovir and inosine pranobex, have now been reported to be effective in the management of primary genital herpes.

Acyclovir is a specific antiherpetic drug which acts by competing with viral thymidine kinase and also inhibits DNA polymerase.[2,3] In a series of clinical trials the oral preparation decreased the duration of viral shedding and symptoms and reduced the time to healing in patients with a first attack of genital herpes.[4-6] Unfortunately, the drug does not seem to prevent subsequent recurrences or reduce their frequency.

Inosine pranobex is an immunomodulator whose action depends upon stimulation of the body's own immune mechanism. It is not a specific antiviral agent, yet clinical studies have suggested that the drug might reduce the duration of viral shedding and the time to healing in patients with first-attack genital herpes.[7,8]

We report here a double-blind trial designed to compare the efficacy of these two drugs in patients with first-attack genital herpes.

Patients and Methods

Patient Selection

Patients with a first attack of genital herpes presenting within five days of onset to the departments of genitourinary medicine at the Middlesex Hospital, London, or the Royal Hallamshire Hospital, Sheffield, were offered the opportunity to participate in the study. Informed consent was obtained from all patients. Exclusion criteria (including: patients under 16 years; females not using adequate contraception; patients unable to attend at the required intervals; and those who had used any antiviral drugs in the preceding 2 weeks) were identical to those in previous studies.[9,10] Also excluded were patients with a history of gout, hyperuricaemia, or immunodepression. Since a high proportion of men attending the Middlesex Hospital clinic were homosexual, with a high attendant prevalence of HIV infection, all men from this centre were excluded.

Treatment

Patients were randomly allocated to three treatment groups: one group received active acyclovir and "dummy" inosine pranobex; one received active inosine pranobex and dummy acyclovir; and the third received both active acyclovir and active inosine pranobex. This last group was investigated to see if the two treatments complemented each other in any way.

The dosage of acyclovir was 200 mg four times daily and of inosine pranobex, 1 g four times daily. Treatment was for seven days.

Clinical Evaluation, Virology, and Safety Tests

Patients were assessed at entry and three times a week until complete healing occurred. Thereafter, patients reattended (or were contacted by telephone) monthly for the next six months and during the first recurrence. At each visit the clinical status of patients was recorded on a standardised schedule.

TABLE I—DEMOGRAPHIC CHARACTERISTICS OF 77 PATIENTS WITH FIRST-ATTACK GENITAL HERPES TREATED WITH ACYCLOVIR, INOSINE PRANOBEX, OR BOTH

—	Acyclovir (n=24)	Inosine pranobex (n=28)	Both (n=25)
Age (yr)*	25·5 (7·02)	23·3 (4·9)	24·3 (7·9)
Duration of symptoms at entry (days)*	4·3 (1·4)	3·9 (1·3)	4·6 (3·3)
Duration of signs at entry (days)*	3·4 (1·8)	3·2 (1·5)	2·9 (1·3)
Women/men	21/3	24/4	21/4
London/Sheffield	11/13	12/16	13/12
External lesions	24 *(100%)*	28 *(100%)*	25 *(100%)*
Internal lesions	15 *(62·5%)*	14 *(50%)*	11 *(44%)*
Type I	9 *(37%)*	13 *(46%)*	12 *(48%)*
Type II	11 *(46%)*	12 *(43%)*	10 *(40%)*
Not typed	4 *(17%)*	3 *(11%)*	3 *(12%)*
Primary/initial	13 *(54%)*	18 *(67%)*	16 *(24%)*

*Mean (SD).

W. BORKOWSKY AND OTHERS: REFERENCES—*continued*

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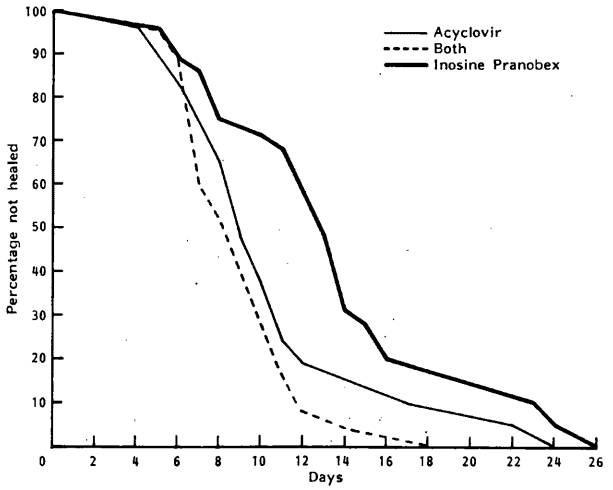

Fig 1—Time to healing for all lesions in the three treatment groups.

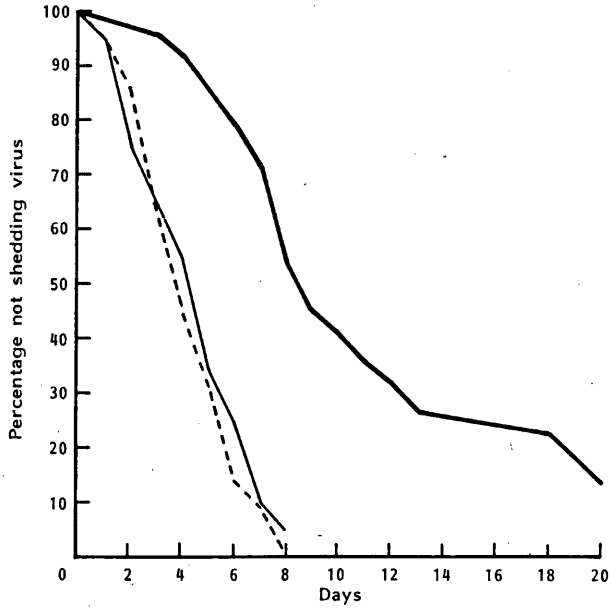

Fig 2—Duration of viral shedding (first day of negative culture) in the three treatment groups.

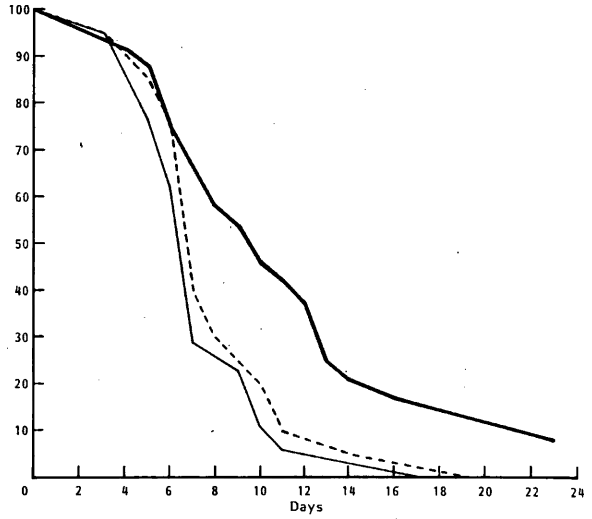

Fig 3—Duration of symptoms in women in the three treatment groups.

If lesions were present swabs were taken for viral culture and handled as described before.[9,10] In London, isolates were typed by an immunofluorescence test with monoclonal antibodies,[11] whereas those from Sheffield were typed by a modified ELISA technique.[12] Acute and convalescent sera were tested for herpes antibodies. Patients with a titre of ≤ 1 in 2 in the acute serum were classed as having primary infection.

At entry to the trial blood was taken for a full blood count, measurement of uric acid, and renal-function and liver-function tests. These were repeated on day 8.

Statistical Analysis

The demographic characteristics and the frequency of recurrences were compared by either the chi-square test or the Mann Whitney U test. Differences between groups in healing time, duration of viral shedding, duration of symptoms, and time to the first recurrence were compared by a log rank test.

Results

Patient Demography

88 patients were recruited (39 in London and 49 in Sheffield). 11 were subsequently excluded—8 who were lost to follow-up after the initial visit, 1 who lost her tablets, 1 who proved to have varicella zoster and not herpes simplex virus, and 1 who was virus-negative with no antibody response. Thus the data from 77 patients were analysed: 24 received acyclovir alone, 25 inosine pranobex alone, and 28 both drugs.

At entry, age, proportion of men and women, viral type, antibody status, or duration of signs and symptoms did not differ between the three treatment groups (table I) or between the two centres. No side-effects were noted.

Healing Time

The median time to healing in the acyclovir group and the group receiving acyclovir and inosine pranobex was shorter than in the inosine-pranobex group (acyclovir *vs* inosine pranobex $p < 0{\cdot}05$; both *vs* inosine pranobex $p < 0{\cdot}001$). By the 11th day 40 (82%) of 49 patients treated with acyclovir

TABLE II—HEALING TIME AND DURATION OF VIRAL SHEDDING AND SYMPTOMS IN THE THREE TREATMENT GROUPS*

—	Acyclovir (n=24)	Insosine pranobex (n=28)	Both (n=25)	Acyclovir *vs* inosine pranobex (p)	Acyclovir *vs* both (p)	Inosine pranobex *vs* both (p)
All Patients						
Healing	9 (4–24)	13 (1–26)	9 (5–18)	<0·05	NS	<0·001
Viral shedding	5 (1–8)	8 (3–20)	4 (1–8)	<0·0005	NS	<0·0005
Dysuria	6 (3–18)	7 (1–21)	7 (1–21)	NS	NS	NS
All symptoms	7 (3–19)	8 (4–23)	7 (3–19)	0·05 >p<0·1	NS	0·05 >p<0·1
Women						
Healing	9·5 (4–24)	13 (1–26)	9 (5–18)	0·05 >p<0·1	NS	<0·005
Viral shedding	5 (1–8)	8 (3–20)	4 (1–8)	<0·005	NS	<0·005
Dysuria	5·5 (3–11)	7·5 (1·21)	6 (3–19)	<0·02	NS	NS
All symptoms	7 (3–19)	9·5 (4–23)	7 (3–19)	<0·05	NS	0·05 >p<0·1

*Median (range). NS, not significant (p > 0·05).

TABLE III—FREQUENCY OF RECURRENCES (PER 28 DAYS OF FOLLOW-UP) IN THE THREE TREATMENT GROUPS BY VIRAL TYPE*

	Treatment group			
Viral type	Acyclovir	Inosine pranobex	Both	All patients
HSV type-I	0·11 (0·13)	0·14 (0·22)	0·21 (0·24)	0·16 (0·2)
HSV type-II	0·49 (0·32)	0·38 (0·51)	0·48 (0·32)	0·45 (0·39)
P value	0·004	0·138	0·044	<0·0005

*Mean (SD).

or both drugs were healed whereas only 8 (32%) of those who received inosine pranobex alone were healed (fig 1).

Duration of Viral Shedding

The duration of virus shedding was longer in patients treated with inosine pranobex than in those in the other two treatment groups ($p < 0·0001$ for both) (fig 2). All patients treated with acyclovir and both drugs were culture-negative by the 8th day whereas 11 (45%) of those treated with inosine pranobex were still shedding virus. 5 (20%) of those treated with inosine pranobex were still culture-positive on the 18th day after entry.

Symptoms

The duration of symptoms did not differ in the three treatment groups. However, a subgroup analysis in the women (who tend to have the most severe symptoms) showed that the duration of dysuria and all symptoms was shorter in those treated with acyclovir than in those treated with inosine pranobex ($p < 0·02$ for dysuria, $p < 0·05$ for all symptoms; fig 3).

Table II summarises the differences in healing time and duration of viral excretion and symptoms in the three treatment groups.

Recurrences

The median time to first recurrence (acyclovir 187·4 days, inosine pranobex 142·5 days, both 132·7 days) and the frequency of recurrences were similar in the three treatment groups (table III). Herpes simplex virus (HSV) type-II infections recurred earlier (median 64 days) than did HSV type-I (median 238·2 days; $p = 0·0015$); HSV type-II infections also recurred more frequently than HSV type-I infections. The differences were irrespective of treatment given (table III).

Discussion

The efficacy of acyclovir in the treatment of first-attack genital herpes has been confirmed in numerous randomised double-blind placebo-controlled trials.[4-6,9,10,13-16] The use of inosine pranobex, on the other hand, has been surrounded by controversy.[17,18] Although several trials have been reported in patients with mucocutaneous herpes,[7,8,19-24] a recent review commented that the "results are difficult to assess because most of the trials are poorly designed or reported".[25] The only randomised double-blind placebo-controlled trial looking exclusively at patients with first-attack genital herpes has not been reported in full.[7] A brief abstract of this trial suggested that inosine pranobex may be beneficial in patients with "primary infections". However, our investigation showed no such benefit. The remainder of the reports were of patients with recurrent genital herpes, labial herpes, or combinations of both.[8,9,24]

We believe that our investigation ends the controversy about the use of inosine pranobex in patients with first-attack gential herpes, and we suggest that the drug no longer has a place in its treatment. Indeed its only remaining justified use is in the context of a controlled trial comparing its "suppressive efficacy" with that of acyclovir.[25] Such trials are in progress.

The observation that neither drug had any impact on the time to first recurrence, or the frequency of recurrences, is of particular interest. It is widely reported that acyclovir when used to treat first-attack gential herpes does not reduce the frequency of subsequent recurrences, probably because the virus has already established latency by the time therapy is initiated. Inosine pranobex on the other hand is said to have both antiviral and immunopotentiating properties. Despite these properties the drug has no apparent effect on the establishment of latency or subsequent reactivation, which suggests that in the context of genital herpes the immunostimulating properties of the drug are unimportant.

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CAMPYLOBACTER PYLORI DETECTED NONINVASIVELY BY THE ^{13}C-UREA BREATH TEST

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Summary The high endogenous urease activity of *Campylobacter pylori* was exploited in a non-invasive test for the presence of this organism in the stomach. When ^{13}C-urea was administered orally after a test meal, urea-derived $^{13}CO_2$ appeared in the respiratory CO_2 of infected individuals at a constant rate for > 100 min. The test was validated in 26 individuals who underwent both the ^{13}C-urea breath test and endoscopic biopsy of the antral mucosa for culture and histological examination. Each positive breath test proved to be correlated with a positive culture or Warthin-Starry silver stain of a mucosal biopsy specimen, or both.

Introduction

MORE than half a century ago, spiral gram-negative bacteria were found attached to human gastric mucosa.[1,2] After several conflicting reports, interest lapsed (reviewed in ref 3) until the 1980s when a major stimulus to research was the development of methods for culturing the organisms from gastric mucosal biopsy material.[4,5] These bacteria were termed campylobacter-like organisms but are now officially recognised as *Campylobacter pylori* (formerly *pyloridis*).[6]

C pylori colonisation of the stomach has been associated with gastric ulcer, duodenal ulcer, non-ulcer dyspepsia, and gastritis.[7-11] Although a role for these organisms in any of these conditions remains unclear, there is growing evidence for a causal relation to gastritis. *C pylori* colonisation of the stomach is associated with gastritis characterised by infiltration of the gastric mucosa by polymorphonuclear leucocytes (PMN).[3,12,14] The causal nature of this association is supported by (i) a positive correlation between the number of *C pylori* organisms and the number of PMN, (ii) the paucity of PMN in parts of the gastric mucosa not associated with *C pylori*, and (iii) the improvement of gastritis associated with therapy directed against the *C pylori* infection.[10,15]

Progress in understanding the relation between *C pylori* and the diseases with which it has been associated has been hampered by the requirement for histological examination or culture of gastric mucosal biopsy specimens to identify *C pylori*. On biochemical characterisation *C pylori* proved to have a very high endogenous urease activity[16-18] and this property has been exploited in attempts to simplify the diagnosis of infection.[19-21] A simple test of urease activity in gastric biopsy material has been reported by Marshall and Langton,[22] who suggested that measurement of the urea content of gastric contents might provide evidence of *C pylori* infection (*C pylori* urease activity resulting in a low urea content).

We report here the development of a simple noninvasive reproducible breath test for *C pylori* infection based on the use of urea labelled with carbon-13—a stable naturally occurring, non-radioactive isotope that can be used repeatedly and can be given to children and pregnant women.

Materials and Methods

Populations

The groups consisted of 54 volunteers (30 men and 24 women, ages 20–57, median 24 yr) and 11 ulcer patients (all men, ages 34–64, median 51·5 yr). Each subject completed a questionnaire concerning symptoms referrable to the upper gastrointestinal tract and gave informed consent. The protocol for this study was approved by the Baylor and VA Hospital Human Investigation Review Boards.

Study Design

In the first phase 26 subjects were accepted without reference to the presence of dyspepsia. They were studied by (i) the ^{13}C-urea breath test, (ii) endoscopic inspection of the oesophagus, stomach, and duodenum, (iii) culture of antral mucosal biopsy specimens for *C pylori*, and (iv) histological evaluation of antral mucosal biopsy specimens for the presence of both gastritis and *C pylori* organisms. Patients with ulcer disease and positive breath tests were included together with sufficient controls with negative breath tests to ensure that microbiological and histological evaluations were done blindly. Results of culture and histopathological evaluation were obtained before the results of breath tests were revealed to the microbiologist or the pathologist. In the second phase, 32 dyspepsia-free subjects and 7 patients with peptic ulcer disease were studied.

Endoscopy

Endoscopic examination was done with a small-diameter, large-biopsy-channel fibrescope (34–JA, Pentax, Orangeburg, NY). In each instance the mucosa of the oesophagus, stomach, and duodenum was inspected and four biopsy specimens were taken from the gastric antrum within 3 cm of the pylorus. The specimens were taken with a large-cup biopsy instrument (FB–13 K, Olympus, Lake Success, NY). The endoscope and biopsy forceps were sterilised before each use. Two biopsy specimens were submitted for culture and the remaining two were submitted for histological examination.

Bacterial Culture

Gastric antral mucosal biopsy specimens were immediately placed in 0·5 ml of Campylobacter albimi cysteine medium. Specimens were delivered to the microbiology laboratory within 10 min and processed within 30 min after collection. Specimens were minced between two sterile glass slides; a small portion of the minced sample was taken for dark-field observations and gram staining, and each specimen was inoculated on two types of blood agar plate—ie, two plates of brain heart infusion agar containing 7% lysed horse blood with amphotericin (2 μg/ml), trimethroprim (5 μg/ml), nalidixic acid (10 μg/ml), and vancomycin (3 μg/ml) (Marshall's blood agar), and two chocolate blood agar plates (BHIA with 7% horse blood).

Culture plates were incubated at 37°C in a microaerophilic bag (Bio-Bag Environmental Chamber Type Cfj, Marion Scientific, Kansas City, MO) with 100% humidity and were examined every 3 days at which time the bags were also changed. Cultures were scored as negative if no typical growth was observed after 12 days of observation. Suspected *C pylori* colonies were tested for cytochrome oxidase, urease, and catalase. Cytochrome oxidase was tested with API Oxidase Kit (API Analytab Products, Plainview, NY). Urease was tested by spreading several isolated *C pylori* suspect colonies on the surface of a Christensen's urea slant (REMEL, Lenexa, KA) followed by 5 min of incubation at 37°C. Catalase tests were performed by lightly touching the surface of a test colony and suspending the cells in 3% H_2O_2.

Histological Evaluation

Biopsy specimens obtained at endoscopy were carefully placed flat on a piece of index card and fixed in 10% buffered formalin. Tissues were processed routinely and embedded in paraffin with special care to obtain optimum orientation in the paraffin block. All specimens from an individual patient were embedded in a single block. Three or four 3 μm paraffin sections were placed on each of ten slides. Two slides were stained with haematoxylin and eosin and

even extremely high doses of radiation are unlikely to completely eliminate all recipient haemopoietic stem cells.

Data from transplants in the congenitally anaemic W/WV mouse indicate that haemopoietic repopulation can occur from a single pluripotent haemopoietic stem cell.[26] For this to occur, reconstitution must be extremely slow, otherwise differentiation will predominate over self-renewal. It is also clear that a proportion of human transplant recipients who show donor engraftment, particularly those with aplastic anaemia, later revert to recipient haemopoiesis after a year or more.[27,28]

Presumably the correlation between transient engraftment, recovery or recipient haemopoiesis, and improved survival, relates to temporary function of the graft. The beneficial effect of temporary engraftment is more likely to occur in mice than in man because engraftment is considerably more rapid in mice,—less than 1 week versus more than 2–3 weeks in man. It is also possible that the transient engraftment is beneficial in other ways, such as by providing accessory cells that stimulate haemopoiesis or by releasing haemopoietic growth factors. Whatever the mechanism of its beneficial effect, temporary engraftment followed by recovery of normal recipient haemopoiesis is a desirable outcome of bone-marrow transplantation; it is preferred to sustained donor engraftment or split chimerism for obvious reasons.

TYPES OF MARROW TRANSPLANTS

The low probability of severe GvHD associated with transplants of T-cell-depleted, HLA-non-identical bone marrow suggests that such transplants may be beneficial in the treatment of radiation victims even though these patients may eventually reject the donor bone-marrow after recovery of recipient haemopoiesis. This possibility can be tested rigorously only by a controlled randomised trial, which is unlikely to be conducted. Other possibilities include the use of fetal liver cells,[29,30] which are similar to HLA-non-identical T-cell-depleted bone-marrow transplants since they contain few T cells, are unlikely to cause GvHD, and have a high probability of being rejected. A final alternative is to identify HLA-matched unrelated bone-marrow donors from large HLA-typed volunteer donor pools. The technical feasibility of these latter approaches was demonstrated at Chernobyl. In the future it may also be possible to culture haemopoietic stem cells in vitro.[31] If large numbers of these cells were available, they might be a source of stem cells for transplantation.

OTHER TREATMENTS FOR RADIATION-INDUCED BONE-MARROW DAMAGE

One must consider what other therapeutic approaches are available since transplants cannot be done on a large scale in an emergency. In animals (including mice and monkeys) molecularly cloned haemopoietic growth hormones such as granulocyte-macrophage colony stimulating factor (GM-CSF) may expedite recovery[32,33] if there are residual haemopoietic stem cells. Although a possible disadvantage of this appoach is that haemopoietic growth factors that favour differentiation over self-replication may result in stem cell depletion, this form of treatment seems promising. In a recent radiation accident in Brazil we used recombinant GM-CSF to treat individuals receiving doses of about 3–6 Gy.[34] This resulted in a prompt increase in granulocytes. A detailed report is in progress (Butturini A, Cesar P, Gale RP, et al, unpublished).

CONCLUSION

The data and considerations discussed here indicate that the use of bone-marrow transplants following nuclear accidents is complex. Each accident imposes unique considerations. Also, the objectives for the transplant may vary. Individual consideration of each situation is required.

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Therapeutics

DOSAGE AND SAFETY OF LONG-TERM SUPPRESSIVE ACYCLOVIR THERAPY FOR RECURRENT GENITAL HERPES

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Summary 131 patients with frequently recurring genital herpes were treated for 1 year with reducing doses of oral acyclovir. The time to first recurrence in patients who commenced therapy on 400 mg twice a day was statistically signficantly shorter than those on 200 mg four times a day ($p < 0.02$) and as the total daily dose and frequency of therapy were lowered so the time to first recurrence was shortened. By the end of 60 days on 200 mg once a day (the lowest daily dose) 56% of patients had recurrences. Patients showed a marked reduction in the frequency of recurrence during therapy (from a mean of 1·1 per 28 days before to 0·11 during treatment, $p = 0.0001$). After stopping treatment the frequency of recurrences (0·71 per 28 days) was signficantly less than the pre-treatment period ($p = 0.001$). No important side-effects were seen. It is concluded that long-term suppression with acyclovir is safe and effective for patients with recurrent genital herpes.

INTRODUCTION

SHORT courses of suppressive doses of oral acyclovir have been extremely effective in reducing both the frequency and severity of recurrences of genital herpes,[1-5] but several questions about this form of treatment remain. How long should treatment continue, is the drug safe, what is the ideal dose, who should be treated, and does acyclovir have any effect on the natural history of the illness?

We have conducted a study to determine the ideal dose of acyclovir required to control attacks in patients with frequently recurring herpes, to examine the drug's long-term safety, and to see whether treatment affected the natural history of infection.

METHODS

Male and female patients aged over 16 years attending this department with at least 8 recurrences per year were enrolled in the study. Patients were excluded if they did not have a culture-positive recurrence in the 2 months before onset of therapy, were known to be immunosuppressed, were unable to attend at the required intervals, and, if female, were either pregnant or not using adequate contraception.

TABLE I—PATIENT CHARACTERISTICS

Characteristics	Schedule A (n = 66)	Schedule B (n = 65)
Mean (SD) age (yr)	31·0 (7·12)	30·4 (6·82)
No of males/females	34/32	33/32
Mean (SD) no of recurrences in last year	14·9 (6·88)	14·2 (6·39)
Mean (SD) no of recurrences in last 3 mo	4·2 (2·12)	3·4 (1·85)
*Mean (SD) pain score**	1·4 (0·89	1·6 (0·79)
Usual site of lesions†		
Vulva or penis	58 *(88%)*	56 *(86%)*
Perineal or perianal	19 *(29%)*	20 *(31%)*
Buttocks	9 *(14%)*	4 *(6%)*
Previous oral HSV infection	24 *(36%)*	13 *(20%)*

*Pain graded 0–3 (none, mild, moderate, severe).
†Some patients had lesions at several sites.

After giving informed consent patients were randomised to receive one of the two different treatment schedules. All patients received an initial therapeutic course of acyclovir 200 mg five times a day for 5 days. Schedule A consisted of acyclovir 200 mg four times a day for the first 12 weeks, then 200 mg thrice a day, 200 mg twice a day, and 200 mg daily for the second, third, and fourth 12 week periods, respectively. For schedule B the doses were 400 mg twice a day, 800 mg once a day, 400 mg once a day, and 200 mg once a day for the four 12-week periods. Patients who had a recurrence during treatment returned to the previous dose and kept to it until the end of the 48 week treatment period. Patients who had a recurrence while on the highest daily dose (either 200 mg four times a day or 400 mg twice a day) doubled their dose. Compliance was assessed by counting the number of missed tablets.

At every visit patients were examined and asked about the date, duration, and severity of recurrences. Patients attended every month during the treatment period and for 6 months after. They were also asked to attend outside these fixed visits whenever they had a recurrence.

Swabs were taken for viral culture if there were any lesions suggestive of herpes and were handled as previously described.[6] Liver function tests, serum urea, serum creatinine, serum electrolytes, and differential blood count were checked at entry and every 12 weeks during treatment and 12 weeks after completing treatment, to assess possible toxicity.

Statistics

Statistical tests included the χ^2 test, the Mann Whitney U test, a log-rank test, a paired t test, and a test of homogeneity of ordered alternatives.[7,8]

RESULTS

Patient Demography (Table I)

134 patients were enrolled. 3 who did not complete treatment were excluded. At presentation the two treatment groups did not differ in age, sex, or frequency, site, duration, and severity of previous recurrences.

Time to First Recurrence (Figure)

The time to first recurrence was related to both the total daily dose of acyclovir and the frequency of tablet taking.

R. P. GALE AND OTHERS: REFERENCES—*continued*

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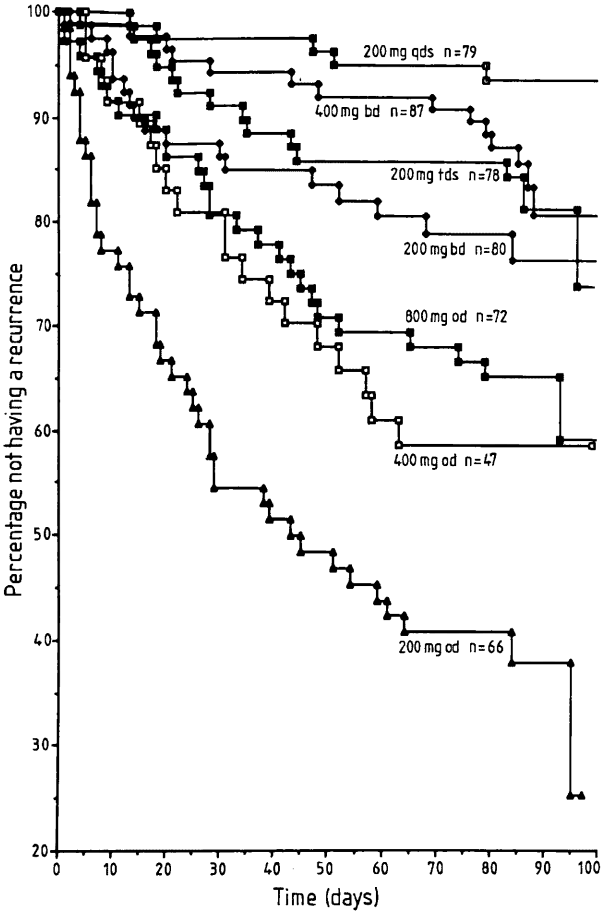

Time to first recurrence with different doses of acyclovir.

od = once daily; bd = twice a day; tds = thrice a day; qds = four times a day.

Only 6% of patients who started therapy on 200 mg four times a day had a recurrence by the end of 84 days, compared with 13% in those who started on 400 mg twice a day ($p < 0.02$). As the total daily dose and the frequency of therapy were lowered, so the time to first recurrence was shortened. For example, at the end of the 60 days 19% of those on 200 mg twice a day had recurrences compared with 31% of those on 800 mg once a day, 39% on 400 mg once a day, and 56% on 200 mg once a day (all higher, $p < 0.05$, than with 200 mg four times a day).

Frequency of Change of Dose (Table II)

1 of the 79 (1%) patients who took acyclovir four times a day had to change dose because of recurrence, compared with 15% on a thrice-daily dose, 13% on a twice-daily dose, and 35% on a once-daily dose ($p < 0.005$).

TABLE II—FREQUENCY OF CHANGE OF DOSE

—	Dose frequency			
	4 × /day*	3 × /day†	2 × /day‡	1 × /day§
Number treated	79	78	167	188
Number *(%)* changing dosage because of recurrence	1 *(1%)*	12 *(15%)*	22 *(13%)*	66 *(35%)*

$p < 0.005$

*Includes only 200 mg four times a day.
†Includes only 200 mg thrice a day.
‡Includes 400 mg twice a day and 200 mg twice a day.
§Includes 800 mg once a day, 400 mg once a day, and 200 mg once a day.

TABLE III—FREQUENCY OF RECURRENCES COMPARING PATIENTS IN THE TWO TREATMENT GROUPS

	All patients	Schedule A	Schedule B	p*
Before treatment	1·11 (0·51)	1·14 (0·53)	1·09 (0·49)	ns
During treatment	0·11 (0·08)	0·09 (0·07)	0·12 (0·1)	ns
After treatment	0·71 (0·55)	0·71 (0·65)	0·68 (0·45)	ns

Findings are given as mean (SD); frequency/28 days.
*For comparisons of before *vs* during, before *vs* after, and during *vs* after, $p = 0.0001$ for all three groups.

Frequency and Duration of Recurrences

The mean (SD) number of recurrences per 28 days was 1·1 (0·5) in the 2 months before treatment compared with only 0·11 (0·08) during treatment ($p = 0.0001$). After withdrawal of treatment the mean number of recurrences was 0·7 (0·55), and this was significantly different from both the pre-treatment and treatment periods ($p = 0.0001$) (table III).

108 recurrences were clinically confirmed during treatment. However, only 29 (27%) of these were culture positive. 24 (36%) of the 67 recurrences that occurred when patients were on once-daily therapy were virus-culture positive, compared with only 5 (12%) of the 41 observed on the more frequent doses ($p < 0.01$).

The duration of recurrences during the treatment period (mean 5·4 [SD 4·1] days) was shorter than those occurring in the pre-treatment (7·8 [3·8]) and post-treatment (7·8 [6·6] periods ($p < 0.005$ for both).

Side-effects and Compliance with Therapy

Several patients reported problems that they thought were caused by the treatment (5 with headaches, 3 each with weight gain, alcohol intolerance, itching, and skin rash, 2 with constipation, and 1 each with thinning of head hair, dry vagina, brittle nails, dizziness, nausea, dry mouth, and tinnitus); in all instances these were short lived and not associated with any detectable clinical abnormality. 20 patients complained of depression. In 8 this had pre-dated treatment and in 4 this was attributable to specific life-events. 1 patient had recently found out he was positive for human immunodeficiency virus (HIV), 1 had recently been made redundant, and the remaining 2 had relationship problems. In the remaining 8 there was no obvious cause for the depression.

24 patients had raised serum bilirubin levels. In 14 the abnormality was noted before treatment was started and it persisted during treatment—probably reflecting Gilbert's syndrome. In the remaining 10 the rise was noted on a single occasion, was very slight, and was not associated with any clinical or other biochemical abnormalities. 9 patients had raised serum aspartate aminotransferase (AST) levels. 1 was taking anabolic steroids; in the remainder there was no obvious cause. All deviations in AST concentration were very slight, were noted on only one occasion, and were not associated with any other biochemical or clinical abnormality. 1 woman who was taking phenytoin for epilepsy had a persistently raised alkaline phosphatase, and 1 male patient who was later found to be HIV-antibody positive and a hepatitis B e-antigen-positive carrier had a persistent thrombocytopenia (platelet count 98–127 $\times 10^9/l$).

Nineteen (15%) of the 131 patients did not miss any tablets, 55 (42%) missed between 1 and 5, 36 (27%) missed between 6 and 20, and 21 (16%) missed more than 20.

DISCUSSION

This trial confirms the efficacy of a year's course of suppressive acyclovir treatment in reducing the frequency of recurrences and shortening the duration of the few remaining recurrences. We were able to confirm the already well-established safety record of acyclovir.[1-5,9,10] The complaint, by a few patients, of depression is being investigated. One possible explanation is that as the patients got to know the investigators well during the study they became willing to discuss personal matters that they had not previously mentioned.

One of our primary aims was to determine the most effective dose for starting and maintaining suppressive acyclovir therapy. Patients who started on treatment with 200 mg four times a day were significantly less likely to have a recurrence than those on 400 mg twice a day, and throughout the study the more frequent the dose, the better the effect. Although breakthrough recurrences occurred with all doses, virus-positive episodes were most common on once-daily treatment. Therefore we recommend that in all patients therapy should start with 200 mg four times a day, and the dose should be reduced to 200 mg three times a day after 2–3 months if the patient is recurrence free. Further reductions to 200 mg twice a day and eventually once a day may be possible. However, it is worth bearing in mind that over 40% of patients will have a recurrence on once-daily therapy.

Are there any alternatives to continuous suppressive therapy? Recent studies have shown that treating each recurrence is less effective and less acceptable to the patient than suppressive therapy.[11,12] Treating patients only at weekends was of little benefit.[13] Thus there seems to be no acceptable alternative to continuous suppression.

How long patients should be treated remains unresolved. Our study suggests that the frequency of recurrences declined after 1 year. Whether this is due to treatment or is the natural history of the infection is unclear. In any event this observation suggests that therapy should be stopped after a year to ascertain whether the frequency of recurrences still warrants suppressive therapy.

We thank Mr J. Pinto-Basto for help with the virology.

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Before our Time

ANOREXIA NERVOSA IN 1888

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A HUNDRED years ago, in the course of just 63 days, no fewer than eleven articles about anorexia nervosa appeared on the pages of *The Lancet*. Included were three reports, an editorial, six letters, and one note. The eleven pieces constitute a curious combination of clinical reportage and editorial panegyric, laced with objurgatory, sarcastic, and pejorative commentary.

BACKGROUND

The episode began on March 17th, 1888, with the publication of an article by Sir William Gull.[1] Gull, a medical elder statesman and a fixture at Guy's Hospital, was nearing the end of his life. He was frail of health, having been afflicted in the autumn of 1887 with a paralysis that compelled him to retire from practice. Although greatly respected for his clinical acumen, Gull was more popular with his patients than with his colleagues, who were put off by his sarcasm and selfassertiveness.[2] Gull's clinical note was brief (forty-two lines) and described the illness and recovery of a 14-year-old girl with anorexia nervosa. The report was accompanied by woodcut portraits of his patient, depicting her appearance during and after her illness. Gull stated that the cause of most cases of anorexia nervosa was "perversions of the 'ego' ".

1 week later[3] the editors commented "The profession will share with us a feeling of much satisfaction that Sir WILLIAM GULL is so far recovered as to have directed the publication of the case of anorexia nervosa . . . The brevity and pithiness of Sir WILLIAM's account. . . . are a happy proof that his keen clinical perceptions have suffered no abatement". They remarked that whereas Sir William had earlier (in his seminal report of 1874[4]) stated that anorexia nervosa was due to "a failure of the powers of the gastric branches of the pneumogastric nerves" he now had taken "a deeper view". The editors also praised Gull for the simplicity of his treatment: "The cure consists of three things—rest, warmth, and the regular and frequent introduction of food, in utter disregard of the anorexia of the patient". The editorial stated "Mr HOVELL is delighted that Sir WILLIAM has abandoned the adjective *Hysterica* in favour of *Nervosa*". (In fact, in his report of 1874, Gull had commented "we might call the state hysterical without committing ourselves to the etymological value of the word, or maintaining that the subjects of it have the common symptoms of hysteria. I prefer, however, the more general term nervosa, since the disease occurs in males as well as females, and is probably central rather than peripheral".)

DEBATE

There had earlier been much rancorous debate about the word hysteria. Whenever this term was printed, one could expect an almost instant riposte from Mr D. de Berdt Hovell, FRCS. Most of Hovell's wrath seemed to be

Comparative Studies of Inosine Pranobex and Acyclovir

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A total of 77 patients with first-attack genital herpes received acyclovir, 400 mg four times per day, inosine pranobex, 1 g four times per day, or both drugs for seven days. Patients treated with acyclovir healed in a shorter time and had a shorter duration of viral shedding and symptoms than those treated with inosine pranobex. Neither acyclovir nor inosine pranobex had any effect on the time to first occurrence or the frequency of subsequent recurrences. Preliminary results from two trials suggest that suppressive acyclovir is more efficacious than inosine pranobex in patients with frequently recurring genital herpes.

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Numerous different treatments have been suggested for managing patients with genital herpes, and these include antiviral drugs and immunomodulators [1,2]. The majority of these preparations have been shown in clinical trials to be ineffective, but many have not been tested in controlled clinical trials. Two drugs, acyclovir and inosine pranobex, have been reported to be efficacious in the management of both first-attack and recurrent genital herpes [3–15]. This review will consider the studies that have compared the efficacy of these two preparations.

One study, comparing the two drugs in patients with first-attack genital herpes, has recently been published [16], and trials using the drugs for suppression of frequently recurring infection are currently in progress.

DRUG THERAPY

Acyclovir

Acyclovir is a specific, anti-herpetic drug that acts by competing with viral thymidine kinase, and also inhibits viral DNA polymerase [17,18]. The oral preparation has been shown in a series of clinical trials to decrease the duration of viral shedding and symptoms, and also to reduce the time to healing in patients with a first attack of genital herpes [3–5]. Unfortunately, the treatment of outbreaks with acyclovir does not appear to prevent the development or reduce the frequency of subsequent recurrences.

Suppressive acyclovir has also been shown to be effective in preventing recurrences or in markedly reducing their frequency and severity in patients with frequently recurring genital herpes [19–21].

Inosine Pranobex

Inosine pranobex is an immunomodulator with an action that stimulates the body's own immune mechanism. The drug is not a specific antiviral agent, but clinical studies have suggested that the drug reduces the duration of viral shedding and the time to healing in patients with first-attack genital herpes, and reduces the severity and frequency of recurrences in those with recurrent attacks [12–15].

TREATMENT OF FIRST-ATTACK GENITAL HERPES

Only one study comparing the efficacy of acyclovir with that of inosine pranobex in patients with first-attack genital herpes has been published [16]. In this study, 77 patients with a first attack of genital herpes, who presented to the Departments of Genito-urinary Medicine, Middlesex Hospital, London, or the Royal Hallamshire Hospital in Sheffield, United Kingdom, were studied.

Patients were randomly allocated to three treatment groups: (1) 24 received active acyclovir and "dummy" inosine pranobex; (2) 28 active inosine

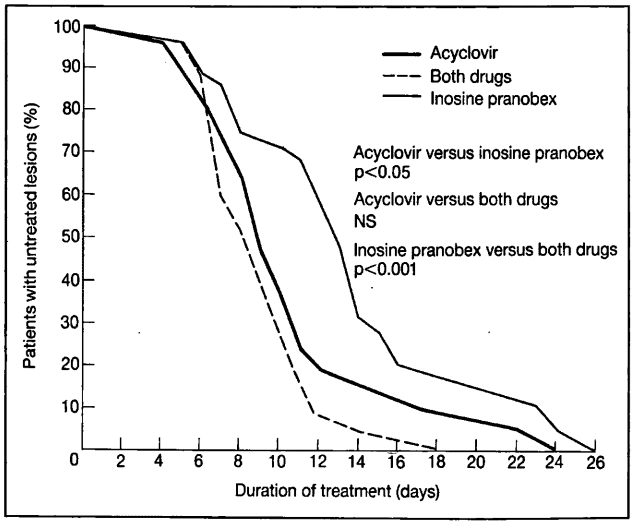

Figure 1. Time to healing of lesions in patients receiving acyclovir, inosine pranobex, or both drugs. Reproduced with permission from Lancet [16].

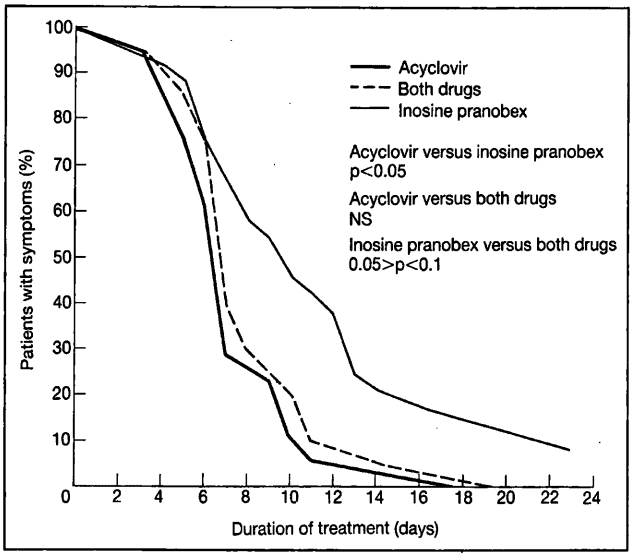

Figure 3. Duration of all symptoms in female patients receiving acyclovir, inosine pranobex, or both drugs. Reproduced with permission from Lancet [16].

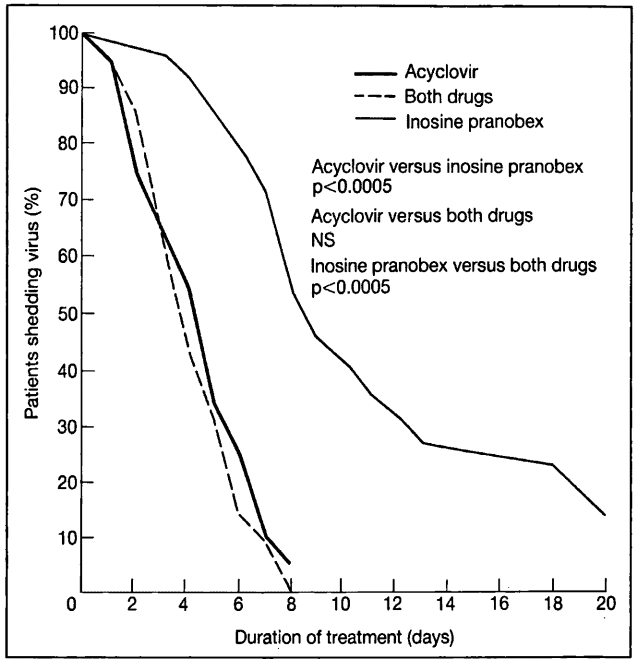

Figure 2. Duration of viral shedding in patients receiving acyclovir, inosine pranobex, or both drugs. Reproduced with permission from Lancet [16].

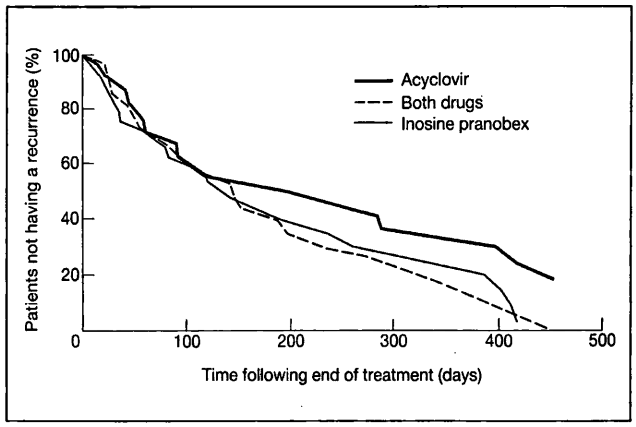

Figure 4. Time to first recurrence in patients receiving acyclovir, inosine pranobex, or both drugs.

pranobex and dummy acyclovir; (3) 25 received both active acyclovir and inosine pranobex. This last group was included to investigate whether the two treatments complemented each other in any way. Acyclovir, 400 mg four times per day, and inosine pranobex, 1 g four times per day, were administered for seven days. Patients were assessed at entry and three times weekly until complete healing occurred. To study the frequency of subsequent recurrences, patients were assessed monthly for six months and the number of recurrences was recorded. Statistical tests included chi-squared, Mann-Whitney U, and a log rank test.

At entry, there were no significant differences in age, sex, viral type, antibody status, or duration of signs and symptoms between the three treatment groups or between the patients from the two centers. No side-effects were noted in any patient.

Healing Time

The median times to healing in the acyclovir group and the group receiving acyclovir and inosine pranobex were both statistically shorter than in the inosine pranobex group ($p < 0.05$, acyclovir versus inosine pranobex; $p < 0.001$, both drugs versus inosine pranobex). By Day 11, over 75 percent of patients treated with acyclovir or with both drugs were healed compared with only 30 percent of those who received only inosine pranobex (**Figure 1**).

Duration of Viral Shedding

The duration of viral shedding was significantly longer in patients treated with inosine pranobex compared with those in the other two treatment groups ($p < 0.0005$ for both groups; **Figure 2**). All culture specimens from patients treated with acyclovir or both drugs yielded negative results by Day 8, whereas 48 percent of those treated with inosine pranobex were still shedding virus. Of those treated with inosine pranobex, 20 percent still had positive culture results on Day 18 after entry.

Symptoms

No significant differences occurred in the duration of symptoms comparing all patients in the three treatment groups. Women treated with acyclovir, however, had a shorter duration of dysuria and all symptoms compared with those treated with inosine

TABLE I

Mean Recurrence Rate Comparing Acyclovir and Inosine Pranobex Patients during the Observation and Treatment Periods

Period	Treatment Group: Acyclovir (n = 12)	Treatment Group: Inosine Pranobex (n = 13)	Value
Pretreatment	1.4* (1.07)†	1.29 (0.79)	NS
Treatment	0.11 (0.16)	1.31 (0.93)	<0.0001
p Value	<0.0005	NS	

*Number of recurrences per month.
†Numbers in parentheses, SD.

pranobex. These differences were statistically significant ($p < 0.02$ for dysuria, $p < 0.05$ for all symptoms; **Figure 3**).

Recurrences

No statistically significant difference occurred in the median time to first recurrence comparing patients in the three treatment groups (acyclovir, 187.4 days; inosine pranobex, 142.5 days; both drugs, 132.7 days; **Figure 4**). Patients with type II infections had earlier recurrences (median, 64 days) than those with type I (median, 238.2 days, $p < 0.0015$). These differences were irrespective of the treatment given. The frequency of recurrences comparing patients in the three treatment groups was similar.

CONCLUSIONS

Patients treated with acyclovir (either alone or in combination with inosine pranobex) healed more quickly, and had a shorter duration of viral shedding and symptoms than those treated with inosine pranobex. Neither preparation appeared to have any effect on the time to first recurrence or the frequency of subsequent recurrences. Acyclovir is the drug of choice for treating patients with first-attack genital herpes.

SUPPRESSIVE THERAPY FOR RECURRENT GENITAL HERPES

Two trials are currently being conducted to compare the efficacy of suppressive acyclovir and inosine pranobex in patients with frequently recurring genital herpes. The first is a multicenter European trial, and results are not yet available. The second is a study being conducted at the Middlesex Hospital, London, United Kingdom. Patients with at least eight recurrences each year are being recruited into the study. Following a two-month observation period, patients are being randomly allocated to receive either active acyclovir, 200 mg four times per day, and dummy inosine pranobex, or active inosine pranobex, 1 g four times per day, and dummy acyclovir; the duration of treatment is 12 weeks. A total of 30 patients have entered the trial and 25 have completed treatment. Interim analysis comparing the frequency of recurrences in the pretreatment and treatment periods in patients treated with either acyclovir or inosine pranobex is shown in **Table I**. During the treatment period, patients treated with acyclovir had a dramatic reduction in the frequency of recurrences compared with the pretreatment frequency ($p < 0.005$). In contrast, the frequency of recurrences in the inosine pranobex group was virtually identical to the frequency prior to treatment.

COMMENTS

Preliminary results comparing the efficacy of suppressive acyclovir with that of inosine pranobex suggest that acyclovir is more efficacious than inosine pranobex. The complete results of these studies will be required, however, to confirm the findings.

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Focus

Screening pregnant women for genital herpes

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Summary – Neonatal herpes leads to serious morbidity and high mortality. The true incidence is unknown due to under reporting and difficulties in diagnosing the condition, but may be increasing. Mothers with primary disease, at term, present a greater infection risk to their offspring than mothers with recurrent disease, but the exact risks remain unknown. Existing prevention policies are inefficient, time-consuming for the doctor and the patient and, where ceasarian section is offered to at-risk mothers, potentially hazardous. Anti-viral therapy offers a rational alternative and requires urgent evaluation.

neonatal herpes / screening

Résumé – Prévention de l'herpès génital chez la femme enceinte. *L'herpès néonatal conduit à une morbidité grave et à des taux élevés de mortalité. Son incidence réelle n'est pas connue en raison des difficultés diagnostiques et de sa sous-déclaration, mais il est possible qu'elle soit en cours d'augmentation. Les mères en primo-infection, au terme de la grossesse, présentent un risque plus élevé de contaminer leur enfant que les mères ayant un herpès récurrent. L'importance exacte des risques respectifs demeure néanmoins inconnue. Les mesures préventives actuelles existantes sont inéfficaces, facteurs de perte de temps pour le médecin et la patiente et, dans les lieux où la césarienne est proposée aux mères à risque, potentiellement risquées. Le traitement antiviral constitue une alternative raisonnable et réclame une évaluation sans tarder.*

herpès néonatal / prévention

Epidemiology of neonatal herpes

In the United States of America, the incidence of neonatal herpes has been variously estimated between 2.6 and 50 per 100 000 live births [22, 28]. In the United Kingdom, a voluntary notification system suggests that the incidence is less than 3 per 100 000 live births [4]. However, ascertaining the true incidence of neonatal herpes is difficult for the following reasons:

1) The disease is not notifiable in the UK nor in the USA; 2) the incubation period of the virus, and shorter in-patient stays during the puerperium mean that more cases may develop after children have left hospital when diagnosis of their condition may be less likely, particularly if infants never develop the classical mucocutaneous lesions; 3) many mothers are asymptomatic at the time of delivery and have no history of genital herpes [25], thus doctors may not suspect the diagnosis.

The clinical presentation of neonatal herpes ranges from minor cases, where only the skin, eye or mouth are involved, to major disease affecting the central nervous system or other internal organs. Mortality and the neurological status of survivors is dependent on the severity of the clinical condition (table I).

Transmission of herpes simplex virus

Although infection is usually thought to be transferred from mother to infant during labour, other routes of infection do occasionally lead to disease (table II). Transplacental infection, inferred when

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Table I. Outcome of neonatal herpes. Percentages with each outcome based on Whitley *et al* (1988).

		Death	*Long term sequelae*	*Normal outcome*
Disseminated Disease	No CNS disease	83	8	9
	CNS disease	74	14	12
Localised	CNS	38	48	14
	Eye	6	40	60
	Skin	14	27	59
Overall		49	26	25

Table II. Sources of infection.

Maternal	Transplacental	
	Birth canal	
		1° HSV
		Recurrent HSV
		Asymptomatic HSV
	Post delivery/oral + ?	other
Paternal	Post delivery	
Other	Medical delivery	
	Medical/paramedical	
	Family	Post delivery
	Foetal monitoring	

infection occurs despite caesarian section before membrane rupture, has been reported from symptomatic and asymptomatic mothers, but is exceptionally rare. The outcome for such infants is poor [14]. Non-genital maternal sources have been documented; frequently an HSV 1 oral lesion [34] but lesions on the thigh and breast have also been implicated [31]. Fathers and other family members as well as medical staff have been thought to be the source of infection in a few cases [28, 34] and baby-to-baby spread has also occurred.

Primary maternal herpes at or around the time of delivery presents a particularly large risk to the neonate. The reasons for this are:

1) Greater quantity of virus present; 2) larger areas from which the virus can be cultured; 3) more frequent involvement of the cervix [9]; 4) longer duration of viral shedding [9]; 5) lesser likelihood of transplacental transfer of maternal antibodies.

In addition, it has been shown that women who have acquired genital herpes early in pregnancy are more likely to shed herpes asymptomatically from both vulva and cervix during that pregnancy, than women whose infection antedates their pregnancy [5].

Two recent prospective studies of pregnant women and their infants [6, 25] identified respectively, 2 mothers with culture proven primary herpes at term, and 5 with primary herpes during the 3rd trimester. Of the 7 infants, 3 had neonatal herpes infection and 2 others had serious perinatal morbidity but herpes was not proven to be the cause. Primary herpes in the mother undoubtedly carries a major risk of transmission to the neonate but in practice, few women acquire a primary infection during pregnancy.

The risk of transmission from women with recurrent disease at delivery is certainly lower. The findings of 3 studies, that looked retrospectively at the mothers of neonates with herpes, are summarized in table III, and would suggest that approximately 1 in 5 of the neonates with herpes are born to mothers with recurrent disease. However, since asymptomatic genital infection is not uncommon, where the true incidence of maternal herpes infection is not determined serologically,

Table III. Maternal characteristics of neonates with herpes.

Neonates with HSV	*Mothers with recurrent HSV*	*Author*
31	8	Yeager and Arvin 1984 [34]
95	17	
196	38	Whitley *et al*, 1988 [32]
26	13	Sullivan-Bolyai *et al*, 1983 [28]
368	76	Total

many patients who have recurrent disease will not be identified by history alone [34]. Prober *et al*, in a prospective study of 6 904 deliveries, showed that fewer than 4% of mothers had a history, but almost 20% exhibited serological evidence of prior HSV 2 infection [25]. Yeager *et al* reviewed the reasons for this absence of a history of genital herpes in mothers of infected neonates and concluded that 20% have primary infections, the mother was not the source in 10%, and in 35% there was serological, but not historical evidence of prior herpes infection [34]. Only 26% gave a history of recurrent genital herpes and in many of these cases the history was elicited only after asking detailed questions; the patients were mostly unaware that their recurrent problem was herpes.

Prospective studies are able to identify women known to have recurrent herpes, who have clinical herpes or are shedding virus at term and then observe the outcome for the infant. The results of such studies are summarised in table IV and suggest that the probability of transmission from mother to neonate is less than 1 in 40. However, this may be an underestimate as the majority of the "recurrences" were asymptomatic.

Table IV. Risk of neonatal herpes from mothers with genital HSV.

Maternal HSV	*Neonatal HSV*	*Author*
12	0	Prober *et al*, 1988 [25]
40	1	Prober *et al*, 1987 [24]
8	0	Arvin *et al*, 1986 [2]
23	1	Nahmias *et al*, 1971 [21]
83	2	Total

The role of maternal antibody in protecting infants from infection or from serious consequences if infected, is not clear and this may be partly due to the diversity of antibodies detected by the assays and the considerable cross-reactivity of the majority of antibodies to HSV 1 and HSV 2. Whitley *et al* did not find any correlation between infant antibody status at the time of disease presentation and eventual outcome [31]. Yeager *et al*, however, demonstrated a protective effect of high titres of transplacentally derived antibody and showed that the titre of neutralising antibody correlated with neonatal acquisition of herpes infection and severity of disease in those who were infected [33]. Sullender *et al*, using type specific antibodies to glycoprotein G have shown a highly significant difference in titres of HSV 2 antibody between neonates exposed to HSV at delivery who remained well (high levels of antibodies) and those who developed neonatal herpes (low levels of antibody) [27].

In women with recurrent genital herpes it is probable that many factors determine whether neonatal infection will occur:

1) the amount of virus present in the lesions cannot easily be quantified but larger amounts increase probability of transmission; 2) the site of the maternal lesions will affect the extent and duration of neonatal contact with the virus (*eg* a cervical lesion will remain in direct contact with the neonate during parturition for longer than a lesion on the labia majora); 3) length of labour and time from membrane rupture to delivery determines the period of potential contact between lesion and neonate; 4) maternal antibody levels (see above); 5) foetal instrumentation (*eg* scalp electrode) may provide a route of entry for the virus.

Unfortunately, few of these variables have been recorded in the studies mentioned above.

Prevention of neonatal herpes

Despite antiviral therapy, acyclovir or vidarabine, the mortality and morbidity for neonatal herpes remains too high for treatment of the neonate at the time of disease presentation to be acceptable. Disease prevention is therefore essential. For any screening policy to be successful, it must use tests which are sensitive, specific and acceptable to the population to be screened. Intervention must improve outcome, at a cost that is appropriate.

Current screening recommendations are that women with a history of recurrent genital herpes have weekly examinations for herpetic lesions and viral cultures from the cervix and/or vulva from 36 wks gestation to term. Such a programme will fail to meet the conditions outlined above. Genital herpes lesions may be asymptomatic, either because of their size and duration or because of their site (*eg* on the cervix). If only those women with a history of genital herpes are screened then the majority of women with serological evidence of recurrent disease will be missed, as may primary infections. The delay between taking a specimen and receiving the result of viral culture means that

women and doctors may be falsely reassured at term by a negative result when a more recent positive swab has yet to be reported, or conversely, may be needlessly alarmed by a recent positive culture when in fact the virus is no longer present at term. Finally, the more frequent clinic visits and genital examinations may make such programmes less acceptable to the patients.

A further consideration when assessing any screening policy is cost, both to the individual and the community. Binkin *et al* calculated that a screening policy in the USA, consisting of weekly viral cultures taken from 32 wks gestation to term from all women with a history of genital herpes, resulted in each averted case of neonatal herpes costing $1.8 million [3].

The identification of mothers at risk of transmitting herpes to their neonates by a past history of genital herpes is clearly very inadequate. The routine use of type specific antibody assays at booking, during the 3rd trimester and at term would identify almost all mothers who have acquired herpes before their pregnancy and the majority who acquire it during pregnancy.

Modified "screening" might then be offered to these women and this would consist of regular examinations by doctors experienced in recognising clinical herpes. Patients could be educated to recognise symptoms of recurrent disease. This would allow earlier intervention when a woman identified as having a recurrence begins labour. It would not require culture tests but would, of course, fail to detect truly asymptomatic viral shedding.

As a result of screening, women are identified who will potentially infect their infants. Three different courses of management are then open; caesarian section, wait-and-see and antiviral treatment (table V). Most screening policies exist to identify women who will be advised that their baby should be delivered by caesarian section. If caesarian section is offered to all women where the most recent culture is positive then, as discussed above, unnecessary operations will be performed. Binkin *et al* calculated that in the USA, screening 121 000 women pa would avert 50 neonatal deaths or cases of severe retardation, but that 3.3 women would die as a result of the increased number of caesarian sections performed [3]. Furthermore, caesarian section may reduce but not prevent transmission. Clearly, infants infected by haematogenous spread would not be helped. It is generally recommended that delivery within 4 h of membrane rupture is necessary to prevent ascending infection, although others have suggested that in the presence of recurrent external genital lesions, when cervical lesions are less likely to be present, caesarian section should be performed regardless of the duration of rupture of membranes [30]. Case reports of infection despite delivery within this time exist [17] but of course prior haematogenous spread cannot be excluded and indeed is suggested by premature rupture of membranes and early infant morbidity in some of these cases.

Antiviral therapy

Acyclovir has been shown to reduce the time to healing and the duration of viral shedding during a primary herpetic episode [7, 9, 10, 12, 16, 18, 20, 23] and when given continuously to patients with frequent recurrences to decrease the frequency of recurrences [11, 13, 15, 19, 26, 29]. Its safety in pregnancy has not been established but no adverse reactions have been reported following inadvertent use during pregnancy [1]. If

Table V. Managment of at-risk pregnancies.

	Advantages	*Disadvantages*
Caesarian section	Does prevent some neonatal infections	Morbidity and mortality Does not prevent all neonatal infections Some are unnecessary Expensive
Wait-and-see	Inexpensive	Does not prevent any infections
Antiviral treatment	? Effective Acceptable to patients	? Who and when to treat

its safety during the 3rd trimester and in neonates were established then several strategies for the reduction of neonatal herpes might be evaluated.

Treatment could be considered for the mother before delivery or for the neonate. Mothers might be treated when experiencing an attack of genital herpes, but this would, of course, fail to treat all of the asymptomatic cases. Alternatively, mothers might be given suppressive acyclovir if they have serological evidence of herpes infection, or have acquired herpes during pregnancy. This form of treatment might be given from, say, 36 wks gestation until term.

Infants may be treated when found to be infected with the herpes virus but this does not prevent morbidity or mortality. Infants born to mothers who are identified serologically to have had prior herpes infection or who are known to have acquired herpes during that pregnancy may be given suppressive therapy for the first few weeks of life. Another option would be to select only those infants with the above criteria who also have other adverse prognostic features such as prematurity, prolonged rupture of membranes or instrumentation during delivery.

Carefully controlled clinical trials will be required to determine which of these options (if any) are useful.

Conclusions

Large scale prospective studies of pregnant women (with or without a history of recurrent genital herpes), with follow-up of any exposed neonates, are needed to provide natural history data before firm recommendations on the management of herpes in pregnancy can be made. Present screening policies are not entirely successful but may prevent some cases of neonatal herpes. Modified screening or anti-viral suppressive treatment may be more acceptable to the patient but require evaluation to establish their safety and efficacy in reducing neonatal mortality and permanent neurological deficit.

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Antiviral Chemotherapy for Genital Herpes

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INTRODUCTION

The introduction of acyclovir, a safe and effective antiviral drug, has revolutionised the treatment of genital herpes. Prior to its introduction, numerous and diverse therapies were used, or suggested, to treat patients with this condition including conventional antivirals (e.g. vidarabine and idoxuridine and ribavirin) immune modulators (e.g. interferons, levamisole, inosine pranobex, thymopentin) and a host of miscellaneous therapies ranging from the conventional (e.g. topical surfactants such as ether, chloroform and nonoxynol-9, antibiotics, topical antiseptics and steroids) to the alternative (e.g. *Aloe vera* extracts, ginseng, red algae and supplemental vitamins).[1,2]

This review will consider briefly the clinical features of genital herpes and the objectives of treatment; antiviral agents with activity against herpes simplex viruses (HSV); the use of acyclovir for the treatment of genital herpes, failure to respond to acyclovir and finally recommendations for the treatment of genital herpes.

THE CLINICAL FEATURES AND NATURAL HISTORY OF GENITAL HERPES

First attack genital herpes can be a severe and prolonged illness particularly in those individuals who have never previously been exposed to HSV. The illness is characterised by both local and systemic symptoms. Pain, dysuria and discharge are the local symptoms and the systemic illness includes fever, malaise, headaches and generalised aches. Erythema of the skin or mucous membranes is followed rapidly by vesiculation. The painful vesicles burst to leave shallow ulcers which heal in 7–10 days. Crops of new vesicles continue to occur for up to 2 weeks and the entire illness may last up to 4 weeks. Lesions may be numerous and widespread affecting the skin and mucous membranes of the genitalia and adjacent areas. Sometimes lesions are found at distant sites such as the finger, mouth or breasts. First attack genital herpes is often very severe in women with genital herpes and homosexual men with perianal or anal herpes. In women involvement of multiple anatomical sites (e.g. vulva, perineum, perianal area and cervix) is not unusual.[3]

Genital herpes may be complicated by a self-limiting viral meningitis and a transient sacral radiculopathy involving the sensory and autonomic nerves. The sacral radiculopathy occurs particularly in men with anal or perianal herpes and is characterised by urinary and faecal difficulties, inability to obtain an erection, absence of the bulbocavernosis reflex and decreased sensation over the sacral dermatomes.[3]

One of the features of infection with most human herpesviruses is the ability to establish latency with subsequent reactivation. Following exposure to HSV at the genital site latency is established in the neurones of the sacral ganglia. There is considerable evidence from animal experiments that latency is established soon after exposure and probably even before lesions have occurred. These findings are of considerable importance as they suggest that antiviral chemotherapy is unlikely to be effective in preventing latency unless it is commenced soon after exposure and almost certainly before lesions have occurred.

Reactivation of the virus occurs periodically thereafter to produce either typical clinical recurrences or inapparent (but nonetheless) infectious viral excretion. The causes of reactivation are not fully understood but several studies have shown that they are often associated with sexual activity (intercourse or masturbation) and menstruation. Other factors often mentioned as being associated with reactivation include intercurrent infection, and physical or emotional stress. Both HSV-1 and HSV-2 may cause genital herpes and both may establish latency. However, genital herpes due to HSV-2 tends to recur earlier and more frequently[4] than HSV-1.

Recurrences are usually less severe and of shorter duration than the first attack, consisting of a single lesion or small crop of lesions mostly on the external genitalia and lasting about 7 days. Many patients have frequent recurrences and 12 or more a year is not unusual. Prodromal symptoms often consisting of tingling sensation at the site where the lesions subsequently occur, or neuralgia-type pain in the dermatomal distribution of the lesions may be more troublesome than the local discomfort associated with the lesions themselves.[5]

Genital herpes is often associated with profound psychological and psychosexual dysfunction. Among the more common psychological problems are: anxiety concerning the chronicity of the disease, anger, disgust and loss of personal esteem and finally difficulty in establishing new sexual relationships and loss of libido. These problems occur particularly in those individuals with frequent recurrences, and in some may be more troublesome than the actual recurrences.[6]

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Table 1. Antiviral agents with activity against HSV

Pyrimidine analogues	
Idoxuridine	IDU
Trifluorothymidine	TFU
Bromovinyl-deoxyuridine	BVDU
Purine analogues	
Vidarabine	
Vidarabine monophosphate	
Ribavirin	
Acyclovir	
Ganciclovir	
Others	
Foscarnet	

The objectives of treatment in primary genital herpes are to decrease the duration of symptoms and viral shedding; decrease the time to healing; prevent complications such as viral meningitis, sacral radiculopathy or urinary retention; and stop the virus establishing latency. The objectives of treatment in recurrent genital herpes are to decrease the severity and duration of the recurrences and prevent the development of further recurrences.

ANTIVIRAL AGENTS WITH ACTIVITY AGAINST HSV

Several antiviral drugs with activity against HSV are shown in Table 1.

Pyrimidine analogues

Idoxuridine (IDU), trifluorothymidine and bromovinyl-deoxyuridine (BVDU) have all been shown *in vitro* and *in vivo* to have activity against HSV. However, systemic toxicity with IDU and trifluorothymidine (mainly profound bone marrow suppression) preclude parenteral use.[7] The antiviral activity of IDU depends on its replacement of thymidine in newly synthesised DNA and its ability to inhibit a variety of enzyme systems. Trifluorothymidine acts by leading to an inhibition of late viral mRNA transcription and preferential synthesis of viral DNA.[7] BVDU depends for its action on phosphorylation, in cells infected by HSV, by an HSV-induced thymidine kinase.[8] Topical IDU is still sometimes recommended for the treatment of genital herpes but a well-conducted double-blind placebo controlled study suggested that it was of questionable benefit.[9] The efficacy of BVDU is still being assessed.

Purine analogues

Vidarabine and vidarabine monophosphate are selective inhibitors of virus-induced DNA polymerase.[10] However, limited topical absorption and toxicity with the parenteral preparation (including bone marrow suppression, gastrointestinal disorders, central nervous system dysfunction, hepatotoxicity and possible teratogenic, mutagenic and carcinogenic effects) preclude their use in genital herpes.[11]

Ribavirin is a synthetic compound structurally related to guanosine. It exerts its antiviral effect after intracellular phosphorylation. It has several modes of action including inhibition of polymerase enzymes, depletion of nucleotide pools and interference with mRNA cap formation.[12] It appears to have some *in vitro* and *in vivo* activity against HSV, although it is certainly less efficacious than the other purine analogues. Side effects including anaemia, gastrointestinal dysfunction, skin rashes and myalgia and its limited oral absorption preclude its widespread use.[13]

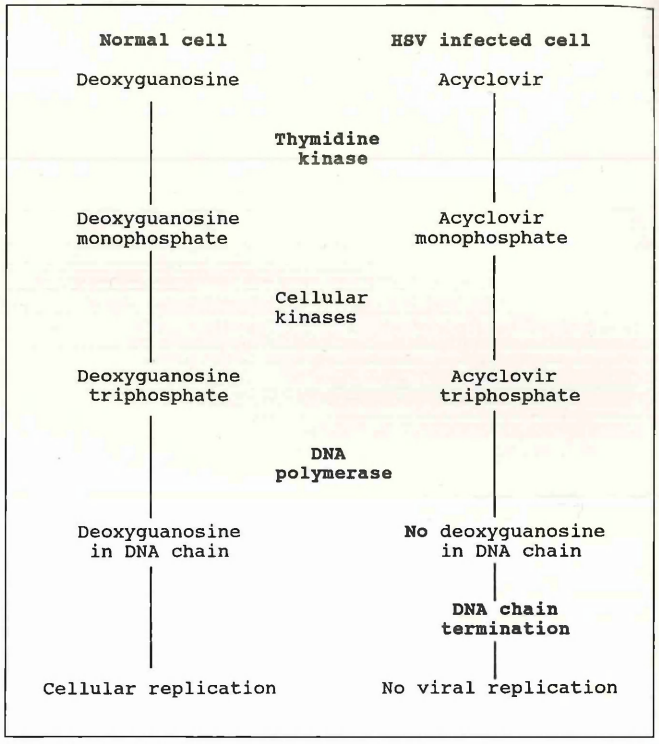

Figure 1. The mechanism of action of acyclovir. The drug acts by competing as a substrate with the deoxynucleosides. Acyclovir triphosphate competes with DNA polymerase and results in DNA chain termination.

Acyclovir is a purine analogue with high potency and selectivity for HSV based on differences between cellular and HSV specified enzymes (Figure 1). First the herpesvirus specified thymidine kinase (TK) phosphorylates acyclovir (whereas cellular thymidine kinase does not) into a monophosphate derivate which is subsequently converted into diphosphate and triphosphate derivatives, presumably by cellular enzymes. The acyclovir triphosphate inhibits viral DNA polymerase resulting in termination of the growing DNA chain. In addition, acyclovir monophosphate inactivates viral DNA polymerase by binding to and inhibiting the enzyme.[15,16] Acyclovir does not appear to have any effect on nonreplicating latently infected cells.

Acyclovir may be used intravenously, orally or topically and its highly selective mode of action and minimal toxicity (discussed in detail below) makes it the drug of choice for the treatment of genital herpes.

The side effects with oral acyclovir are unusual and mostly unimportant and include nausea, skin rashes, headache, fever and malaise.[16] Long term safety with oral acyclovir appears to be excellent. More serious side effects including encephalopathic changes and transient renal tubular abnormalities have been reported on very rare occasions with intravenous acyclovir but not with the oral

preparation. The renal toxicity is due to deposition of acyclovir crystals in the renal tubules and occurs when patients are severely dehydrated or the drug is given by bolus intravenous injection.[17]

Ganciclovir has a similar mode of action to acyclovir in that the virus specified TK phosphorylates acyclovir whereas cellular TK does not.[18] However, the drug is poorly absorbed orally and causes anaemia and neutropenia and is consequently of limited use for the treatment of genital herpes.

Foscarnet

This is a unique agent whose mode of action is dependent on the selective inhibition of viral DNA polymerase. It is poorly absorbed orally and needs to be given intravenously. As a consequence of its different mode of action foscarnet may be of use in patients with anogenital herpes infections which are resistant to treatment with acyclovir.[19] (Resistance is discussed in detail below.) Foscarnet is nephrotoxic; may cause hyper- or hypocalcaemia and rarely genital ulceration.

Immune modulators

Several drugs said to have immunopotentiating properties, including various interferons, levamisole, thymopentin and inosine pranobex have been used or suggested for use in patients with genital herpes. There is no convincing evidence that any of these agents has any effect either on the acute course or the natural history of the infection. Inosine pranobex is still widely recommended in parts of Europe and the UK. However, two double-blind controlled trials comparing acyclovir and inosine pranobox have shown that acyclovir is statistically significantly superior for both the treatment of acute and the suppression of frequently recurring genital herpes.[20,21]

ACYCLOVIR FOR THE TREATMENT OF GENITAL HERPES

First attack genital herpes

There have been numerous randomised double-blind placebo controlled clinical trials using acyclovir in patients with first attack genital herpes with several different formulations of the drug including intravenous, oral and topical.[22–30] These studies have shown that patients treated with acyclovir have a statistically significant reduction in the time to healing, the duration of viral shedding, pain and the other associated symptoms compared with placebo recipients. The reduction in viral shedding was the most dramatic and consistent finding, with acyclovir treated patients shedding virus for a mean of 2–3 days compared with 8–10 days in placebo recipients. These findings have an important practical implication, in that the effect of the drug on healing and symptoms is dependent upon its antiviral effect. If treatment is started early before extensive vesiculation and ulceration are present the results are excellent. However, if treatment is delayed and there is extensive ulceration, the reduction in viral shedding will have only a minimal effect on total symptoms and the time to healing. There appears to be no benefit in combining oral and topical therapy nor in prolonging oral treatment beyond 5 days.

The current recommended dose is 200 mg 5 times daily and studies looking at alternative dosing regimes are under way. One of the disappointing aspects of treatment has been the observation that acyclovir does not prevent or reduce the likelihood of the development of recurrences or decrease their frequency. Even prolonged treatment of the first attack fails to achieve this objective.[31] Consequently patients treated with acyclovir for first attack of genital herpes need to be informed that the drug has no effect on the development of subsequent recurrences.

Acyclovir for the treatment and prevention of recurrent genital herpes

The treatment of each recurrence with either topical or oral acyclovir has proved disappointing. Although several studies have shown a statistically significant reduction in the duration of viral shedding and the time to healing[27–30,32] the actual relevance of this to the patient is questionable. Most of these studies showed that healing times were approximately one day shorter in acyclovir recipients compared with controls such that taking acyclovir tablets or using cream for 5 days reduced the time to healing from 6 days to 5 days; at best a marginal improvement. Using treatment early in the attack or during the prodrome appears to be a little better and may be suitable for some patients. However, not all patients have a clear cut prodrome and often prodromal symptoms occur without a subsequent clinical recurrence. Single courses of treatment with acyclovir do not affect the frequency or severity of subsequent recurrences.

An alternative approach is to use continuous suppressive acyclovir to prevent recurrences. This approach has already proved highly successful in preventing life threatening herpes infections in immunocompromised patients, particularly transplant recipients and those having cancer chemotherapy.

Several double-blind placebo controlled trials using suppressive acyclovir therapy in patients with frequently recurring genital herpes have been conducted. The initial studies showed that continuous oral acyclovir used for periods of 3–6 months was a highly effective form of therapy for patients with frequently recurring herpes.[33–37] The majority of patients on acyclovir had either no recurrences or very few minor episodes, whereas those treated with placebo continued to have recurrences at the same frequency and with similar severity as before. There are several additional benefits of suppressive therapy, including a decrease in prodromal symptoms and neuralgia pains, a decreased risk of transmission to sexual partners and an improvement in both psychological and psychosexual well being.

The frequency of medication varied in the initial trials from 2 to 5 times daily and the total daily dosage from 600 mg to 1 g; however, all the treatments showed a reduction in the frequency of recurrences compared with placebo. Three important questions raised by these studies will be discussed below.

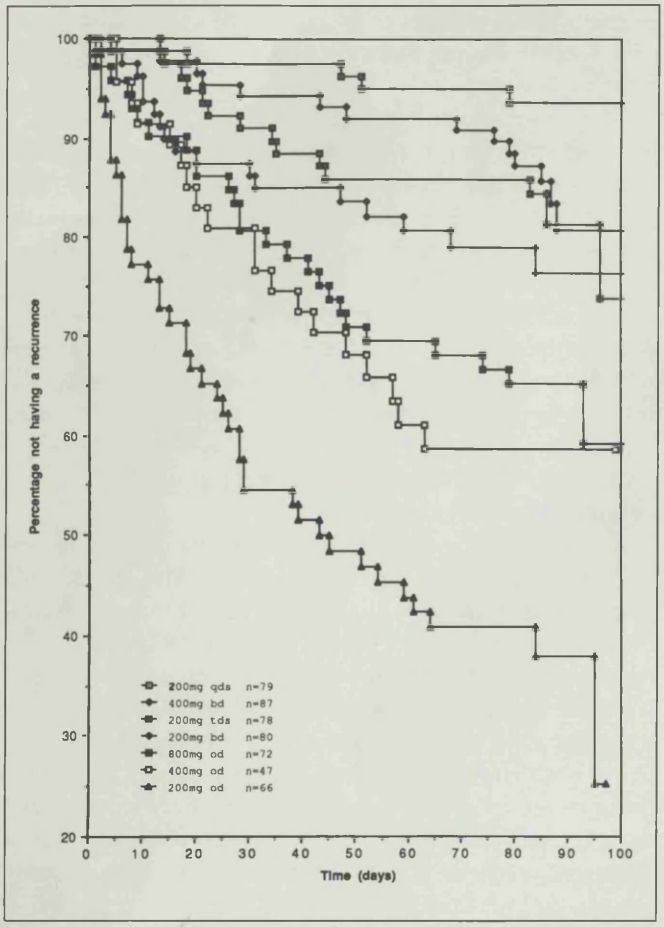

Figure 2. The time to first recurrence in patients with frequently recurring genital herpes comparing different doses of acyclovir. The lower and less frequent the dose, the more likely the patient is to have recurrences. From Mindel *et al.* (1988).[38]

What is the ideal dosage for suppression?

Two studies have been conducted to determine the most efficacious dose for commencing and maintaining suppressive acyclovir therapy.[38,39] These two studies have shown that the most effective dose for commencing suppression is 200 mg q.d.s. Patients on 400 mg b.d., 200 mg t.d.s., 200 mg b.d., 800 mg o.d., 400 mg o.d. and 200 mg o.d. are statistically significantly more likely to have a recurrence than those on 200 mg q.d.s. (Figure 2). In these studies, as the total daily dose and/or the frequency of tablet taking were lowered so the likelihood of having a recurrence was increased. For example, in one of the studies at the end of 60 days on suppression 10% of patients on 200 mg q.d.s. had had a recurrence compared with 14% on 200 mg t.d.s., 19% on 200 mg b.d. and 56% or 200 mg o.d. Once daily therapy is particularly likely to lead to breakthrough recurrences irrespective of dose. On 800 mg o.d. 30% will have recurred after 60 days, compared with 41% on 400 mg o.d. and 56% on 200 mg o.d. Whilst breakthrough recurrences can occur on all doses, virus-positive episodes are more common on once daily therapy. On the basis of these studies we would recommend that all patients should commence therapy on 200 mg q.d.s. and this should be reduced, to 200 mg t.d.s. after 2–3 months if the patient is recurrence free. Further reductions to 200 mg b.d. and eventually once daily may be possible. However, as mentioned above, it is worth bearing in mind that over 40% of patients will have a recurrence on once daily therapy.

How long should treatment continue?

The question of how long patients should be treated before stopping remains unresolved. Studies from the UK and USA suggest that the frequency of recurrences declines after 1 or 2 years of treatment.[38,40] Whether this is due to treatment or is the natural history of the infection is unclear. In any event this observation suggests that therapy should be stopped after a year to ascertain if the frequency of recurrences warrants further treatment.

Which patients should be treated?

Whilst the efficacy of the therapy is undisputed, the question of who to treat remains controversial. Several factors should be taken into consideration when deciding who to treat, including the following:

1. Frequency of recurrences.
2. Duration of recurrences.
3. Severity of symptoms.
4. Associated psychological or psychosexual morbidity.
5. Total duration of illness.
6. Likelihood of transmission to sexual partner.

Each of these factors should be considered and discussed with the patient. My own view is that all patients with 8 or more recurrences per year should be offered suppression, irrespective of the severity or other factors mentioned above. In those with between 6 and 8 attacks per year, all the factors above need to be considered and those with less than 6 attacks per year (unless each attack is very prolonged) should not be considered for therapy.

We have found that the easiest way of doing this is to follow patients prospectively from the time of presentation until the observer is confident, first that the patient does indeed have herpes and second that the recurrences are sufficiently frequent or severe to warrant therapy. Patients who present with primary herpes should not be given suppressive acyclovir until sufficient time has passed to assess that the patient is having at least 6 recurrences per year.

Patients who are immunocompromised (e.g. those with a malignancy, receiving chemotherapy or other immunosuppressive drugs, or those with human immunodeficiency virus (HIV) infection should be handled differently, as more serious consequences may occur. These include chronic progressive cutaneous lesions where localised sores (particularly in the anal, genital or oral area) fail to heal and may become larger, deeper and more painful; acute mucocutaneous dissemination where the lesions spread widely over the body and systemic spread where the infection disseminates to the internal organs in particular the bowel and liver.[41] These patients should probably be offered suppressive oral acyclovir as soon as recurrences become either more frequent or more severe than they were previously. It has been suggested that higher doses of the drug (400 mg q.d.s.) are required in immunocompromised patients, however, clinical trials comparing different doses have not been conducted and our experience is that most patients can successfully be suppressed on 200 mg q.d.s.

One of the considerations in regard to long term therapy is cost. The drug is certainly expensive, but I do not believe that withholding therapy on financial grounds is

acceptable. Where finance is an issue either for the individual, the hospital or the Health Authority, initial use of lower doses (e.g. 400 mg b.d. or 200 mg b.d.) may be considered, although this is clearly not the optimum dose. As mentioned above, some patients, particularly those with infrequent recurrences, may successfully be managed by treating each recurrence with either oral or topical acyclovir.

Are there any alternatives to continuous suppressive therapy for patients with frequent recurrences? Several studies have shown that treating each recurrence with acyclovir is less efficacious and less acceptable to patients than suppressive therapy.[42] Another approach of treating patients only at weekends[43] again showed little benefit. One is led to the conclusion that for most patients, at present, there is no acceptable alternative to suppression.

FAILURE TO RESPOND TO ACYCLOVIR THERAPY

The majority of patients with genital herpes treated with acyclovir (either the first attack or suppression of recurrences) respond to therapy, but a small number fail to do so. There are several reasons for failure of therapy including patients not taking the drug in sufficient dose, malabsorption[44] (which may be a particular problem in patients with diarrhoea or those with HIV infection), the condition being due to some other pathology or finally resistance to therapy.

Resistance can result from alteration in two loci on the HSV genome—the regions coding for TK and DNA polymerase enzymes. Viruses with reduced sensitivity to acyclovir (mostly TK negative strains) have been reported, although the number of reports is small and mostly in immunocompromised patients who have received long or repeated courses of therapy.[19,45–47] A handful of reports suggest that resistant isolates may rarely be found in patients with normal immunity—even prior to the administration of acyclovir. It is of interest that recovery of resistant virus may not correlate with the clinical response, and that virus isolated from patients who previously demonstrated resistant strains may be sensitive to subsequent treatment.

Although resistance remains uncommon, vigilance will be required to see that it remains so. It is interesting to postulate 'biological situations' that may be likely to give rise to resistant strains. Repeated courses of treatment using sub-optimal doses (e.g. repeated short courses of topical acyclovir for recurrent oral or genital herpes or long term suppression with once daily dosing) may favour the emergence of such strains, whereas suppressive therapy (in sufficient dose) may prevent their emergence by stopping viral replication. On the other hand, it has been suggested that long term suppression may increase the likelihood of the emergence of drug resistant strains.[48] Viral lesions often contain mixtures of clonal types, most sensitive to acyclovir, and a few possibly resistant, and acyclovir suppression may subsequently suppress 'wild type' virus and allow TK negative mutants to replicate. TK negative strains occur spontaneously and are probably eliminated by the immune system; however, in immunocompromised patients this may not occur. Making sure that all patients, particularly those who are immunocompromised, receive adequate doses of acyclovir to prevent reactivation may be important. Further studies are required to determine whether either repeated courses of oral or topical acyclovir, or long term suppression are important in the subsequent development of resistance.

As the majority of clinically significant strains of resistant virus are TK negative, most will respond to treatment with foscarnet,[19] which as mentioned above acts by selective inhibition of viral DNA polymerase. Unfortunately, foscarnet has to be given intravenously and consequently is less suitable for long term suppression.

OTHER POTENTIAL USES OF ACYCLOVIR

Prevention of genital herpes

Experiments on animals have shown that if acyclovir is administered within 48 h of exposure to HSV, both clinical lesions and latency can be prevented.[49] The potential use of acyclovir in humans for preventive therapy is therefore a possibility. The problem is that the majority of people who contract herpes do so from someone who is unaware that they are infected at the time and consequently a controlled trial of acyclovir in this situation would be difficult to organise. Nonetheless, it would seem worthwhile to treat any individual presenting within 48 h who had been inadvertently exposed to HSV.

Prevention of neonatal herpes

Neonatal herpes is a serious infection resulting in neurological damage or severe disseminated infection in many infants. Without treatment 60% of infants die. The introduction of antiviral chemotherapy (vidarabine and acyclovir) has reduced the mortality. Nonetheless, a considerable number of infants will either die or be left with severe neurological impairment.[50]

The majority of infections are contracted from the mother's birth canal at the time of delivery, usually as a consequence of primary infection in the mother at or around the time of delivery. Caesarean section has been used to prevent neonatal herpes, presumably by allowing the baby to bypass the infected birth canal. In an attempt to identify the women at risk of infecting the baby during delivery screening procedures involving genital examinations and viral cultures have been adopted. However, these have recently come in for severe criticism. The grounds for these criticisms are first that the women at risk are not necessarily identified and that caesarean sections themselves carry a mortality and morbidity.

It has been suggested that suppressive oral acyclovir given during the last 4 weeks of pregnancy to women with a history of recurrent herpes could prevent both neonatal herpes and the need for caesarean section by preventing reactivation of latent infection and the possible development of infectious lesions at the time of delivery.

Stray Pederson[51] has recently reported the results of a study in which pregnant women with a history of recurrent

genital herpes were either treated for the last week of pregnancy with oral acyclovir or received no treatment. There was a statistically significant reduction in the number of caesarean sections in the treated group. These results are unfortunately suspect as the study was open and unrandomised and there was little evidence that the two groups were comparable. Carefully controlled clinical trials will be needed to evaluate this therapy, both in terms of its efficacy and safety. Preliminary analysis of the inadvertent use of acyclovir in pregnancy has not shown any adverse events, although the number of patients reported in these studies has been small.

RECOMMENDATIONS FOR THE MANAGEMENT OF GENITAL HERPES

Acyclovir is the only drug currently available that has any consistent efficacy for the treatment of first attacks and the suppression of recurrent genital herpes and the following treatment recommendations can be made.

Treatment of first attack genital herpes

Acyclovir 200 mg orally 5 times daily for 5 days

1. Treatment should be started as early as possible.
2. There is no benefit in prolonging treatment.
3. Intravenous therapy should be reserved for the most severely ill patients.
4. Patients should be counselled that despite therapy recurrences may occur.

Treatent of recurrent genital herpes

1. Patients with frequently occurring herpes may benefit from long term suppressive oral acyclovir.
2. The decision on who to treat with long term suppression will depend upon a consideration of the frequency, duration and severity of recurrences, any associated psychosexual morbidity and the likelihood of spread to a sexual partner.
3. Suppressive therapy should commence at a dose of 200 mg q.d.s. and be reduced sequentially to the lowest dose at which the patient remains recurrence-free.
4. Suppression should be stopped after 1 year to reassess the necessity to treat.
5. A small number of patients may be adequately managed using repeated courses of topical or oral acyclovir.

Recurrences in immunocompromised patients

1. Severe recurrences should be treated with oral acyclovir 200 mg 5 times daily for 5–10 days.
2. All patients with frequent or severe recurrences should be considered for long suppression to prevent cutaneous or systemic dissemination.

Recurrent genital herpes in pregnancy

1. The efficacy and safety of acyclovir suppression to prevent neonatal herpes is still being assessed.

Acyclovir resistant genital herpes

1. Consider foscarnet.

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Recurrent genital herpes: clinical and virological features in men and women

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Recurrent genital herpes: clinical and virological features in men and women

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SUMMARY One hundred and forty eight patients (69 women and 79 men) with often recurring genital herpes were observed for two months. Men had 119 observed recurrences and women 104. The attacks were significantly longer in men than women (8·7 days *v* 6·6 days, p = 0·005). Significantly more women complained of symptoms, however, and when symptoms occurred they were more severe. Other significant differences between men and women included age (men were older than women); more men had previously had sexually transmitted diseases; more men had infected a sexual partner, but fewer knew the source of their infection; and men had more lesions at each attack. Positive viral culture results were shown to depend on the amount of erythema, the number of lesions, and the presence of vesicles.

Numbers of patients with genital herpes attending sexually transmitted disease (STD) clinics in the United Kingdom (UK) and the United States of America (USA) have increased dramatically in recent years.[1–3] Most of these patients have severe first episode genital herpes, but the proportion attending again with recurrent infection has increased significantly.[4] Although primary attacks last longer and are more severe than recurrences,[5] it is the recurrent nature of the condition that is responsible for the anxiety and psychosexual dysfunction often seen in these patients.[6,7]

Despite many reports on genital herpes, only a handful of studies have looked at the clinical features, viral isolation, and likelihood of transmission in patients with recurrent infection,[5,8–12] and only small numbers of patients were studied in all but one of these studies.[5]

We undertook the study published here to review the natural history of recurrent herpes, to gather information concerning the source and transmission of the infection, to assess the patients' understanding of the condition, and to compare these features in men and women.

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Patients and methods

Patients with recurrent genital herpes who had participated in a trial of suppressive acyclovir treatment were entered into the study. All were aged 19 or over and gave a history of at least six attacks of herpes a year. We used a standardised schedule to record the frequency and severity of previous recurrences and treatments, the source of the infection and whether other sexual partners had been infected, and each patient's knowledge about herpes. We observed patients for two months while they received no treatment. During each recurrence patients were asked to return to the clinic, where a history was taken, clinical features noted, and specimens sent to the laboratory for viral culture. Symptoms were graded on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Statistical tests used included the χ^2 and Mann Whitney U-tests. For ethical reasons homosexual men were not tested for antibodies to human immunodeficiency virus (HIV).

Results

PATIENT DEMOGRAPHY AND HISTORY OF PREVIOUS ATTACKS

The study population comprised 69 women and 79 men; 14 of the men were homosexual and the remaining heterosexual. Table 1 shows that the men were significantly older than the women (mean ages 31·8 *v*

Table 1 *Demographic characteristics and history of attacks in men compared with women with frequently recurring genital herpes. Figures are numbers (percentages) except where otherwise stated.*

	Men (n = 79)	*Women (n = 69)*	*p Value*
Mean (SD) age (years)	31·8 (6·8)	29·1 (6·3)	<0·01
Median (range) duration of attacks (days)	9 (3–35)	7 (3–14)	<0·001
Mean (SD) pain score	1·1 (0·8)	1·7 (0·6)	<0·001
Prodrome never experienced	9 (12)*	10 (15)	NS
Precipitating factors:			
Sexual intercourse	23 (29)	9 (13)	0·02
Stress	29 (37)	31 (45)	NS
Previous sexually transmitted diseases (STDs):			
Non-specific genital infection	33 (42)	11 (16)	<0·005
Gonorrhoea	21 (27)	4 (6)	<0·005
Warts	8 (10)	13 (19)	NS
Syphilis	4 (5)	0	NS
Any STD	51 (65)*	27 (40)†	<0·01

*data missing in one case.
†data missing in two cases.

29·1 years, $p < 0·01$). The median duration of attacks was significantly longer in men (nine days in men *v* seven days in women, $p < 0·001$), but the mean (SD) pain score was higher in women (1·7 (0·57) *v* 1·1 (0·77), $p < 0·001$). Twenty six women identified menstruation as a precipitating factor, and significantly more men than women thought that attacks were associated with sexual intercourse (23 *v* 9, $p = 0·02$).

A history of STDs was more common in men than women. Thirty three men and only 11 women had been treated for non-specific genital infection ($p < 0·005$) and gonorrhoea had occurred in 21 men and only four women ($p < 0·005$). Similar numbers of men and women had received antiviral treatment in the past, the commonest being acyclovir cream.

Seventy two men had experienced penile lesions, and 58 women had a history of vulval attacks. Other genital and perigenital sites, including the perineum, perianal region, natal cleft, buttock, and anus, were affected in a few patients. Extragenital herpes, predominantly orolabial, was reported by 27 men and 21 women.

SOURCE AND TRANSMISSION

Table 2 shows that genital herpes was present in the current sexual partner of 15 men and 11 women. The source of infection was known by 47 men and 58 women ($p = 0·001$). Five of the homosexual men knew the source of infection, compared with 42 of the heterosexual men ($p = 0·05$), but the difference between heterosexual men and women remained significant ($p = 0·01$).

Seventeen men, but only six women, had infected a sexual contact ($p = 0·03$). Fifty six men had informed their current sexual partner of their condition, compared with 32 women ($p = 0·02$).

Table 2 *Source of infection and history of transmission comparing men and women with recurrent genital herpes. Figures are numbers (percentages)*

	Men (n = 79)	*Women (n = 69)*	*p Value*
Infection in current partner	15 (19)	11 (16)*	NS
Source of infection known	47 (60)	58 (84)	0·001
Contact infected by patient	17 (22)	6 (9)	0·03
Current partner informed	56 (71)	32 (46)	0·02

*Data missing in one case

KNOWLEDGE ABOUT HERPES

Fifty men and 48 women said that they had received advice about not having sexual intercourse during attacks. Forty one women considered that cervical cytology was necessary yearly, but 24 did not realise the need for cytology at all.

DOCUMENTED ATTACKS

During the two month observation period, the mean number of attacks was 1·51 in both sexes (range 1–4). The total number of attacks observed was 119 in men and 104 in women. These attacks were confirmed virologically from at least one site in 75 of the attacks in men and in 64 of the attacks in women. The mean time between attacks was 24·7 days in men and 28·5 days in women (not significant). The mean (SD) duration of attacks was 8·7 (5·7) days in men and 6·6 (3·2) days in women ($p = 0·005$).

Symptoms

Table 3 shows that more women than men complained of local symptoms (pain, itching, or dysuria). For example, pain occurred in 54 attacks in women compared with only 43 in men ($p = 0·02$). The systemic symptoms of headache and malaise were also more common in women; malaise was associated with 52 out of 104 of attacks in women compared with only

Table 3 *Symptoms comparing men with women*

Symptoms	No (%) of attacks with symptoms			Mean (SD) symptom score* in attacks with symptoms		
	Men (n = 119)	Women (n = 104)	p Value	Men	Women	p Value
Local:						
Pain	43 (36)	54 (52)	0·02	1·4 (0·6)	1·6 (0·7)	0·04
Itching	51 (43)	63 (61)	0·008	1·5 (0·7)	1·8 (0·8)	0·04
Dysuria	8 (7)	26 (25)	0·002	1·1 (0·4)	1·5 (0·8)	NS
Systemic:						
Fever	18 (15)	9 (9)	NS	1·2 (0·5)	1·0 (0·0)	NS
Headache	15 (13)	24 (23)	0·04	1·1 (0·5)	1·3 (0·4)	NS
Malaise	41 (35)	52 (50)	0·02	1·2 (0·4)	1·1 (0·4)	NS

*Symptoms graded 0 (none), 1 (mild), 2 (moderate), or 3 (severe).

41 out of 119 in men (p = 0·02). In those who had symptoms, the mean symptom scores for pain and itching were significantly higher in the women (p = 0·04).

Signs and virology

One hundred and one attacks in men affected the penis, and 69 attacks in women affected the vulva. Less common sites were the natal cleft, perianal region, suprapubic area, buttock, perineum, and cervix. Two sites were simultaneously affected in four attacks in men and 10 attacks in women. Three or more sites were affected in one attack in only one man.

The mean (SD) number of lesions in men was greater than in women (2·9 (2·41) *v* 2·0 (1·20)), p = 0·001. The number of lesions correlated significantly with a positive viral culture result (p < 0·001), but positive culture results did not depend on the anatomical site of the lesion.

Inguinal lymphadenopathy was present in 27 attacks in men and 29 attacks in women, and as many patients with as without enlarged lymph nodes had positive viral culture results. The degree of erythema (graded 0–3) correlated significantly with a positive viral culture result (p = 0·04), as did the presence of vesicles (p = 0·001). Even at the crusting stage five of 14 lesions yielded positive culture results.

Discussion

This study showed that significantly more women with recurrent herpes suffer from pain, itching, dysuria, headache, and malaise than their male counterparts, and that these symptoms tended to be more severe. As a third of women reported that their attacks were associated with menstruation, some of the symptoms in women could be related to premenstrual and menstrual factors. It is of interest, however, that men had significantly longer attacks than women. HIV infection could be a possible reason for the longer duration of symptoms in men, though this was unlikely to be important in this study as only 14 of the men were homosexual and only a quarter of homosexual men attending this clinic are known to be HIV positive.[13] The differences in symptomatology between men and women are similar to those reported by Corey and colleagues from Seattle.[5]

In this study more women than men knew the source of their infection, but fewer had infected a contact or informed their current sexual partner of their condition. These findings suggest that the women were more careful in the way that they conducted their sexual relationships, but were less open about their condition, perhaps reflecting a fear that disclosure would receive an unsympathetic response from the partner. A surprising feature of this study was the large number of patients who claimed that they had not received advice about abstaining from sexual intercourse during attacks or about the need for cervical cytology. The need to reinforce information to all patients is apparent, particularly to men about transmission and to women about cytology and about risks to neonates.

Men had significantly more lesions at each attack than women. These findings are similar to those of Corey *et al*,[5] though they reported more lesions per episode (7·5 for men, 4·8 for women) than we found. Our findings in this respect agree more closely with those of Guinan *et al*, who found that 78% of women had only a single lesion at each recurrence.[11]

Positive viral culture results were shown to depend on the amount of erythema, the number of lesions, and the presence of vesicles. Other studies have confirmed that the optimum time for taking samples for herpes culture is at the early stages of recurrence, when erythema is at its maximum and vesicles are still present.[5,11] Even at the crusting stage, however, 36% of lesions in our study were culture positive. This suggests that even when crusts are present a viral culture may still be worthwhile and, as such lesions are potentially infectious, patients should be advised to refrain from sexual intercourse until healing is complete. The infection can also be transmitted when

patients are asymptomatic,[14] but this issue was not addressed in our study.

In summary, we have identified the following differences between men and women; women get worse symptoms, but men have longer duration of attacks and more lesions at each attack. Men were more conscious of attacks being provoked by sexual activity, and had previously had a sexually transmitted disease. More women knew the source of their infection, but fewer told or infected a new sexual partner. These factors may be important when diagnosing, treating, and counselling patients with herpes.

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Suppression of frequently recurring genital herpes: acyclovir *v* inosine pranobex

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Suppression of frequently recurring genital herpes: acyclovir *v* inosine pranobex

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SUMMARY The suppressive action of acyclovir and inosine pranobex was compared in a randomised double blind controlled trial in patients with frequently recurring genital herpes. Fourteen patients received acyclovir and 17 inosine pranobex. Treatment continued for 12 weeks. The time to the first recurrence was significantly longer and the frequency of recurrences significantly less in the recipients of acyclovir. No important side effects were noted. It is concluded that acyclovir is the treatment of choice to suppress often recurring genital herpes.

Frequently recurring genital herpes may cause profound emotional and sexual disturbances,[1 2] and until recently little could be done to help. Suppressive treatment with two drugs, acyclovir and inosine pranobex, has, however, been reported to reduce the frequency of recurrences.[3–10] Acyclovir is a specific antiviral compound with pronounced antiherpetic activity,[11 12] and inosine pranobex is reported to have both antiviral and immune potentiating properties.[13 14]

The aim of this study was to compare the suppressive action of the two preparations in a randomised double blind trial in patients with frequently recurring genital herpes.

Patients and methods

We recruited men and women patients who had at least eight recurrences of genital herpes a year. Exclusion criteria were identical to those used in previous studies.[5 6] In addition, patients who had not had a culture positive recurrence in the two months before the onset of treatment were excluded, as were those with a history of gout, hyperuricaemia, or severe atopic eczema. Informed consent was obtained from all the participants.

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The treatment was randomised, double blind, and double dummy. Patients received either active acyclovir and dummy inosine pranobex or active inosine pranobex and dummy acyclovir. The dosage of acyclovir was 200 mg and of inosine pranobex 1 g, each four times a day. Treatment was for 12 weeks. Compliance was assessed by counting the number of tablets missed.

Patients attended every two weeks during the treatment period and once a month for six months after stopping treatment. Additional visits were made during any recurrence. We undertook liver function tests and full and differential blood counts and measured serum concentrations of uric acid, creatinine, urea, and electrolytes at entry and every four weeks during treatment. All information was recorded on a standardised recording schedule.

Statistical tests used included the χ^2, Mann Whitney U, and a log rank test.

Results

PATIENT CHARACTERISTICS

The trial was initially designed to include 100 patients, but after only 32 had been treated some were obviously deriving no benefit from treatment whereas the condition of others had improved considerably. After careful assessment of our previous experience of using suppressive acyclovir,[6] we considered it unethical to continue, and halted the trial prematurely.

One of the 32 patients was lost to follow up after two weeks, and was excluded from the analysis. Table 1

Table 1 *Demographic characteristics of 31 patients with recurrent herpes simplex virus (HSV) receiving one of two treatments*

	Acyclovir (n = 14)	*Inosine pranobex (n = 17)*
Mean (SD) age (years)	34·2 (6·8)	32·3 (6·8)
No of men/women	9/5	6/11
Mean (SD) years with HSV	5·7 (4·7)	5·5 (4·2)
Mean (SD) No of attacks in:		
Previous 12 months	11·8 (3·4)	16·2 (10·6)
Previous 3 months	3·6 (1·8)	4·9 (3·1)
Mean (SD) duration of attacks (days)	6·4 (1·4)	6·8 (4·2)
Mean (SD) % with prodrome	72·1 (34·7)	69·1 (39·1)
No (%) with orolabial HSV	4 (28·6)	4 (23·5)

shows the demographic characteristics of the remaining 31 patients. No significant differences in age, sex, or the frequency, severity, or duration of previous recurrences were seen between patients receiving each treatment.

RECURRENCES DURING TREATMENT

All 17 recipients of inosine pranobex experienced recurrences during treatment, compared with five of the 14 (36%) recipients of acyclovir ($p < 0·001$), each of whom experienced their first recurrences within the first five days. The time to first recurrence was significantly shorter in the recipients of inosine pranobex (see figure; $p < 0·0001$).

Table 2 shows that the mean (SD) number of recurrences in 28 days of treatment was 0·16 (0·28) in patients receiving acyclovir compared with 1·22 (0·8) in those receiving inosine pranobex ($p = 0·0001$).

RECURRENCES AFTER TREATMENT

After stopping treatment the mean (SD) frequency of recurrences was similar in the two treatment groups: 1·03 (0·53)/28 days in those receiving acyclovir compared with 1·0 (0·9)/28 days in those receiving inosine pranobex (table 2).

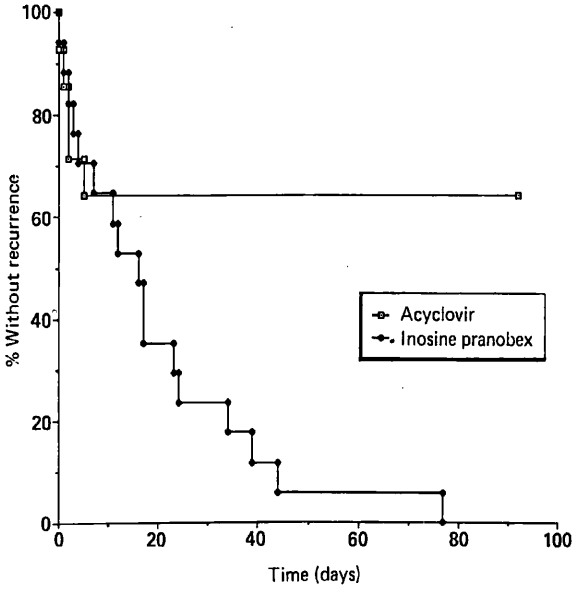

Figure *Time to first recurrence comparing 14 patients receiving acyclovir with 17 receiving inosine pranobex.*

Table 2 *Mean (SD) frequency (number/28 days) of recurrences comparing patients receiving one of two treatments*

	Period of observation	*Acyclovir*	*Inosine pranobex*	*p Value*
Before treatment	2 months	1·3 (0·9)	1·99 (0·76)	NS
During treatment	12 weeks	0·16 (0·28)	1·22 (0·8)	0·0001
After treatment	6 months	1·03 (0·53)	1·0 (0·9)	NS

Before *v* during treatment with acyclovir, $p < 0·005$; during *v* after treatment with acyclovir, $p < 0·001$. Before *v* during treatment and during *v* after treatment with inosine pranobex, not significant.

SAFETY AND COMPLIANCE

No side effects were noted, and the mean number of missed tablets was similar in the two treatment groups.

Discussion

This trial showed that acyclovir is the drug of choice for suppressive treatment of patients with frequently recurring genital herpes. Patients treated with acyclovir showed a significant reduction in the frequency of recurrences, whereas those treated with inosine pranobex continued to have attacks without any apparent reduction. The results of this trial were similar to those of previous trials that compared suppressive acyclovir with placebo.[3-7] In those studies patients treated with acyclovir showed a pronounced reduction in the frequency of recurrences, whereas those who received placebo did not.

The only recurrences in patients receiving acyclovir occurred within the first five days of treatment, which suggests that viral reactivation of the virus before the onset of treatment was responsible for these outbreaks. Early attacks can be prevented by giving a therapeutic course of acyclovir (200 mg five times a day for five days) before starting suppression.[5,6]

A previous study showed that inosine pranobex was inferior to acyclovir for treating first attacks of genital herpes,[15] and the study published here raises the question of whether inosine pranobex has any remaining role in treating genital herpes.

Acyclovir is therefore the drug of choice both for treating the first attack and for suppressing recurrences of genital herpes. Any new antivirals will have to be compared with it.

We thank Mr G Pinto Basto for help with the virology.

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Prophylaxis for Genital Herpes
Should it be Used Routinely?

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1. Treatment Options for Genital Herpes

Many patients with genital herpes have recurrences, and although these are usually less severe and of shorter duration than the first episode, they often cause physical discomfort, psychological morbidity, and interfere with normal sexual relations (Marks & Patrick 1983; Sacher 1983). The frequency of recurrences is variable; many patients only have occasional episodes, whereas others have 12 or more a year (Mindel et al. 1988).

Numerous therapies have been recommended for herpes (table I), ranging from conventional antiviral drugs such as vidarabine (adenine arabinoside, Ara-A) [Adams et al. 1976], idoxuridine (iododeoxyuridine) [Hutfield 1964; Silvestri et al. 1982] and aciclovir (Bryson et al. 1983; Corey et al. 1982, 1983; Douglas et al. 1984; Fiddian et al. 1983; Halsos et al. 1985; Kinghorn et al. 1983, 1985; Mertz et al. 1984; Mindel et al. 1982, 1984; Nilsen et al. 1982; O'Brien & Campoli-Richards 1989; Reichman et al. 1984; Straus et al. 1984; Thin et al. 1985) to vitamins, essential amino acids and a range of less conventional remedies including ginseng and aloe vera extracts (Mindel & Sutherland 1983). However, the only drug that has been shown in a series of clinical trials to have any efficacy for the treatment of genital herpes is aciclovir (Bryson et al. 1983; Corey et al. 1982, 1983; Douglas et al. 1984; Fiddian et al. 1983; Halsos et al. 1985; Kinghorn et al. 1983, 1985; Mertz et al. 1984; Mindel et al. 1982, 1984; Nilsen et al. 1982; O'Brien & Campoli-Richards 1989; Reichman et al. 1984; Straus et al. 1984; Thin et al. 1985).

2. Aciclovir

Aciclovir is a nucleoside analogue, whose activity depends on suppression of DNA synthesis. Aciclovir competes as a substrate with the deoxynucleosides and is selectively phosphorylated by viral thymidine kinase (Elion 1982); therefore, the drug targets infected as opposed to uninfected cells (fig. 1). Aciclovir monophosphate is convered into di- and triphosphate by cellular enzymes (Miller & Miller 1980). Aciclovir triphosphate is the active metabolite of the drug and competes selectively with the deoxynucleoside triphosphates for viral DNA polymerase (Furman et al. 1979) and also by direct inhibition of viral DNA polymerase (Elion 1982). The substrate activity of aciclovir triphosphate is self limiting and results in DNA chain termination (Furman et al. 1979).

2.1 Effect on Recurrent Attacks

In the first attack of genital herpes aciclovir significantly reduces the duration of viral shedding, the duration of symptoms and the time to healing (Bryson et al. 1983; Corey et al. 1982, 1983; Fiddian et al. 1983; Kinghorn et al. 1983; Mertz et al. 1984; Mindel et al. 1982; Nilsen et al. 1982). Treating each recurrence with aciclovir (either oral or topical) is less successful (Corey et al. 1982; Nilsen

Table I. Suggested treatments for genital herpes

Miscellaneous
Topical surfactants
  Ether
  Chloroform
  Nonoxinol 9
  Thymol
Photodynamic inactivation
  Neutral red
  Proflavine
Lysine (L-lysine)
2′-Deoxy-*D*-glucose
Zinc
Lithium
Dimethylsulfoxide (DMSO)
Povidone iodine
Oral and/or topical antibiotics
Topical steroids
Methyl alcohol (methanol)
Gentian violet
Copper sulphate
Potassium permanganate
Boric acid ointment
Urea
Tannic acid ointment
Tocopherol (vitamin E), ascorbic acid (vitamin C), and cyanocobalamin (vitamin B12)
Ginseng
Aloe vera extracts
Red algae
Laser therapy
Cryotherapy

Antivirals
Vidarabine (adenine arabinoside, Ara-A)
Aciclovir
Idoxuridine (iododeoxyuridine)
Foscarnet (phosphonoformate)
Brivudine (bromovinyldeoxyuridine, BVDU)

Immune modulators
Interferons
Levamisol
Inosine pranobex (metisoprinol methisoprinol, 'Isoprinosine')
Thymopentin (TP5)
Vaccines
  BCG
  Smallpox
  Polio
  Influenza
  Yellow fever

et al. 1982; Silvestri et al. 1982). The drug certainly reduces the duration of viral shedding; however, the effect on healing and symptoms is minimal. While early treatment, particularly during prodromal symptoms, may be more efficacious (Reichman et al. 1984), not all patients have prodromal symptoms, and many have prodromal symptoms and then do not develop a full-blown outbreak (Mindel et al. 1988a). Nonetheless, some patients, particularly those with infrequent recurrences, may be managed successfully with intermittent oral or topical aciclovir.

An alternative approach is to use continuous oral aciclovir to suppress or prevent recurrences. Numerous double-blind placebo-controlled trials for periods ranging from 12 weeks to 2 years have shown that this form of treatment is highly successful for patients with frequent recurrences (Douglas et al. 1984; Halsos et al. 1985; Kinghorn et al. 1985; Mertz et al. 1988; Mindel et al. 1984; Straus et al. 1984; Thin et al. 1985). Several studies have shown that continuous aciclovir is superior to intermittent therapy (Mertz et al. 1988; Sacks et al. 1988; Straus et al. 1986). Most patients on suppressive aciclovir have either no recurrences or very few minor episodes (fig. 2).

These studies have raised several important issues, including: how long should treatment continue, what is the ideal dosage, is the drug safe, and most importantly, which patients should be treated? Several studies have provided some answers concerning the duration of treatment. The efficacy of

suppressive aciclovir appears to be undiminished in studies over 1 and 2 years, and an additional benefit is that the frequency of recurrences after stopping prolonged therapy is significantly reduced (Mindel et al. 1988b; Straus et al. 1988). It would therefore seem sensible to stop treatment after 1 year and ascertain whether the patient is still having frequent recurrences, and if so to restart treatment.

2.2 Dosage

In regard to dosage, over 80% of patients will remain recurrence free on 200mg 4 times daily or 400mg twice daily (Mindel et al. 1988b). However, at least one study has shown that recurrences are statistically significantly more likely to occur on

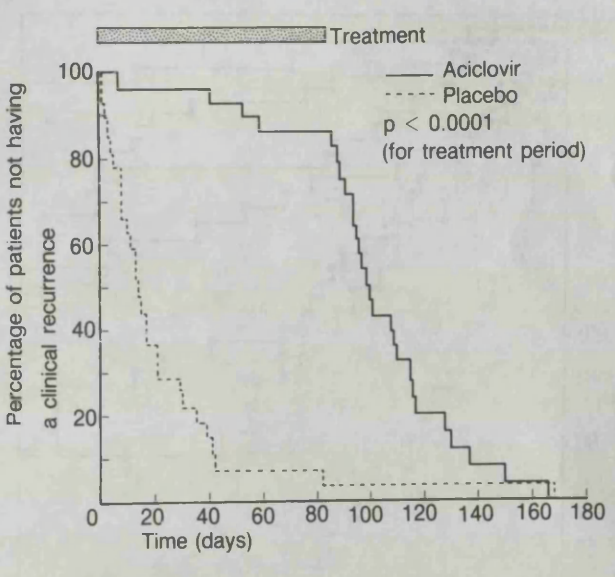

Fig. 2. Time to first recurrences in patients with frequently recurring genital herpes, comparing patients receiving aciclovir or placebo (from Mindel et al. 1984, with permission).

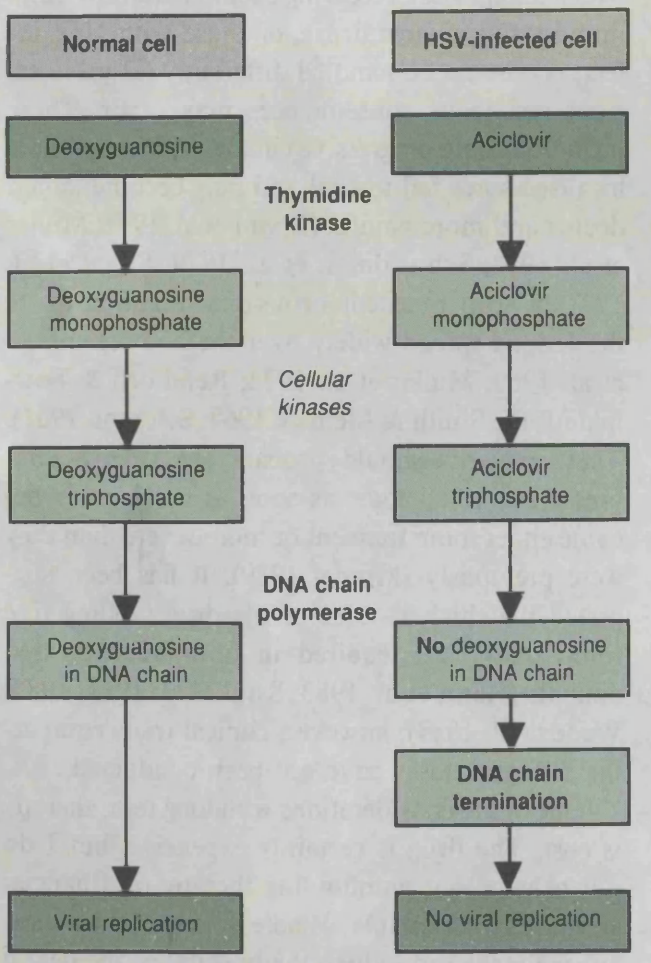

Fig. 1. Mechanism of action of aciclovir. HSV = herpes simplex virus.

400mg twice daily than 200mg 4 times daily (Mindel et al. 1988b). Patients receiving lower doses (e.g. 200mg 3 times daily or 200mg twice daily) are more likely to have a recurrence (approximately 20% at 3 months), and those on once-daily therapy (800mg, 400mg, 200mg) have a 40 to 60% chance of a recurrence within 3 months (Mindel et al. 1988b) [see fig. 3]. Therefore, it would seem sensible to commence therapy on 200mg 4 times daily and reduce the dose to 200mg 3 times daily and then 200mg twice daily over the coming months if there are no further recurrences.

2.3 Adverse Effects

Adverse effects of oral aciclovir are unusual and mostly unimportant, and include nausea, skin rashes, headache, fever and malaise (Tilson 1988). More serious adverse effects, including encephalopathic changes (Wade & Meyers 1983) and transient renal tubular abnormalities (Mindel et al. 1982; Weller et al. 1983), have been reported on very rare occasions with intravenous aciclovir but not with the oral preparation. Long term safety with suppressive oral aciclovir appears to be excellent (Mertz et al. 1988; Mindel et al. 1988b; Straus et al. 1988).

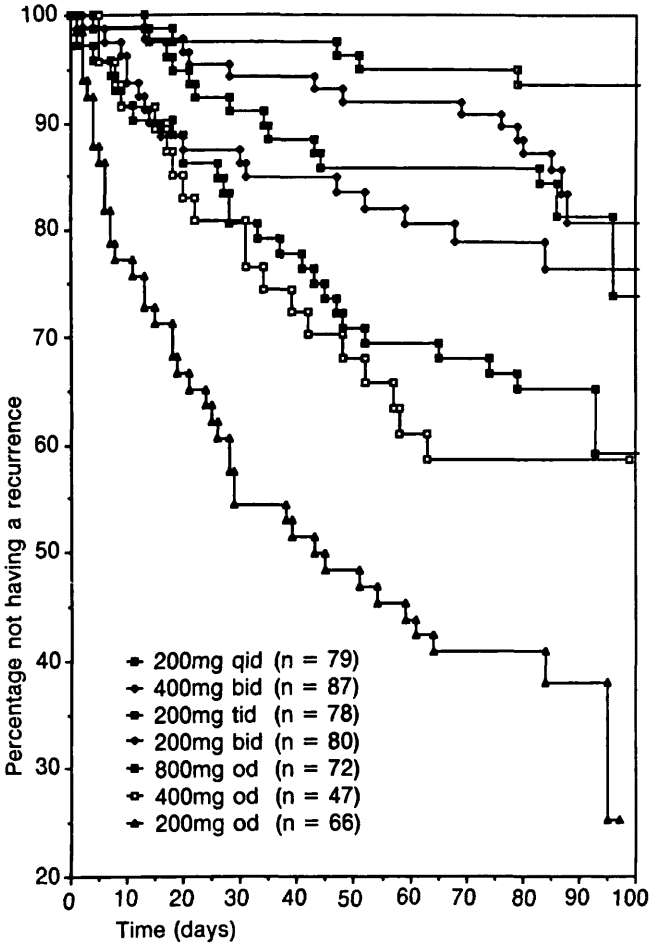

Fig. 3. Time to first clinical recurrence comparing different dosages of oral aciclovir (from Mindel et al. 1988b, with permission).

2.4 Who to Treat?

Deciding which patients need treatment is more difficult. Patients with 12 or more recurrences a year each lasting 10 to 14 days certainly require treatment, whereas those with one minor recurrence a year do not. Where one draws the line between these two extremes is a matter of clinical judgement and discussion between the patient and the physician. There are several factors that should be taken into consideration when making this decision, including the frequency and duration of recurrences, the severity of symptoms (including local pain and discomfort, neuralgia and malaise), any associated psychological or psychosexual problems, the type of relationship the person is in, and finally the risk of spread to a sexual partner.

Considering all of these factors, the easiest to assess are the frequency, duration and severity of recurrences. My own belief is that patients with 8 or more recurrences per year generally require suppression, whereas those with fewer than 6 probably do not. Between 6 and 8 it is important to assess the duration and severity of recurrences and the other factors mentioned above. We have found that the easiest way of doing this is to follow patients prospectively from the time of presentation until the observer is confident, firstly that the patient does indeed have herpes, and secondly that the recurrences are sufficiently frequent or severe to warrant therapy. Patients who present with primary herpes should not be given suppressive aciclovir until sufficient time has passed to assess that the patient is having at least 6 recurrences per year.

Patients who are immunosuppressed (e.g. those with a malignancy, receiving chemotherapy or other immunosuppressive drugs, or those with HIV infection) should be handled differently, as more serious cutaneous consequences may occur. These include chronic progressive cutaneous lesions where localised sores fail to heal and may become larger, deeper and more painful (Logan et al. 1971; Muller et al. 1972; Schneidman et al. 1979; Siegal et al. 1981) or acute mucocutaneous dissemination where the lesions spread widely over the body (Lynfield et al. 1969; Muller et al. 1972; Rendtorff & Fowinkle 1965; Smith & Melnick 1962; Solomon 1961). These patients should probably be offered suppressive oral aciclovir as soon as recurrences become either more frequent or more severe than they were previously (Mindel 1989). It has been suggested that higher doses of the drug (400mg five times daily) are required in immunosuppressed patients (Hann et al. 1983; Saral et al. 1981, 1983; Wade et al. 1984); however, clinical trials comparing different doses have not been conducted.

One of the considerations with long term therapy is cost. The drug is certainly expensive, but I do not believe that withholding therapy on financial grounds is acceptable. Where finance is an issue either for the individual, the hospital or the health authority, initial use of lower doses (e.g. 400mg twice daily, or 200mg twice daily) may be consid-

ered, although this is clearly not the optimum dose. As mentioned above, some patients may successfully be managed by treating each recurrence with either oral or topical aciclovir.

2.5 Drug Resistance

Occasionally patients may fail to respond to suppressive therapy. There are several reasons for this, including patients not taking the drug or taking an insufficient dose, malabsorption (Mindel & Carney 1988), the condition being due to some other pathology, and finally, resistance to therapy. Resistance can result from alteration in 2 loci on the HSV genome – the regions coding for thymidine kinase (TK) and DNA polymerase enzymes (Coen & Schaffer 1981; Field & Darby 1980; Schnipper & Crumpacker 1980). Viruses with reduced sensitivity to aciclovir (mostly TK negative strains) have been reported, although the number of reported resistant isolates is small and mostly in immunocompromised patients who have received long or repeated courses of therapy (Burns et al. 1982; Chatis et al. 1989; Crumpacker et al. 1982; Erlich et al. 1989; Norris et al. 1988; Schinazi et al. 1986; Sibrack et al. 1982; Wade et al. 1983). A handful of reports suggest that resistant isolates may rarely be found in patients with normal immunity even prior to the administration of aciclovir (McLaran et al. 1983; Straus et al. 1984). It is of interest that recovery of resistant virus may not correlate with poor clinical response and that virus isolated from patients with previously demonstrated resistance strains may be sensitive to subsequent treatment.

It has recently been suggested that the widespread use of suppressive aciclovir may encourage the emergence of resistant strains (Hirsch & Schooley 1989). Viral lesions often contain complex mixtures of clonal types, the majority sensitive to aciclovir but some drug resistant. These drug-resistant mutants may normally be at a selective disadvantage, but in the presence of aciclovir may compete successfully with drug-sensitive strains. On the other hand suppressive aciclovir may discourage the emergence of resistant mutants which occur particularly when viral titres are high (that is, in the absence of antiviral chemotherapy). Also, drug-resistant mutants have occasionally been recovered from individuals never exposed to aciclovir (McLaran et al. 1983; Straus et al. 1984). Finally, as mentioned above, individuals with a previously treated resistant virus may on subsequent recurrence be found to have a sensitive isolate. It is of interest that clinically resistant mutants have thus far only been reported in immunosuppressed patients and perhaps this issue is of no relevance in those with normal immunity. It remains to be determined whether drug-resistant mutants can be transmitted and whether they can establish ganglionic latency. Further studies are required to address these issues.

3. Conclusion

In summary, long term suppressive oral aciclovir is a highly effective and safe treatment for patients with frequently recurring genital herpes. It should be reserved for those with 6 or more attacks per year. Treatment should commence at a dose of 200mg four times daily and should be reduced sequentially to the lowest effective dose. After one year, treatment should stop in order to ascertain whether the recurrences are still sufficiently frequent to warrant further suppression. Immunosuppressed patients should also be considered for therapy and closely monitored for the possible emergence of drug-resistant mutants.

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