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Limited Value of Acyclovir in the Treatment of Uncomplicated Herpes Zoster: A Placebo-controlled Study

Summary: The effect of intravenous acyclovir (at a dosage of 30 mg/kg per day for five days) on uncomplicated herpes zoster was investigated in 51 patients in a double-blind study. Although existing herpes zoster lesions tended to heal more rapidly and new lesions ceased to appear somewhat earlier in the acyclovir group, these differences were not statistically significant. During treatment, patients on acyclovir had significantly lower pain scores than placebo-treated patients. At follow-up, however, there was no difference between the two groups. Complications of herpes zoster occurred only in the placebo groups (generalization in two and keratitis in two cases). With the possible exception of trigeminal zoster or severe pain, acyclovir seems to offer little benefit for immunocompetent patients with herpes zoster.

Zusammenfassung: *Begrenzter Wert von Acyclovir in der Therapie des unkomplizierten Herpes zoster: Eine Plazebo-kontrollierte Studie.* Die Wirkung von Acyclovir intravenös (in einer Dosis von 30 mg/kg pro Tag für fünf Tage) auf den unkomplizierten Herpes zoster wurde bei 51 Patienten in einer Doppelblindstudie geprüft. Obwohl bei den vorhandenen Herpes zoster-Läsionen eine Tendenz zu rascherer Heilung bestand und das Neuauftreten von Läsionen in der Acyclovir-Gruppe etwas früher aufhörte, waren diese Unterschiede statistisch nicht signifikant. Unter der Behandlung war die Schmerz-Score bei Patienten, die Acyclovir erhielten, signifikant niedriger als bei Patienten, die Placebo erhielten. Bei der Verlaufsbeurteilung fanden sich zwischen den Gruppen jedoch keine Unterschiede. Zu Komplikationen des Herpes zoster kam es nur in der Plazebo-Gruppe (in je zwei Fällen Generalisation und Keratitis). Mit der möglichen Ausnahme des Zoster im Trigeminus-Bereich oder starker Schmerzen scheint Acyclovir bei immunkompetenten Patienten mit Herpes zoster nur von geringem Wert zu sein.

Introduction

Acyclovir is a new antiviral drug with activity against Varicella zoster virus *in vitro* (1). In the present study, the value of acyclovir in the treatment of uncomplicated herpes zoster was assessed.

Patients and Methods

In the period from January 1981 to January 1983, all patients with a clinical diagnosis of shingles who presented within 72 hours after the onset of the rash were entered into the study. Exclusion was made for neurologic or ocular complications of herpes zoster, granulocyte counts below 0.1×10^9/l, chemotherapy for cancer and pregnancy. After informed consent was obtained, the patients were randomly allocated to receive either acyclovir 10 mg/kg (= 0.4 ml/kg) or placebo (0.4 ml/kg) at eight hour intervals, 15 doses in all. In the first nine patients the drug or placebo was administered by intravenous injection, but when it became known that the administration of acyclovir in this way led to phlebitis and elevation of serum creatinine (2), the required dose was diluted in a volume of at least 100 ml and given over 30–60 min as side-infusion to a rapidly flowing (about 250 ml in 60 min) infusion of saline or 5% glucose. If necessary, the dose was adjusted to renal function according to the scheme proposed by *Blum* et al. (3). No further treatment for herpes zoster was given. Analgesics (initially paracetamol) were prescribed when the patients asked for pain relief. The presence or absence of papules, pustules, ulcerations, crusts or healed lesions, fever, pain (scored as none, slight, moderate or severe by questioning the patient), change of pain (scored as increased, unchanged or decreased) and use of analgesics were recorded daily during the course of the treatment, and approximately ten days after termination of the treatment, by one of us who was unaware of the randomization code. Hemoglobin, leukocytes and platelets, as well as liver enzymes and serum creatinine, were checked before, during and after treatment.

Virology: Swabs from skin lesions were taken from all patients for viral culture. For transport the specimens were held in Gly medium and then cultured by inoculation onto human fetal diploid fibroblasts. The presence of antibodies to herpes zoster virus in serum was demonstrated with an immune adherence hemagglutination test (4).

Statistical analysis: Wilcoxon's two-sample test was used for the statistical analysis. Skin lesions, pain score and analgesic use in the two groups were compared by computing the areas under the curves.

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Table 1: Characteristics of the patients.

	Placebo	Acyclovir
Number of patients	24	26
Male	12	16
Female	12	11
Age (median [range])	69 (20–89)	59 (12–87)
Underlying disease	1*	4**
Duration of symptoms until onset of rash (hours; median [range])	50 (1–120)	23 (0–120)
Time between onset of rash and start of therapy (hours; median [range])	36 (12–72)	25 (6–72)

* Renal transplant;
** Two cases of renal transplantation, one of cured Hodgkin's disease and one of chronic lymphatic leukaemia.

Results

Fifty-one patients were enrolled in the study. Forty-two of these patients were referred by their general practitioner. All but two of the patients were examined by one of the two physicians who conducted this clinical trial. One patient was not evaluable due to lack of follow-up data, and all but one of the patients were hospitalized. Placebo was given to 24 and acyclovir to 26 patients. There were no statistically significant differences as to sex, age, underlying disease duration of symptoms, or time elapsed between the onset of the rash and the start of treatment (Table 1), although the patients in the acyclovir group had a shorter duration of complaints than those in the placebo group. On entry into the trial, the localization and extension of the rash, pain score and use of analgesics did not differ significantly. However, the higher number of patients with trigeminal zoster in the acyclovir group may be important. Comparison of the patients with trigeminal zoster with the other patients, regardless of treatment group, showed that the former had less pain on Day 4 ($p = 0.04$), the papules disappeared earlier ($p = 0.002$) and crust formation and healing were faster ($p = 0.02$). This accelerated recovery in trigeminal zoster patients was previously described by *Wildenhoff* et al. (5).
The evolution of the skin lesions did not differ greatly be-

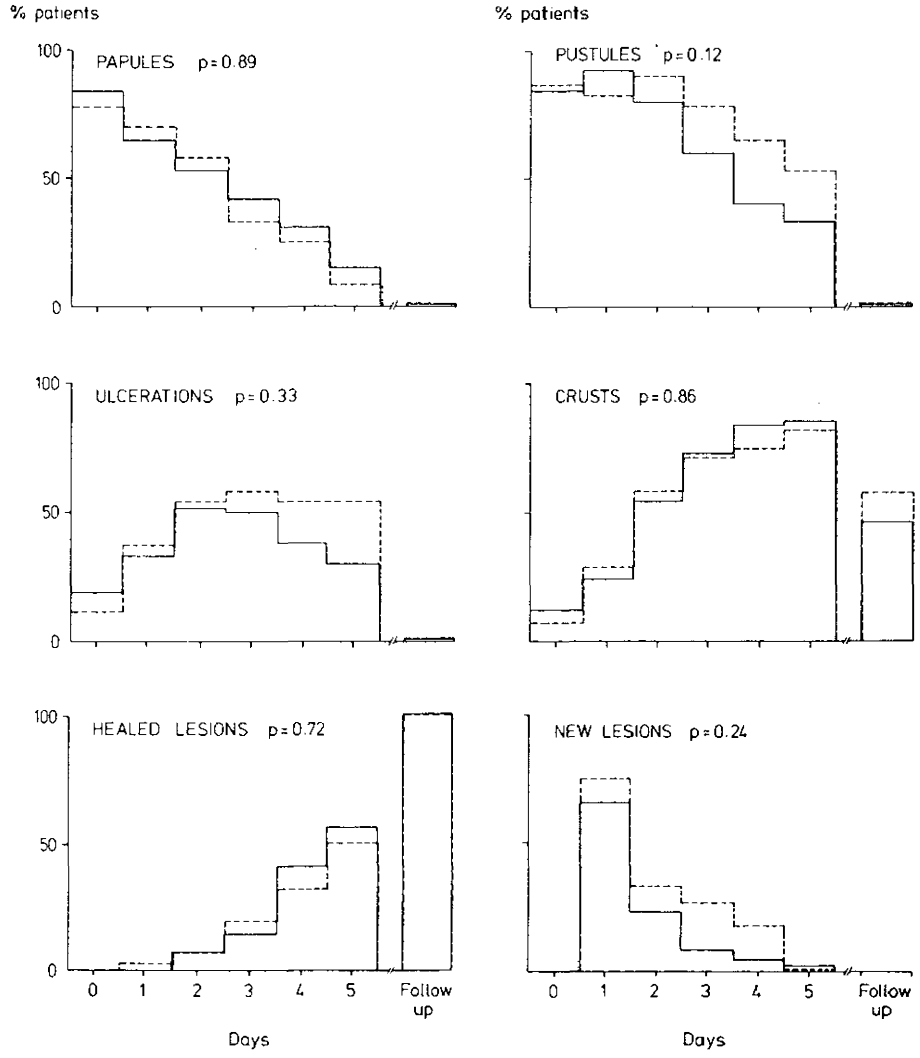

Figure 1: Evolution of the skin lesions in the patients on acyclovir (——) and in the placebo group (- - - -). The percentage of patients with the indicated lesion is shown on the y axis.

Table 2: State of the disease at enrollment in the trial.

	Number of patients	
	Placebo	Acyclovir
Localization		
Trigeminal nerve	5	10
Cervical	7	1
Thoracic	10	12
Lumbar	2	2
Sacral	0	1
Extension of the disease		
Scanty discrete	2	6
Profuse discrete	3	1
Semi-confluent	15	17
Confluent	4	2
Pain		
None	7	10
Slight	5	8
Moderate	7	4
Severe	5	4
Use of analgesics	5	4
Fever (≥ 37.5° C)	14	13

tween the acyclovir and placebo groups (Figure 1). Papules regressed at the same rate; pustules and ulcerations disappeared more rapidly in the acyclovir group, but this difference was not statistically significant. Crusts appeared and lesions healed at the same time in both groups. New lesions ceased to appear earlier in the acyclovir group: on the mean, no new lesions were observed after 2.77 days (SD = 0.99) in the acyclovir-treated patients and 3.42 days (SD = 1.32) in the placebo-treated patients ($p = 0.13$).

Patients on acyclovir had a significantly lower mean pain score than patients receiving placebo (Figure 2A) ($p = 0.05$). The difference was most marked on Days 3, 4 and 5. This finding corresponds with a larger proportion of patients already indicating decrease of pain already on Day 2 in the acyclovir group (Figure 2B), but after about the tenth day after termination of the treatment, there was no difference. Correspondingly, less analgesics were used in the acyclovir group (Figure 2C; $p = 0.06$).

Complications of herpes zoster occurred only in the placebo group and concerned two patients with keratitis, which is a complication of trigeminal zoster, and two patients with generalization of the herpes zoster to other skin areas. Thus, two of the five patients who had trigeminal zoster and were on placebo developed keratitis as opposed to none of ten patients with trigeminal zoster on acyclovir ($p = 0.19$) (Fisher's exact test).

Serious side-effects of treatment were not encountered: phlebitis at the infusion site was seen in three acyclovir and four placebo recipients. All three cases of phlebitis occurred in the period during which acyclovir was given as intravenous injection. No differences were observed in either group as to changes in the serum creatinine level during the administration of acyclovir or placebo.

There was no doubt concerning the diagnosis of herpes zoster in any of the patients. The clinical diagnosis was confirmed in nine patients by both serology (four-fold rise in titer) and culture, in 25 by serology and in two by culture alone. In nine patients the diagnosis was not confirmed by either of these methods, and for five patients such data were lacking. No effect of acyclovir on antibody response was found.

Discussion

In this study, slight and statistically non-significant differences in the evolution of the skin lesions were found be-

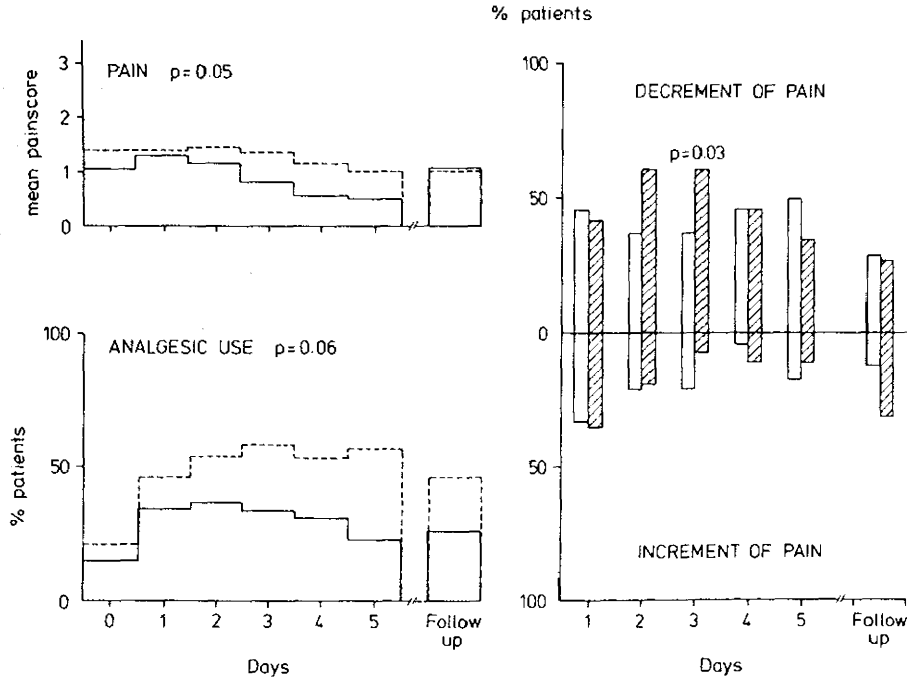

Figure 2: Mean pain score (A), percentage of patients reporting a decrease or increase of pain (B) and percentage of patients using analgesics (C) for the acyclovir-treated patients (—— and ▨) and placebo-treated patients (- - - - and □).

tween the acyclovir group and the placebo group. The appearance of new lesions ceased on average 15 hours earlier in the acyclovir than in the placebo group, and regression of the skin lesions was seen at an earlier stage in the acyclovir group.

A significant but transient decrease in pain during treatment with acyclovir was seen, but after treatment there was no difference between the two groups. The somewhat earlier entrance into the study of the patients alotted to the acyclovir treatment can be a disadvantage for acyclovir: the patients have not yet reached the height of the disease, in contrast to the patients in the placebo group. On the other hand, the higher incidence of rapidly healing ophthalmic zoster (5) and the somewhat lower age in the acyclovir group could have had a favourable impact on healing in this group.

Complications accompanying herpes zoster only occurred in the placebo group. Generalization, which is not a severe complication in immunocompetent patients, was seen twice. The severe complication, keratitis, was also seen twice. This complication did not occur in the acyclovir group despite the relatively large number of patients with trigeminal zoster in this group. *Juel-Jensen* et al. (6), using the same dose of acyclovir, also observed that none of their patients with ophthalmic zoster and on acyclovir developed complications, whereas three of the four patients on placebo developed complications.

The side-effects of acyclovir were minimal in the present series; we did not encounter the high incidence of renal toxicity reported by *Bean* et al. (7), who used the same intravenous dose of acyclovir.

The results of the present study are less favourable than those reported by *Peterslund* (8), who used a dose of 15 mg/kg per day in a series of 56 patients and reported more rapid healing of skin lesions and less pain. *Bean* et al. (7) made similar findings in a smaller group of patients (19 on acyclovir, ten on placebo) treated with a high dose of acyclovir (500 mg/m^2). Like us, these authors saw recurrence of pain after acyclovir was discontinued. In a study comprising 37 patients, *McGill* et al. (9) found accelerated healing of skin lesions in acyclovir-treated patients (15 mg/kg/day) but no statistically significant effect on the pain during the acute phase of the disease or at three months.

In view of the small differences found in our study and in the published series (6–9), we conclude that except perhaps in patients with trigeminal zoster or severe pain, acyclovir offers minimal benefit, even when administered intravenously to immunocompetent patients.

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