MEDICAL TREATMENT OF CHRONIC INFLAMMATORY BOWEL DISEASES

clinical and pharmacokinetic aspects, with emphasis on 5-aminosalicylic acid delivering drugs

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een wetenschappelijke proeve op het gebied van
de medische wetenschappen, in het bijzonder de geneeskunde

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Katholieke Universiteit te Nijmegen,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op
maandag 29 april 1991
des namiddags te 1.30 uur precies

door

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geboren op 26 januari 1953
te Eindhoven

1991
druk: ICG Printing BV, Dordrecht

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The studies presented in this thesis were perfomed in the Division of Gastrointestinal and Liver Diseases (Head: Dr. J.H.M. van Tongeren), Department of Internal Medicine, University Hospital Nijmegen, The Netherlands.

Part of these studies were supported by grants of Kabi Pharmacia (Uppsala, Sweden).

The financial support by Kabi Pharmacia Nederland BV and Glaxo Nederland BV for the printing of this thesis is gratefully acknowledged.

aan mijn ouders

aan Herlin

CONTENTS

CHAPTER 1

INTRODUCTION

Sulphasalazine (salicylazosulphapyridine) and corticosteroids have been used extensively in the treatment of ulcerative colitis and Crohn's disease. Many therapeutical trials have been performed, showing effectivity of both drugs in active ulcerative colitis and active Crohn's disease, and relapse preventing properties of sulphasalazine in quiescent ulcerative colitis.

Still, some questions as to the optimal use of both drugs, single or combined, remain unanswered. To date, the additive effect of prednisone to sulphasalazine in patients with active Crohn's disease has not been defined.

The appreciation of the fact that 5-aminosalicylic acid (5-ASA) is the active moiety of sulphasalazine, whereas sulphapyridine is responsible for the majority of the side effects, has led to the development of new, merely 5-ASA containing drugs. As all these drugs have different mechanisms for the release of 5-ASA, comparative pharmacokinetic studies are necessary to define their possible role in the treatment of chronic inflammatory bowel diseases in different locations and under different circumstances, for instance normal and accelerated intestinal transit.

Moreover, clinical trials are needed to demonstrate the efficacy and safety of the new 5-ASA containing drugs in comparison with placebo and of course sulphasalazine, the mainstay of treatment up till now.

The yardstick for measuring disease activity, and, consequently, therapeutic effect in the two inflammatory bowel diseases is still subject to debate. In Crohn's disease, several clinical activity indices, composed of a number of objective and sometimes subjective data are available. Apart from the fact that no agreement exists about the optimal activity index, they are too complicated to be used in daily practice. Several studies have shown that the serum levels of some acute phase reactants reflect the severity of inflammation of the bowel, and this might provide a simple and easily obtainable substitute for the more cumbersome clinical activity indices.

Aim of this study

The aim of this study was to investigate some unexplored areas in the medical treatment of chronic inflammatory bowel disease. A general survey of our knowledge of epidemiology, etiology, measurement of disease activity, medical treatment and prognosis of ulcerative colitis and Crohn's disease is given in Chapter 2. In Chapter 3 a clinical trial comparing the therapeutic effect of sulphasalazine plus prednisone with sulphasalazine plus placebo in patients with active Crohn's disease is described. In Chapter 4 the value of the determination of the acute phase reactants orosomucoid and C-reactive protein in the measurement of the disease activity of Crohn's disease is investigated.In Chapters 5, 6 and 7 the disposition of sulphasalazine and the sulphapyridine-free, 5-ASA containing drugs olsalazine (Dipentum^{R}), Pentasa^{R}, Asacol^{R} and Salofalk^{R} is investigated in normal volunteers without diarrhoea, healthy volunteers with drug induced diarrhoea and patients with inflammatory bowel disease, with and without diarrhoea.

In Chapter 8 the efficacy and safety of sulphasalazine and olsalazine are compared in patients with active ulcerative colitis, and in Chapter 9 a comparative study of the relapse-preventing properties and safety of these two drugs in patients with quiescent ulcerative colitis is described.

CHAPTER 2

INTRODUCTORY REMARKS ABOUT THE EPIDEMIOLOGY, AETIOLOGY, MEASUREMENT OF DISEASE ACTIVITY, MEDICAL TREATMENT AND PROGNOSIS OF ULCERATIVE COLITIS AND CROHN'S DISEASE

An expanded version of this paper has been accepted for publication in Chirurgische Gastroenterologie - Interdisziplinäre Gespräche

INTRODUCTION

Ulcerative colitis and Crohn's disease are chronic inflammatory bowel diseases of unknown origin, which can be active for many years. Often a distinction between them can be made on the basis of certain features, but sometimes it is not possible to classify a patient immediately as having either disease. In these cases the nature of the disease becomes evident only after a course of time, and sometimes not at all. A common feature of both diseases is their tendency to chronicity with fluctuating disease activity, hampering daily life in varying degrees. Although this regularly leads to severe somatic and psycho-social disability, both diseases run a rather mild course in most patients, allowing a more or less normal life (1,2).

EPIDEMIOLOGY

Crohn's disease and ulcerative colitis are prone to occur at early adult age (between 15 and 40 years). In patients attending the Nijmegen University Hospital the incidence is low above the age of 40 (3), but in other studies a second incidence peak is detected around the age of 70, both for ulcerative colitis and for Crohn's disease (4,5). There is no clear sex predisposition.

The incidence rates of ulcerative colitis vary in several studies from the western world from 3 to more than 10 per 100,000, without a change in the last few decades. Prevalences range from 40 to 120 per 100,000 (6). In contrast to ulcerative colitis the incidence rates of Crohn's disease show a clear tendency to increase, probably only partly attributable to improved diagnostic tools (see Figure 1). The prevalence varies from 26 to 75 per 100,000 (22). The incidence rates of both diseases are said to be higher for Jews than for other populations, but the figures reported from Israel are lower than from other western countries (23).

AETIOLOGY

In spite of numerous hypotheses about possible causative factors and mechanisms the aetiology of Crohn's disease and ulcerative colitis remains unclear.

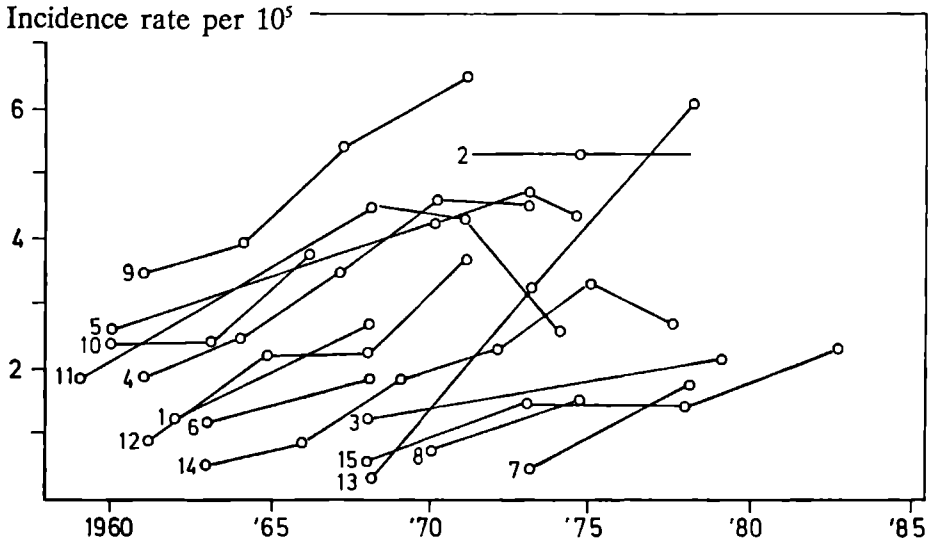

Figure 1. *Incidence rates of Crohn's disease since 1960 in different locations: 1 = Basel, Switzerland (7); 2 = North Tees, UK (8); 3 = Faroe Islands, DK (9); 4 = Stockholm, Sweden (10); 5 = Cardiff, UK (11); 6 = Clydesdale, UK (12); 7 = Beer Sheva, Israel (13); 8 = Tel Aviv, Israel (14); 9 = Malmö, Sweden (15); 10 = Uppsala, Sweden (16); 11 = Scotland, UK (17); 12 = Nottingham, UK (18); 13 = Blackpool, UK (19); 14 = Copenhagen, DK (20), 15 = Scotland, UK (21).* Modified figure from Binder V, Schweiz Med Wschr 1988; **118:** 738-42, copied with permission of the editor.

Genetic factors

Chronic inflammatory bowel diseases occur more often among relatives of patients than in the general population: 10-15% in case of ulcerative colitis and 0-30% in case of Crohn's disease (24-26). Sometimes a relative of a patient with Crohn's disease has ulcerative colitis, and vice versa. The genetic relationships do not follow simple mendelian rules. Possibly genes on multiple loci play a role. No consistent relationship has been found between blood groups or HLA-types and the occurrence of both diseases (27).

Infectious factors.

Both ulcerative colitis and Crohn's disease show a close resemblance with certain bowel inflammations with a known infectious cause. Therefore, great efforts has been made to find such a cause for both diseases. Several bacteria, fungi and chlamydia have been suggested as the causative agent for ulcerative colitis (28), but reproducible results have never been obtained. It was reported possible to isolate a cytopathogenic factor, possibly a virus, from bowel tissue of patients with ulcerative colitis and to pass it serially in tissue cultures (29). This finding, however, has never been confirmed.

Because Crohn's disease closely resembles infections that are caused by mycobacteria (tuberculosis in humans and Johne's disease in sheep) the possible role of these microorganisms has been investigated intensively. In an open study, quadruple anti-mycobacterial chemotherapy was effective in half of patients with refractory Crohn's disease (29a). Recent attention has specifically been paid to M. paratuberculosis (30), but the positive results of one group still await confirmation by others. Moreover, it was not possible to detect serum antibodies directed against mycobacteria in patients with Crohn's disease (31), or to demonstrate mycobacterial DNA in diseased tissue with immunohistochemical (32) or modern molecular-biological (33,34) techniques. The T-cell mediated immune response to sonicates of M. paratuberculosis, M. kansasii, M. tuberculosis and M. avium is in patients with Crohn's disease as frequently positive as in controls (34a).

Although, until now, no microorganism has met the Koch's postulates, it is not excluded that an infectious agent initiates a chronic bowel inflammation that subsequently leads its own life.

Nutritional and toxicologic factors

No clear relationship has been demonstrated between intake of certain foods and development of ulcerative colitis or Crohn's disease (35,36). In some studies it was found that the intake of refined carbohydrates was higher in patients with Crohn's disease than in controls; the importance of this finding remains unclear

(37).

In recent years considerable attention has been paid to the relationship between smoking habits and inflammatory bowel diseases. Patients with Crohn's disease would more often be smokers, whereas a negative correlation has been found between ulcerative colitis and smoking (38,39). Ex-smokers would particularly be at risk. Some authors report an increased risk for Crohn's disease amongst contraceptive pill users (40,41).

Psychosocial factors

Although some patients feel that stressful or traumatic events initiated or aggravated their disease, evidence for this hypothesis is lacking (42). Neither can specific pre-morbid personality characteristics consistently be found in patients with ulcerative colitis or Crohn's disease (43). Nevertheless, patients can be severely mentally distressed by problems related to their illness, and in addition some therapeutical agents, especially corticosteroids, may cause mental adverse effects. Of course the attending physician should be mindful of this and pay ample attention to these aspects of disease. Often the mental problems disappear when the bowel disease goes into remission.

Immunological factors

The chronic bowel inflammation with ongoing destruction of intestinal mucosa may be interpreted as an inadequate immunological reaction. Therefore, great efforts has been made to investigate the immunological apparatus in patients with inflammatory bowel diseases. There is no firm evidence that a primary immunological defect is involved in the aetiology of one of the two diseases. The humoral immune response is normal, and the levels of circulating and mucosal immunoglobulins are not decreased as a rule (44). The cell-mediated immunity may be impaired in active disease (the cutaneous anergia in severe Crohn's disease is well-known), but restoration occurs after resection of the diseased bowel or achievement of a remission. However, although no primary

immunological defect can be demonstrated, an immune reaction, once started, causes the tissue damage characteristic for these diseases. In inflamed bowel tissue the number of lymphocytes, both immunoglobulin producing and T-lymphocytes, is increased (45). This is not specific to inflammatory bowel disease; it is also found in bacterial enteritis (46). Indications exist for both antibody-induced and cell-mediated tissue damage. Many patients with chronic inflammatory bowel disease have antibodies directed against colon epithelium (47). Some investigators found these antibodies to cross-react with E. Coli lipopolysaccharides (48). It may be conjectured that an immunological response, initiated as a defence against E. Coli, is directed by cross-antigenicity against own intestinal tissue, but this does not tally with the finding that such antibodies can also be demonstrated in patients with bowel diseases not characterized by chronic inflammation (49). Moreover, high antibody titres against various colonic bacteria (50,51) and cow's milk (52) are often found in serum and mucosa. These antibodies might form immune complexes in the mucosa with the corresponding antigens, thus starting a type III (Arthus) inflammatory reaction, leading to tissue damage. Probably the high antibody titres are not a primary event but a consequence of epithelial damage. There are also indications of T-cell mediated cytotoxicity in patients with inflammatory bowel disease. The existence of T-cells sensitized for autologous colon epithelial cells has been demonstrated (53). Recently, serum anticolon antibody and in vitro anticolon antibody production by peripheral blood and mucosal lymphocytes was found increased in a majority of patients with ulcerative colitis, as opposed to healthy controls and patients with Crohn's disease (53a). This gives support to the conception that ulcerative colitis is, at least partially, an autoimmune disorder. Ulcerative colitis is also more often than Crohn's disease associated with HLA class II related autoimmune diseases, such as primary sclerosing cholangitis (53b).

None of the above-mentioned immunological phenomena is made acceptable as a primary cause of the inflammatory process, nor are they specific of Crohn's disease or ulcerative colitis. They are probably epiphenomena of an existing inflammation, which nevertheless can amplify the inflammatory process by means

of production of inflammatory mediators such as complement, prostaglandins, leucotrienes and oxygen radicals, thereby worsening the tissue damage. This also explains the favourable effect of aspecific inhibitors of inflammation such as corticosteroids, and the effect of 5-aminisalicylic acid which, among other things, influences leucotriene production (54) and scavenges oxygen radicals (55).

The question as to the primary event that starts the inflammation is still open. Do ulcerative colitis and Crohn's disease have different causes or are they the ends of a spectrum of one disease? The fact that sometimes features of both diseases can be found in one patient, and the occurrence of both diseases in one family support this hypothesis. On the other hand it is imaginable that various aetiologic factors can result in the same clinical picture, since the gut has only limited possibilities to respond to an inflammatory stimulus. The clinical and histological picture of a Yersinia infection can often not be distinguished from Crohn's disease, as shigellosis cannot be distinguished from ulcerative colitis. Possibly the individual immunological characteristics of a patient are also important for the appearance of the inflammation.

THE MEASUREMENT OF DISEASE ACTIVITY

There is a great need for a uniform yardstick to measure the disease activity of inflammatory bowel disease. Such an instrument is necessary to define the characteristics of patients taking part in therapeutic trials, and to compare the results of treatment. It might also be useful in decision-making in the management of an individual patient.

A workable activity index should meet several requirements. An ideal activity index consists of as few factors as possible, factors easily obtainable in any hospital, is reproducible, independent of the subjectivity of patient and observer, and truly reflects the severity of inflammation.

Both for ulcerative colitis and Crohn's disease numerous measures of disease activity have been proposed and actually used in clinical trials. A classification can be made in clinical activity indices, composed of several factors that relate to

physical status, signs, symptoms and laboratory data, further endoscopic indices, other imaging techniques, and single or multiple laboratory indices. Indices can be based on the intuition of the authors (e.g. Truelove-Witts classification for ulcerative colitis) or be derived from multiple variables by means of stepwise multiple regression analysis (e.g. the CDAI and AI for Crohn's disease), and may exist of discrete classes or a continuous numerical scale. It is generally accepted that, because of the different clinical presentation of ulcerative colitis and Crohn's disease, no single measure of disease activity can be applied to both diseases.

Measures of disease activity in ulcerative colitis

In 1955, Truelove and Witts proposed a three-grade scale of absent, mild, moderate and severe disease (56), shown in Table 1.

Although this provides an easily obtainable and reproducible scale of disease activity, it has certain disadvantages. It is not stated how a patient with features from different catagories should be classified. Several factors, such as pulse rate, fever and anaemia, are interrelated. In a three-grade scale less pronounced changes of disease activity can be overlooked; patients answering the minimal requirements for the 'severe' scale are not severely ill in our opinion, so this scale can accommodate a large variation of disease activities.

Table 1. *Truelove-Witts severity catagories of ulcerative colitis*

Mild:	Diarrhoea <4 motions/day, non-bloody
	No fever
	Pulse rate < 90/min
	No severe anaemia
	ESR <30 mm/hr
Severe:	Diarrhoea >6 motions/day, bloody
	Evening temperature > 37.5°C
	Pulse rate >90/min
	Haemoglobin 75% or below
	ESR >30 mm/hr
Moderate:	Intermediate between mild and severe

Another activity index with 15 constituent factors was proposed by Talstad et al (57) but to our knowledge has never been used in practice, probably because of low feasibility. The same disadvantage applies to the numerical index of Powell-Tuck et al. (58) which consists of 11 items. So far, the Truelove-Witts classification

remains the most frequently used clinical index for ulcerative colitis.

As the inflamed bowel is easily accessible by sigmoidoscope or colonoscope, endoscopic judgement is at least as important in ulcerative colitis. The gradings of Dick et al. who distinguished five degrees of severity (59), has also be used in other studies, but in many therapeutic trials of ulcerative colitis a modified endoscopic index is proposed. Recently, Rachmilewitz presented a numerical endoscopic index, in which granularity, vascular pattern, vulnerability and mucosal damage can be scored at several levels (60). The added score is than a measure of the endoscopically assessed severity of inflammation. The endoscopic index described by van der Heide et al, composed of eight items with three levels each starts from the same principle (61). Although granularity, vascular pattern, erythema, friability, bleeding and ulceration are invariably parts of any endosopic score, no general agreement exist as to how these factors should constitute an index.

Segal et al were the first to demonstrate that the faecal excretion of reinjected ^{111}In-labelled homologous leucocytes correlated with the presence of inflammatory bowel disease (62). Leddin et al found that the amount of ^{111}In in stools correlated significantly with their own activity index for ulcerative colitis, based upon clinical picture, colonoscopic and histological findings, and less well with the Truelove-Witts classification (63).

After the publication of Dearing et al (64), indicating that serum levels of the acute phase reactant orosomucoid were elevated in patients with ulcerative colitis, serum levels of many serum proteins such as albumin, pre-albumin, immunoglobulins, α_1-antichymotrypsin, orosomucoid, α_1-antitrypsin, and C-reactive protein were studied in their relation to disease activity and response to treatment (65,66). Orosomucoid and C-reactive protein are most consistently found to be elevated in active ulcerative colitis, and to correlate with disease activity (66,67). In one study, the level of C-reactive protein at admission was found to correlate well with the outcome of the attack (68), but this finding awaits confirmation.

At present, the best way to judge the extent and severity of inflammation of ulcerative colitis remains endoscopy, while a clinical index is useful to measure the

impact of the inflammation on the health status. Because of the above-mentioned disadvantages of the Truelove-Witts classification, a more accurate index is desirable. In chapter 8 such an index is proposed, and actually used in a therapeutic trial.

Measures of disease activity in Crohn's disease

Measuring disease activity in Crohn's disease is much more complicated than in ulcerative colitis. Whereas in ulcerative colitis the extent of inflammation and development of mucosal damage is rather uniform, Crohn's disease can present with many patterns of anatomic distribution and intestinal injuries, from shallow aphthous ulcers to perforation, fistulas and stenoses. Therefore it is very difficult, if not impossible, to compare all conceivable appearances of Crohn's disease in one activity scale. Meanwhile, several activity indices have been developed, composed of the factors listed in Table 2.

For the American National Cooperative Crohn's Disease Study the need for an appropriate activity index was felt, resulting in the Crohn's Disease Activity Index (CDAI) (69). Harvey and Bradshaw developed a simplified version of this index, necessitating the assessment for only one day instead of one week (70). Lloyd-Still devised a clinical score for inflammatory bowel disease in children, taking into account important paediatric factors such as growth and school activity (71). Because it was felt that the CDAI was too dependent on subjective data as well-being and pain, a Dutch group developed the so-called van Hees Activity Index (AI), consisting merely of objective parameters (72). Others found the equations, necessary for the calculation of the CDAI and AI, too cumbersome and proposed a binary 10-item index, the so-called Oxford Index, scoring for the presence or absence of each parameter (73). The "Cape Town Index", published by South-African investigators, is a complicated version of this index, allowing four degrees of severity for each of ten almost identical items (74). Recently, Pinchbeck et al devised a Crohn's Activity Group Scale by performing a discriminant function analysis on several demographic, anthropomorphic, clinical and laboratory data

Table 2. *Factors assessed in various activity indices*

Factor assessed	CDAI	Harvey & Bradshaw CDAI	van Hees AI	Oxford Index	Cape Town Index
Abdominal pain	x	x		x	x
Bowel habits	x	x	x	x	x
Perianal complications				x	x
Other complications	x	x	x	x	x
Palpable mass	x	x	x	x	x
Body weight/build	x			x	x
Haemoglobin/haematocrit	x			x	x
Well-being	x	x			x
Use of anti-diarrhoeal drugs	x				
Quetelet index*			x		
Temperature			x	x	x
Serum albumin			x		
ESR			x		
Sex			x		
Previous resection			x		
Tenderness				x	x
Fistula				x	

Quetelet index: weight/length^2 (kg/m^2)

that was found to have predictive value as to the future course of disease (75), but the 15-item equation appears too complicated to gain much popularity.

Members of the International Organization for the Study of Inflammatory Bowel Disease, all clinicians with a wide experience in the field, conducted an important exercise by calculating all the activity indices available at that time for a number of paper cases and real patients. In a report by De Dombal only the CDAI and AI are discussed thoroughly (76). The AI appeared less subject to interobserver variation than the CDAI. The correlation between AI and CDAI is rather poor (72).

The divergence between the outcomes of the activity indices is easy to understand as each index measures a different aspect of disease. The AI, consisting of objective factors, reflects the severity of inflammation, whereas the CDAI is more a general measure of illness.

In contrast to ulcerative colitis, endoscopy is less feasible to assess the extent and severity of inflammation in Crohn's disease. Still, a standardized endoscopic evaluation, providing the opportunity to calculate a Crohn's disease endoscopic index, as proposed by Mary and Modigliani (77), can be useful in the judgement of medical or surgical intervention. The correlation between colonoscopic findings and the CDAI is reported to be poor (78).

As in ulcerative colitis, the loss of ^{111}In-labelled leucocytes in faeces has been used to quantify the degree in Crohn's disease (62), with different results in various studies. In the study of Leddin, loss of ^{111}In-labelled leucocytes correlated well with the AI, but not with the CDAI (63), which is explained by the nature of the two indices. In the experience of the Leiden group, faecal ^{111}Indium loss correlates of all indices only with the AI, and only if the disease is localized in the colon (79). On the basis of these results the authors conclude that activity indices are poor indicators of intestinal inflammation. As they found even poorer correlations between faecal loss of ^{111}In-labelled leucocytes with serum orosomucoid and C-reactive protein levels, it may be questioned whether faecal ^{111}Indium loss is much better.

Of the acute phase reactants, orosomucoid and C-reactive protein are those most intensively studied in Crohn's disease after André and co-workers found that these proteins correlated best with the disease activity (66). The course of C-reactive protein levels corresponds closely to relapse, remission and response to therapy (80), and the levels of C-reactive protein and orosomucoid in periods of quiescent disease correlate with the probability of a future relapse (81,82). Orosomucoid and C-reactive protein may rise some months before a relapse of Crohn's disease becomes apparent (83). In chapter 4 of this thesis a study of the predictive value of orosomucoid and C-reactive protein in active Crohn's disease is described.

Because of the many divergent clinical pictures the gold standard for Crohn's

disease is even more difficult to define than that for ulcerative colitis. For clinical trials an overall estimation of the severity of disease, as measured with clinical activity indices, is the most useful. The choice of one of the indices remains more or less a matter of philosophy. In our opinion the AI, which avoids subjective feelings of the patients and has the least interobserver variation, deserves preference.

Possibly measurement of acute phase reactants will prove useful in the management of an individual patient. In one study it was possible to select a group of patients with quiescent Crohn's disease for prophylactic treatment with corticosteroids on the basis of high serum levels of orosomucoid and C-reactive protein (84).

THERAPY

General measures

Both for patients with ulcerative colitis and with Crohn's disaese it is important to aim for a good general condition. In case of severe anaemia blood transfusions should be given, deficiencies of fluid and electrolytes should be supplemented; especially hypokalaemia should be corrected as this may bring about a toxic megacolon.

Nutritional measures

The nutritional status is often poor, as a consequence of the inflammation and of the - sometimes bizarre - dietary measures imposed on the patient by himself or by the attending physician. For ulcerative colitis it has never been demonstrated in controlled trials that any diet has a favourable effect on the course. Care should be taken that the patient, who is often in a catabolic state, has a sufficient

oral intake of calories in a palatable form. Only poorly tolerated foods should be left out of the diet. A small proportion of the patients have lactose intolerance and profit from lactose restriction. This may also apply to patients who have only a short length of functional bowel after resections. The possibility should be kept in mind of the occurrence of deficiencies of vitamin B12 and folic acid, and of iron, calcium, magnesium and zinc, and these should be supplemented whenever necessary. Withholding oral foods and administration of parenteral nutrition do not influence the course of ulcerative colitis (85,86).

In Crohn's disease long-term administration of parenteral nutrition or an elementary diet may lead to an improvement of the inflammation, and sometimes to closure of fistulas, but it is questionable whether these effect persists in the long run (86,87). In one study the disease remained quiescent for some time after reinstitution of oral feeding (88). Generally, however, an operation cannot be avoided by these dietary measures. In our opinion it is not proper to try to improve the general and nutritional state by means of parenteral nutrition in the hope of diminishing the risk of operation. The fastest way to improve the general condition is a resection of the diseased bowel segment. The improvements induced by parenteral nutrition do not outweigh the long time necessary to achieve a substantial effect and the complications inherent in parenteral nutrition.

Medical therapy

As the causes of both chronic inflammatory bowel diseases are unknown, medical therapy has necessarily an empirical character. In mild or moderate disease salicylazosulphapyridine (Salazopyrine) and drugs containing 5-aminosalicylic acid are effective. In more severe cases administration of corticosteroids is necessary. The various drugs are discussed in more detail in the paragraphs below.

Salazopyrine and other 5-aminosalicylic acid containing drugs

Salicylazosulphapyridine (SASP) consists of sulphapyridine and 5-aminosalicylic acid (5-ASA), linked together with an azo bond. It has been used for almost 50

years in the treatment of patients with ulcerative colitis. Over the years it has become apparent that 5-ASA is the active part of SASP (89,90), and that sulphapyridine is responsible for the majority of adverse effects caused by SASP. Both parts are released in the bowel lumen after splitting of the azo bond by bacterial enzymes (91). 5-ASA constitutes almost 40% of the molecular weight of SASP, so equivalent doses of 5-ASA and SASP relate to each other as 1 : 2.5. A number of new drugs have been developed that contain only 5-ASA and no sulphapyridine. Plain 5-ASA cannot be given by mouth because it is largely absorbed in the proximal parts of the small bowel and reaches the distal small bowel and colon in insufficient amounts (92). In the new drugs sustained or delayed release of 5-ASA is achieved by the application of a acrylic resin coating that dissolves at a certain pH (Asacol^{R} and Salofalk^{R}), by packing 5-ASA in ethylcellulose vesicles that permit slow diffusion of 5-ASA (Pentasa^{R}), or by the coupling of two 5-ASA molecules via an azo bond that is, like SASP, split by intestinal bacteria (olsalazine, Dipentum^{R}). Last but not least enemas and suppositories are important application forms of 5-ASA, resulting in high concentrations in the distal colon, with excellent therapeutic results (93-95).

SASP and 5-ASA in ulcerative colitis

Several studies demonstrated that SASP is more effective than placebo for the achievement of remission in patients with mildly or moderately active ulcerative colitis (96,97), and that it diminishes the risk of recurrence in patients with ulcerative colitis in remission (98,99). With the exception of Pentasa^{R} all new 5-ASA containing drugs have been investigated in patients with active ulcerative colitis and they appeared to be more effective than placebo (100-102) or as effective as SASP (60,103,104). Efficacy equal to SASP in maintaining remission has been demonstrated for Dipentum^{R} (105), Asacol^{R} (106), Pentasa^{R} (107) and Claversal^{R} (108), which is identical to Salofalk^{R}.

SASP and 5-ASA in Crohn's disease

SASP is effective in the treatment of active Crohn's disease, especially if localized in the colon, according to the American National Cooperative Crohn's Disease Study and the European Cooperative Crohn's Disease Study (109,110). Effectiveness in patients with terminal ileitis also has been described (111). Until recently no studies were available that showed effectiveness of SASP in maintaining remission of Crohn's disease, or in reducing the risk of recurrence after resection. It has to be kept in mind, however, that the compliance to therapy of patients without symptoms is often poor, which might explain the lack of effect in the prevention of relapses. Recently it could be demonstrated in one study that SASP in a dosage of three grams per day reduced the risk of recurrence after resection (112). Data on the effectiveness of the new 5-ASA containing drugs in Crohn's disease are still scarce. In a placebo-controlled trial in patients with small bowel Crohn's disease the course of disease was more favourable in patients treated with Pentasa^{R}, but this effect was not statistically significant (113).

Dosages of 5-ASA and adverse effects

The effect of 5-ASA drugs is the result of the locally achieved concentrations and not of serum concentrations, which are at least a 1000 times lower (114). Therefore the highest possible concentration at the site of inflammation has to be aimed for.

In most studies SASP is given in a dosage of 3 to 4 grams in active disease, and 1 to 2 grams during remission. In our experience a considerable proportion of patients with active disease tolerate a daily dose of 6 gram well, although some patients will experience adverse effects. These adverse effects are the most important restriction on the use of SASP. Most adverse effects such as headache, nausea and abdominal discomfort, anorexia and myalgia are not severe and dose-dependent (96,97,99,115). Skin rash, often on parts exposed to sunlight, and fever are probably dose-independent (115). Severe adverse effects such as hepatitis, pancreatitis, interstitial pneumonitis, bone marrow suppression and the Stevens-

Johnson syndrome are rare. SASP interferes with the intestinal absorption of folic acid, sometimes resulting in folic acid deficiency and anaemia (116). Another frequent cause of SASP-related anaemia is haemolysis (117). Finally the frequently occurring male infertility, which is reversible after discontinuation of SASP, should be mentioned (118).

With the new 5-ASA containing drugs, adverse effects, although less frequent, are not completely absent. In patients intolerant of SASP who are treated with olsalazine or slow-release 5-ASA adverse effects occur in 13 to 25% of cases (119). Especially skinrash appears to be caused sometimes by the 5-ASA component (120). 5-ASA is also reported to provoke an exacerbation of the disease (121,122). Olsalazine causes diarrhoea in some patients (123), as a result of impaired absorption of water, sodium and chloride in the small intestine (124-126). Incidentally, diarrhoea has also been mentioned as an adverse effect of slow-release 5-ASA (120). Meanwhile, pancreatitis also is reported as an adverse effect of olsalazine (127), Asacol^{R} (128) and Claversal^{R} (129).

Finally, the possibly 5-ASA-related renal damage should be discussed. In the rat 5-ASA has nephrotoxic properties (130). Case reports on occurrence of a nephrotic syndrome (131) and interstitial nephritis (132) during 5-ASA therapy have been published, and in one trial a rise of serum creatinine was observed in some patients during treatment with Asacol (102). In the absence of sulphapyridine-related adverse effects high doses of 5-ASA (more than 3 grams per day) for longer periods look tempting, but in the light of these reports, caution is indicated.

Because of the short time for which the new 5-ASA containing drugs have been available, their relative efficacies have not been compared so far. Therefore it is not possible to give a firmly based preference to any one of these drugs in specific clinical situations. Choices can only be made on the basis of pharmacokinetic studies. Of some drugs, the proportions recovered in ileostomy effluent after oral intake have been measured, permitting calculation of the proportions absorbed in the small intestines. After intake of Pentasa^{R}, 35% of 5-ASA appeared to be released in the small bowel (133), as against less than 1%

after intake of olsalazine (134). Another approach to investigate the site of release of 5-ASA is measurement of the amount of (acetyl)-5-ASA in urine in relation to time after ingestion, and of the amount of acetylated 5-ASA in faeces. A considerable proportion of 5-ASA excreted into the urine shortly after intake indicates that it has been released and absorbed in the proximal parts of the digestive tract (92,135). 5-ASA is acetylated by bowel mucosa and by intestinal bacteria (136,137). Therefore, large amounts of acetyl-5-ASA in faeces indicate early release of 5-ASA, whereas little or no acetyl-5-ASA indicates (too) late release from the drug concerned. In the chapters 5, 6 and 7 of this thesis these principles are applied to investigate the disposition of 5-ASA from several 5-ASA delivering drugs in healthy volunteers without diarrhoea, in healthy volunteers with diarrhoea induced by bisacodyl, and in patients with inflammatory bowel diseases, with and without diarrhoea. The results of these studies inspired some recommendations concerning the treatment of patients with inflammatory bowel disease, which are discussed in the summary.

Corticosteroids

Corticosteroids are very effective in patients with active ulcerative colitis (56) or Crohn's disease (109,110). Corticosteroids appeared generally ineffective in the prevention of relapses (109,110,138), but it should be kept in mind that the compliance to therapy is always a problem in patients on long-term therapy, the more so when they are free of complaints. In a small study the risk of relapse of Crohn's disease was smaller during corticosteroid maintenance therapy in patients with elevated serum levels of acute phase proteins (139). The most frequently prescribed drugs are prednisone and prednisolone. Prednisone is not active by itself, but is, after absorption, rapidly transformed in the liver into the active metabolite prednisolone. Orally administered prednisone is as effective as prednisolone, except in patients with severe liver failure. For rectal administration only prednisolone is appropriate.

Prednisone or prednisolone are indicated in ulcerative colitis in patients with moderately or severely active disease, where insufficient efficacy of 5-ASA drugs is

to be expected. If the inflammation is limited to the rectum or rectosigmoid region, corticosteroids, like 5-ASA, can successfully be applied locally as enemas or suppositories (140).
In Crohn's disease, also corticosteroids are prescribed in moderate and severe cases, the more so if fever or considerable weight loss is present. Initial dosages and tapering-off schedules vary widely in literature.

It has never been investigated whether the combination of SASP and prednisone is better than SASP alone. In chapter 3 a comparative study of these treatment modalities in patients with active Crohn's disease is described.
In a small proportion of patients it is not possible, even in the long run, to lower the dosage of prednisone to less than 10 or 15 mg per day. When these dosages of corticosteroids have to be continued for longer than one or two years, resection of the diseased bowel segment, or, if that is not feasible (e.g. because of the risk of a short bowel syndrome), institution of treatment with azathioprine has to be considered.
All physicians and most patients are well aware of the many possible adverse effects of corticosteroids. However, when the duration of administration is limited to a few months, the side effects are well surveyable in our experience and their importance is certainly outweighed by the efficacy of corticosteroids, which is not equaled by any other form of medical therapy (141).
At this moment some corticosteroids are being investigated which presumably have the same local efficacy as prednisolone, but fewer systemic adverse effects because of low intestinal absorption or considerable first-pass inactivation in the liver (142). If the first promising results are confirmed they will be an appreciated adjunct to the therapeutic arsenal.

Immunosuppressive drugs

In a chronic inflammation with destruction of tissue immunosuppressive drugs may be expected to be useful. In inflammatory bowel diseases experience has been gathered with azathioprine, its metabolite 6-mercaptopurine, and with

cyclosporine, which interferes with the T-cell mediated immune response.

Data on the effectiveness of azathioprine in patients with ulcerative colitis are scarce. In two controlled trials azathioprine appeared to decrease the need for corticosteroids (143) or the disease activity (144). In another study, however, no effect was observed (145). Reports on a favourable effect of cyclosporine in ulcerative colitis remain sporadic (146).

More data are available on the efficacy of immunosuppressives in Crohn's disease. In several studies a prednisone-sparing effect of azathioprine and 6-mercaptopurine was found (147,148). However, the long period (two months or more) sometimes elapsing before an effect can be observed, and the considerable frequency of adverse effects such as bone marrow suppression, pancreatitis, fever and nausea are drawbacks of this therapy (149). Therefore these immunosuppressive drugs should be reserved for cases refractory to protracted treatment with corticosteroids, or immediately relapsing after lowering the dosage, if resection of the diseased bowel is not feasible for whatever reason.

Cyclosporine has appeared to be effective in patients with Crohn's disease with insufficient response to or intolerance of corticosteroids (150). In a considerable proportion of patients a deterioration occurred after lowering the dose.

Metronidazole

Metronidazole in a dosage of 800 mg per day is more effective than placebo (151) or as effective as SASP (152) in patients with Crohn's disease, especially with locations in the colon. Perianal fistules in particular may sometimes respond well to local or systemic application of metronidazole. Unfortunately, the inflammation often flares up immediately after discontinuation of therapy, and prolonged administration is not rarely complicated by severe polyneuropathy which is not always reversible. Metronidazole does not seem to be effective in ulcerative colitis (153).

PROGNOSIS

Ulcerative colitis

The course of ulcerative colitis is very variable and unpredictable. In the majority of patients the disease activity is intermittent, with alternating exacerbations and remissions. Less than 5% have only one attack without a relapse in the next 15 years, and in approximately 10% the disease is more or less continuously active (154). At a random moment in the course of disease about half the patients are free of symptoms (155).

The mortality of a first attack of ulcerative colitis has decreased with time and is now less than 2% (154,155,156). The vast majority of deaths occur in severe colitis, mostly corresponding with colitis of the entire colon. Other factors that might be associated with increased mortality are a short history before the onset of a severe attack and advanced age at presentation (157-159). The mortality of toxic megacolon ranges from 13 to 30%.

In our own patients no clear correlation between the severity and extension of the first attack on the one hand and the probability of a prolonged remission and mortality on the other could be found (3). In other studies the long-term prognosis is related to the severity of the first attack: increasing severity is connected with an increased risk of relapses later on and increased 5-year mortality.

Crohn's disease

The course of Crohn's disease is highly unpredictable in the individual patient. Usually the disease has a continuously fluctuating nature (160,161).

In the National Cooperative Crohn's Disease Study the cumulative probability of an operation was about 50% after 5 years and about 75% after 10 years. The risk was greatest for patients with ileocolitis (162). The figures for second operations are of the same order. In unselected populations from defined geographic areas the figures are lower. In the Leiden region (Netherlands) the cumulative risk of a reoperation was 25% after 10 years and 60% after 20 years (163). In this study, the risk of a second resection was greater if the patient was over 30 years of age

at the time of the first operation. In the Copenhagen region (Denmark) 55% of the patients had undergone at least one operation after 10 years (161).

The mortality in patients with Crohn's disease in unselected populations was higher than in the normal population, especially in the first three years of illness in one study (164), but in another study it was not clearly increased (161).

REFERENCES

1. Hendriksen C, Binder V. Social prognosis in patients with ulcerative colitis. Br Med J 1980, ii: 581-3.
2. Sorensen VZ, Olsen BG, Binder V. Life prospects and quality of life in patients with Crohn's disease. Gut 1987, **28:** 382-5.
3. Perenboom RM, Rijk MCM, Rikken G, van Tongeren JHM Het ziektebeloop bij colitis ulcerosa. Nederl Tijdschr Geneesk 1990, **134:** 438-42.
4. Garland CF, Lilienfield AM, Mendeloff AI, Markowitz JA, Terrell KB, Garland FC. Incidence rates of ulcerative colitis and Crohn's disease in fifteen different areas in the United States. Gastroenterology 1981, **81:** 1115-24.
5. Fabricius PJ, Gyde AN, Shoulder P, et al. Crohn's disease in the elderly. Gut 1985, **26:** 461-5.
6. Mayberry JF. Some aspects of the epidemiology of ulcerative colitis. Gut 1985; **26:** 968-74.
7. Fahrländer H, Baerlocher CH. Clinical features and epidemiological data on Crohn's disease in the Basel area. Scand J Gastroenterol 1971; **6:** 657-62.
8. Devlin HB, Datta D, Dellipiani AW. The incidence and prevalence of inflammatory bowel disease in North Tees health district World J Surg 1980; **4:** 183-93
9. Berner J, Kjær T. Ulcerative colitis and Crohn's disease on the Faroe Islands 1964-1983. Scand J Gastroenterol 1986, **21:** 188-92.
10. Hellers G. Crohn's disease in Stockholm County 1955-1974. Acta Chir Scand 1979, (suppl): 490.
11. Mayberry J, Rhodes J, Hughes LE. Incidence of Crohn's disease in Cardiff between 1934 and 1977. Gut 1979; **20:** 602-8.
12. Smith IS, Young S, Gillespie G, O'Connor J, Bell JR. Epidemiological aspects of Crohn's disease in Clydesdale 1961-1970. Gut 1975; **16:** 62-7.
13. Krawiec J, Odes HS, Lasry Y, Krugliak P, Weitzman S. Aspects of the epidemiology of Crohn's disease in the Jewish population in Beer Sheva, Israel. Isr J Med Sci 1984, **20:** 16-21.
14. Rozen O, Zonia J, Yekutiel P, Gilst T. Crohn's disease in the Jewish population of Tel Aviv-Yafo. Gastroenterology 1979; **76:** 25-30.
15. Brahme F. Crohn's disease in a defined population. Gastroenterology 1975, **69:** 342-51.
16. Norlén BJ, Krause U, Bergman L. An epidemiological study of Crohn's disease Scand J Gasroenterol 1970, **5:** 385-90.
17. Kyle J. An epidemiological study of Crohn's disease in northeast Scotland. Gastroenterology 1971; **61:** 826-33.

18. Miller DS, Keighley AC, Langman MJS. Changing patterns in epidemiology in Crohn's disease. Lancet 1974; **ii:** 691-3.

19. Lee FI, Costello FT. Crohn's disease in Blackpool-incidence and prevalence 1968-1980. Gut 1985; **26:** 274-8.

20. Binder V, Both H, Hansen PK, Hendriksen C, Kreiner S, Torp-Pedersen K. Incidence and prevalence of ulcerative colitis and Crohn's disease in the County of Copenhagen, 1962 to 1978. Gastroenterology 1982; **83:** 563-8.

21. Barton JR, Gillon S, Ferguson A. Incidence of inflammatory bowel disease in Scottish children between 1968 and 1983; marginal fall in ulcerative colitis, three-fold rise in Crohn's disease. Gut 1989; **30:** 618-22.

22. Mayberry JF, Rhodes J. Epidemiological aspects of Crohn's disease: a review of the literature. Gut 1984; **25:** 886-99.

23. Gilat T, Ribak J, Benaroya Y, Zemishlany Z, Weissman I. Ulcerative colitis in the Jewish population of Tel Aviv Jafo. I. Epidemiology. Gastroenterology 1974; **66:** 335-42.

24. Lewkonia RM, Mc Connell RB. Familial inflammatory bowel disease-hereditary or environment? Gut 1976; **17:** 235-43.

25. Farmer RG, Michener WM, Mortimer EA. Studies of family history among patients with inflammatory bowel disease. Clin Gastroenterol 1980; **9:** 271-8.

26. Weterman IT, Pena AS. Familial incidence of Crohn's disease in the Netherlands and a review of the literature. Gastroenterology 1984; **86:** 449-52.

27. Elson CO, Kagnoff MF, Fiocchi C, Befus AD, Targan S. Intestinal immunity and inflammation: recent progress. Gastroenterology 1986; **91:** 746-68.

28. Swarbrick ET, Kingham JGC, Price HC, Blackshaw AJ, Griffiths PD, Darougar S, Buckell NA. Chlamydia, cytomegalovirus, and Yersinia in inflammatory bowel disease. Lancet 1979; ii: 11-2.

29. Gitnick GL, Rosen VJ, Arthur MH, Hertwecks A. Evidence for the isolation of a new virus from ulcerative colitis patients. Dig Dis Sci 1979; **24:** 609-619.

29a Hampson SJ, Parker MC, Saverymutti SH, Joseph AE, McFadden JP, Hermon-Taylor J. Quadruple antimycobacterial chemotherapy in Crohn's disease: results at 9 months of a pilot study in 20 patients. Aliment Pharmacol Therap 1989; **3:** 343-52.

30. Thayer WR, Coutu JA, Chiodini RJ, Van Kruiningen HJ, Markal KS.Possible role of mycobacteria in inflammatory bowel disease.Dig Dis Sci 1984; **29:** 1080-5.

31. Kobayashi K, Brown WR, Brennan PJ, Blaser MJ. Serum antibodies to mycobacterial antigens in active Crohn's disease. Gastroenterology 1988; **94:** 1404-11.

32. Kobayashi K, Blaser MJ, Brown WR. Immunohistochemical examination for mycobacteria in intestinal tissues from patients with Crohn's disease. Gastroenterology 1989; **96:** 1009-15.

33. Yoshimura HH, Graham DY, Estes MK, Merkal RS. Investigation of association of

mycobacteria with inflammatory bowel disease by nucleic acid hybridization J Clin Microbiol 1987; **25**: 45-51.

34. Butcher PD, McFadden JJ, Hermon-Taylor J. Investigation of mycobacteria in Crohn's disease tissue by Southern blotting and DNA hybridisation with cloned mycobacterial genomic DNA probes from a Crohn's disease isolated mycobacteria. Gut 1988, **29**: 1222-8.

34a Seldenrijk CA, Drexhage HA, Meuwissen SGM, Meijer CJLM. T-cellular immune reactions (in macrophage inhibition factor assay) against Mycobacterium paratuberculosis, Mycobacterium kansasii, Mycobacterium tuberculosis, Mycobacterium avium in patients with chronic inflammatory bowel disease. Gut 1990; **31**: 529-35.

35. Hodgson HJF. Inflammatory bowel disease and food intolerance. J Roy Coll Phys London 1986; **20**: 45-8.

36. Kirsner JB, Shorter RG. Recent developments in "nonspecific" inflammatory bowel disease. N Eng J Med 1982; **306**: 775-85.

37. Thornton JR, Emmett PM, Heaton KW. Smoking, sugar and inflammatory bowel disease.Br Med J 1985; **290**: 1786-7.

38. Tobin MV, Logan RFA, Langman MJS, Mc Connell RB, Gilmore IT Cigarette smoking and inflammatory bowel disease. Gastroenterology 1987, **93**: 316-21.

39. Lindberg E, Tysk C, Andersson K, Järnerot G. Smoking and inflammatory bowel disease. A case control study. Gut 1988, **29**: 352-7.

40. Rhodes JM, Cockel R, Allan RN, Hawker PC, Dawson J, Elias E. Colonic Crohn's disease and use of oral contraception. Br Med J 1984; **288**: 595-6.

41. Lesko SM, Kaufman DW, Rosenberg L, et al. Evidence for an increased risk of Crohn's disease in oral contraceptive users. Gastroenterology 1985, **89**: 1046-9.

42. Monk M, Mendeloff AI, Siegel CI, Lilienfeld A. An epidemiological study on ulcerative colitis and regional enteritis among adults in Baltimore. III. Psychological and possible stress precipitating factors. J. Chron. Dis. 1970; **22**: 565-578.

43. McKegney FP, Gordon RO, Levine SM. A psychosomatic comparison of patients with ulcerative colitis and Crohn's disease. Psychsom. Med. 1970; **153**: 153-166.

44. Hodgson HJF, Jewell DP. The humoral immune system in inflammatory bowel disease. Am. J. Dig. Dis. 1978; **23**: 123-8.

45. Fiocchi C, Battisto JR, Farmer RG. Gut mucosal lymphocytes in inflammatory bowel disease-isolation and preliminary functional characterization. Dig. Dis. Sci. 1979, **24**: 705-717.

46. Scott BB, Goodall A, Stephenson P, Jenkins D. Rectal mucosal plasma cells in inflammatory bowel disease. Gut 1983; **24**: 519-24.

47. Broberger O and Perlmann P. Autoantibodies in human ulcerative colitis. J Exper Med 1963; **110**: 657-74

48. Perlmann P, Hammarstrom S, Lagercrantz R, Gustafsson BE. Antigen from colon of

germfree rats and antibodies in human ulcerative colitis. Ann. NY Acad. Sci. 1965; **124:** 377-394.

49. McGiven ART, Ghose T, Nairn RC. Autoantibodies in ulcerative colitis. Br. Med. J. 1967; **ii:** 19.
50. Eckhart R, Heinish M, Meyer zum Buschenfelde KH. Cellular immune reactions against common antigen, small intestine and colon antigen in patients with Crohn's disease, ulcerative colitis and cirrhosis of the liver. Scand J Gastroenterol 1976; **11:** 49-54.
51. Monteiro E, Fossey J, Shiner M, Drasar BS, Allison AC. Antibacterial antibodies in rectal and colonic mucosa in ulcerative colitis. Lancet 1971; **i:** 249-51.
52. Jewell DP, Truelove SC. Circulating antibodies to cow's milk proteins in ulcerative colitis. Gut 1972; **13:** 796-801.
53. Shorter RG, McGill DB, Bahn RC. Cytotoxicity of mononuclear cells for autologous colonic epithelial cell in colonic diseases. Gastroenterology 1984; **86:** 13-22.

53a. Hibi T, Ohara M, Toda K, et al. In vitro anticolon antibody production by mucosal or peripheral blood lymphocytes from patients with ulcerative colitis. Gut 1990; **31:** 1371-6.

53b. Snook JA, de Silva HJ, Jewell DP. The association of autoimmune disorders with inflammatory bowel disease. Q J Med 1989; **72:** 835-40.

54. Peskar BM, Dreyling KW, May B, Schaarschmidt K, Goebell H. Possible mode of action of 5-aminosalicylic acid. Dis Dis Sci 1987; **32:** (suppl) 51S-56S.
55. Miyachi Y, Yoshioka A, Imamura S, Niwa Y. Effect of sulphasalazine and its metabolites on the generation of reactive oxygen species. Gut 1987; **28:** 190-5.
56. Truelove SC, Witts LJ. Cortisone in ulcerative colitis. Final report on a therapeutic trial. Br Med J 1955; **2:** 1041-8.
57. Talstad I, Gjone E. The disease activity of ulcerative colitis and Crohn's disease. Scand J Gastroenterol 1976; **11:** 403-8.
58. Powell-Tuck J, Bown RL, Lennard-Jones JE. A comparison of oral prednisone given as single or multiple daily doses for active ulcerative colitis. Scand J Gastroenterol 1978; **13:** 833-7.
59. Dick AP, Grayson MJ, Carpenter RG, Petrie A. Controlled trial of sulphasalazine in the treatment of ulcerative colitis. Gut 1964; **5:** 437-42.
60. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in treatment of active ulcerative colitis: a randomised trial. Br Med J 1989; **298:** 82-6.
61. Van der Heide H, Van den Brandt-Gadel V, Tytgat GNJ et al. Comparison of beclomethason dipropionate and prednisolone 21-phophate enemas in the treatment of ulcerative proctitis. J Clin Gastroenterol 1988; **10:** 54-8.
62. Segal AW, Ensell J, Munro JA, Sarner M. Indium-111 tagged leucocytes in the diagnosis of inflammatory bowel disease. Lancet 1980; **ii:** 230-2.

63 Leddin DJ, Paterson WG, DaCosta LR, Dinda PK, Depew WT, Markotich J, McKaigney JP, Groll A, Beck IT Indium-111-labeled autologous leucocyte imaging and fecal excretion-a comparison with conventional methods of assessment of inflammatory bowel disease Dig Dis Sci 1987, **32:** 377-87

64 Dearing WH, McGuckin WF, Elveback LR Serum α_1-acid glycoprotein in chronic ulcerative colitis Gastroenterology 1969, **56:** 295-303

65 Weeke B, Jarnum S Serum concentration of 19 serum proteins in Crohn's disease and ulcerative colitis Gut 1971, **12:** 297-302

66 Andre C, Descos L, Landais P, Fermanian J Assessment of appropriate laboratory measurements to supplement the Crohn's disease activity index Gut 1981, **22:** 571-4

67 Jensen KB, Jarnum S, Koudahl G, Kristensen M Serum orosomucoid in ulcerative colitis Its relation to clinical activity, protein loss, and turnover of albumin and IgG Scand J Gastroenterol 1976, **11:** 177-83

68. Buckel NA, Lennard-Jones JE, Hernandez MA, Kohn J, Riches PG, Wadsworth J Measurement of serum proteins during attacks of ulcerative colitis as a guide to patient management Gut 1979, **20:** 22-7

69 Best WR, Becktel JM, Singleton JW Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI) Gastroenterology 1979, **77:** 843-6

70 Harvey RF, Bradshaw JM A simple index of Crohn's disease activity Lancet 1980, **i:** 514

71. Lloyd-Still JD, Green OC A clinical scoring system for chronic inflammatory bowel disease in children Dig Dis Sci 1979; **24:** 620-4

72 Van Hees PAM, van Elteren Ph, van Lier HJJ, van Tongeren JHM An index of inflammatory activity in patients with Crohn's disease Gut 1980, **21:** 279-86

73 Myren J, Bouchier IAD, Watkinsom G, Softley A, Clamp SE, de Dombal FT The OMGE multinational inflammatory bowel disease survey 1976-1982 A further report on 2657 cases Scand J Gastroenterol 1984 Suppl 95 1-27

74 Wright JP, Marks IN, Parfitt A. A simple clinical index of Crohn's disease activity-the Cape Town index. S Afr Med J 1985, **68:** 502-3

75 Pinchbeck BR, Imes S, Dinwoodie A, Thomson ABR Discriminant function analysis to calculate a Crohn's activity group scale to predict future inactive or active disease J Clin Gastroenterol 1988, **10:** 498-504

76 De Dombal FT, Softley A. IOIBD report no 1 observer variation in calculting indices of severity and activity in Crohn's disease Gut 1987, **28:** 474-81

77 Mary JY, Modigliani R Development and validation of an endoscopic index of the severity of Crohn's disease. a prospective multicentre study Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID) Gut 1989, **30:** 983-9

78 Gomes P, Du Boulay C, Smith CL, Holdstock G Relationship between disease activity

indices and colonoscopic findings in patients with colonic inflammatory bowel disease Gut 1986, **27:** 92-5

79 Crama Bohbouth G, Pena AS, Biemond I, Verspaget HW, Blok D, Arndt JW, Weterman IT, Pauwels EKJ, Lamers CBHW Are activity indices helpful in assessing active intestinal inflammation in Crohn's disease? Gut 1989; **30:** 1236-40

80 Fagan EA, Dyck RF, Maton PN, Hodgson HJF, Cahdwick VS, Petric A, Pepys MB Serum levels of C-reactive protein in Crohn's disease and ulcerative colitis Eur J Clin Invest 1982, **12:** 351-9

81 Boirivant M, Leoni M, Tariciotti D, Fais S, Squarcia O, Pallone F The clinical significance of C-reactive protein levels in Crohn's disease Results of a prospective longitudinal study J Clin Gastronterol 1988, **10:** 401 5

82 Brignola C, Campieri M, Bazzochi G, Farraguzia P, Tragnone A, Lanfranchi GA. A laboratory index for predicting relapse in asymptomatic patients with Crohn's disease Gastroenterology 1986, **91:** 1490-4

83 Wright JP, Alp MN, Young GO, Tigler-Wybrandi Predictors of acute relapse of Crohn's disease A laboratory and clinical study Dig Dis Sci 1987, **32:** 164-70

84 Brignola C, Campieri M, Farraguzia P, Tragnone A, Pasquali S, Iannone P, Lanfranchi GA, Barbara L. The possible utility of steroids in the prevention of relapses of Crohn's disease in remission A preliminary study J Clin Gastroenterol 1988, **10:** 631-4 39

85 Dickinson RJ, Ashton MG, Axon ATR, Smith RC, Yeung CK, Hill GL Controlled trial of intravenous hyperalimentation and total bowel rest as an adjunct to the routine therapy of acute colitis Gastroenterology 1980, **79:** 1199-204

86 McIntyre PB, Powell-tuck J, Wood SR, Lennard-Jones JE, Lerebours E, Hecketsweiler P Galmiche J-P, Clin R Controlled trial of bowel rest in the treatment of severe acute colitis Gut 1986, **27:** 481-5

87 O'Morain C, Segal AW, LeviAJ Elemental diet as primary treatment of acute Crohn's disease a controlled trial Br Med J 1984, **288:** 1859 62

88 Muller JM, Keller HW, Erasmi H, Pickelmaier H Total parenteral nutrition as the sole therapy in Crohn's disease-a prospective study Br J Surg 1983, **70:** 40 3

89 Khan AKA, Piris J, Truelove SC An experiment to determine the active therapeutic moiety of sulfasalazine Lancet 1977, ii 892 5

90 Van Hees PAM, Bakker JH, van Tongeren JHM Effect of sulphapyridine, 5-aminosalicylic acid and placebo in patients with idiopathic proctitis a study to determine the active therapeutic moiety of sulphasalazine Gut 1980, **21:** 632 5

91 Peppercorn MA, Goldman P The role of intestinal bacteria in the metabolism of salicylazosulfapyridine J Pharmacol Exp Ther 1972, **181:** 555-62

92 Myers B, Evans DNW, Rhodes J Evans BK, Hughes BR, et al Metabolism and urinary

excretion of 5-aminosalicylic acid in healthy volunteers when given intravenously or released for absorption at different sites in the gastrointestinal tract. Gut 1987; **28**: 196-200.

93. Campieri M, Lanfranchi GA, Bazzocchi G, Brignola C, et al. Treatment of ulcerative colitis with high dose 5-aminosalicylic acid enemas. Lancet 1981; **ii**: 270-1.
94. Danish 5-ASA group. Topical 5-aminosalicylic acid versus prednisolone in ulcerative proctosigmiditis. A randomized, double-blind multicenter trial. Dig Dis Sci 1987; **32**: 598-602.
95. Biddle WL, Greenberger NJ, Swan T, McPhee MS, Miner PB Jr. 5-aminosalicylic acid enemas: effective agent in maintaining remission in left-sided ulcerative colitis. Gastroenterology 1988; **94**: 1075-9.
96. Baron JH, Connell AM, Lennard-Jones JE, Avery Jones F. Sulphasalazine and salicylazosulphadimidine in ulcerative colitis. Lancet 1962; **i**: 1094-6.
97. Dissanayake AS, Truelove SC. A controlled therapeutical trial of ulcerative colitis with sulphasalazine (Salazopyrine). Gut 1973; **14**: 923-6.
98. Dissanayake AS, Truelove SC. A controlled therapeutic trial of long-term maintenance treatment of ulcerative colitis with sulphasalazine. Gut, 1973; **14**: 923-26.
99. Khan AKA, Howes DT, Piris J. Truelove SC. Optimum dose of sulphasalazine for maintenance treatment in ulcerative colitis. Gut 1980; **21**: 232-40.
100. Selby WS, Barr GD, Ireland A, Mason CH, Jewell DP. Olsalazine in ulcerative colitis. Br Med J 1985; **291**: 1373-5.
101. Meyer S, Sachar DB, Present DH, Janowitz HD. Olsalazine sodium in the treatment of ulcerative colitis among patients intolerant of sulfasalazine. A prospective, randomized, placebo-controlled, double-blind, dose-ranging clinical trial. Gastroenterology 1987; **93**: 1255-62.
102. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1987; **317**: 1625-9.
103. Riley SA, Mani V, Goodman MJ, Herd ME, Dutt S, Turnberg LA. Comparison of delayed release 5-aminosalicylic acid (mesalazine) and sulphasalazine in the treatment of mild to moderate ulcerative colitis relapse. Gut 1988; **29**: 669-74.
104. Rao SSC, Dundas SAC, Holdsworth CD, Cann PAN, Palmer KR, Corvett CL. Olsalazine or sulphasalazine in first attacks of ulcerative colitis? A double blind study. Gut 1989; **30**: 675-9.
105. Ireland A, Mason CH, Jewell DP. Controlled trial comparing olsalazine and sulphasalazine for the maintenance treatment of ulcerative colitis. Gut 1988; **29**: 835-7.
106. Riley SA, Mani V, Goodman MJ, Herd ME, Dutt S, Turnberg LA. Comparison of delayed release 5-aminosalicylic acid (mesalazine) and sulphasalazine as maintenance treatment of ulcerative colitis. Gastroenterology 1988; **94**: 1383-9.
107. Mulder CJJ, Tytgat NJ, Weterman IT, Dekker W, Blok P, Schrijver M, v.d. Heyde H. Double-blind comparison of slow-release 5-aminosalicylic acid and sulfasalazine in remission

maintenance in ulcerative colitis. Gastroenterology 1988; **95:** 1449-53.

108. Rutgeerts P. Comparative efficacy of coated, oral 5-aminosalicylic acid (Claversal^{R}) and sulpahsalazine for maintaining remission of ulcerative colitis. Aliment Pharmacol Therap 1989; 3: 183-91.
109. Summers RW, Switz DM, Session JT Jr, et al. National cooperative Crohn's disease study: results of drug treatment. Gastroenterology 1979; **77:** 847-69.
110. Malchow H, Ewe K, Brandes JW, et al. European cooperative Crohn's disease study (ECCDS): results of drug treatment. Gastroenterology 1984; **86:** 249-66.
111. Van Hees PAM, van Lier HJJ, van Elteren Ph, et al. Effect of sulphasalazine in patients with active Crohn's disease: a controlled double-blind study. Gut 1981; **22:** 404-9.
112. Ewe K, Herfarth C, Malchow H, Jesdinsky HJ. Postoperative recurrence of Crohn's disease in relation to radicality of operation and sulfasalazine profylaxis: a multicenter trial. Digestion 1989;**42:** 224-32.
113. Rasmussen SN, Lauritsen K, Tage-Jensen U, Nielsen OH, et al. 5-Aminosalicylic acid in the treatment of Crohn's disease. A 16 week double-blind, placebo-controlled, multicentre study with Pentasa. Scand J Gastroenterol 1987; **22:** 877-83.
114. Bondesen S, Nielsen OH, Schou JB, et al. Steady-state kinetics of 5-aminosalicylic acid and sulfapyridine during sulfasalazine profylaxis in ulcerative colitis. Scand J Gastroenterol 1986; **21:** 693-700.
115. Das KM, Eastwood MA, McManus JPA, Sircus W. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. N Eng J Med 1973; **289:** 491-5.
116. Halsted CH, Ghandi G, Tamura T. Sulfasalazine inhibits the absorption of folates in ulcerative colitis. N Eng J Med 1981; **305:** 1513-7.
117. Van Hees PAM, van Elferen LW, van Rossum JM, van Tongeren JHM. Hemolysis during salicylazosulfapyridine therapy. Am J Gastroenterol 1979; **70:** 501-5.
118. Toovey S. Hudson E, Hendry WF, Levi AJ. Sulphasalazine and male infertility: reversibility and possible mechanisms. Gut 1981; **22:** 445-51.
119. Turunen U, Elomaa I, Autilla V-J, Seppälä K. Mesalazine tolerance in patients with inflammatory bowel disease and previous intolerance or allergy to sulphasalazine or sulphonamides. Scand J Gastroenterol 1987; **22:** 198-802.
120. Rao SS, Cann PA, Holdsworth CD. Clinical experience of the tolerance of mesalazine and olsalazine in patients intolerant of sulphasalazine. Scand J Gastroenterol 1987; **22:** 332-6.
121. Austin LA, Cann PA, Jones TH, Holdsworth CD. Exacerbation of diarrhoea and pain in patients treated with 5-aminosalicylic acid for ulcerative colitis. Correspondence. Lancet 1984; **i:** 917-8.
122. Chakaborty TK, Bhatia D, Heading RC, Ford MJ. Salicylate induced exacerbation of

ulcerative colitis. Gut 1987; **28:** 613-5.

123. Järnerot G. Clinical tolerance of olsalazine. Scand J Gastroenterol 1988; **23:** (suppl 148) 21-23.
124. Mohsen AQM, Mulvey D, Priddle JD, Parsons DS. Effects of olsalazine in the jejunum of the rat. Gut 1987; **28:** 346-52.
125. Goerg KJ, Wanitschke K, Diehl PH, Meyer zum Büschenfelde KH. Secretory effect of azodisalicylate (azodisal sodium) on the short circuited mucosa of the rat ileum in vitro. Gut 1988; **29:** 336-41.
126. Sandberg-Gertzén H, Järnerot G, Bukhave K, Lauritsen K, Rask-Madsen J. Effect of azodisal sodium and sulfasalazine on ileostomy output of fluid and luminal concentrations of PGE_2 and PGF_2 in subjects with a permanent ileostomy. Gut 1986; **27:** 1306-11.
127. Poldermans D, van Blankenstein M. Pancreatitis induced by disodium azodisalicylate. Am J Gastroenterol 1988; **83:** 578-80.
128. Sachedina B, Saibil F, Cohen LB, Whittey J. Acute pancreatitis due to 5-aminosalicylic acid. Ann Int Med 1989; **110:** 490-2.
129. Deprez P, Descamps Ch, Fiasse R. Pancreatitis induced by 5-aminosalicylic acid. Lancet 1989; **ii:** 445-6.
130. Calder SC, Funder CC, Green CR, Ham KN, Tange JD. Nefrotoxic lesions from 5-aminosalicylic acid. Br Med J 1972; **i:** 152-4.
131. Novis BH, Korzets Z, Chen P, Bernheim J. Nephrotic syndrome after treatment with 5-aminosalicylic acid. Br Med J 1988; **i:** 1442.
132. von Mühlendahl KE. Nephritis durch 5-aminosalicylsäure. Dtsch Med Wochensch 1989; **114:** 236.
133. Rasmussen SN, Bondesen S, Hvidberg EF, Hansen SH, Binder V, Halskov S, Flach SH. 5-Aminosalicylic acid in a slow-release preparation: bioavailability, plasma level, and excretion in humans. Gastroenterology 1982; **83:** 1062-70.
134. Sandberg-Gertzén H, Ryde H, Järnerot G. Absorption and excretion of a single 1 g dose of azodisal sodium in subjects with ileostomy. Scand J Gastroenterol 1983; **18:** 107-11.
135. Nielsen OH, Bondesen S. Kinetics of 5-aminosalicylic acid after jejunal instillation in man. Br J Clin Pharmac 1983, 16, 738-740.
136. Dull BJ, Salata K, Goldman P. Role of intestinal flora in the acetylation of sulfasalazine metabolites. Biochem Pharmacol 1987, 36, 3772-3774.
137. Allgayer H, Ahnfelt NO, Kruis W, Klotz U,Frank-Holmberg K, Söderberg HNA, Paumgartner G. Colonic N-acetylation of 5-aminosalicylic acid in inflammatory bowel disease. Gastroenterology 1989, 97, 38-41.
138. Lennard-Jones JE, Misciewicz JJ, Connell AM, Baron JH, Jones FA. Prednisone as maintenace treatment for ulcerative colitis in remission. Lancet 1965; **i:** 188-9.

139. Brignola C, Campieri M, Farrugia P, et al. The possible utility of steroids in the prevention of Crohn's disease in remission. J Clin Gastroenterol 1988; **10:** 631-4.

140. Truelove S. Treatment of ulcerative colitis with local hydrocortisone hemisuccinate. A report on a controlled therapeutic trial. Br Med J 1958; **2:** 1072-7.

141. Lennard-Jones JE. Towards optimal use of corticosteroids in ulcerative colitis and Crohn's disease. Gut 1983; **24:** 177-81.

142. Mulder CJJ, Rondas AALM, Wiltink EHH, Tytgat NGJ. Topical corticosteroids in inflammatory bowel disease. Neth J Med 1989; **35:** S27-34.

143. Rosenberg JL, Wall AJ, Levin B, Binder HJ, Kirsner JB. A controlled trial of azathioprine in the management of chronic ulcerative colitis. Gastroenterology 1975; **69:** 96-9.

144. Kirk AP, Lennard-Jones JE. Controlled trial of azathioprine in chronic ulcerative colitis. Br Med J 1982; **284:** 1291-2.

145. Jewell D, Truelove SC. Azathioprine in ulcerative colitis: final report on a controlled therapeutic trial. Br Med J 1974; **4:** 627-30.

146. Gupta S, Keshavarzian A, Hodgson HJF. Cyclosporin in ulcerative colitis. Lancet 1984; **i:** 1277-8.

147. Rhodes J, Bainton D, Beck P, Campbell H. Controlled trial of azathioprine in Crohn's disease. Lancet 1971; **ii:** 1273-6.

148. O'Donoghue DP, Dawson AM, Powell- Tuck J, Bown RL, Lennard-Jones JE. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. Lancet 1978; **ii:** 955-7.

149. Singleton JW, Law DH, Kelley ML Jr, Mekhjian HS, Sturdevant RAL. National cooperative Crohn's disease study: adversereactions to study drugs. Gastroenterology 1979; **77:** 870-82.

150. Brynskow J, Freund L, Rasmussen SN, Lauritsen K, et al. A placebo-controlled, double-blind, randomized trial fo cyclosporine therapy in active chronic Crohn's disease. N Engl J Med 1989; **321:** 845-50.

151. Keighley MR. Infection and the use of antibiotics in Crohn's disease. Can J Surg 1984; **27:** 438.

152. Ursing B, Alm T, Barany F, Bergelin I, et al. A comparative study of metronidazole and sulfasalazine for active Crohn's disease. The cooperative Crohn's disease study in Sweden (CCDSS). Gastroenterology 1982; **83:** 550-62.

153. Gilat T, Suissa A, Leichtman G, Delpre G, Pavlotzky M, Grossman A. Fireman Z. A comparative study of metronidazole and sulfasalazine in active, not severe ulcerative colitis. An Israeli multicenter trial. J Clin Gastroenterol 1987; **9:** 415-7.

154. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. Gut 1983; **4:** 299-315.

155. Hendriksen C, Kremer S, Binder V. Long term prognosis in ulcerative colitis-based on

results from a regional patient group from the County of Copenhagen. Gut 1985; **26:** 158-63.

156. Järnerot G, Rolny P, Sandberg-Gertzén H. Intensive intravenous treatment of ulcerative colitis. Gastroenterology 185; **89:** 1005-13.
157. Watts JM, de Dombal FT, Watkinson G, Goligher JC. Long-term prognosis of ulcerative colitis.Br Med J 1966; **i:** 1447-53.
158. Jalan KN, Prescitt RJ, Sircus W, Card WI, et al. An experience of ulcerative colitis. III. Long term outcome. Gastroenterology 1970; **59:** 598-602.
159. Bonnevie O, Binder V, Anthonissen P, Riis P. The prognosis of ulcerative colitis. Scand J Gastroenterol 1974; **9:** 81-91.
160. Bergman L, Krause U. Crohn's disease: A long term study of the clinical course of 186 patients. Scand J Gastroenterol 1977; **12:** 937-44.
161. Binder V, Hendriksen C, Kremer S. Prognosis in Crohn's disease-based on results from a regional patient group from the county of Copenhagen. Gut 1985; **26:** 146-50.
162. Mekhjian HS, Switz DM, Watts HD, Deren JJ, Katon RM, Beman FM. National cooperative Crohn's disease study: factors determining recurrence of Crohn's disease after surgery. Gastroenterology 1979; **77:** 907-13.
163. Shivananda S, Hordijk MC, Pena AS, Mayberry JF. Crohn's disease: risk for recurrence and reoperation in a defined population. Gut 1989; **30:** 990-5.
164. Mayberry JF, Newcombe RG, Rhodes J. Mortality in Crohn's disease. Quart J Med 1980; **193:** 63-8.

CHAPTER 3

EFFECT OF SULPHASALAZINE AND PREDNISONE COMPARED WITH SULPHASALAZINE AND PLACEBO IN TREATING ACTIVE CROHN DISEASE

A double-blind, randomized, multicenter trial

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Annals of Internal Medicine 1991; **114:** 15 march (in press)

ABSTRACT

Objective: To determine whether sulphasalazine plus prednisone is more effective than sulphasalazine alone in treating active Crohn's disease.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Multicenter trial in one university hospital and nine general hospitals.

Patients: Patients with active Crohn's disease and a Van Hees Activity Index of 140 or more. Of 71 patients who were randomly assigned 60 completed treatment and were analyzed.

Interventions: For 16 weeks, 30 patients received sulphasalazine 6 g/d (or 4 g/d if adverse effects occurred) and prednisone 30 mg/d initially. Prednisone therapy was tapered in steps of 5 mg/2wk to 10 mg/d after 8 weeks. Thirty other patients received sulphasalazine and a placebo.

Measurements and Main Results: In the first 6 weeks of treatment, the Van Hees Activity Index decreased to a median of 70% (interquartile range 57 to 81%) of the initial value in patients treated with sulphasalazine and prednisone and to a median of 87% (interquartile range 70 to 94%) in patients treated with sulphasalazine alone ($P = 0.001$). In the last 4 weeks of treatment, the corresponding figures were 63% (interquartile range 40 to 75%) and 70% (interquartile range 54 to 90%) ($P = 0.10$). The Crohn's Disease Activity Index decreased in the first 6 weeks to a median of 65% (interquartile range 57 to 86%) in patients receiving sulphasalazine and prednisone and to a median of 75% (interquartile range 58 to 101%) in patients receiving sulphasalazine alone ($P = 0.13$). In the last 4 weeks of treatment, the corresponding figures were 65% (interquartile range 42 to 90%) and 76% (49 to 110%) ($P = 0.19$).

Conclusions: The use of prednisone in addition to sulphasalazine in patients with active Crohn's disease results in a significantly faster initial improvement, but not in a significantly better result after 16 weeks of treatment, when disease activity is measured by the Van Hees Activity Index.

INTRODUCTION

Both sulphasalazine and prednisone are widely used in the treatment of patients with Crohn's disease. Sulphasalazine is generally used for patients with mildly or moderately active Crohn's disease, and corticosteroids are used as well when the disease is severe or the condition worsens during treatment. The superiority of sulphasalazine to placebo has been proved in several studies (1-3). In the National Cooperative Crohn's Disease Study sulphasalazine was shown to be effective in treating Crohn's colitis and ileocolitis (1), whereas, in the European Cooperative Crohn's Disease Study, it was effective only for treatment of colonic involvement (2). The study of Van Hees and colleagues (3) showed the effectiveness of sulphasalazine in treating both small- and large-bowel disease. In both studies, the effectiveness of corticosteroids in treating patients with active disease in different locations was shown. In the National Cooperative Crohn's Disease Study, corticosteroids alone were not effective in treating colonic disease (1).

An additive effect from combination therapy with corticosteroids and sulphasalazine in patients with active Crohn's disease might be expected, but so far has not been investigated. Nor has it become clear whether severely ill patients will benefit more from addition of corticosteroids than do mildly or moderately ill patients. We therefore compared the effect of therapy with sulphasalazine and prednisone with the effect of therapy with sulphasalazine and placebo in 60 patients with active Crohn's disease in a double-blind, randomized, multicenter trial designed to answer three questions: Does combination therapy with sulphasalazine and prednisone induce more rapid improvement in active Crohn's disease than does sulphasalazine alone? Does such therapy result in a better improvement at the end of treatment than does therapy with sulphasalazine alone? Is combination therapy with prednisone and sulphasalazine especially effective in treating Crohn's disease that manifests in certain locations or in treating severe Crohn's disease?

Patient selection and diagnostic criteria for Crohn's disease

Ten Dutch hospitals participated in the study. The reference committee of the University Hospital Nijmegen determined whether diagnoses of Crohn's disease were correct and approved the application of criteria for inclusion, exclusion (Table 1), and premature withdrawals. From February 1982 to May 1986, 175 patients with active Crohn's disease were examined for eligibility for the trial. Patients were diagnosed as having Crohn's disease if they had a chronic inflammatory bowel disease (for at least 3 months) and their radiographs showed typical features of Crohn's disease (4). In several patients, the diagnosis was confirmed by endoscopy; however, only radiologic criteria were used for patient selection because this procedure allowed central and uniform judgment. Only patients with a Van Hees Activity Index of 140 or more (*see* next section) were included. Patients with a first attack as well as patients with a relapse who had been medically or surgically treated in the past were eligible. For patients receiving maintenance treatment with sulphasalazine, corticosteroids, or both, a washout period of 14 days was instituted. Patients who met one or more of the criteria listed in Table 1 were excluded from the study.

The study protocol was reviewed and approved by the ethics committee of the University Hospital Nijmegen. Patients were fully informed, and their written consent was obtained in accordance with the declarations of Helsinki and Tokyo.

Assessment of inflammatory activity

The activity index developed by Van Hees and colleagues (5) was used to assess inflammatory activity and to evaluate the effects of therapy. In addition, all variables included in the Crohn's Disease Activity Index were collected to permit computation this index according to Best and colleagues (6). The variables in the Van Hees Activity Index are stool consistency, the presence of extra-intestinal lesions, the presence of an abdominal mass, temperature, the Quetelet index

(weight divided by height squared), sex, previous resections, erythrocyte sedimentation rate, and serum albumin level. Values of less than 100 indicate quiescent disease, of 100 to 150 indicate mild disease, of 150 to 210 indicate moderately severe disease and values of more than 210 indicate severe or very severe disease. The variables in the Crohn's Disease Activity Index are the number of liquid or soft stools, the number of perianal and extra-intestinal lesions, the presence of an abdominal mass, the percentage of body weight that is below standard weight, hematocrit results, abdominal pain, well-being, and use of opiates. A Crohn's Disease Activity Index of less than 150 denotes quiescent disease, of 150 to 450 indicates active disease, and of more than 450 indicates very severe disease.

Study design and randomization

Patients who satisfied the diagnostic and study criteria and had given their written informed consent were assigned to receive either sulphasalazine and prednisone or sulphasalazine and placebo. Patients were allocated to treatment groups using a modification of the standardized range method presented by Begg (7) to ensure equal distribution of prognostic factors between both treatment groups. The modification consisted of standardization of the variance method. The balancing variables were the Van Hees Activity Index, the location of disease, first attack or recurrence, the duration of symptoms, previous medical or surgical therapy, and attending physician.

The duration of treatment was 16 weeks. The dose of sulphasalazine was initially 6 g/d in four doses and was reduced to 4 g/d when side effects attributable to sulphasalazine occurred. Prednisone and placebo were given as externally indistinguishable capsules, each containing 5 mg. Double-blindness appeared to be maintained throughout the study in all patients. The dose of prednisone was 30 mg/d during the first 2 weeks. Prednisone therapy was tapered in steps of 5 mg/2 wk to 10 mg/d after 8 weeks and remained at that level until the end of the study.

All patients were interviewed and examined at inclusion and every 2 weeks

Table 1 *Criteria for exclusion*

Criteria
Severe illness
presence of abscesses or large infiltrates
very poor general condition (inclusion in the trial would entail an unacceptable risk)
Surgery is likely to be needed soon (for example, severe stenosis, extensive fistulae)
Presence of a blind loop, ileostomy, proximal colostomy, or ileorectal anastomosis
Location of Crohn's disease in the proximal small or entire small bowel
Reinstitution of treatment within the 4 weeks before study entry
Van Hees Activity Index of 140 or less
Elevation of at least two out of four liver function variable (bilirubin, alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase levels) to more than twice the upper margin of the normal range, or evidence of liver cirrhosis
Creatinine clearence of less than 30 mL/min
Diabetes mellitus
Conditions influencing Van Hees Activity Index variables (for example the nephrotic syndrome, hyperthyroidism, malabsorption not caused by Crohn's disease and diseases associated with raised erythrocyte sedimentation rate such as rheumatoid arthritis)
Need for antibiotics or corticosteroids (for any reason)
Proved allergy to sulphadrugs, salicylates, or sulphasalazine
Pregnancy
Uncooperativeness

during the study period: At each visit, a medical history was taken, patients were questioned about the intake of the capsules; a physical examination was done, with an emphasis on the findings needed to establish the Van Hees Activity Index and the Crohn's Disease Activity Index, and blood was drawn for determining all of the laboratory variables included in the two indices and for measuring serum levels of sulphapyridine. All patients recorded their complaints on a diary chart during the week before each visit.

Criteria for premature discontinuation of treatment

Therapy was considered to be no longer justified and was discontinued when a patient's temperature was persistently over 38.0°C, the Van Hees Activity Index value increased by more than 25% to more than 200, or when this index was more than 200 for more than 8 weeks. When therapy was stopped for one of these reasons, the patient was included in the evaluation as a treatment failure. Patients who were withdrawn for reasons other than the three above were not included in the analysis.

Assessment of the response to therapy and statistical analysis

The response to treatment was examined and tested by comparing the relative changes in the activity indices of both treatment groups in the early phase and at the end of the treatment period. In Van Hees and colleagues study (3), the most substantial decrease in activity in patients receiving sulphasalazine was reached after 6 weeks of treatment. In our study, the means of the data obtained at weeks 2, 4 and 6 were considered to represent the initial response, and the means of the data obtained at weeks 12, 14 and 16 were considered to represent the final response. Comparisons were made between the two treatment groups as a whole and after subdivision according to the location of disease (in the small bowel only, in the small bowel and colon, and in the colon only) and according to the initial Van Hees Activity Index value (< 175 or ≥ 175).

In cases of premature withdrawal due to treatment failure the values of the activity indices at all later times were set at the values they had been at the time of withdrawal. The test of Shapiro-Wilk was used to assess normality. Because of the non-normal distribution of the responses, the Wilcoxon two-sample test was used.

Differences in sulphasalazine intake and serum sulphapyridine levels were also examined with the Wilcoxon two-sample test. Correlations between stool frequency and the activity index were examined with the Spearman correlation coefficient (r_s). The chi-square test was used to test the dependance of the disease activity on the location of disease. Only two-sided test results were used.

P-values of less than 0.05 were considered significant. Data were analyzed with the Statistical Analysis System (SAS Institute, Cary, North Carolina).

RESULTS

Composition of treatment groups

During the entire study period, 175 patients were examined for eligibility. One hundred and four of them were excluded because of too low an Activity Index value (67 patients), recent start of drug treatment (12), need for surgery (11), severe illness (5), refusal to provide informed consent (3), previous adverse reactions to test drugs (2) and other reasons (4 patients). Seventy-one patients were randomly assigned. Eleven of them dropped out before the end of the study for reasons that made them not evaluable: adverse effects of sulphasalazine (3 patients), uncooperativeness (2 patients), false diagnosis of Crohn's disease (2 patients), need for surgery within 14 days (2 patients), break in drug use (1 patient) and cerebrovascular accident (1 patient). Sixty patients remained for analysis. Thirty were assigned to receive sulphasalazine and prednisone and 30 to receive sulphasalazine and placebo. The main characteristics of both treatment groups are shown in Table 2. The distribution of the initial values for the Van Hees Activity Index did not differ significantly according to the location of disease in either treatment group. The number of patients per center ranged from 4 to 17.

The mean intake of sulphasalazine, as judged by the biweekly questionnaire, was 5.4 ± 0.7 g/d (mean ± SD) in the group assigned to receive sulphasalazine and prednisone and 5.0 ± 1.1 g/d in the group assigned to receive sulphasalazine and placebo. No significant difference in serum levels of sulphapyridine was found between the two treatment groups, indicating similar compliance to therapy.

Response to therapy

Four patients had a premature treatment failure. One was treated with sulphasalazine and prednisone and was excluded from the study after 8 weeks

Table 2. *Comparability of treatment groups*

Patient characteristics	Treatment group	
	sulphasalazine plus prednisone (n = 30)	sulphasalazine plus placebo (n = 30)
Men : women	8:22	7:23
Mean age ± SD, y	29.4 ± 14.0	27.9 ± 11.0
Bowel involvement, n		
Small bowel only	10	11
Small bowel and colon	10	9
Colon only	10	10
First attack : relapse	26:4	24:6
Maintenance treatment with		
Prednisone	0	1
Sulphasalazine	3	4
Mean Van Hees Activity Index ± SD	178.4 ± 30.2	173.2 ± 27.3
Initial Van Hees Activity Index > 175	13	11
Mean Crohn's Disease Activity Index ± SD	304.9 ±105.0	254.8 ± 79.1
Number of liquid or very soft stools per week ± SD	31.6 ± 27.1	20.1 ± 15.7

There was no significant difference between the two groups

because the Van Hees Activity Index remained above 200 for that time. The other three patients, treated with sulphasalazine and placebo, were excluded after 2 and 4 weeks (because of persistent high fever), and 8 weeks (because of a Van Hees Activity Index that remained above 200), respectively. The course of the relative Van Hees Activity Index, as compared with the initial value, in both treatment groups is shown in Figure 1.

1. *Initial response*

The mean relative changes in activity indices in the first 6 weeks of treatment

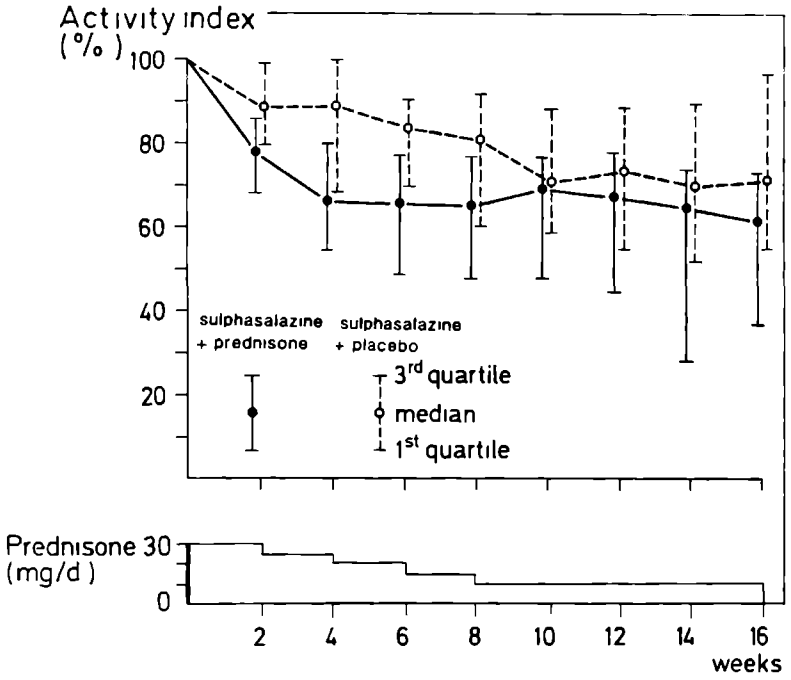

Figure 1. *The Van Hees Activity Index value as a proportion of the initial value in patients treated with sulphasalazine and prednisone (●) or sulphasalazine and placebo (O). The daily dose of prednisone in the patients treated with sulphasalazine and prednisone is shown in the bottom panel. Data are presented as medians and quartiles. The median and the first and third quartiles of a sample are the values which include 50%, 25%, and 75% of the observations, respectively.*

are presented in Table 3. In the initial phase of treatment a significantly faster decrease in the Van Hees Activity Index was seen in all of the patients who were treated with sulphasalazine and prednisone, in the subgroups of patients whose Crohn's disease was located in the small bowel and the colon and in the colon only, and in the subgroup with a high and the subgroup with a low initial Van Hees Activity Index value. When the Crohn's Disease Activity Index was used as an indicator of the degree of illness, the conditions of patients who were treated with sulphasalazine and prednisone also showed more improvement during the first 6 weeks than did the conditions of those who

Table 3. *Relative values of the Van Hees Activity Index and the Crohn's Disease Activity Index in the first 6 weeks of treatment*[*].

	mean Van Hees Activity Index			mean Crohn's Disease Activity Index		
	sulphasalazine plus prednisone	sulphasalazine plus placebo	P-value	sulphasalazine plus prednisone	sulphasalazine plus placebo	P-value
Disease location						
Small bowel only	73 (64-86) N = 10	87 (72- 89) N = 11	0.27	72 (52-86) N = 9	93 (55-121) N = 11	0.17
Small bowel and colon	68 (54-81) N = 10	86 (70-100) N = 9	0.04	58 (56-88) N = 9	72 (50- 98) N = 9	0.79
Colon only	64 (47-79) N = 10	88 (59- 93) N = 10	0.03	65 (61-87) N = 10	71 (66-110) N = 10	0.38
Initial activity index						
<175	75 (64-84) N = 17	86 (74- 89) N = 19	0.04			
> 175	63 (51-72) N = 13	88 (60-103) N = 11	0.02			
All	70 (57-80) N = 30	87 (70- 94) N = 30	0.001	65 (57-86) N = 28	75 (58-100) N = 30	0.13

[*] The relative values are expressed as percentages of the initial values. The data are the medians of the mean values obtained at week 2, 4 and 6, with quartile ranges in parentheses. N = number of patients.

were treated with sulphasalazine and placebo; however, this difference was not significant. This finding applied to the whole group of patients and to all subgroups according to disease location.

2. *Final response*

The values of the relative activity indices in the last 4 weeks of treatment (the mean of the values obtained at weeks 12, 14 and 16) are presented in Table

4. Although the improvement at the end of the treatment period, as measured with both activity indices, was larger in patients treated with sulphasalazine and prednisone, this benefit was not significant when all patients were taken together. When subgroups were considered separately, significant benefit from the additional use of prednisone was seen only in patients with a high initial Van Hees Activity Index value.

The proportion of patients in each treatment group that showed improvement in the components of the two indices in the initial and final phases is shown in Table 5. Of the components of the Van Hees Activity Index, serum albumin, erythrocyte sedimentation rate, and Quetelet score improved most often in both treatment groups in the last 4 weeks. These components also improved in the first 6 weeks in patients who were treated with sulphasalazine and prednisone. In the first 6 weeks of treatment with sulphasalazine and placebo, improvement in the erythrocyte sedimentation rate and in Quetelet score was far less frequent. The number of liquid and very loose stools, scores for abdominal pain and well-being, and body weight were the components of the Crohn's Disease Activity Index that improved most frequently in both treatment groups in the initial and final phases of treatment.

Before the start of treatment, the number of liquid or very soft stools per week was almost significantly higher in patients assigned to receive sulphasalazine and prednisone (Table 2). In this group, there was no significant correlation between the mean relative change in the Van Hees Activity Index in the first 6 weeks and the number of liquid or very soft stools at the start of treatment. In the group assigned to receive sulphasalazine and placebo, however, the mean relative decrease in the Van Hees Activity Index in the first 6 weeks correlated negatively with the number of liquid or very soft stools at the start of treatment (r_s = -0.47; P = 0.009; n = 30). In other words, the higher the frequency of diarrhea was, the less improvement there was in the initial phase. In this group, some correlation remained between the mean decrease in the Van Hees Activity Index in the last 4 weeks and the number of liquid or very soft stools at the start of treatment (r_s

Table 4. *Relative values of the Van Hees Activity Index and the Crohn's Disease Activity Index in the last 4 weeks of treatment**.

	mean Van Hees Activity Index			mean Crohn's Disease Activity Index		
	sulphasalazine plus prednisone	sulphasalazine plus placebo	P-value	sulphasalazine plus prednisone	sulphasalazine plus placebo	P-value
Disease location						
Small bowel only	73 (63-80) N = 10	71 (53- 80) N = 11	0.81	69 (55-90) N = 10	71 (50-100) N = 11	0.70
Small bowel and colon	62 (38-75) N = 10	70 (52- 98) N = 9	0.21	42 (33-92) N = 10	70 (53- 90) N = 9	0.33
Colon only	52 (35-68) N = 10	71 (53- 92) N = 10	0.09	73 (44-92) N = 10	98 (42-129) N = 10	0.47
Initial activity index						
< 175	71 (62-76) N = 17	71 (54- 80) N = 19	0.94			
> 175	42 (36-68) N = 13	70 (49-101) N = 11	0.02			
All	63 (40-75) N = 30	70 (54- 90) N = 30	0.10	65 (42-90) N = 30	76 (49-110) N = 30	0.19

* The relative values are expressed as percentages of the initial values. The data are the medians of the mean values obtained at week 12, 14 and 16, with quartile ranges in parentheses. N = number of patients.

= -0.36; P = 0.05; n = 30).

DISCUSSION

Our results show that the use of prednisone, in the dose prescribed, in addition to sulphasalazine in the treatment of patients with active Crohn's disease results in markedly faster initial improvement, as measured with the Van Hees Activity Index. This advantage remains at the end of the 16-week treatment period. However, is then far smaller and insignificant. This pattern can be seen in all

Table 5. *Improvement in the components of the Van Hees Activity Index and the Crohn's Disease Activity Index during treatment with sulphasalazine plus prednisone and during treatment with sulphasalazine plus placebo*[*]

Components	sulphasalazine plus prednisone		sulphasalazine plus placebo	
	first 6 weeks	last 4 weeks	first 6 weeks	last 4 weeks
	← % →			
Van Hees Activity Index				
Serum albumin level	100	96	89	92
Erythrocyte sedimentation rate	70	75	33	65
Quetelet score	87	97	40	74
Abdominal mass	30	34	20	26
Temperature	40	38	24	27
Stool consistency	46	52	48	58
Extra-intestinal lesions	3	0	7	7
Crohn's Disease Activity Index				
Loose stools	90	86	57	58
Abdominal pain	90	89	63	73
Well-being	66	68	57	65
Perianal and Extra-intestinal lesions	43	43	40	40
Abdominal mass	30	35	20	27
Haematocrit result	43	45	57	42
Weight	87	93	47	69

[*] percentage of patients with improvement

patient subgroups made according to the location of disease, and for patients with ileocolonic and colonic disease the difference in initial improvement was significant. A real difference may have remained undiscovered as a result of the

small numbers in each subgroup. Prednisone therapy may have produced a better result at 16 weeks had it been tapered off more slowly.

When patients were subdivided according to the severity of disease at the start of treatment, both those with a high ($\geq$ 175) and those with a low ($<$ 175) initial Van Hees Activity Index value benefited significantly from use of prednisone in addition to sulphasalazine in the first 6 weeks of treatment. In the last 4 weeks, however, this advantage remained significant only for patients with a high initial value. When the initial Van Hees Activity Index value was low, the use of prednisone in addition to sulphasalazine made no difference at all at the end of the treatment period. In other words, the conditions of all of the patients improved faster when sulphasalazine was combined with prednisone, but the end result was only better in cases of severe disease. The location of disease and the initial value of the Van Hees Activity Index did not appear to be related to each other.

The course of the Van Hees Activity Index in this study is consistent with that noted in the study of van Hees and colleagues (3), in which the mean initial value in patients treated with sulphasalazine was 185 $\pm$ 30 and the median proportional decrease after 16 weeks of treatment with sulphasalazine was approximately 30%. In our study, the mean initial value of patients treated with sulphasalazine and placebo was 173 $\pm$ 27 and the median proportional decrease after 16 weeks 29% (95% CI 17% to 39%).

Although the Crohn's Disease Activity Index did not show a significant difference between the two treatment groups, the trends were in the same direction as those obtained with the Van Hees Activity Index. The course of the Crohn's Disease Activity Index during treatment with sulphasalazine alone in our study was less favorable than in the National Cooperative Crohn's Disease Study. The mean initial value was 255 $\pm$ 79 in our study and 256 $\pm$ 71 in the National Cooperative Crohn's Disease Study. After 15 weeks of treatment in that study, the mean value of the Crohn's Disease Activity Index had maximally decreased to approximately 60% of its initial value. After 16 weeks of treatment in our study, this figure was about 78%. Comparison of our findings with the results of the National and the

European Cooperative Crohn's Disease Study should be made cautiously, however, because the duration of treatment and the dosages used in that studies were different from those used in our study (1,2).

When patients have diarrhea with an accelerated intestinal transit time, the time of mucosal contact is shortened and, moreover, the splitting of sulphasalazine is less complete (8,9), resulting in decreased availability of 5-aminosalicylic acid to the diseased intestine. We found a negative correlation between the number of liquid or very soft stools and a decrease in the Van Hees Activity Index in the first 6 weeks and even in the last 4 weeks of treatment in the patients who received sulphasalazine and placebo. Patients who do not respond to therapy may continue to have accelerated intestinal transit times, causing incomplete splitting of sulphasalazine and resulting in a diminished therapeutic effect. These correlations were not found in patients treated with sulphasalazine and prednisone, thus warranting the conclusion that sulphasalazine alone, compared with prednisone, which has an uptake largely independent of intestinal transit time, is not effective in patients with severe diarrhea.

The value of the Crohn's Disease Activity Index at the start of the treatment, which was not a balancing variable at the time of assignment, was higher in the group of patients treated with sulphasalazine and prednisone ($P = 0.057$, the Wilcoxon test). On one hand, a high initial disease activity may be attended by a higher probability of treatment failure, thus implying a disadvantage for treatment with sulphasalazine and prednisone. On the other hand, patients with a high initial Crohn's Disease Activity Index value may react better than patients with a lower initial value to administration of prednisone. We tried to correct for the difference between the initial values by using relative instead of absolute values.

The finding that the Crohn's Disease Activity Index, as compared with the Van Hees Activity Index, showed less pronounced differences between the treatment groups might be caused in part by the large variability of the data and the relatively small number of patients. This finding does not indicate that the first index is better than the latter; however, it shows how important the choice of the yardstick of disease activity is for measuring the effectiveness of treatment. The

existence of many activity indices for Crohn's disease indicates that none of them is perfect. The Van Hees Activity Index is composed of some readily accessible laboratory variables and other objective items that mostly indicate inflammatory activity (5), whereas the Crohn's Disease Activity Index contains more subjective variables, like general well-being and abdominal pain (6), that do not necessarily relate to inflammation. In our study, serum albumin, erythrocyte sedimentation rate, and weight were the most frequently improving components of the Van Hees Activity Index. In the Crohn's Disease Activity Index, abdominal pain and well-being were also among the components most frequently improving. So, although the two indices measure different aspects of disease, changes in inflammatory parameters and subjective parameters appear to parallel each other quite well in practice.

REFERENCES

1. Summers RW, Switz DM, Sessions JT Jr, et al National Cooperative Crohn's Disease Study: results of drug treatment. Gastroenterology 1979, **77:** 847-69
2. Malchow H, Ewe K, Brandes JW, et al European Cooperative Crohn's Disease Study (ECCDS). results of drug treatment Gastroenterology 1984, **86:** 249-66.
3. Van Hees PAM, van Lier HJJ, van Elteren Ph, et al Effect of sulphasalazine in patients with active Crohn's disease a controlled double-blind study Gut 1981; **22:** 404-9
4. Marshak RH, Lindner AE. Roentgen features of Crohn's disease. Clin Gastroenterol 1972, **1:** 265-77.
5. Van Hees PAM, van Elteren Ph, van Lier HJJ, van Tongeren JHM. An index of inflammatory activity in patients with Crohn's disease. Gut 1980, **21:** 279-86
6. Best WR, Becktel JM, Singleton JW Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI) Gastroenterology 1979, **77:** 843-6
7. Begg CB, Iglewicz B. A treatment allocation procedure for sequential clinical trials. Biometrics 1980; **36:** 81-90
8. Van Hees PAM, Tuinte JHM, van Rossum JM, van Tongeren JHM. Influence of intestinal transit time on azo-reduction of salicylazosulphapyridine (Salazopyrin) Gut 1979, **20:** 300-4
9. Rijk MCM, van Hogezand RA, van Schaik A, van Tongeren JHM. Disposition of 5-aminosalicylic acid from 5-aminosalicylic acid-delivering drugs during accelerated intestinal transit in healthy volunteers. Scand J Gastroenterol 1989, **24:** 1179-85.

CHAPTER 4

DETERMINATION OF SERUM LEVELS OF OROSOMUCOID AND C-REACTIVE PROTEIN IN PATIENTS WITH ACTIVE CROHN'S DISEASE

DETERMINATION OF SERUM LEVELS OFOROSOMUCOID AND C-REACTIVE PROTEIN IN PATIENTS WITH ACTIVE CROHN'S DISEASE

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SUMMARY

In 103 patients with Crohn's disease the van Hees Activity Index, the Crohn's Disease Activity Index and serum levels of the acute phase reactants orosomucoid and C-reactive protein were measured and their mutual correlations calculated. The predictive power of the initial value of the acute phase reactants and of their change early in treatment was investigated in 30 patients treated with sulphasalazine and prednisone and 30 patients treated with sulphasalazine alone. Coefficients of correlation between the clinical activity indices and the acute phase reactants did not exceed 0.56. In patients with high initial orosomucoid levels (>175mg/100 ml) the response of the van Hees Activity Index was better in the last 4 weeks of treatment with sulphasalazine and prednisone (median 40.8% of initial value, interquartile range 34.9-66.2%) as compared with sulphasalazine alone (median 62.6%, interquartile range 47.1-85.7%; p=0.07). The changes of the acute phase reactants after 2 and 4 weeks of treatment did not distinguish patients with a good and a poor response. We conclude that the acute phase reactants cannot be put in place of clinical activity indices and are of limited predictive value as to the response to therapy.

INTRODUCTION

Many methods are available for the measurement of the activity of Crohn's disease. Clinical activity indices are composed of factors that are considered important for the judgement of the severity of the disease. Factors can be related to the patient's physical status, such as weight and previous resections, to symptoms of inflammation such as stool frequency, extra-intestinal manifestations and fever, to subjective complaints such as abdominal pain and well-being, and to objective laboratory data as ESR, haemoglobin, haematocrit or serum albumin. The Crohn's Disease Activity Index (CDAI) and the Van Hees Activity Index (AI), presented in Table 1, are examples of such composite indices (1, 2).

In several studies it was found that the serum concentrations of some acute phase reactants such as orosomucoid, C-reactive protein and alpha-1-antitrypsin correlated well with disease activity, and therefore might serve as a substitute for or as an adjunct to other indices (3-7). Moreover, the level of one or more of the acute phase reactants, and the value of an index composed of these, were closely related to a future relapse of Crohn's disease in patients in a quiescent phase (7-9).

We investigated the course of the AI, CDAI, and serum levels of orosomucoid and C-reactive protein in patients with active Crohn's disease, their mutual correlations and the value of the measurement of the serum

Table 1. *Composition of the Van Hees Index (AI) and the Crohn's Disease Activity Index (CDAI)*

Factor assessed	AI	CDAI
Stool habits	x	x
Extra-intestinal lesions	x	x
Abdominal mass	x	x
Temperature	x	
Quetelet score (lenght/height^2)	x	
Weight related to ideal weight		x
Sex	x	
Previous resections	x	
ESR	x	
Serum albumin	x	
Haemoglobin/haematocrit		x
Pain		x
General well-being		x
Anti-diarrhoeal drugs		x

AI < 100: quiescent disease,
AI 100-150: mild disease,
AI 150-210: moderately severe disease.
AI > 210: (very) severe disease.

CDAI < 150: quiescent disease,
CDAI 150-450: active disease,
CDAI > 450: very severe disease.

For formulas of AI and CDAI see ref. 1 and 2.

concentrations of these acute phase reactants to predict the response to two defined treatment schemes.

METHODS

Patients and treatment

As described Chapter 3 (10), 175 patients with active Crohn's disease were examined as to their eligibility for a clinical trial, designed to compare the therapeutic effect of salazosulphapyridine (SASP) and prednisone with SASP and placebo. One-hundred-and-four patients were not admitted to the trial, most of them because of an AI lower than 140 points. Of the 71 patients entering the trial eleven were withdrawn for reasons other than treatment failure. Of the remaining 60 patients 30 were assigned to SASP and prednisone, and 30 to SASP and placebo. The dosage of SASP was 4 to 6 g per day. Prednisone was given in an initial dose of 30 mg daily and tapered down to 10 mg after 8 weeks. The total duration of the study was 16 weeks. Control visits took place every two weeks. At each control visit data were collected to calculate the CDAI and AI, and blood was drawn for the determination of orosomucoid and C-reactive protein. The effect of treatment was assessed by the value of the AI and CDAI at the end of the study, expressed as a proportion of the initial value. The mean of available data of week 12, 14 and 16 was considered representative for the end of the treatment period, and was called "final response".

In the group of patients treated with SASP and prednisone the median final response of AI was 63.2% and the median final response of CDAI 65.2%. In patients assigned to SASP and placebo the median final response of AI was 70.4% and of CDAI 75.9% (10).

In 48 of the 104 patients excluded from the trial values of AI, orosomucoid and C-reactive protein were available, and in only 22 of them (mostly seen at the University Hospital Nijmegen) also all data needed for the calculation of the CDAI. In seven out of the 60 patients treated according to the trial protocol data of orosomucoid and C-reactive protein at entry, and in two patients the initial

CDAI were missing. In two out of the eleven patients who were withdrawn prematurely not because of a treatment failure, all data at entry were available. Data from included and excluded patients were combined to establish correlations between the levels of acute phase reactants and activity indices. In the group examined the AI ranged from 50 to 243 (median 153) and the CDAI from 10 to 470 (median 195).

Determination of orosomucoid and C-reactive protein

Serum of patients was stored at -20°C until analysis. Orosomucoid and C-reactive protein levels were measured by means of a radial immunodiffusion method (LC-Partigen^R for C-reactive protein, NOR-Partigen^R for orosomucoid, both from Behringwerke AG, Marburg, W. Germany). The normal range of orosomucoid is 55-140 mg/100 ml, and of C-reactive protein 6-10 mg/l.

Assessment of the value of orosomucoid and C-reactive protein

The measurement of the serum levels of orosomucoid and C-reactive protein was presumed to be of clinical importance if they could replace the clinical activity indices or if their value at the start, or their change in the initial phase of treatment (after 2 or 4 weeks) would have predictive value with regard to the final response to treatment.

To determine the correlations between orosomucoid and C-reactive protein on the one side and AI and CDAI on the other side data from all patients participating in the trial before the start of treatment were taken, and moreover from patients excluded from the trial, as far as all data needed were available. Also, mutual correlation coefficients during the course of treatment were calculated.

The possible predictive value of C-reactive protein and orosomucoid in both treatment groups was examined in two ways. Firstly, we examined whether patients with a high initial level of orosomucoid or C-reactive protein were more likely to profit from the addition of prednisone to SASP than those with a low initial level. Secondly, we studied the correlations between the proportional decrease of the

acute phase reactants in the initial phase of treatment (after two and four weeks) and the final response.

Statistical analysis

Correlations between concentrations of orosomucoid and C-reactive protein and activity indices were examined with Spearman's rank correlation coefficient. Wilcoxon's two-sample test was used to examine differences in proportional changes of the activity indices in both treatment groups. All tests were two-sided. A p-value of 0.05 or less was considered significant.

If a patient was withdrawn from the study because of treatment failure the relative value of AI and CDAI at subsequent times was set at the value at the time of withdrawal.

RESULTS

The correlation coefficients between the acute phase reactants and the activity indices in 103 patients with quiescent and active disease are presented in Table 2. The correlation coefficients of the AI with the acute phase reactants are somewhat higher than of the CDAI.

Table 2. *Spearman's rank correlations between serum orosomucoid, serum C-reactive protein and Van Hees Activity Index (AI) and Crohn's Disease Activity Index (CDAI) in patients with Crohn's disease. All values measured before the start of treatment.*

	AI	CDAI
orosomucoid	r = 0.56	r = 0.34
	p < 0.001	p = 0.003
	n = 103	n = 75
C-reactive protein	r = 0.56	r = 0.32
	p <0.001	p = 0.005
	n = 103	n = 75

From Figures 1 and 2 it is obvious that the mean values of the activity indices run closely together with the mean values of the serum levels of orosomucoid, and far less with C-reactive protein. C-reactive protein responds much faster to treatment, especially in patients treated with SASP and prednisone, than the other parameters. In patients treated

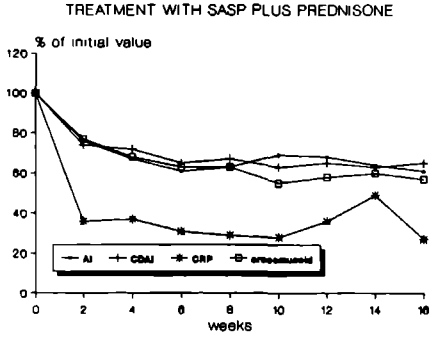

Figure 1 *Course of the mean proportional value of AI, CDAI, orosomucoid and C-reactive protein (CRP) in patients with active Crohn's disease, treated with sulphasalazine and prednisone*

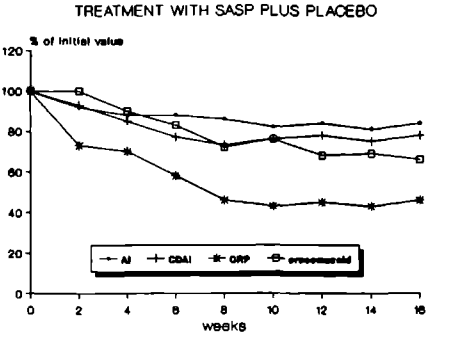

Figure 2. *Course of the mean proportional value of AI, CDAI, orosomucoid and C-reactive protein (CRP) in patients with active Crohn's disease, treated with sulphasalazine and placebo*

with sulphasalazine and prednisone the mean value of C-reactive protein had decreased after 2 weeks to 36 ± 31% of its initial value, whereas orosomucoid had decreased to only 77 ± 23%, the AI to 76 ± 15% and the CDAI to 74 ± 18%. In patients treated with sulphasalazine and placebo the values of C-reactive protein, orosomucoid, AI and CDAI had decreased to 73 ± 66%, 99 ± 42%, 92 ± 28% and 93 ± 44%.

In Table 3 correlation coefficients at the start of treatment and after 2 and 16 weeks are presented. The coefficients of correlation with the CDAI were generally much lower. Although the Figures 1 and 2 suggest that the correlation between activity indices and orosomucoid is fairly good, the r-values never exceeded 0.71, due to a large spread of values. Furthermore, the r-values showed a considerable week-to-week fluctuation.

In the group of patients with a high initial serum orosomucoid (higher than the median value of 175 mg/100 ml) or a high initial C-reactive protein (higher than the median value of 50 mg/l) the final response of AI and CDAI was better in those treated with SASP and prednisone than in those treated with SASP and placebo, but this failed to reach statistical significance (the lowest p-value was 0.07 for the difference in response of AI in patients with high and low initial orosomucoid). In patients with a low initial orosomucoid or C-reactive protein the responses to SASP and prednisone and to SASP and placebo were similar (Table

Table 3. *Spearman's rank correlations between serum orosomucoid, serum C-reactive protein (CRP) and Van Hees Activity Index (AI) in patients with Crohn's disease, measured during treatment with sulphasalazine and prednisone or sulphasalazine alone.*

	Correlation coefficients with AI					
	At the start of treatment with		After 2 weeks of treatment with		After 16 weeks of treatment with	
	SASP plus prednisone	SASP plus placebo	SASP plus prednisone	SASP plus placebo	SASP plus prednisone	SASP plus placebo
orosomucoid	r = 0.59	r = 0.41	r = 0.29	r = 0.50	r = 0.69	r = 0.70
	p = 0.01	p = 0.04	p = 0.13	p = 0.01	p = 0.003	p = 0.008
	n = 28	n = 26	n = 29	n = 23	n = 16	n = 13
CRP	r = 0.48	r = 0.31	r = 0.34	r = 0.14	r = 0.45	r = 0.71
	p = 0.01	p = 0.11	p = 0.08	p = 0.54	p = 0.07	p = 0.007
	n = 27	n = 27	n = 28	n = 23	n = 16	n = 13

4). The choice of any other cut-off point for high and low values of the acute phase reactants did not result in a better prediction of the result of therapy. It is apparent however from the data in Table 4 that patients treated with SASP and prednisone who have high initial orosomucoid levels respond far better than those with low initial levels (no overlap in quartile ranges of final respons, $p < 0.001$).

The correlations between the change of acute phase reactants in the first four weeks of treatment and the final response of the AI are shown in Table 5. As none of the r-values of the correlations with the CDAI exceeded 0.31, these correlation coefficients are not mentioned. With the exception of orosomucoid in patients treated with SASP and placebo, the relative value of orosomucoid and C-reactive protein after four weeks correlated significantly with the final response of AI in the whole group of patients and in both treatment groups. However, the change of the acute phase reactants after four weeks in individual cases had little predictive power with regard to the final response. For, when patients were divided according to the height of the relative values after four weeks (more or

Table 4. *Relative values of AI and CDAI (expressed as percentages of the initial value) in the last four weeks of treatment,in subgroups of patients according to initial height of the acute phase reactants. Figures are medians of the mean values of week 12, 14 and 16, with quartile ranges in parenteses.*

	mean AI in the last four weeks			mean CDAI in the last four weeks		
	SASP + prednisone	SASP + placebo	p	SASP + prednisone	SASP + placebo	p
orosomucoid <175	75.1 (67.3-82.2) n = 13	71.7 (55.0-88.3) n = 16	0.48	75.7 (59.0-96.7) n = 13	70.8 (51.9-107.3) n = 16	0.98
orosomucoid >175	40.8 (34.9-66.2) n = 15	62.6 (47.1-85.7) n = 10	0.07	45.9 (33.5-72.7) n = 13	87.0 (50.4-102.3) n = 9	0.12
C-reactive protein <50	71.9 (54.9-76.5) n = 14	66.3 (52.2-80.6) n = 14	0.84	70.5 (54.7-91.9) n = 14	69.8 (42.1- 90.5) n = 14	0.91
C-reactive protein >50	60.8 (35.4-71.4) n = 13	72.3 (51.9-90.7) n = 13	0.095	59.6 (31.0-85 0) n = 11	90.3 (53.6-110.0) n = 12	0.19

Units of orosomucoid: mg/100 ml; units of C-reactive protein: mg/ml.
p. P-values of the difference between the SASP plus prednisone treated and the SASP plus placebo treated group.

less than the median value), the difference in final response of AI between these groups was not significant, neither when other cut-off points were chosen. This was due to a large overlap in final response of AI between both groups. The correlations between the relative changes of the acute phase reactants after two weeks and the final responses of the activity indices were even lower than after four weeks, so the relative change after two weeks does not provide any information as to the final outcome.

Table 5. *Spearman's rank correlations between the relative value of serum orosomucoid, C-reactive protein after four weeks of treatment, expressed as percentage of the initial value, and the final response of the Van Hees Activity Index (AI), expressed as the mean of available relative values of week 12, 14 and 16, in patients with Crohn's disease treated for 16 weeks with sulphasalazine (SASP) and prednisone or SASP and placebo.*

	Final response of AI		
Proportional value after four weeks of	Patients treated with SASP and prednisone	Patients treated with SASP and placebo	All patients
orosomucoid	r = 0.65 p = 0.0003 n = 26	r = 0.31 p = 0.13 n = 25	r = 0.53 p = 0.0001 n = 0.51
C-reactive protein	r = 0.51 p = 0.02 n = 22	r = 0.54 p = 0.007 n = 24	r = 0.49 p = 0.0004 n = 46

DISCUSSION

Serum levels of C-reactive protein and orosomucoid are considered to reflect the severity of acute inflammation. The question whether this holds for patients with active Crohn's disease cannot be answered in this study, as our "gold standards" were clinical activity indices, partly consisting of factors, e.g. haemoglobin and body weight, that certainly do not immediately respond to acute inflammation. But, even if acute phase reactants cannot be expected to correlate closely with the activity indices - what they actually did not in this study - they would be of value if they were good predictors of the outcome of therapy.

We found significant correlations between the activity indices and the acute phase reactants, but indeed the correlation coefficients were too low to permit the

replacement of the first by the latter. Furthermore, the r-values changed considerably during the course of both treatments, being particularly low shortly after the start. This inconsistency makes acute phase reactants even less suitabable to substitute the clinical activity indices.

In this study, the average course of the activity indices was well reflected by the average course of the serum levels of orosomucoid, and less by the course of C-reactive protein, that responds much faster to treatment. Measurement of C-reactive protein would be of importance if this early occurring change would be a good predictor of the final outcome of therapy. However, similar to orosomucoid, the initial value of C-reactive protein was not a good predictor of the response to treatment, neither did its relative value after four weeks correlate well with the final response of the activity indices in any treatment group.

In the group of patients with a high orosomucoid level at the start of treatment patients assigned to SASP and prednisone tended to do better than those assigned to SASP and placebo, but the difference just failed to be significant ($p = 0.07$). Still, this might be considered an argument to add prednisone to SASP therapy in patients with high orosomucoid levels.

The relative values of the acute phase reactants after four weeks of treatment correlate significantly with the final response of AI, but, due to a large overlap in final response between patients with a high and a low relative value after four weeks, these values cannot be safely used to predict the individual response to therapy.

André et al found correlations between a simple, four-grade clinical index of disease activity and orosomucoid, C-reactive protein and ESR strong enough to advise addition of one or more of these parameters to a practical clinical index of Crohn's disease activity (3). We feel that the addition of an extra parameter to an activity index is of little use unless it possesses additional proporties, e.g. the power to predict the future course of disease.

Starting from the results of our study, we believe that the determination of the acute phase reactants is of limited additional value in the assessment of disease activity and in the management of the individual patient. Only the initial serum

levels of orosomucoid show a trend to significance in predicting the outcome of treatment in active disease. This is in contrast with the situation of quiescent disease, where a high level of acute phase reactants correlates with an early flare-up (7-9), and may even be helpful in selecting patient groups that could profit of relapse preventing use of corticosteroids (11).

Of course, criticism can be raised against the fact that we judge the usefulness of the acute phase reactants by the AI and CDAI as the gold standards. The choice of the gold standard is less a matter of mathematics than of philosophy. Some authors consider endoscopical and histological findings as the ultimate criterion of disease activity and criticize clinical activity indices and laboratory indicators, including acute phase reactants, for their lack of correlation with endoscopy and histology (12). It can be argued, however, that endoscopy assesses only the internal surface of the gut, histology providing two or three millimeters deeper insight, with ample space for sampling error.

Composite clinical indices as the AI and the CDAI provide more information about the effects of inflammation on metabolism and/or the patient as a whole. After all, activity indices are the quantification of the clinical judgement of its designers, who take decisions in patient management on the basis of its components, not on the basis of whatever single laboratory measurement. The results of this study indicate that clinical activity indices cannot be replaced by a single determination of serum orosomucoid or C-reactive protein, and that these acute phase proteins are of limited prognostic value during treatment of active disease. It should be emphasised, however, that these results apply only to situations where patients are treated according to the described medication scheme.

REFERENCES

1. Best WR, Becktel JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). Gastroenterology 1979; **77**: 843-6.
2. Van Hees PAM, van Elteren Ph, van Lier HJJ, van Tongeren JHM. An index of inflammatory activity in patients with Crohn's disease. Gut 1980; **21**: 279-86.

3. Andre C, Descos L, Landais P, Fermanian J. Assessment of appropriate laboratory measurements to supplement the Crohn's disease activity index. Gut 1981; **22:** 571-4.
4. Fagan EA, Dyck RF, Maton PN, Hodgson HJF, Cahdwick VS, Petrie A, Pepys MB. Serum levels of C-reactive protein in Crohn's disease and ulcerative colitis. Eur J Clin Invest 1982; **12:** 351-9.
5. Macfarlane PI, Miller V, Wells F, Richards B. Laboratory assessment of disease activity in childhood Crohn's disease and ulcerative colitis. J Pediatr Gastroenterol Nutr 1986; **5:** 93-6.
6. Chambers RE, Stross P, Barry RE, Whicher JT. Serum amyloid A protein compared with C-reactive protein, alpha 1-antichymotrypsin and alpha 1-acid glycoprotein as a monitor of inflammatory bowel disease. Eur J Clin Invest 1987; **17:** 460-7.
7. Boirivant M, Leoni M, Tariciotti D, Fais S, Squarcia O, Pallone F. The clinical significance of C-reactive protein levels in Crohn's disease. Results of a prospective longitudinal study. J Clin Gastronterol 1988; **10:** 401-5.
8. Wright JP, Alp MN, Young GO, Tigler-Wybrandi. Predictors of acute relapse of Crohn's disease. A laboratory and clinical study. Dig Dis Sci 1987; **32:** 164-70.
9. Brignola C, Campieri M, Bazzochi G, Farraguzia P, Tragnone A, Lanfranchi GA. A laboratory index for predicting relapse in asymptomatic patients with Crohn's disease. Gastroenterology 1986; **91:** 1490-4.
10. Rijk MCM, van Hogezand RA, van Lier HJJ, van Tongeren JHM. The effect of sulphasalazine and prednisone compared with sulphasalazine and placebo in patients with active Crohn's disease. A double-blind, randomized, multi-centre trial. Ann Int Med, accepted for publication.
11. Brignola C, Campieri M, Farraguzia P, Tragnone A, Pasquali S, Iannone P, Lanfranchi GA, Barbara L. The possible utility of steroids in the prevention of relapses of Crohn's disease in remission. A preliminary study. J Clin Gastroenterol 1988; **10:** 631-4.
12. Gomes P, Du Boulay C, Smith CL, Holdstock G. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut 1986; **27:** 92-5.

CHAPTER 5.1

DISPOSITION OF 5-AMINOSALICYLIC ACID BY 5-AMINOSALICYLIC ACID DELIVERING COMPOUNDS IN HEALTHY VOLUNTEERS

Scandinavian Journal of Gastroenterology 1988; **233:** 107-112

Disposition of 5-Aminosalicylic Acid by 5-Aminosalicylic Acid-Delivering Compounds

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Rijk MCM, van Schaik A, van Tongeren JHM Disposition of 5-aminosalicylic acid by 5 aminosalicylic acid delivering compounds Scand J Gastroenterol 1988, 23, 107–112

The disposition of 5-aminosalicylic acid (5-ASA) from 5-ASA-delivering drugs was studied in eight healthy volunteers Time-related urinary excretion and faecal excretion of 5-ASA and acetyl-5-ASA were measured after a single oral dose of the azo compounds sulphasalazine and olsalazine, of the slow-release compounds Pentasa®, Asacol®, and Salofalk®, and of plain 5-ASA Plain 5-ASA was rapidly excreted into urine and had a low faecal recovery, indicating fast absorption proximally in the intestine and little availability to the colon After ingestion of both azo compounds and slow-release compounds, urinary excretion of 5-ASA was markedly delayed and reduced, and faecal excretion was enhanced At all points of time there was a significant but not very marked difference in urinary excretion of 5-ASA after ingestion of the azo compounds and the slow-release compounds, in favour of the azo compounds A significantly larger proportion of the ingested 5-ASA, moreover, was excreted in faeces after intake of azo compounds as compared with slow-release compounds

Key words 5 Aminosalicylic acid, azodisal sodium (olsalazine), metabolism, salicylazosulphapyridine

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For many years salazosulphapyridine (sulphasalazine, Salazopyrine®, Azulfidine® (SASP)) has been used in the treatment of inflammatory bowel disease (1–6) Unfortunately, adverse effects due to SASP occur not infrequently, necessitating dose reduction or even withdrawal of the drug

After it had become clear that SASP is split by intestinal bacteria into 5-aminosalicylic acid (5-ASA) and sulphapyridine (SP) (7, 8), studies have been performed to identify the active moiety It has been demonstrated that 5-ASA is the active part (9, 10)

Since nearly all side effects are attributable to SP, the development of SP-free alternatives to SASP was a logical next step 5-ASA in suppositories and enemas is now successfully used in the treatment of idiopathic proctitis and distal colitis For more extensive ulcerative colitis and Crohn's disease rectal application is insufficient, and in such situations 5-ASA has to be given by mouth Plain 5-ASA, however, is rapidly absorbed and excreted into urine (11), suggesting that it is largely taken up in the small bowel This is likely to reduce the luminal 5-ASA concentrations in the distal intestine to insufficient levels This problem has been dealt with in two ways

First, 5-ASA has been given such a galenic formulation that it is released gradually or after a certain delay in an environment with a neutral pH Several of these slow-release or sustained-release formulations are now being developed by various pharmaceutical companies, which all coat and buffer 5-ASA in a different manner Pentasa® (Ferring A/S Vanlose, Denmark, 5-ASA in microgranules with an ethyl cellulose membrane), Asacol® (Tillotts Laboratories, Henlow, UK, 5-ASA coated with Eudragit-S, an acrylic-based

resin), and Salofalk® (Falk GmbH Freiburg, FRG, 5-ASA buffered with sodium carbonate and glycine in an enteric soluble film) are now available in some European countries

Secondly, 5-ASA can be coupled with another carrier instead of sulphapyridine via an azo bond Analogous to sulphasalazine, such a compound is also split by intestinal bacteria, resulting in the release of 5-ASA at the proper site The carrier can be an indifferent molecule, such as in ipsalazide or balsalazide (12), or another 5-ASA molecule, thus constituting azodisalicylate (ADS) or olsalazine (Dipentum®, Pharmacia) The latter molecule has the advantage that it does not contain superfluous substances Both olsalazine and slow-release formulations have been tested in patients with active or quiescent ulcerative colitis or Crohn's disease These compounds were claimed to be as effective as sulphasalazine or more active than placebo and were generally tolerated well (13–17)

We wondered whether all 5-ASA-delivering drugs are equally capable of delivering 5-ASA to the distal bowel If one drug would release 5-ASA more proximally in the gut than the others, it would be less appropriate for use in colonic inflammatory bowel disease Reports on the disposition of the new 5-ASA-delivering drugs have been published They all suggest that the disposition is roughly comparable with that of sulphazalazine (18–22) Differences in study design, study subjects, and dosages make it impossible to compare the results We therefore compared the disposition of six 5-ASA-delivering drugs (SASP, ADS, Pentasa, Asacol, Salofalk, and plain 5-ASA) in the same subjects, adhering to a fixed protocol A basic assumption was that 5-ASA liberated early in the proximal small bowel would be absorbed promptly and excreted rapidly into the urine The more 5-ASA is excreted into urine at an early stage, therefore, the less becomes available to the colon We therefore measured the time-related urinary excretion of 5-ASA after a single oral dose of the drugs considered and, in addition, the faecal recovery Both 5-ASA and its major metabolite acetyl-5-ASA were determined

Table I Dosages and 5-ASA contents of the drugs administered in this study

Drugs administered	Dose (mg)	5-ASA content (μmol)
Azo compounds		
Salazopyrine®	1500	3760
Dipentum®	500	2890
Slow-release compounds		
Pentasa®	500	3268
Asacol®	400	2614
Salofalk®	500	3268
Plain 5-ASA	500	3268

Subjects and methods

The study was approved by the hospital's ethical committee

Eight healthy volunteers, six men and two women, took part after giving their informed consent Their age ranged from 20 to 38 years None had a history of gastrointestinal disorders Dosages and 5-ASA content of the drugs administered are listed in Table I The sequence of administration was random, and the washout period after intake of one of the drugs was at least 7 days On the day of administration of the drug the volunteers fasted from midnight until 1300 h Drinking was not restricted At 0900 h the drug was taken by mouth During the first 8 h thereafter, urine was collected in four 2-h portions The fifth portion covered the rest of the first day During the next 3 days urine was collected every 24 h Faeces were collected per 4-day period Urine was collected in plastic containers and immediately placed in dry ice Faeces were collected in plastic containers with $HgCl_2$ and, after thorough shaking, also placed in dry ice Both urine and faeces were stored at −20°C until analysis These measures were taken to prevent (so far as possible) further acetylation and breakdown of 5-ASA and intact parent molecules by bacterial enzymes (23)

Analysis for 5-ASA, ac-5-ASA, SASP, and ADS was done with a sensitive and specific high-performance liquid chromatography (HPLC) method combined with fluorescence spectrophotometry, as described elsewhere (23)

The two-sided Wilcoxon test was used in com-

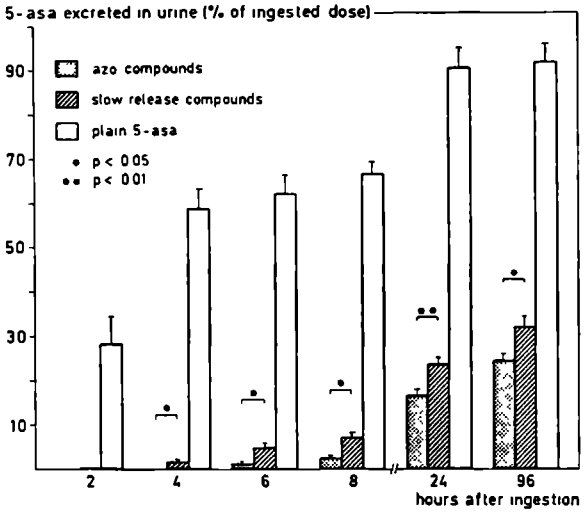

Fig. 1. Cumulative excretion of 5-ASA (acetylated + unacetylated) in urine after ingestion of a 5-ASA-delivering drug, expressed as a percentage of the dose ingested. Azo compounds (SASP and ADS) and slow-release compounds are represented as groups. Bars represent means ± SEM of eight healthy volunteers.

paring the results. P values of <0.05 were considered to be significant.

RESULTS

Fig. 1 shows the cumulative excretion of total 5-ASA (5-ASA plus ac-5-ASA) in urine, expressed as a percentage of the dose ingested. In this figure azo compounds (SASP and ADS) and slow-release compounds are presented as groups.

Plain 5-ASA is excreted very rapidly. After 4 h 58.9% is found in the urine, after 24 h 90.0%, and after 96 h 91.5%. After ingestion of both azo compounds and slow-release compounds, urinary excretion of 5-ASA is markedly delayed and reduced. After 8 h only 2.6% of the 5-ASA administered is recovered in the urine after ingestion of the azo compounds, and 7.3% after ingestion of slow-release tablets. After 24 h the percentages are 16.5 and 23.6, and at 96 h 24.2 and 32.0%, respectively. At all points of time the difference in excretion between the two groups was significant.

Fig. 2 shows the cumulative urinary excretion after 8, 24, and 96 h for all the drugs separately. No significant differences within one group were present. The faecal excretion of 5-ASA and ac-5-ASA after ingestion of the test drugs is shown in Table II.

The faecal recovery of 5-ASA from azo compounds was significantly higher than that from slow-release compounds ($p < 0.05$). Again, no significant differences within one group were found. The faecal excretion of the intact parent molecule was 6.4 ± 1.8% after ingestion of SASP and 4.1 ± 1.1% after ingestion of ADS.

The total recovery rate of 5-ASA from the azo compounds and slow-release compounds ranged from 71.5% (Salofalk) to 81.8% (SASP).

DISCUSSION

The therapeutic effect of 5-ASA is probably related to its local concentration in the bowel lumen and not to serum levels, which are always very low owing to the very rapid excretion of 5-

Table II Faecal excretion of 5 ASA and acetyl 5-ASA in 96 h after ingestion of 5-ASA delivering drugs by eight healthy volunteers, expressed as a percentage (mean ± SEM) of the dose ingested

	5-ASA	Acetyl 5-ASA	Total 5-ASA	Intact parent molecule
SASP	12 8 ± 2 2	45 4 ± 3 4	58 3 ± 4 8	6 6 ± 1 8
ADS	8 2 ± 1 3	39 1 ± 3 4	47 4 ± 3 5	4 1 ± 1 1
Pentasa®	9 0 ± 1 5	38 4 ± 2 4	47 3 ± 2 5	
Asacol®	7 0 ± 1 4	33 2 ± 2 3	40 2 ± 2 0	
Salofalk®	5 2 ± 1 3	32 1 ± 4 2	37 3 ± 4 4	
Plain-5 ASA	0 1 ± 0 1	15 7 ± 2 1	15 8 ± 2 1	
Mean of azo compounds	10 5 ± 1 6	42 3 ± 2 7	52 8 ± 3 5	
Mean of slow-release compounds	7 1 ± 0 9	34 6 ± 2 1	41 7 ± 2 0	

NS

** $P < 0.01$
* $P < 0.05$

inside the bowel could of course not be prevented

Recently, Myers et al (25) published the results of a study in which they measured time-related urinary excretion after ingestion of 500 mg plain 5-ASA and 2 4 g 5-ASA coated with Endragit-S (equivalent to the Asacol used in this study) The proportional urinary excretion of total 5-ASA after 4 h was closely comparable with our results, for plain 5-ASA, 48 2% (58 6% in our study), and for Asacol, 0% (0% in our study)

They found a total urinary recovery from plain 5-ASA of 78% and from Asacol of 21%, these are somewhat smaller percentages than we found in this study This may be partly due to a different method of analysis Unfortunately, they did not measure faecal excretion of 5-ASA Although it seems justified to favour azo compounds in the treatment of distal inflammatory bowel disease on the basis of the results of our study, some precautions should be taken

In this study the total amount of 5-ASA administered was not exactly the same for all the drugs as a result of the different 5-ASA content of some of the tablets Giving equal amounts would mean that some tablets would have to be broken, thus destroying the slow-release mechanism It seems unlikely, however, that the small differences in 5-ASA content have influenced the outcome of this study

The study was performed in healthy volunteers who had a normal intestinal transit time In this respect they resemble patients with quiescent inflammatory bowel disease In active inflammatory bowel disease transit time is often accelerated This may have an unfavourable effect on the release of 5-ASA from the 5-ASA-delivering drugs The release from slow-release tablets takes place more distally in the bowel, and when transit time is very fast, the tablet could be excreted more or less intact We do not know whether this applies equally to each of these slow-release drugs The start of the release of 5-ASA from azo compounds does not depend on the time since ingestion but on the presence of intestinal bacteria The release of 5-ASA from azo compounds starts in the distal small bowel and colon or in more proximal bowel loops when bacterial overgrowth is present, which might be the case in small-bowel segments affected with Crohn's disease (26) This might explain the beneficial effect of SASP in small-bowel Crohn's disease reported in one study (6) On the other hand, splitting of azo compounds will be less complete when intestinal transit time is accelerated, also resulting in impaired delivery of 5-ASA to the colon (27)

Another difference between healthy persons and patients is the reduced capacity of the

inflamed colon mucosa to absorb 5-ASA (28) This results in a higher luminal 5-ASA concentration after ingestion of both slow-release and azo compounds

Firm conclusions can therefore only be drawn when the comparison made in this study has also been made in patients with inflammatory bowel disease with increased transit time For the time being, we think that azo compounds are the most appropriate for distally localized inflammatory bowel disease Being much cheaper than all other 5-ASA-delivering drugs, salazosulphapyridine should be the first choice When salazosulphapyrine is not tolerated well, treatment with olsalazine should be considered

This study shows once again that plain 5-ASA is rapidly absorbed and excreted into urine It is not appropriate for the treatment of distal inflammatory bowel disease It may be suitable for Crohn's disease located in the stomach, duodenum, and jejunum

REFERENCES

1 Misciewicz JJ, Lennard-Jones JE, Connell AM, Baron JH, Avery Jones F Lancet 1965, 1, 185–189
2 Azad Khan AK, Howes DT, Piris J, Truelove SC Gut 1980, 21, 232–240
3 Dissanayake AS, Truelove SC Gut 1973, 14, 923–926
4 Dick AP, Grayson MJ, Carpentier RG, Petrie A Gut 1964, 5, 437–442
5 Summers RW, Switz DM, Sessions JT Jr, Becktel JM, Best WR, Kern F Jr, Singleton JW Gastroenterology 1979, 77, 847–869
6 Van Hees PAM, Van Lier HJJ, Van Elteren Ph, Driessen WMM, van Hogezand RA, Ten Velde GPM, Bakker JH, et al Gut 1981, 22, 404–409
7 Peppercorn MA, Goldman P J Pharmacol Exp Ther 1972, 181, 555–562
8 Schröder H, Lewkonia RM, Evans DAP Clin Pharmacol Ther 1973, 14, 802–809
9 Azad Khan AK, Piris J, Truelove SC Lancet 1977, 892–897
10 Van Hees PAM, Bakker JH, Van Tongeren JHM Gut 1980, 21, 632–635
11 Nielsen OH, Bondeson S Br J Clin Pharmacol 1983, 16, 738–740
12 Chan RP, Pope PJ, Gilbert AP, Sacra PJ, Baron JH, Lennard-Jones JE Dig Dis Sci 1983, 28, 609–615
13 Sandberg-Gertzén H, Järnerot G, Kraaz W Gastroenterology 1986, 90, 1024–1030
14 Selby WS, Barr GD, Ireland A, Mason CH, Jewell DP Br Med J 1985, 291, 1373–1375
15 Dew MJ, Harries AD, Evans N, Evans BK, Rhodes J Br Med J 1983, 287, 23–24
16 Dew MJ, Hughes PJ, Harries AD, Williams G, Evans BK, Rhodes J Br Med J 1982, 285, 1012–1014
17 Rasmussen SN, Binder V, Maier K, Bondesen S, Fischer C, Klotz U, Hansen SH, et al Gastroenterology 1983, 85, 1350–1353
18 Willoughby CP, Aronson JK, Agback H, Bodin NO, Truelove SC Gut 1982, 23, 1081–1087
19 Van Hogezand RA, van Hees PAM, Zwanenburg B, Van Rossum JM, van Tongeren JHM Gastroenterology 1985, 85, 717–722
20 Dew MJ, Ebden P, Kidwai NS, Lee G, Evans BK, Rhodes J Br J Clin Pharmacol 1984, 17, 474–476
21 Rasmussen SN, Bondesen S, Hvidberg EF Gastroenterology 1982, 83, 1062–1070
22 Klotz U, Maier KE, Fischer C, Bauer KH Arzneimittelforsch Drug Res 1985, 35, 636–639
23 Van Hogezand RA, van Balen HCJG, van Schaik A, Tangerman A, van Hees PAM, Zwanenburg B, van Tongeren JHM J Chromatogr 1984, 305, 470–476
24 Bondesen S, Nielsen OH, Schou JB, Jensen PH, Lassen LB, Binder V, Krasilnikoff PA, et al Scand J Gastroenterol 1986, 21, 693–700
25 Myers B, Evans DNW, Rhodes J, Evans BK, Hughes BR, Lee MG, Richens A, et al Gut 1987, 28, 196–200
26 Keighley MRB, Arabi Y, Dimock F, Burdon DW, Allan RN, Alexander-Williams J Gut 1978, 19, 1099–1104
27 Van Hees PAM, Tuinte JHM, van Rossum JM, van Tongeren JHM Gut 1979, 20, 300–304
28 Campieri M, Lanfranchi GA, Boschi S, Brignola C, Bazzocchi G, Gionchetti P, Minguzzi MR, et al Gut 1985, 26, 400–405

CHAPTER 5.2

ADDENDUM TO CHAPTER 5.1

Only after the publication of the paper presented in chapter 5 it was fully appreciated that considerable differences exist in disposition of the individual 5-ASA delivering drugs, and that the results of the two azo compounds on the one side and of the slow-release compounds on the other cannot be simply lumped together. It is therefore considered appropriate to re-evaluate the data of the drugs separately and to subject them to additional statistical analysis.

The urinary excretion of (acetyl)-5-ASA after eight hours, representing the early release of 5-ASA from the drugs, is shown on the left side of Figure 2. The figures for Salazopyrin^R and Dipentum^R were significantly lower than for Pentasa^R and Salofalk^R. The early release from Asacol^R was intermediate, not differing significantly from any other drug.

The total urinary excretion of (acetyl)-5-ASA after 96 hours is shown on the right side of Figure 2. At this point of time the figures for Salazopyrin^R and Dipentum^R were still significantly lower than for Salofalk^R, and moreover, the excretion from Salazopyrin^R was significantly lower than from Asacol^R.

The proportions of 5-ASA, acetyl-5-ASA and unsplit parent molecule excreted in faeces are shown in Table 2.

None of the differences in faecally excreted 5-ASA was significant. As for the faecal excretion of acetyl-5-ASA, only the differences between Salazopyrin^R and Salofalk^R and between Salazopyrin^R and Asacol^R were significant.

The consideration of the individual drugs instead of azo and slow-release groups does not substantially alter the conclusions with regard to the early release in the first eight hours after ingestion. Eight hours represents quite well the transit through stomach and small bowel, as the median gastric emptying time in fasting subjects is aprroximately one hour, and the median small bowel transit time is four to eight hours (1,2). Both azo-compounds release significantly less 5-ASA at an early stage than the slow-release drugs Pentasa^R and Salofalk^R. Asacol^R takes an intermediate position. These results indicate that Pentasa^R and Salofalk^R are probably more fit for the treatment of small bowel locations of Crohn's disease,

and that more 5-ASA is saved for the colon when given in the form of Salazopyrin^{R} and Dipentum^{R}, and, to a lesser extent, Asacol^{R}. That the azo-compounds do not release 5-ASA too late can be derived from the high proportion of acetyl-5-ASA in the faeces, for Salazopyrin^{R} even significantly higher than for Asacol^{R} and Salofalk^{R}. The proportion of unacetylated 5-ASA, the therapeutically active substance (3), recovered in faeces is low for all drugs, the least low for Salazopyrin^{R}.

It is concluded that in healthy volunteers without diarrhoea, early release of 5-ASA is largest after intake of Pentasa^{R} and Salofalk^{R}, and least after intake of Salazopyrin^{R} and Dipentum^{R}. The latter two compounds have a disposition profile that is the most in agreement with good availability to the colon. It should be emphasised that for all drugs the ratio of acetyl-5-ASA to 5-ASA in faeces is high to such an extent, that the bulk of 5-ASA must have been released at considerable time before defaecation, and only little unreleased or unacetylated 5-ASA can have reached the rectum. This contrasts with the situation with an accelerated intestinal transit, either artificially generated, or present in patients with active disease, as will be pointed out in the chapters 6 and 7.

Additional references

1. Fallingborg J, Christensen LA, Ingeman-Nielsen M, Jacobsen BA, Abildgaard K, Rasmussen HH. pH-Profile and regional transit times of the normal gut measured by a radiotelemetry device. Aliment Pharmacol Ther 1989; 3: 605 - 13.
2. Hardy JG, Healy, JNC, Lee SW, Reynolds JR. Gastrointestinal transit of an enteric coated delayed release 5-aminosalicylic acid tablet. Aliment Pharmacol Ther 1987; 1: 209 - 19.
3. Van Hogezand RA, van Hees PAM, van Gorp JPWM, et al. Effect of 5-aminosalicylic acid (5-ASA) and acetyl-5-aminosalicylic acid (ac-5-ASA) suppositories in patients with idiopathic proctitis. A double blind study. Aliment Pharmacol Therap 1988; 2: 33-40.

CHAPTER 6

DISPOSITION OF 5-AMINOSALICYLIC ACID BY 5-AMINOSALICYLIC ACID DELIVERING DRUGS DURING ACCELERATED INTESTINAL TRANSIT IN HEALTHY VOLUNTEERS

Scandinavian Journal of Gastroenterology 1989; **24:** 1179-1185

Disposition of 5-Aminosalicylic Acid from 5-Aminosalicylic Acid-Delivering Drugs during Accelerated Intestinal Transit in Healthy Volunteers

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Rijk MCM, van Hogezand RA, van Schaik A, van Tongeren JHM. Disposition of 5-aminosalicylic acid from 5-aminosalicylic acid-delivering drugs during accelerated intestinal transit in healthy volunteers. Scand J Gastroenterol 1989, 24, 1179–1185

In eight healthy volunteers accelerated intestinal transit time was induced with bisacodyl, and urinary and faecal excretion of sulphasalazine, olsalazine, 5-aminosalicylic acid (5-ASA), and acetyl-5-ASA was studied after a single oral dose of 3.3 mmol sulphasalazine, olsalazine, Pentasa®, and Salofalk® and 2.6 mmol of Asacol®. The faecal and urinary excretion of acetyl-5-ASA was lowest after intake of sulphasalazine and olsalazine and highest after intake of Pentasa and Salofalk. The figures for Asacol were intermediate. This indicates insufficient release of 5-ASA from sulphasalazine and olsalazine. When the results of this study are compared with those of a previous study without accelerated transit time, the disposition of 5-ASA from all the 5-ASA-delivering drugs is influenced unfavourably by an accelerated gut transit but most pronounced in the case of sulphasalazine, olsalazine, and Asacol. The impaired release from the azo compounds sulphasalazine and olsalazine is a result of far less complete splitting of the diazo bond.

Key words 5-Aminosalicylic acid; azodisal sodium (olsalazine); metabolism, salicylazosulphapyridine

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In recent years several sulphapyridine-free, 5-aminosalicylic acid (5-ASA)-containing alternatives for sulphasalazine have been developed for the treatment of patients with inflammatory bowel disease. In olsalazine (Dipentum®) two 5-ASA molecules are linked together via an azo bond, which is split by intestinal bacteria, resulting in the delivery of only 5-ASA to the bowel and no superfluous substances (1, 2). 5-ASA can also be packed in a slow-release tablet that delivers 5-ASA gradually after dwelling a certain time in an environment with a pH above 5.5 or 6.5. Pentasa®, Asacol®, and Salofalk® are such presently available slow-release formulations (3–5).

Orally administered 5-ASA should not be released too early or too late, because in both instances insufficient concentrations and exposure times will be accomplished in the distal small bowel and in the colon. The time-related urinary excretion of 5-ASA and the amount of acetylated 5-ASA in the faeces can serve as indicators of proper delivery. When 5-ASA is released too early, it is rapidly absorbed and excreted into the urine, resulting in a high urinary output of 5-ASA shortly after intake. When it is released too late, very little is absorbed, and the total urinary excretion is low. The longer 5-ASA resides in the bowel lumen, the more of it is acetylated. So a considerable proportion of acetylated 5-ASA in the faeces indicates that release has not taken place too late. Thus, after ingestion of the 'ideal' 5-ASA-containing tablet little 5-ASA will be

excreted into the urine in the first hours after ingestion, and a considerable proportion of 5-ASA in the faeces will be acetylated

On the basis of these assumptions we compared in a previous study sulphasalazine, olsalazine, Pentasa, Asacol, and Salofalk in healthy volunteers with normal intestinal transit (6) After ingestion of sulphasalazine and olsalazine the early urinary recovery was significantly less, and the proportion of acetylated 5-ASA in the faeces greater than after ingestion of the slow-release tablets, indicating that azo compounds are preferable to slow-release tablets It may be assumed, however, that some patients with inflammatory bowel disease have an accelerated intestinal transit, which influences the disposition of 5-ASA We therefore investigated the disposition of 5-ASA from the above-mentioned 5-ASA-delivering drugs in healthy volunteers with accelerated intestinal transit, induced by bisacodyl The results obtained per drug during accelerated transit were compared, and, moreover, the results from this study were compared with those from the previous study in volunteers, who were all different individuals, with normal intestinal transit

MATERIALS AND METHODS

The study protocol was approved by the ethics committee of the University Hospital Nijmegen, and the study was performed in accordance with the Declaration of Helsinki

Eight healthy volunteers (three men and five women, aged 20 to 62 (median 27) years) without a history of gastrointestinal complaints participated in the study after having given their written informed consent

Diarrhoea was induced with bisacodyl in a dose of 5 to 10 mg three times daily Bisacodyl was started on the evening before intake of the study drug and maintained during the period that urine and faeces were collected The participants were instructed to adjust the dose in such a manner that a stool frequency between four and eight times per day was established On the 1st day of each investigation period a single dose of one of the study drugs was taken by mouth during breakfast together with 20 radiopaque rings The dosages of the study drugs were chosen to contain approximately equal amounts of 5-ASA (Table I) Urine was collected every 2 h during the first 8 h and thereafter in a 4-h portion, and the sixth portion covered the last 12 h of the first day On the 2nd and 3rd day urine was collected per 24 h Each urine portion was placed on dry ice immediately after voiding and later stored at −20°C until analysis Faeces were collected in containers with 1% $HgCl_2$ and, after thorough shaking also immediately placed on dry ice and later stored at −20°C These measures were taken to prevent further acetylation and breakdown of 5-ASA The time of each defaecation was noted

Faeces were radiographed for the presence of the radiopaque rings Intestinal transit time was defined in accordance with Hinton et al (7) as the time at which 80% of the ingested rings were recovered in the faeces Transit time was measured during administration of each of the 5-ASA-containing drugs, together with Bisacodyl and also on one separate occasion without administration of bisacodyl Urine and faeces were analysed for 5-ASA, acetyl-5-ASA and in the case of sulphasalazine and olsalazine for the intact parent molecule with a sensitive and specific high-performance liquid chromatography method, combined with fluorescence spectrophotometry (8)

In the previous study with normal transit time eight healthy volunteers, all different from the subjects in the present study, took part (6) They had all normal bowel habits, with a defaecation frequency of once or twice a day Six were male,

Table I Dose and 5-ASA content of the administered drugs

	Accelerated transit time		Normal transit time	
	Dose (mg)	5-ASA (μmol)	Dose (mg)	5-ASA (μmol)
Sulphasalazine	1290	3234	1500	3760
Olsalazine	560	3237	500	2890
Pentasa®	500	3268	500	3268
Asacol®	400	2614	400	2614
Salofalk®	500	3268	500	3268

Table II Intestinal transit times defined as the time at which 80% of ingested radiopaque markers are recovered in faeces during simultaneous intake of 5-ASA delivering drugs and bisacodyl and under basal conditions without intake of bisacodyl (mean ± SD)

	Transit time (h)
Bisacodyl together with	
Sulphasalazine	21 6 ± 14 2
Olsalazine	20 2 ± 19 5
Pentasa®	17 2 ± 7 9
Asacol®	24 8 ± 15 4
Salofalk®	14 2 ± 6 5
Without intake of bisacodyl	53 2 ± 13 8

two female, and their age ranged from 20 to 38 (median, 34) years Sex distribution (chi-square test) and age (rank sum two-sample test) did not differ significantly from those of the present study The protocol of the previous study was identical to that of the present study, except for the intake of bisacodyl, small differences in 5-ASA content of the study drugs, and the duration of the collection period of urine and faeces The dosages used in the previous study are listed in Table I The collecting period in the previous study was 96 h instead of 72 h However, data on urinary recovery after 72 h are available, and these figures are used for comparison with the present study Faeces of 96 h were mixed together, so no data on faecal recovery after 72 h during normal intestinal transit are available

Data obtained during accelerated intestinal transit were compared by means of the two-tailed Wilcoxon test for paired observations Results during accelerated intestinal transit time were compared with results during normal intestinal transit by the rank sum two-sample test, which enables comparison of unpaired observations P values less than 0 05 were considered significant

RESULTS

Without bisacodyl the intestinal transit time in the group of volunteers also studied during intake of bisacodyl was 53 2 ± 13 8 h (mean ± SD) The transit times during intake of bisacodyl are presented in Table II None of the differences in accelerated transit times were significant

The amounts of 5-ASA, acetyl-5-ASA, and parent molecule recovered in urine and faeces and expressed as percentage of the ingested dose are presented in Table III The 5-ASA recovered in urine is almost exclusively in the acetylated form The early urinary excretion of 5-ASA (excretion within the first 8 h) was 1 1 ± 0 4% for sulphasalazine, 0 9 ± 0 4 for olsalazine, 10 0 ± 1 7% for Pentasa, 1 2 ± 0 7 for Asacol, and 10 6 ± 3 3% for Salofalk It is clear that the early excretion of 5-ASA in urine is very small, indicating that no drug released too much 5-ASA at an early stage

After 72 h significantly less 5-ASA in urine was recovered from sulphasalazine and olsalazine as compared with Pentasa and Salofalk The difference between Pentasa and Salofalk was also significant in this respect The urinary excretion after intake of Asacol was intermediate and did not differ significantly from any of the other drugs The urinary excretion of unsplit parent azo molecules was very small 2 2 ± 0 8% for sulpha-

Table III Urinary and faecal excretion of 5-ASA, acetyl-5-ASA and parent molecules in 72 h after ingestion of 5-ASA-delivering drugs by eight healthy volunteers with drug-induced diarrhoea Figures are percentages of the ingested dose (mean ± SEM)

	Urine	Faeces		
	(Ac-)5-ASA	Ac-5-ASA	5-ASA	Parent molecule
Sulphasalazine	4 5 ± 1 5	6 6 ± 2 1	15 9 ± 3 4	41 5 ± 6 5
Olsalazine	4 9 ± 1 5	8 4 ± 2 7	17 6 ± 4 8	52 2 ± 11 5
Pentasa®	14 5 ± 2 5	21 2 ± 3 4	30 4 ± 7 6	
Asacol®	10 1 ± 4 1	9 5 ± 4 3	38 6 ± 8 5	
Salofalk®	26 7 ± 4 9	18 6 ± 6 0	22 3 ± 5 9	

salazine and 0.5 ± 0 1% for olsalazine (mean ± SEM).

The amount of acetylated 5-ASA in the faeces, to be regarded as an indicator of the release of 5-ASA in proper time, was significantly smaller after intake of sulphasalazine and olsalazine, on the one hand, and Pentasa, on the other The difference between olsalazine and Salofalk was also significant, and the difference between sulphasalazine and Salofalk was nearly significant ($p = 0.06$). From Table III it is apparent that a large proportion of the parent molecules sulphasalazine and olsalazine is excreted unsplit in the faeces. The total recovery of ingested 5-ASA was 70.6 ± 4.0% for sulphasalazine (mean ± SEM), 83.6 ± 5.3% for olsalazine, 66 1 ± 5.3% for Pentasa, 58.1 ± 7.6% for Asacol, and 67.6 ± 4.8% for Salofalk.

When the results of the present study are compared with those from the previous study, in which the intestinal transit time was not accelerated, it is clear that shortening of the transit time results in a marked reduction of the urinary 5-ASA excretion and of the amount of acetylated 5-ASA in the faeces (Table IV and Figs. 1 and 2). This applies to all the drugs investigated, and the results for normal and accelerated intestinal transit are significant except for Salofalk.

Shortening of the intestinal transit time also results in a significant increase of unsplit sulphasalazine and olsalazine.

DISCUSSION

The present study shows that acceleration of the intestinal transit causes an impairment of the delivery of 5-ASA from all investigated 5-ASA-containing drugs. The impairment is most pronounced for sulphasalazine, olsalazine, and Asacol. The impaired delivery of 5-ASA from the azo drugs is obviously the result of far less complete splitting of these drugs. During accelerated intestinal transit there is probably not enough time for intestinal bacteria to split the diazo bond. The azo reduction is not directly influenced by bisacodyl (9). The modes of action of bisacodyl include stimulation of peristaltic contractions, stimulation of mucus production, and conversion of net water and sodium absorption into secretion. It is not known to what extent each of these mechanisms contributes to its effect, but *it is certain that the end result is reduction of the* intestinal transit time, which is the condition that we wanted to investigate in this study.

It might be disputed whether it is permissible to compare the data of the present study with data from the previous study with normal intestinal transit, in volunteers who were all different from those in the present study. The subjects were not, however, significantly different with regard to age and sex distribution. Some minor inter-study differences in dosages of study drugs existed, as did minor intra-study differences in 5-ASA content of the drugs, inherent in the various amounts of 5-ASA packed in one tablet. This problem can be solved by comparing the proportions of the ingested 5-ASA recovered in faeces and urine, instead of using absolute figures. Seventy-two-hour faecal excretion of (ac-)5-ASA during accelerated transit is compared with 96-h excretion during normal transit. The urinary excretion of ac-5-ASA from 72 to 96 h during normal intestinal

Table IV. Urinary excretion of (ac-)5-ASA in 72 h and faecal excretion of 5-ASA, acetyl-5-ASA, and parent molecules in 96 h after ingestion of 5-ASA-delivering drugs by eight healthy volunteers, all different from the subjects mentioned in Table III, with normal intestinal transit time Figures are percentages of the ingested dose (mean ± SEM)

	Urine	Faeces		
	(Ac-)5-ASA	Ac-5-ASA	5-ASA	Parent molecule
Sulphasalazine	23.3 ± 2 1	45 4 ± 3.4	12 8 ± 2 2	6 6 ± 1 8
Olsalazine	24 5 ± 2 5	39 1 ± 3.4	8.2 ± 1 3	4.1 ± 1.1
Pentasa®	28.0 ± 3.2	38 4 ± 2.4	9.0 ± 1.5	
Asacol®	31 1 ± 2.8	33 2 ± 2.3	7 0 ± 1.4	
Salofalk®	36.1 ± 2 5	32 1 ± 4 2	5.2 ± 1.3	

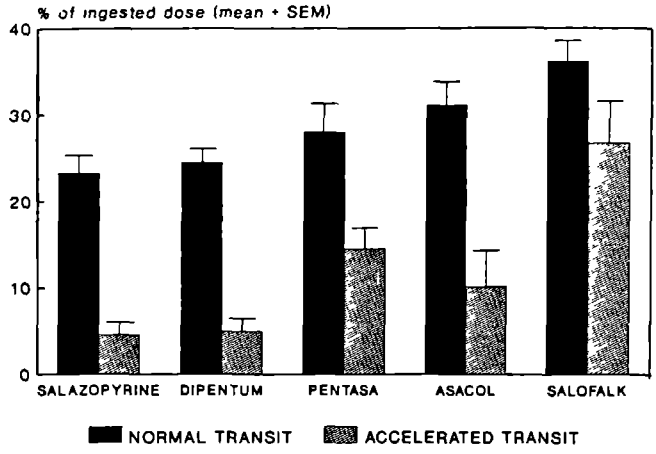

Fig 1 Urinary excretion of (acetyl-)5-ASA in 72 h after ingestion of a single dose of 5-ASA delivering drugs by eight healthy volunteers during accelerated intestinal transit time and eight different healthy volunteers during normal intestinal transit time Bars represent means ± SEM

transit, however was very low, indicating that only negligible amounts of 5 ASA could have remained in the bowel at that time

Although not statistically significant some differences existed in the gut transit times during administration of the various drugs A short transit time could indicate a disadvantage, but the shortest transit times (Pentasa and Salofalk) were

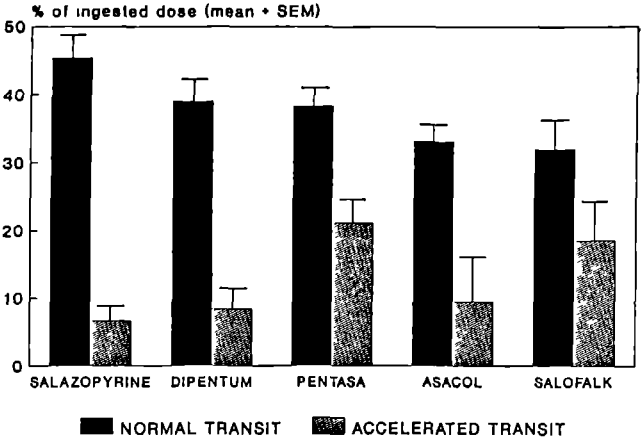

Fig 2 Faecal excretion of acetyl-5-ASA in 72 h after ingestion of a single dose of 5-ASA-delivering drugs by eight healthy volunteers during accelerated intestinal transit time and faecal excretion in 96 h in eight different healthy volunteers during normal intestinal transit time Bars represent means ± SEM

associated with the most favourable disposition, which perhaps even blunted the real difference. The results are in accordance with two other studies on the influence of transit time on 5-ASA disposition. In a study by Van Hees et al. (9) the disposition of sulphasalazine was investigated under conditions of normal and accelerated intestinal transit time during maintenance treatment. The proportion of unsplit sulphasalazine in faeces increased from 0 5% to 45.4%, the proportion of 5-ASA excreted in urine decreased from 18.5% to 5.9%, and the proportion of total 5-ASA in faeces decreased from 74.5% to 45.5%. Unfortunately, figures for acetylated and unacetylated 5-ASA were not mentioned separately. Christensen et al. (10) studied the disposition of Pentasa and found that a fivefold speeding up of the gut transit resulted in a decrease of the proportion of urinary excreted 5-ASA from 34% to 23% and a decrease of faecal acetyl-5-ASA from 38% to 30%.

The crucial question is to which patients the results of the present study are applicable. Not every patient with active inflammatory bowel disease has clearly accelerated intestinal transit In a study of patients with ulcerative colitis Rao et al. (11) did not find an accelerated intestinal transit but rather proximal colonic stasis. Frequent stools were not attributable to rapid bowel transit but to mucus secretion and impaired compliance of the rectum. Other authors, however, found no evidence of colonic stasis in patients with active ulcerative colitis and even demonstrated a shortened transit time (12). The observation that serum sulphapyridine levels during sulphasalazine therapy are lower in the active phase of inflammatory bowel disease than in the quiescent phase supports the assumption that splitting of sulphasalazine is impaired during active disease, most likely due to accelerated intestinal transit (9).

The shortening of transit time induced with bisacodyl was considerable in this study: from a mean of 53.2 h to a mean of 19.6 h Probably few patients will have such a short transit time, but it is conceivable that the same trends in 5-ASA disposition will be found at less accelerated transit times, albeit less pronounced.

The total recovery of ingested 5-ASA did not reach 100% for any of the study drugs. This problem is encountered in all studies dealing with disposition of 5-ASA-delivering compounds and is probably caused by breakdown of 5-ASA and acetyl-5-ASA to unknown substances, which are not detected with the presently applied method of analysis.

We conclude that during accelerated intestinal transit the disposition of 5-ASA from Salofalk and Pentasa is more favourable than that from sulphasalazine and olsalazine, with Asacol in an intermediate position. As compared with normal intestinal transit, the disposition of all 5-ASA-delivering drugs is impaired, especially from the azo compounds. Salofalk and Pentasa are therefore to be preferred when intestinal transit is clearly accelerated.

REFERENCES

1 Willoughby CP, Aronson JK, Agback M, Bodin NO, Truelove SC. Distribution and metabolism in healthy volunteers of disodium azodisalicylate, a potential therapeutic agent for ulcerative colitis Gut 1982, 23, 1081–1087
2. Van Hogezand RA, Van Hees PAM, Zwanenburg B, Van Rossum JM, Van Tongeren JHM. Disposition of disodium azodisalicylate in healthy subjects. Gastroenterology 1985, 88, 717–722
3 Rasmussen SN, Bondesen S, Hvidberg EF, et al 5-Aminosalicylic acid in a slow-release preparation: bioavailability, plasma level, and excretion in humans. Gastroenterology 1982, 83, 1062–1070
4 Dew MJ, Hughes PJ, Lee MG, Evan BK, Rhodes J. An oral preparation to release drugs in the human colon Br J Clin Pharmacol 1982, 14, 405–408
5. Klotz U, Maier KE, Fischer C, Bauer KH A new slow-release form of 5-aminosalicylic acid for the oral treatment of inflammatory bowel disease. Arzneimittelforsch 1985, 35, 636–639
6 Rijk MCM, Van Schaik A, Van Tongeren JHM Disposition of 5-aminosalicylic acid by 5-aminosalicylic acid-delivering compounds. Scand J Gastroenterol 1988, 23, 107–112
7. Hinton JM, Lennard-Jones JE, Young AC A new method for studying gut transit times using radioopaque markers. Gut 1969, 10, 842–847
8. Van Hogezand RA, Van Balen HCJG, Van Schaik A, et al Determination of disodium azodisalicylate, salicylazosulfphapyridine and their metabolites in serum, urine and faeces by high-performance liquid chromatography. J Chromatogr 1981, 305, 470–476
9. Van Hees PAM, Tuinte JHM, van Rossum JM, van Tongeren JHM. Influence of intestinal transit time on azo-reduction of salicylazosulphapyridine (Salazopyrin). Gut 1979, 20, 300–304
10 Christensen LA, Slot O, Sanchez G, et al Release of 5-aminosalicylic acid from Pentasa® during normal and accelerated intestinal transit time Br J Clin Pharmac 1987, 23, 365–369
11 Rao SSC, Read NW, Brown C, Bruce C, Holdsworth CD Studies on the mechanism of bowel disturbances in ulcerative colitis Gastroenterology 1987, 93, 934–940
12 Allison MC, Dick R, Pounder RE A controlled study of faecal distribution in ulcerative colitis and proctitis Scand J Gastroenterol 1987, 22, 1277–1280

CHAPTER 7

DISPOSITION OF 5-AMINOSALICYLIC ACID (5-ASA) FROM 5-ASA DELIVERING DRUGS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE, WITH AND WITHOUT DIARRHOEA

DISPOSITION OF 5-AMINOSALICYLIC ACID (5-ASA) FROM 5-ASA DELIVERING DRUGS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE, WITH AND WITHOUT DIARRHOEA

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Submitted for publication

SUMMARY

The disposition of 5-aminosalicylic acid (5-ASA; mesalazine) from the azo-compounds sulphasalazine and olsalazine (Dipentum^{R}), and from the slow-release mesalazine drugs Pentasa^{R}, Asacol^{R} and Salofalk^{R}, was studied in 20 patients with inflammatory bowel disease. Ten of them had diarrhoea and 10 had normal stools. On the last two days of a seven-day maintenance treatment with each of the study drugs urine and faeces were collected for determination of 5-ASA, acetyl-5-ASA and unsplit azo-compound. A large proportion of acetyl-5-ASA in urine, and especially in faeces, was considered an indicator of timely release of 5-ASA in the bowel. The median intestinal transit time was 20.6 hours in patients with diarrhoea and 39.1 hours in patients without diarrhoea. In patients with and without diarrhoea the urinary and the faecal excretion of acetyl-5-ASA was lowest during treatment with olsalazine. The proportion of acetyl-5-ASA in faeces was highest during treatment with Pentasa^{R} in both groups. The presence of diarrhoea was associated with a decrease of the proportion of acetyl-5-ASA in faeces during treatment with all drugs, not significant only for Pentasa^{R}. The proportion of unsplit azo-compound in faeces increased in case of diarrhoea to almost 50%.

It is concluded that in patients with inflammatory bowel disease diarrhoea substantially influences the disposition from all these drugs, except Pentasa^{R}.

INTRODUCTION

Sulphapyridine-free alternatives for sulphasalazine are now widely used in the treatment of patients with inflammatory bowel disease.

Pentasa^{R}, Asacol^{R} and Salofalk^{R} contain mesalazine (5-aminosalicylic acid, 5-ASA) in a sustained release or slow-release formulation, and Dipentum^{R} contains olsalazine, consisting of two 5-ASA molecules linked together by an azo bond. The slow-release formulations are necessary to prevent premature absorption of 5-ASA in the proximal part of the small intestine, resulting in insufficient availability of 5-ASA in the more distal parts, where the inflammation is often the most severe. Intact olsalazine is hardly absorbed in the small bowel (1), but the azo bond is split by intestinal bacteria in the terminal ileum and colon, resulting in the release of 5-ASA at these sites.

The disposition of 5-ASA delivering drugs has been studied and compared rather extensively in healthy volunteers (2-6), sometimes after induction of diarrhoea (7-9), far less often however in patients with inflammatory bowel disease (IBD) (10,11). It has been demonstrated in healthy volunteers that the disposition is markedly influenced by a change in intestinal transit time (7-9).

Table 1 *Clinical characteristics of patients in the two groups*

	no diarrhoea (n = 10)	diarrhoea (n = 10)
median age (range)	37.5 (28-75)	33 (23-67)
male : female	6 : 4	6 : 4
Crohn's disease	6	9
ileitis (resected)	4 (3)	3 (3)
ileocolitis	1	3
colitis	1	3
Ulcerative colitis	4	1

When 5-ASA is released in the colon it is subject to acetylation, partly by intestinal bacteria (12), partly by the intestinal mucosa (13). The proportion of acetylated 5-ASA in the faeces is therefore an indicator of the availability of 5-ASA to the distal intestine. When 5-ASA is released too late, or not at all, little or no acetyl-5-ASA is found in faeces. When it is

released too early in the proximal small intestine, it is rapidly absorbed, acetylated and excreted into the urine, resulting in a large amount of acetyl-5-ASA in urine and little (acetyl)-5-ASA recovered in faeces (6,14,15).

Starting from these principles, the disposition of 5-ASA from 5-ASA delivering drugs was compared in ten patients with IBD and a normal stool frequency, and in ten different patients with IBD and diarrhoea.

PATIENTS AND METHODS

Twenty patients with inflammatory bowel disease agreed to take part in the study and gave their informed consent in accordance with the Declaration of Helsinki.

Ten patients reported three or less bowel motions per day and are referred to as patients without diarrhoea. The ten patients who reported four or more bowel motions per day were called patients with diarrhoea. The main characteristics of both patient groups are listed in Table 1. All patients without diarrhoea had clinically quiescent disease, characterized by a normal ESR and serum albumin levels and the absence of blood in the stools. Of the patients with diarrhoea the patient with ulcerative colitis had moderately severe disease according to the criteria of Truelove and Witts (16). The nine patients with Crohn's disease had quiescent or at most moderately severe disease with a Van Hees Activity index (17) at most 167 (values of less than 100 denote quiescent disease, of 100 to 150 indicate mild disease, of 150 to 210 indicate moderately severe disease, and of more than 210 indicate very severe disease). In two of them the diarrhoea was attributed mainly to bile acid overflow after ileocoecal resection. All patients were treated on an out-patient basis.

Before the start of the study, all patients were treated with sulphasalazine or another 5-ASA containing drug. At entry, the pre-study drug was withdrawn and medication according to the study protocol was immediately started. None of the patients received corticosteroids or intrarectal medication.

Study protocol

During five consecutive weeks the patients received a daily dose of 3000 mg of sulphasalazine (Salazopyrin^R), 1500 mg of olsalazine (Dipentum^R), 1500 mg of Pentasa^R, 1200 mg of Asacol^R and 1500 mg of Salofalk^R, divided in three gifts, each during one week, in a random order. In the mornings of the last three days of each week a capsule with 20 radio-opaque rings, of a different size for each day, was taken by mouth. On the last two days of each week urine and faeces were collected.

Processing of urine and stool specimens

Urine was collected in plastic containers and immediately after voiding placed on dry ice. Stools were collected separately in plastic containers with $HgCl_2$ 1% to prevent further breakdown and acetylation of 5-ASA (18), and after thorough shaking also immediately placed on dry ice. The time of each defaecation was noted. Urine and faeces were later stored at -20°C until analysis. After radiographing of the separate stools, faeces of each 48-hour collection period were pooled and subsequently thoroughly homogenized and mixed. Samples were taken for duplicate analysis. Urine and stool specimens were analyzed for 5-ASA, acetylated 5-ASA and unsplit SASP and olsalazine by means of HPLC, combined with fluorescence spectrophotometry (18). The values obtained were divided by two to obtain the amounts excreted per 24 hours.

Calculation of the intestinal transit time

All stool specimens were radiographed separately to determine the number and size of the radio-opaque rings. Initially it was intended to calculate the intestinal transit time (ITT) according to the single stool method of Cummings (19). This requires the presence of at least two different forms of radio-opaque rings in one stool. Especially when the ITT was short, this condition was often not met. Therefore the ITT was considered to be the time at which 80% of one of the forms of rings was recovered, as proposed by Hinton (20). In some instances the ITT could be determined both according to Cummings and to Hinton. From these

cases a regression equation was calculated, allowing for transformation of the ITT according to Cummings to an ITT according to Hinton on those occasions where only the ITT according to Cummings was available.

Statistical analysis

The daily amounts of excreted 5-ASA, acetyl-5-ASA and unsplit parent drug were obtained by dividing the amounts, excreted in 48 hours, by two, and expressed as proportions of the daily ingested dose. The urinary excretions of acetylated 5-ASA, unacetylated 5-ASA and unsplit parent molecule are not mentioned separately, as the last two constitute only a very small part of 5-ASA excreted in urine (less than 2%). Therefore only the total amount of urinary excretion of 5-ASA is presented, and referred to as acetyl-5-ASA. Data within one group of patients (with normal stools or diarrhoea) were tested with the Wilcoxon's signed rank test, and comparisons between the two groups were tested with the rank sum test. For correlations Spearman's rank correlation was used. Only two-sided results were used. P-values of 0.05 or less were considered significant.

RESULTS

The disposition of 5-ASA from the 5-ASA delivering drugs in patients without diarrhoea is shown in Figures 1 (daily urinary excretion) and 2 (daily faecal excretion). The urinary disposition of 5-ASA from olsalazine was significantly lower than that from SASP, Pentasa^R and Salofalk^R, and the urinary excretion of acetyl-5-ASA from Salofalk^R was significantly higher than that from olsalazine, Asacol^R and Pentasa^R. The faecal excretion of acetylated 5-ASA from olsalazine and Asacol^R was significantly lower than that from Salofalk^R and Pentasa^R. The faecal excretion of unacetylated 5-ASA was highest after ingestion of Asacol^R. A significantly larger part of olsalazine was recovered unsplit in faeces, as compared with SASP.

The results from the group of patients with diarrhoea are presented in Figures 3 and 4. In this group of patients the urinary excretion of acetyl-5-ASA from

olsalazine was significantly lower than that from all other drugs. The faecal excretion of acetyl-5-ASA was significantly higher during treatment with Pentasa^R than during treatment with all other drugs, while the faecal excretion of acetyl-5-ASA from olsalazine was significantly lower than that from all other drugs, except Asacol^R.

In Table 2 the data from the two groups of patients are compared. In patients with diarrhoea the proportion of unsplit SASP and olsalazine in faeces was significantly higher, and the urinary excretion of acetyl-5-ASA from SASP and olsalazine was significantly less than in patients without diarrhoea. The faecal excretion of acetylated 5-ASA after intake of olsalazine, Asacol^R and Salofalk^R was significantly less in patients with diarrhoea than in patients without diarrhoea. All patients during all study periods had at least one bowel motion per 48 hours.

The ITTs in both groups of patients are listed in Table 3. The correlation between the ITT according to Cummings and the ITT according to Hinton was derived from simultaneously available data in 35 cases and could be described by the formula $y = 0.85x + 11.6$ in which y = ITT according to Hinton and x = ITT according to Cummings ($r = 0.73$, $p < 0.001$) . In patients without diarrhoea, the ITT according to Hinton was available in 30 of 50 cases and could be derived from the ITT according to Cummings in 10 cases, leaving 10 cases in which no sufficient data at all were present. In the group of patients with diarrhoea these numbers were 33, 8 and 9 respectively.

Within one group of patients no significant differences in ITT occurred. The ITT in the group of patients with diarrhoea was shorter than in patients without diarrhoea during intake of all five drugs, not significant only for SASP and nearly significant for Asacol^R.

Regression of the proportion of excreted metabolites of 5-ASA versus the ITT's showed significant correlations between the proportions of acetyl-5-ASA excreted in faeces and the ITT for all drugs except for Pentasa^R (Table 4). The correlation between the unsplit sulphasalazine in faeces and the ITT failed to reach significance ($r = -0.47$, $n = 16$, $p = 0.07$), but the correlation between unsplit olsalazine and the ITT was very significant ($r = -0.69$, $n = 16$, $p = 0.003$).

Table 2. *Disposition of 5-ASA during maintenance treatment with 5-ASA delivering drugs in IBD patients without and with diarrhoea. Figures are the daily excretions, calculated by dividing the amounts excreted on two consecutive collection days by two, and are expressed as the proportion of the ingested dose, with SEM in parentheses*

	patients without diarrhoea (n = 10)	patients with diarrhoea (n = 10)	p
	Urinary excretion of 5-ASA (acetylated + unacetylated)		
Sulphasalazine	26.2 (4.3)	11.8 (2.4)	0.009
Olsalazine	12.9 (1.9)	5.4 (2.1)	0.03
Pentasa®	25.1 (3.2)	22.7 (4.2)	0.73
Asacol®	24.3 (5.7)	16.2 (3.4)	0.27
Salofalk®	34.7 (3.2)	22.8 (5.1)	0.16
	Faecal excretion of 5-ASA		
Sulphasalazine	24.3 (4.5)	22.3 (5.2)	0.62
Olsalazine	22.3 (2.2)	13.1 (4.0)	0.02
Pentasa®	16.2 (3.2)	29.2 (2.8)	0.02
Asacol®	34.2 (6.7)	50.7 (11.2)	0.47
Salofalk®	20.9 (3.9)	27.0 (5.0)	0.52
	Faecal excretion of acetyl-5-ASA		
Sulphasalazine	29.6 (8.7)	11.9 (3.7)	0.09
Olsalazine	16.7 (2.8)	4.3 (1.5)	0.003
Pentasa®	39.5 (3.5)	27.4 (2.5)	0.38
Asacol®	18.4 (2.8)	9.0 (2.6)	0.02
Salofalk®	27.9 (7.8)	13.7 (3.2)	0.01
	Faecal excretion of unsplit parent molecule		
Sulphasalazine	5.3 (1.6)	42.9 (12.2)	0.004
Olsalazine	15.2 (3.7)	47.2 (10.0)	0.03
	Total recovery of ingested drug		
Sulphasalazine	81.9 (14.2)	88.8 (9.6)	0.47
Olsalazine	67.0 (5.6)	70.1 (5.9)	0.79
Pentasa®	80.9 (11.8)	79.4 (6.5)	0.97
Asacol®	76.9 (6.4)	75.9 (13.8)	0.97
Salofalk®	83.5 (8.2)	63.2 (9.2)	0.79

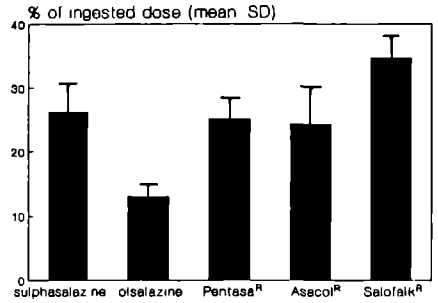

Figure 1. *Urinary excretion of acetyl-5-ASA from 5-ASA delivering drugs in ten patients with inflammatory bowel disease without diarrhoea. Bars represent the amounts excreted on day 6 and 7 of a seven-day treatment period, divided by two, and expressed as the proportion of the daily ingested dose*

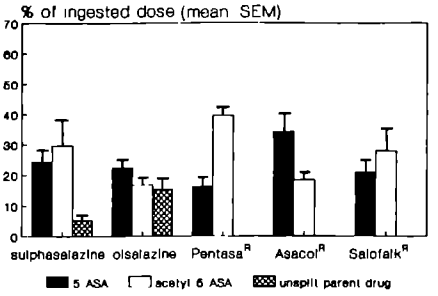

Figure 2 *Faecal excretion of 5-ASA, acetyl-5-ASA and unsplit parent drug from 5-ASA delivering drugs in ten patients with inflammatory bowel disease without diarrhoea Bars represent the amounts excreted on day 6 and 7 of a seven-day treatment period, divided by two, and expressed as the proportion of the daily ingested dose*

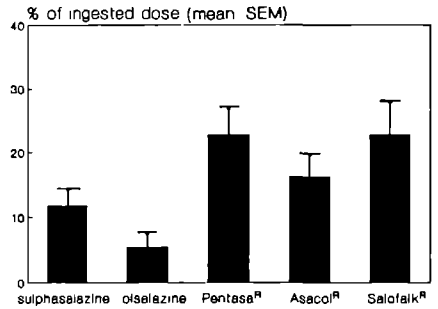

Figure 3. *Urinary excretion of acetyl-5-ASA from 5-ASA delivering drugs in ten patients with inflammatory bowel disease and diarrhoea. Bars represent the amounts excreted on day 6 and 7 of a seven-day treatment period, divided by two, and expressed as the proportion of the daily ingested dose*

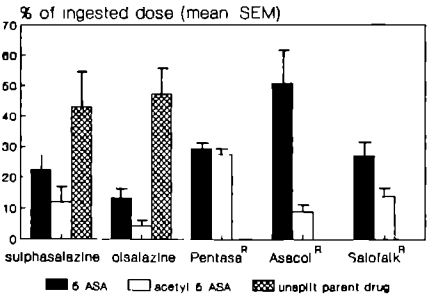

Figure 4. *Faecal excretion of 5-ASA, acetyl-5-ASA and unsplit parent drug from 5-ASA delivering drugs in ten patients with inflammatory bowel disease and diarrhoea Bars represent the amounts excreted on day 6 and 7 of a seven-day treatment period, divided by two, and expressed as the proportion of the daily ingested dose*

DISCUSSION

From previous studies in healthy volunteers it is known that a marked acceleration of the ITT profoundly influences the disposition of 5-ASA from 5-ASA delivering drugs (7-9). This is confirmed in the present study. In the group of patients with diarrhoea, with median ITTs ranging from 15.1 (olsalazine) to 23.8 hours (Salofalk^{R}) there were marked differences in disposition between the study drugs, and also marked differences in comparison with the non-diarrhoea group. In the first place azo compounds are far less completely split in case of diarrhoea. This has a marked unfavourable effect on the availability of 5-ASA in the bowel lumen, reflected in a decrease of both the proportion of 5-ASA excreted in urine and of acetyl-5-ASA in faeces. The disposition of olsalazine appears to be impaired somewhat more than the disposition of SASP.

The disposition of Asacol^{R} in patients with diarrhoea is characterized by a high proportion of 5-ASA excreted in faeces, but little in the acetylated form, indicating that release must have taken place distally, if at all.

Although the disposition from Salofalk^{R} and Pentasa^{R} is also impaired in case of diarrhoea, the changes are far less substantial and the disposition remains rather favourable. Specifically the faecal excretion of acetyl-5-ASA from Pentasa^{R} is

Table 3. *Intestinal transit time according to Hinton in patients with and without diarrhoea. Figures are median values (hours), with the range in parentheses.*

	patients without diarrhoea	patients with diarrhoea	p
Sulphasalazine	38.2 (16.3-66.0)	21.7 (13.7-59.8)	0.17
Olsalazine	39.7 (15.0-54.5)	15.1 (6.8-30.6)	0.006
Pentasa^{R}	34.6 (13.0-75.5)	15.6 (6.4-28.4)	0.02
Asacol^{R}	38.8 (11.8-65.5)	23.1 (6.0-30.6)	0.057
Salofalk^{R}	45.8 (26.5-53.2)	23.8 (4.6-33.0)	0.02
All treatments	39.1 (11.8-75.5)	20.6 (4.6-59.8)	<0.0001

No significant internal differences in either group of patients

Table 4. *Coefficients of correlation between the proportion of acetyl-5-ASA in faeces and the intestinal transit time.*

	r*	n	p
Sulphasalazine	0.54	16	0.032
Olsalazine	0.90	16	<0.001
Pentasa	0.16	15	0.58
Asacol	0.86	16	<0.001
Salofalk	0.73	18	0.001

* Spearman rank correlation

significantly higher than from all other drugs under conditions with an accelerated intestinal transit. This also finds expression in the fact that Pentasa^{R} was the only drug without a significant correlation between the proportion of acetyl-5-ASA in faeces and the ITT.

These results are in full agreement with those obtained in healthy volunteers after administration of a single dose of these 5-ASA delivering drugs, with and without induction of diarrhoea with bisacodyl (6,9).

The proportion of acetyl-5-ASA that is excreted in urine of patients with quiescent disease is almost identical to that of normal volunteers (6), with the exception of olsalazine, which has a lower urinary recovery in patients (mean 12.9 vs 24.8%).

The faecal excretion of acetyl-5-ASA in patients without diarrhoea was about identical to the data of healthy volunteers as far as Salofalk^{R} and Pentasa^{R} are concerned, but lower for SASP, olsalazine and Asacol^{R} (9). Also, the proportion of unsplit olsalazine was higher in patients without diarrhoea than in volunteers (mean 15.2 and 4.1% respectively). The cause of these differences might be the fact that even in patients without diarrhoea the ITT was shorter than in normal persons. Indeed, we found in a previous study in normal persons a mean ITT according to Hinton of 53.2 hours (9), and in the present study mean ITTs ranging from 36.4 to 42.0 hours. Obviously, olsalazine is influenced most by this slight acceleration of ITT, while the disposition of Salofalk^{R} and Pentasa^{R} is not substantially altered.

Our results are also in agreement with the study of van Hees (7), who measured the disposition of sulphasalazine in volunteers during normal and accelerated intestinal transit and found the proportion of unsplit drug in faeces to increase

from 0.5 to 45.4%, and the proportion of 5-ASA in urine to decrease from 18.5 to 5.9%.

In the study of Christensen et al. (8) concerning the disposition of Pentasa^R during normal and accelerated ITT the differences in urinary excretion of 5-ASA were larger than in our study, probably due to a five-fold speeding up of the ITT by bisacodyl. Their figures for faecal excretion are almost identical to ours.

Staerk Laursen et al (21) investigated the disposition of olsalazine, Pentasa^R, Asacol^R and Salofalk^R in 14 patients with ulcerative colitis in remission (less than two bowel motions per day). As in our study they found that the urinary excretion of acetyl-5-ASA and faecal excretion of acetyl-5-ASA were highest after ingestion of Pentasa^R and Salofalk^R. The intraluminal colonic concentrations of 5-ASA, as measured by equilibrium in vivo dialysis, was highest after intake of olsalazine and Asacol^R, which is consistent with predominantly colonic release of 5-ASA by these drugs in the absence of diarrhoea.

With the method of processing the faeces used in the present study it was not possible to distinguish released 5-ASA from 5-ASA still captured in a slow-release tablet (Salofalk^R and Asacol^R) or in ethylcellulose vesicles (Pentasa^R). It is possible that some tablets were excreted with an intact coat, which was not broken until the homogenization of the faeces. If this happens to most tablets, only low proportions of acetyl-5-ASA in urine and faeces can be expected. After homogenizing a dispersed Pentasa^R tablet and an Asacol^R tablet with faeces we measured a recovery of 5-ASA of more than 80% for both tablets, indicating that the homogenization procedure was vigorous enough to disrupt the majority of the small ethylcellulose vesicles of Pentasa^R and the resin coat of Asacol^R. This means that we cannot distinguish released 5-ASA from still captured 5-ASA, and that the measurement of acetyl-5-ASA in faeces is indispensable to estimate timely release in the colon.

Although it was initially suggested that acetyl-5-ASA was also effective in the treatment of ulcerative colitis (22), this could not be confirmed by others (23, 24), and at present only 5-ASA is considered to have important anti-inflammatory properties. So, although a high proportion of acetyl-5-ASA is an indicator of

timely release in the gut, it is inactive in itself, and a very high ratio of acetylated to unacetylated 5-ASA in faeces is therefore not desirable for patients with inflammation in the distal colon.

The results of the present study entail important consequences for the choice of 5-ASA delivering drugs under specific clinical circumstances. In patients without diarrhoea, too late release of 5-ASA does not appear to be a major problem, as the proportion of acetyl-5-ASA in faeces is considerable, olsalazine being on the low side with 16%. The fact that the mean faecal excretion of acetyl-5-ASA after ingestion of Pentasa^R is as high as 39.5% and the proportion of unacetylated 5-ASA in faeces only 16.2% might even indicate that 5-ASA is released too early for patients with inflammation in the distal colon, without diarrhoea. This is confirmed by the presence of low colonic intraluminal concentrations of 5-ASA during intake of Pentasa^R by patients with quiescent ulcerative colitis (21). On the other hand, Pentasa^R has been proven to possess relapse preventing properties equal to sulphasalazine in patients with quiescent ulcerative colitis (25). Therefore, it is hard to express a preference for one drug to the other when no frank diarrhoea is present. However, when a patient does suffer from diarrhoea and ITT is substantially shortened, important differences in disposition become apparent. Under these circumstances, olsalazine clearly has the least favourable, and Pentasa^R, and to a somewhat lesser extent Salofalk^R, the most favourable disposition profile. This should be taken into account when prescription of a 5-ASA delivering drug is considered.

REFERENCES

1. Sandberg-Gertzén H, Ryde H, Järnerot G. Absorption and excretion of a single 1 g dose of azodisal sodium in subjects with ileostomy. Scand J Gastroenterol 1983; **18**: 107 - 11.
2. Rasmussen SN, Bondesen S, Hvidberg EF, Hansen SH, Binder V, Halskov S, Flachs H. 5-Aminosalicyloc acid in a slow-release preparation: bioavailability, plasma level, and excretion in humans. Gastroenterology 1982; **83**: 1062-70.
3. Dew MJ, Hughes PJ, Lee MG, Evan BK, Rhodes J. An oral preparation to release drugs in the human colon. Br J Clin Pharmac 1982; **14**: 405-8.
4. Van Hogezand RA, Van Hees PAM, Zwanenburg B, Van Rossum JM, Van Tongeren JHM.

Disposition of disodium azodisalicylate in healthy subjects. Gastroenterology 1985; **88:** 717-22.

5. Klotz U, Maier KE, Fischer C, Bauer KH. A new slow-release form of 5-aminosalicylic acid for the oral treatment of inflammatory bowel disease. Drug Res 1985; **35:** 636-9.
6. Rijk MCM, Van Schaik A, Van Tongeren JHM. Disposition of 5-aminosalicylic acid by 5-aminosalicylic acid-delivering compounds. Scand J Gastroenterol 1988; **23:** 107-12.
7. Van Hees PAM, Tuinte JHM, van Rossum JM, van Tongeren JHM. Influence of intestinal transit time on azo-reduction of salicylazosulphapyridine (Salazopyrin). Gut 1979; **20:** 300-4.
8. Christensen LA, Slot O. Sanchez G, et al. Release of 5-aminosalicylic acid from Pentasa^{R} during normal and accelerated transit time. Br J Clin Pharmac 1987; **23:** 365-9.
9. Rijk MCM, Van Hogezand RA, Van Schaik A, Van Tongeren JHM. Disposition of 5-amino-salicylic acid from 5-aminosalicylic acid-delivering drugs during accelerated intestinal transit in healthy volunteers. Scand J Gastroenterol 1989; **24:** 1179-85.
10. Klotz U, Maier KE, Bauer KH. A new slow-release form of 5-aminosalicylic acid for the oral treatment of inflammatory bowel disease. Drug Res 1985; **3:** 636-9.
11. Lauritsen K, Staerk Laursen L, Bukhave K, Rask-Madsen J. Longterm olsalazine treatment: pharmacokinetics, tolerance and effects on local eicosanoid formation in ulcerative colitis and Crohn's colitis. Gut 1988; **29:** 974-82.
12. Dull BJ, Salata K, Goldman P. Role of intestinal flora in the acetylation of sulphasalazine metabolites. Biochem Pharmacol 1987: **36:** 3772-4.
13. Allgayer H, Ahnfelt NO, Kruis W, Klotz U,Frank-Holmberg K, Söderberg HNA, Paumgartner G. Colonic N-acetylation of 5-aminosalicylic acid in inflammatory bowel disease. Gastroenterology 1989; **97:** 38-41.
14. Nielsen OH, Bondesen S. Kinetics of 5-aminosalicylic acid after jejunal instillation in man. Br J Clin Pharmac 1983; **16:** 738-40.
15. Myers B, Evans DNW, Rhodes J, Evans BK, Hughes BR, Lee MG, Richens A, Richards D. Metabolism and urinary excretion of 5-aminosalicylic acid in healthy volunteers when given intravenously or released for absorption at different sites in the gastrointestinal tract. Gut 1987: **28:** 196-200.
16. Truelove SC and Witts LJ. Cortisone in ulcerative colitis. Final report on a therapeutical trial. Br Med J 1955; **ii:** 1041-8.
17. Van Hees PAM, van Elteren Ph, van Lier HJJ, van Tongeren JHM. An index of inflammatory activity in patients with Crohn's disease. Gut 1980; **21:** 279-86.
18. Van Hogezand RA, Van Balen HCJG, Van Schaik A, Tangerman A, Van Hees PAM, Zwanenburg B, Van Tongeren JHM. Determination of disodium azodisalicylate, salicylazosulphapyridine and their metabolites in serum, urine and faeces by high-performance liquid chromatography. J Chromatogr 1984; **305:** 470-476.
19. Cummings JH, Wiggins HS. Transit through the gut measured by analysis of a single stool.

Gut 1976; **17**: 219-23.

20. Hinton JM, Lennard-Jones JE, Young AC. A new method for studying gut transit times using radioopaque markers. Gut 1969; **10**: 842-7.
21. Staerk Laursen L, Stokholm M. Bukhave K, Rask-Madsen J, Lauritsen K. Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations: comparison of intraluminal colonic concentrations, serum values, and urinary excretion. Gut 1990; **31**: 1271-6.
22. Willoughby CP, Piris J, Truelove SC. The effect of topical N-acetyl-5-aminosalicylic acid in ulcerative colitis. Scand J Gastroenterol 1980; **15**: 715-9.
23. Binder V, Halskov S, Hvidberg E, et al. A controlled study of 5-acetyl-aminosalicylic acid (5-AC-ASA) as enema in ulcerative colitis (abstract). Scand J Gastroenterol 1981; **16**: 1122.
24. Van Hogezand RA, van Hees PAM, van Gorp JPWM, et al. Effect of 5-aminosalicylic acid (5-ASA) and acetyl-5-aminosalicylic acid (ac-5-ASA) suppositories in patients with idiopathic proctitis. A double blind study. Aliment Pharmacol Therap 1988; **2**: 33-40.
25. Mulder CJJ, Tytgat NJ, Weterman IT, Dekker W, Blok P, Schrijver M, v.d. Heyde H. Double-blind comparison of slow-release 5-aminosalicylic acid and sulphasalazine in remission maintenance in ulcerative colitis. Gastroenterology 1988; **95**: 1449 - 53.

CHAPTER 8

THE EFFICACY AND SAFETY OF SULPHASALAZINE AND OLSALAZINE IN PATIENTS WITH ACTIVE ULCERATIVE COLITIS.

THE EFFICACY AND SAFETY OF SULPHASALAZINE AND OLSALAZINE IN PATIENTS WITH ACTIVE ULCERATIVE COLITIS.

A prospective, double-blind, randomized multicentre study.

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Submitted for publication

SUMMARY

Fifty-five patients with active ulcerative colitis were treated at random in a prospective, double-blind, multicentre trial with sulphasalazine 6 g/d or olsalazine 3 g/d for six weeks, to be continued for another six weeks if no remission had been achieved. Clinical and laboratory evaluation was performed every two weeks, and endoscopic evaluation at 0, 6 and 12 weeks. After 6 weeks 6 of 27 evaluable patients (22.2%) on sulphasalazine and 9 of 28 patients (32.1%) on olsalazine had achieved a remission (95% CI of the difference -33.3 to 13.4%). After 12 weeks 11 of 27 patients (40.7%) on sulphasalazine and 14 of 26 patients (53.8%) on olsalazine were in remission (95% CI of the difference -39.8 to 13.6%). Substantial endoscopic improvement was eventually achieved in 48.2% of patients on sulphasalazine and 65.4% of patients on olsalazine (95% CI of the difference -43.4 to 9.0%). Six patients from each group were withdrawn because of adverse effects or increasing severity of disease. By means of a newly developed numerical Ulcerative Colitis Activity Index no significant difference as to the effect of treatment between both groups could be demonstrated. Olsalazine is at least as effective and as well tolerated as sulphasalazine in patients with active ulcerative colitis.

INTRODUCTION

Since it is recognized that 5-aminosalicylic acid (mesalazine) is the active part of sulphasalazine (1,2), whereas sulphapyridine is the cause of the majority of adverse effects (3), sulphapyridine-free drugs have been developed for the treatment of patients with inflammatory bowel disease. As plain mesalazine is rapidly absorbed in the proximal small bowel (4), measures have been taken to delay release by enveloping mesalazine with a special coating, or by binding it to another molecule that greatly reduces absorption in the small bowel. Olsalazine (Dipentum^{R}) consists of two mesalazine molecules, linked together with an azo bond, and is hardly absorbed in the small bowel (5). On the analogy of sulphasalazine (6) it is split by intestinal bacteria in terminal ileum and colon, resulting in the release of two mesalazine molecules at that site (7). Olsalazine is more effective than placebo in active ulcerative colitis (8). We compared the efficacy and safety of olsalazine and sulphasalazine in patients with active ulcerative colitis.

PATIENTS AND METHODS

The study was prospectively carried out in a double-blind, randomized, multicentre fashion.

Patient selection

Fourteen Dutch hospitals participated in this study. From october 1985 to april 1989 patients with active ulcerative colitis, extending 25 cms or more from the anal verge, and with an Ulcerative Colitis Activity Index (see next section) of 120 or more, were considered eligible for the trial. The diagnosis of ulcerative colitis was made on the basis of typical clinical, endoscopic and histological appearances, and the absence of positive stool cultures for Salmonella, Shigella, Campylobacter jejuni and Yersinia enterocolica. Patients with a first attack as well as patients with a relapse were eligible. Criteria for exclusion are listed in Table 1.

Table 1. *Criteria for exclusion of patients*

1. Uncooperativeness.
2. Colitis with a specific cause (infectious colitis, pseudomembranous colitis, radiation-induced colitis).
3 Presence of features of Crohn's disease.
4. Colitis extending less than 25 cm from the anal verge.
5. Use of prednisone, prednisolone or more than 3 g of sulphasalazine daily in the last two weeks
6. Proven hypersensitivity to sulpha drugs or salicylates.
7. Pregnancy or desire to become pregnant.
8. Only slightly active colitis (UCAI <120).
9. Temperature of 39°C or more due to ulcerative colitis.
10. Severe illness, i.e.
    a. severe blood loss requiring transfusions,
    b. severe diarrhoea (>10 motions/day),
    c. any other condition that makes, in the opinion of the attending physician, the risk involved in the participation in the trial unacceptable (e g toxic megacolon)
11. Need (for whatever reason) for antibiotics or corticosteroids.
12 Presence of colostomy or ileo-rectal anastomosis.
13. Two or more abnormal liver function tests (bilirubin, alkaline phosphatase, ALAT or ASAT more than twice the upper limit of normal), or signs of cirrhosis of the liver.
14. Clearly impaired kidney function (endogenous creatinine clearance <30 ml/min).
15. Acute intermittent porphyria.

Protocol review

The study protocol was reviewed and approved by the ethics committee of the University Hospital Nijmegen, and by the local ethics committees of the participating hospitals. Patients were fully informed and their written consent was obtained in accordance with the declarations of Helsinki and Tokyo.

Study design and randomization

Patients who satisfied the diagnostic criteria, lacked the exclusion criteria and gave

their written informed consent were assigned to receive either sulphasalazine or olsalazine. Patients were allocated to treatment groups with a modification of the standardized variance allocation method as described by Begg and Iglewicz (9), in order to ensure equal distribution of prognostic factors among both treatments. The modification consisted of standardization of the variance method. The factors taken into account were age (less than 40 years; 40 years and older), sex, duration of disease (less than 2 months; 2 months to 2 years; more than 2 years), extent of colitis (distal to splenic flexure, beyond splenic flexure), Ulcerative Colitis Activity Index (see below) and attending physician.

The duration of treatment was six weeks, to be continued for another six weeks if no clinical remission according to Truelove and Witts, and endoscopic remission was achieved. The dose of sulphasalazine was 6 g daily and of olsalazine 3 g daily, divided in three doses, to be taken on top of a meal, and to be reduced to 4 and 2 g daily respectively when adverse effects occurred. Sulphasalazine and olsalazine were given in externally indistinguishable capsules, containing 333 mg of sulphasalazine or 167 mg of olsalazine, provided by Pharmacia AB, Uppsala, Sweden, in sealed plastic containers. On day 1 and 2 the dosage was one-third, and on day 3 and 4 three two-thirds of the full dose.

Control visits were performed every two weeks. At the inclusion visit and each control visit a medical history was taken, patients were questioned about the intake of capsules and the occurrence of possible adverse effects, and a physical examination was made with emphasis on the findings necessary for the calculation of the Truelove-Witts catagory and the UCAI. Blood was drawn for determination of the laboratory data included in these activity indices and, in order to recognize possible adverse effects, also of leucocytes, platelets, glucose, creatinine, liver function parameters (bilirubin, alkaline phosphatase, ALAT, ASAT and lactate dehydrogenase) and haptoglobin. Urine was analyzed for the presence of protein and glucose. Before entry, faeces were cultured for Salmonella, Shigella, Campylobacter jejuni and Yersinia enterocolitica.

All patients recorded their complaints on a diary card during the whole treatment period.

Criteria for premature discontinuation of treatment

Treatment was stopped prematurely, and cases were consequently considered a treatment failure, if on account of the severity of the disease continuation of the "blind" therapy was not longer regarded as warranted in the opinion of the attending physician, or if adverse effects neccessitated a decrease of the dose of the study drug to less than two-thirds of the full dose. Patients withdrawn for these reasons were included in the evaluation and considered a treatment failure.

Assessment of inflammatory activity

The inflammatory activity was assessed by means of two clinical activity indices, an endoscopic index and a histological score.

Clinical assessments

First, the severity index as described by Truelove and Witts (10) was used. Because it is not clear from their description in which grade of severity a patient has to be classified when a patients meets criteria of different catagories of illness, we devised a modification as shown in Table 2.

Secondly, we devised an Ulcerative Colitis Activity Index (UCAI) because it was supposed that the three-grade Truelove-Witts classification would limit the statistical processing of data and would offer insufficient opportunity to assess minor changes of disease activity.

The UCAI was developed in a similar way as has been done for Crohn's disease (11). From the files of 89 patients with ulcerative colitis, treated in the period 1956-1984 in the University Hospital Nijmegen, 112 sets of simultaneous observations of the following 15 variables were obtained: sex, Quetelet index (weight divided by height squared), stool frequency, well-being, abdominal pain, cramps, megacolon, loss of blood in stools, body temperature, ESR, haemoglobin concentration, leucocytes and serum albumin. The maximum number of sets of observations of the same patient was three. These 112 sets of observations were duplicated. In a random order the resulting 224 sets were rated by five

Table 2. *Modified Truelove-Witts classification for the severity of ulcerative colitis.*

Mild colitis: at least 3 of the 4 criteria ad I and 1 of the 2 criteria ad II are fulfilled.

I. - mean frequency of defaecation ≤ 4/day
- small amounts of macroscopic blood in stools
- no fever (evening temperature <37.5°C)
- no tachycardia (pulse rate <90/min)

II. - haemoglobin male ≥8.0 mmol/l; female ≥7.4 mmol/l
- ESR <20 mm

Severe colitis: at least 3 of the 4 criteria ad III and 1 of the 2 criteria ad IV are fulfilled.

III. - mean frequency of defaecation ≥ 7/day
- always substantial amounts of macroscopic blood in stools
- evening temperature 38.0°C on at least 3 out of 5 consecutive days
- tachycardia (pulse rate >90/min)

IV. - haemoglobin male <6.5 mmol/l; female < 6.0 mmol/l
- ESR ≥30 mm

Moderately severe colitis: neither the criteria for the mild nor for the severe modality are fulfilled.

Colitis in remission:

- mean frequency of defaecation ≤ 3/day
- no blood in stools
- no fever
- no tachycardia
- haemoglobin normal or returning towards normal
- ESR normal or returning towards normal

gastroenterologists with the scores 1, 2, 3 and 4, denoting no, mild, moderate and severe activity of the colitis respectively. Comparing the scores awarded to the duplicate sets never more than a difference of 1 point (in 18% of the cases) was found. Pearson correlation coefficients between the sum of duplicate scores of the physicians two and two were at least 0.90. Having established in this way a

sufficient intra- and interrater consistency the 10 ratings of the five physicians were added. The sum of these ratings now can be considered a reliable measure of the severity of colitis according to the common judgement of the five physicians.

By stepwise multiple linear regression a function of 6 of the 15 variables has been constructed predicting the sum score of a patient with sufficient accuracy. We refrained from adding another variable because the multiple correlation coefficient exceeded 0.95 after inclusion of the sixth variable. The activity index is this function multiplied by 6 in order to obtain a similar scale as in the activity index for Crohn's disease mentioned before. The ulcerative colitis activity index (UCAI) is defined as follows:

UCAI = 24.6T - 1.86Alb + 24.9Bl - 5.54HB + 15.6MC + 0.205ESR - 746.

Where T = body temperature (°C)

Alb = serum albumin (g/l)

Bl = blood loss in stools (1 = no, 2 = mild (not always present or only blood streaks), 3= always clearly present).

Hb = haemoglobin concentration (mmol/l)

MC = megacolon (1=absent, 2=present, 3=severe)

ESR = erythrocyte sedimentation rate (mm in 1 h)

The maximum difference between the index and the sum of the ten original ratings multiplied by 6 is 37, that is 0.62 in the 1,2,3,4 scale of the original ratings. The residual standard deviation is 18.4 or 0.31 in the 1,2,3,4 rating scale.

The fractional contribution of a variable to the UCAI is taken as the standard deviation of that variable times the absolute value of its coefficient in the UCAI and devided by the sum of such products for all variables. These fractions are 32.4% (T), 21.4% (Alb), 22.5% (Bl), 9.7% (HB), 6.9% (MC) and 7.1% (ESR) respectively.

Endoscopic assessment

Patients underwent a flexible sigmoidoscopy or colonoscopy before entry in the

study, after 6 and, if suitable, after 12 weeks of treatment.

In order to obtain reproducible judgements of the endoscopic severity of inflammation a standardized five-parameter assessment, with maximally four levels for each parameter, was used. The assessment was always performed 20-30 cm from the anal verge. Parameters and the resulting grading of severity are shown in Table 3.

Histological score

Biopsies for histological examination were taken in the 20-30 cm region, and, if no macroscopically recognizable inflammation was present at that site, also at 5 cm from the anal verge. The biopsies were judged by the local pathologist and scored for the absence or presence of inflammation.

Assessment of response to therapy and statistical analysis

The following end-points were used to measure the response to treatment.

1. The number of patients achieving endoscopic and clinical (according to the modified Truelove-Witts criteria) remission.
2. The number of patients achieving a "success" as assessed with the Truelove-Witts classification. Success is defined as the achievement of remission (grade 0) or a decrease of severity by two grades or more.
3. The number of patients achieving a "success" as assessed with endoscopy. Success is defined as the achievement of remission (grade 0) or a decrease of severity by two grades or more.
4. The number of patients achieving histological remission.
5. The relative value of the UCAI (expressed as the proportion of the initial value) after 6 and twelve weeks of treatment.

If a patient left the trial after 6 weeks because of achievement of remission, he was also counted as a remission and a success at 12 weeks.

In case of premature withdrawal due to treatment failure or adverse effects the exact values of the above mentioned parameters were set on an arbitrary value

higher than the values of any other patient. As this results in a non-normal distribution medians and quartiles are presented instead of mean and standard deviation. The Wilcoxon two-sample test was used to test differences in the proportional UCAI, and Fisher's exact test for differences in success rates. Only two-sided test results were used, and p-values of less than 0.05 were considered significant.

Reflections about the size of the treatment groups

The null-hypothesis in this study was that no difference in therapeutic effect and in incidence of adverse effects between the two groups would exist. It was calculated that 75 patients in each treatment group would be needed in order to obtain a probability of 80% to find a significant test result at the 5% level for a 28% difference between both treatment groups. However, due to lower than expected enrollment this number was not reached in reasonable time, and it was decided to stop the trial after inclusion of 55 evaluable patients. All treatment results are now presented with their 95% confidence intervals.

RESULTS

During the entire study period 65 patients were randomized. Ten of them dropped out in the first 6 weeks for reasons other than treatment failure or adverse effects: four because of uncooperativeness, two because of a major protocol violation (visit at 6 weeks postponed for more than 7 days), two because of too severe disease at the intended starting day, one because of prolonged need for antibiotics in relation with a pneumonia, and one patient because he soon appeared to suffer from Crohn's disease. These patients were not included in the analysis. Of the remaining 55 patients, 27 were assigned to sulphasalazine and 28 to olsalazine. The characteristics of both treatment groups are shown in Table 4. Two more patients dropped off after 6 weeks because of uncooperativeness. They were included in the analysis at 6 weeks, but excluded from the analysis at 12 weeks.

Table 4. *Main characteristics of both treatment groups.*

	Patients treated with	
	sulphasalazine (n = 27)	olsalazine (n = 28)
median age (range)	36 (12-78)	33 (13-76)
male : female	18 : 9	18 : 10
duration of disease		
≤2 months	7	9
2 months - 2 years	13	11
>2 years	7	8
extent of colitis		
not beyond splenic flexure	14	14
beyond splenic flexure	11	13
unknown*	2	1
Ulcerative Colitis Activity Index		
120 - 139	16	14
140 - 179	10	13
≥180	1	1
severity according to Truelove and Witts		
mild	10	8
moderately severe	10	13
severe	2	0

* splenic flexure not reached at endoscopy

In the first 6 weeks of treatment 6 patients assigned to sulphasalazine, and 6 assigned to olsalazine were withdrawn for the reasons mentioned in Table 5, and consequently added to the evaluable patients as treatment failures. Patients were defined as having increasing diarrhoea if an increasing frequency of loose stools was the only event observed. If patients also experienced increasing fever, if laboratory parameters of inflammation (haemoglobin and ESR) clearly deteriorated or the endoscopic appearance substantially worsened, the patients were considered having an increasing severity of disease.

The results after 6 and 12 weeks of treatment are mentioned in Table 6. Although every end point with the exception of clinical improvement after 6 weeks showed a trend in favour of olsalazine, due to wide confidence limits at neither point of time significant differences occurred in the rates of achievement of clinical and endoscopic remission, clinical or endoscopic success, or in the relative value of the UCAI. The achievement of remission was not dependent on

Table 5. *Reasons for patient withdrawal*

sulphasalazine group		olsalazine group	
upper abdominal complaints	4*	increasing severity of colitis	3
rash	1	increasing diarrhoea (>10/day)	2
depression, insomnia	1	pancreatitis	1

* one of the four patients also had headache

the severity according to Truelove-Witts at entry, as 9 of 18 patients with mild disease came into remission after 12 weeks, 15 of 35 patients with moderately severe disease and 1 of the 2 patients with severe disease.

Biopsies were not available from all patients evaluable at 6 and 12 weeks. Some patients, withdrawn shortly after entry or being severely ill, refused endoscopy. Thus, after 6 weeks judgeable biopsies were available in 41 patients, and after 12 weeks in 25 patients. At 6 weeks, no histologically active inflammation was found in 4 out of 21 patients treated with sulphasalazine and in 3 out of 20 patients treated with olsalazine. At 12 weeks, inflammation was absent in 3 out of 14 and 4 out of 11 patients respectively. All together, six patients from the sulphasalazine group had no histologically active inflammation any more at the time they left the trial, and seven patients from the olsalazine group. None of the differences in histological outcome between the two treatments was significant. On 19 occasions histological signs of inflammation were still present whilst the endoscopic appearance was quiet, and in one patient with clinical and endoscopic signs of inflammation the histological appearance was normal.

Minor adverse effects that disappeared spontaneously or after dose-reduction by less than one-third occurred in 11 patients (40.7%) treated with sulphasalazine and 6 patients (21.4%) treated with olsalazine, as shown in Table 7. Some patients experienced more than one adverse effect. The 95%-confidence intervals of the difference are -5 and 43%. No major abnormalities in laboratory tests

Table 6. *Results of therapy: remission and success rates with 95%-confidence intervals, and course of UCAI.*

	After 6 weeks of treatment			After 12 weeks of treatment		
	treatment group			treatment group		
	sulphasalazine	olsalazine	95% CI of difference	sulphasalazine	olsalazine	95% CI of difference
endoscopic and clinical remission	6/27 (22.2%)	9/28 (32.1%)	-33.3 - 13.4%	11/27 (40.7%)	14/26 (53.8%)	-39.7 - 13.6%
endoscopic success*	9/27 (33.3%)	11/28 (39.3%)	-31.3 - 19.4%	13/27 (48.2%)	17/26 (65.4%)	-43.5 - 9.0%
clinical (Truelove-Witts) success*	12/27 (44.4%)	11/28 (39.3%)	-20.8 - 31.2%	15/26 (57.7%)**	16/26 (61.5%)	-30.5 - 22.8%
median relative UCAI***	65.0 (56.8-79.1)	72.2 (62.0-83.1)		73.1 (59.2 -112.6)	71.3 (60.8-129.9)	

* success defined as remission or decrease of severity by two grades or more.

** in one patient insufficient laboratory data were collected after 12 weeks for determination of the Truelove-Witts catagory.

*** expressed as the proportion of the initial dose [%], with quartile range in parentheses.

For patients in remission after 6 weeks, values of UCAI at 6 weeks were used to calculate the 12 weeks median and quartile range.

None of the differences between the treatment groups were significant

occurred in both groups. In one patient of each treatment group mild, transient leucopenia to a minimal count of $3.4x10^9/l$ (on sulphasalazine) and $2.9\ 10^9/l$ (on olsalazine) was encountered. In four patients treated with sulphasalazine and one treated with olsalazine haptoglobin decreased to levels under the normal range, indicating low grade haemolysis.

The daily intake of the study drugs was similar in both treatment groups. Sixteen of the 27 patients assigned to sulphasalazine and 14 of the 28 assigned to olsalazine were able to take the full dose throughout the study, as derived from the diaries. In the sulphasalazine group the mean intake was 5.4 g (90% of the full dose) after 6 weeks, and 5.0 g (83%) after 12 weeks. In the olsalazine group these figures were 2.6 g (87%) and 2.8 g (94%), respectively.

Validation of the UCAI

The mean value of the UCAI increased from low to high Truelove-Witts catagories. At entry, the initial UCAI was 131 ± 12 (mean ± SD) in patients in Truelove-Witts catagory 1, 145 ± 19 in catagory 2, and the two patients in Truelove-Witts catagory 3 had a UCAI of 151 and 153. This trend was significant

Table 7. *Minor adverse effects, not necessitating withdrawal.*

sulphasalazine (n = 27)		olsalazine (n = 28)	
upper abdominal complaints	6	upper abdominal complaints	3
headache	3	increasing diarrhoea (>10/day)	2
dizziness	2	lower abdominal pain	1
tinnitus	1		
feeling of tension	1		
burning retrosternal pain	1		
number of patients with adverse effects	11*		6

* some patients had more than one adverse effect

(p = 0.0004, trend-test). The UCAI-values in catagory 1 differed significantly from the values in catagory 2 and 3. The Spearman correlation coefficient between the Truelove-Witts catagories and the UCAI at entry was 0.47 (n = 55, p = 0.0002). Also, the change of UCAI after 6 weeks correlated significantly with the change in Truelove-Witts catagory (r = 0.51, n =39, p = 0.0008)

DISCUSSION

In this study, sulphasalazine and olsalazine were equally effective, as measured by the number of patients achieving clinical, endoscopic and histological remission, and by the decrease of the Ulcerative Colitis Activity Index. This is in accordance with other studies in patients with active ulcerative colitis, where olsalazine was as effective as sulphasalazine (12), or more effective than placebo (6,13). The present study differs from these previous studies as to the choice of its major end-points (clinical and sigmoidoscopic remission instead of improvement), the additional use of an Ulcerative Colitis Activity Index with continuous scale, the longer duration (6 to 12 weeks instead of 2 to 4 weeks), and the higher dosages of olsalazine and sulphasalazine. The choice of remission as major end-point is logical, because this is the goal one is aiming at when treating patients with active colitis. As it is well known from clinical experience that it takes usually longer than four weeks to achieve remission by sulphasalazine alone, we chose for a treatment duration up to 12 weeks. The dosage of 3 g olsalazine, and especially of 6 g sulphasalazine per day, is higher than used elsewhere. Notwithstanding the high incidence of adverse effects, reported in the litterature with such high or even lower dosages of sulphasalazine (12), our personal impression is that a reasonable part of patients with active disease tolerate this dosage well. Meanwhile, it has been demonstrated for olsalazine (13) and it is reasonable to expect from sulphasalazine that the efficacy is dose-related. Feurle et al, comparing olsalazine with placebo suggested that the lack of a significant difference as to clinical and histological parameters was a consequence of the low dose of 2 g olsalazine per day (14). In our study, using daily dosages of 6 g of

sulphasalazine or 3 g of olsalazine about half of the patients were able to take the full dose throughout the study, and the mean intake in both study groups was about 90% of the full dose. With this regimen, 40.7% of patients treated with sulphasalazine and 53.8% treated with olsalazine had achieved clinical and endoscopic remission after 12 weeks. As other studies on olsalazine do not mention remission rates, the figures are not well comparable. In studies on slow-release mesalazine drugs divergent remission rates are reported. Habal and Greenberg treated patients with active ulcerative colitis in an open study with 3.2 g daily of Asacol^{R} (slow-release mesalazine), equivalent to the dosages used in this study, and found a remission rate after 3 months of 29% (15). They pointed out that the success rate was strongly dependent of the severity of disease at entry. Sixty-four percent of patients with mild or moderate disease, and none of the patients with severe disease (according to a self-devised grading) achieved remission. In the present study the remission rate was independent of the Truelove-Witts catagory or the height of the UCAI, probably because severely ill patients were hardly admitted.

In another trial with even higher dosages of 4.8 g Asacol^{R} only 24% of patients with mildly and moderately active ulcerative colitis had achieved remission after six weeks (16). In a multicentre study reported by Rachmilewitz, 49% of patients taking 1.5 g Mesasal (coated mesalazine) and 47% of patients taking 3 g sulphasalazine were in endoscopic remission after eight weeks (17). These figures are comparable with those from the present study.

In addition to achievement of remission, an all or nothing criterium, and decrease of severity according to Truelove-Witts or to endoscopic aspect, that allows only a limited number of grades, we used an Ulcerative Colitis Activity Index with a continuous scale in order to detect more subtle differences between the treatment groups. Also with this activity index we were unable to find significant differences between the effects of sulphasalazine and olsalazine. Although the UCAI consist of partly different factors, its correlation with the Truelove-Witts catagories is significant, as is the correlation between the changes of both indices during treatment. This corroborates the idea that the UCAI might be a useful

instrument.

The use of high dosages in the present study was accompanied by a withdrawal of six patients in both treatment groups (22.2% for sulphasalazine and 21.4% for olsalazine). These figures are higher than from some studies with lower doses of olsalazine (12-14), but comparable with the withdrawal rate in both arms of the Mesasal-sulphasalazine trial (17). In a study to the relapse preventing effect of 2 g olsalazine in patients with quiescent ulcerative colitis the withdrawal rate for side effects was 24% (18).

It is interesting that the reasons for withdrawal were different for both treatment groups. Most withdrawals from the sulphasalazine group took place because of upper gastrointestinal complaints, whereas increasing severity of the colitis and increasing frequency of loose stools were the most frequent reasons for withdrawal from olsalazine. Increasing severity of the colitis can stand for a treatment failure, but also for an adverse effect of 5-aminosalicylic containing drugs (19,20). Increasing numbers of loose stools is a known side-effect of olsalazine, as a result of impaired absorption of water and electrolytes in the small intestines (21,22). The frequency reported in other studies ranges from 2.2 to 12.5% (12-14,23,24). In the present study two patients were withdrawn for this reason, and one other had only transient complaints. So, in this study loose stools caused by olsalazine are not a major problem. The case of pancreatitis during treatment with olsalazine deserves some elaboration. It is not absolutely sure that olsalazine was the cause of this event, as the patient had already some abdominal discomfort a few days before the start of treatment. On the 13th day of treatment, however, she developed a frank pancreatitis. No predisposing factors such as gallstones, alcohol abuse, hypercalcaemia or hyperlipidaemia were present. After withdrawal of the drug she recovered completely, and two years later she was treated with olsalazine 1.5 g daily without problems. Interestingly, some cases of pancreatits caused by olsalazine (25) and coated mesalazine (26) are reported in the literature.

In the present study less patients treated with olsalazine experienced minor adverse effects, as compared with sulphasalazine (21.7 vs 40.7%). The incidence is

especially high for sulphasalazine, but it is reassuring that all these adverse effect disappeared spontaneously or after dose reduction to two-thirds. The comparison of the incidence of adverse effects is the more in favour of olsalazine when it is realized that most patients entering this study had taken sulphasalazine before, so that the study group is more or less selected for its tolerance of sulphasalazine. The adverse effects of sulphasalazine are similar as reported in the litterature.

It is concluded that olsalazine is as effective as sulphasalazine in patients with mildly and moderately active colitis, that it is accompanied by the same withdrawal rate, and by a lower incidence of minor adverse effects. Both olsalazine and sulphasalazine are reasonably well tolerated in higher dosages than usually administered (3 and 6 g daily respectively). In patients intolerant of sulpha drugs olsalazine deserves the preference over sulphasalazine. This also counts for males at reproductive age, desiring to father children, as the seminal abnormalities induced by sulphasalazine (27,28) disappear on olsalazine (21).

Acknowledgements

Marno C.M. Rijk received a grant from Pharmacia AB, Uppsala, Sweden, who also kindley gave further financial support and supplied the study drugs. The authors wish to thank Hans Bakker, hospital pharmacist, who excellently took care for the distribution and dispense of the study drugs.

References

1. Khan AKA, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet 1977; ii: 892 - 5.
2. Van Hees PAM, Bakker JH, van Tongeren JHM. Effect of sulphapyridine, 5-aminosalicylic acid and placebo in patients with idiopathic proctitis: a study to determine the active therapeutic moiety of sulphasalazine. Gut 1980; 21: 632 - 5.
3. Das KM, Eastwood MA, McManus JPA, Sircus W. Adverse reactions during salicylazosulphapyridine therapy and the relation with drug metabolism and acetylator phenotype. N Eng J Med 1973; 289: 491 - 5.

4. Myers B, Evans DNW, Rhodes J Evans BK, Hughes BR, et al. Metabolism and urinary excretion of 5-aminosalicylic acid in healthy volunteers when given intravenously or released for absorption at different sites in the gastrointestinal tract. Gut 1987; **28:** 196 - 200.
5. Sandberg-Gertzén H, Ryde H, Järnerot G. Absorption and excretion of a single 1 g dose of azodisal sodium in subjects with ileostomy. Scand J Gastroenterol 1983; **18:** 107 - 11.
6. Peppercorn MA, Goldman P. The role of intestinal bacteria in the metabolism of salicylazosulphapyridine. J Pharmacol Exp Ther 1972; **181:** 555 - 62.
7. Van Hogezand RA, van Hees PAM, Zwanenberg B, van Rossum JM, van Tongeren JHM. Disposition of disodium azodisalicylate in healthy subjects. A possible new drug for inflammatory bowel disease. Gastroenterology 1985; **88:** 717 - 22.
8. Selby WS, Barr GD, Ireland A, Mason CH, Jewell DP. Olsalazine in ulcerative colitis. Br Med J 1985; **291:** 1373 - 5.
9. Begg CB, Iglewicz A. A treatment allocation procedure for sequential clinical trials. Biometrics 1980; **36:** 81 - 90.
10. Truelove SC, Witts LJ. Cortisone in ulcerative colitis. Final report on a therapeutic trial. Br Med J 1955; **2:** 1041 -8.
11. Van Hees PAM, van Elteren PH, van Lier HJJ, van Tongeren JHM. An index of inflammatory activity in patients with Crohn's disease. Gut 1980: **21:** 279-86.
12. Rao SSC, Dundas SAC, Holdsworth CD, Cann PAN, Palmer KR, Corvett CL. Olsalazine or sulphasalazine in first attacks of ulcerative colitis? A double blind study. Gut 1989; **30:** 675 - 9.
13. Meyers S, Sachar DB, Present DH, Janowitz HD. Olsalazine sodium in the treatment of ulcerative colitis among patients intolerant of sulphasalazine. A prospective, randomized, placebo-controlled, double-blind, dose-ranging clinical trial. Gastroenterology 1987; **93:** 1255 - 62.
14. Feurle GE, Theuer D, Velasco S, et al. Olsalazine versus placebo in the treatment of mild to moderate active colitis: a randomized double blind trial. Gut 1989; **30:** 1354 - 61.
15. Habal FM, Greenberg GR. Treatment of ulcerative colitis with oral 5-aminosalicylic acid including patients with adverse reactions to sulphasalazine. Am J Gastroenterol 1988; **83:** 15 - 9.
16. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1987; **317:** 1625 - 9.
17. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in treatment of active ulcerative colitis: a randomised trial. Br Med J 1989; **298:** 82-6.
18. Ireland A, Mason CH, Jewell DP. Controlled trial comparing olsalazine and sulphasalazine for the maintenance treatment of ulcerative colitis. Gut 1988; **29:** 835 - 7.

19. Austin LA, Cann PA, Jones TH, Holdsworth CD. Exacerbation of diarrhoea and pain in patients treated with 5-aminosalicylic acid for ulcerative colitis. Correspondence. Lancet 1984; **i:** 917 - 8.

20. Chakaborty TK, Bhatia D, Heading RC, Ford MJ. Salicylate induced exacerbation of ulcerative colitis. Gut 1987; **28:** 613 - 5.

21. Sandberg-Gertzén H, Järnerot G, Bukhave K, Lauritsen K, Rask-Madsen J. Effect of azodisal sodium and sulphasalazine on ileostomy output of fluid and luminal concentrations of PGE_2 and PGF_2 in subjects with a permanent ileostomy. Gut 1986; **27:** 1306 - 11.

22. Mohsen AQM, Mulvey D, Priddle JD, Parsons DS. Effects of olsalazine in the jejunum of the rat. Gut 1987; **28:** 346 - 52.

23. Ireland A, Jewell DP. Olsalazine in patients intolerant of sulphasalazine. Scand J Gastroenterol 1987; **22:** 1038 - 40.

24. Azodisal sodium in the treatment of ulcerative colitis. A study of tolerance and relapse-prevention properties. Sandberg-Gertzén H, Järnerot G, Kraaz W. Gastroenterology 1986; **90:** 1024 - 30.

25. Poldermans D, van Blankenstein M. Pancreatitis induced by disodium azodisalicylate. Am J Gastroenterol 1988; **83:** 578 - 80.

26. Sachedina B, Saibil F, Cohen LB, Whittey J. Acute pancreatitis due to 5-aminosalicylic acid. Ann Int Med 1989; **110:** 490 - 2.

27. Toovey S. Hudson E, Hendry WF, Levi AJ. Sulphasalazine and male infertility: reversibility and possible mechanisms. Gut 1981; **22:** 445 -51.

28. O'Morain C, Smethurst P, Doré CJ, Levi AJ. Reversible male infertility due to sulphasalazine: studies in man and rat. Gut 1984; **25:** 1078 - 84.

CHAPTER 9

THE RELAPSE PREVENTING EFFECT AND SAFETY OF SULPHASALAZINE AND OLSALAZINE IN PATIENTS WITH ULCERATIVE COLITIS IN REMISSION.

THE RELAPSE PREVENTING EFFECT AND SAFETY OF SULPHASALAZINE AND OLSALAZINE IN PATIENTS WITH ULCERATIVE COLITIS IN REMISSION.

A prospective, double-blind, randomized multicentre study.

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Submitted for publication

SUMMARY

Fourty-nine patients with ulcerative colitis in remission were entered into a prospective, double-blind, multicentre trial comparing the relapse preventing effect and safety of 4 g sulphasalazine and 2 g olsalazine daily during 48 weeks. Of the 46 evaluable patients 23 were assigned to sulphasalazine and 23 to olsalazine. Seven of 23 patients (30.4%) relapsed on sulphasalazine and six of 23 patients (26.1%) on olsalazine (95% confidence interval of the difference -22.0% to 30.3%). The relapse-free survival curves did not differ significantly at any time during the trial period. In both treatment groups three patients dropped out because of adverse effects. Four patients on sulphasalazine and six patients on olsalazine experienced minor adverse effects. One patient on sulphasalazine had mild leucopenia, and four patients on sulphasalazine and one patient on olsalazine had decreased levels of haptoglobin.

Thus, sulphasalazine and olsalazine are equally effective in maintaining remission of ulcerative colitis and are accompanied by a similar incidence of adverse effects.

INTRODUCTION

Sulphasalazine has been the mainstay of treatment for patients with ulcerative colitis in remission, as it was the first drug that proved to be more effective than placebo in maintaining remission (1). Its relapse preventing effect is dose-dependent, but unfortunately adverse effects become more frequent when higher dosages are used (2). For this reason, the dosage during remission is usually limited to 2 or 3 g per day. Since it has become evident that the sulphapyridine part of sulphasalazine is responsible for the majority of adverse effects (3), and that 5-aminosalicylic acid (mesalazine) is the active moiety (4,5), sulphapyridine-free, mesalazine containing alternatives have been developed. As plain mesalazine is rapidly absorbed in the proximal part of the small intestine and the effect of mesalazine is dependent on its local concentration, measures must be taken to delay release, in order to deliver mesalazine more distally. Therefore, slow-release forms of mesalazine have been developed. Olsalazine (Dipentum^{R}) consists of two mesalazine molecules, linked together via an azo bond, and is hardly absorbed in the small bowel (6). On the analogy of sulphasalazine (7), the azo bond in olsalazine is split by bacteria in the distal ileum and colon, resulting in the release of two mesalazine molecules distally in the gut (8) with avoidance of superfluous and potentially harmful substances.

Olsalazine is more effective than placebo in the prevention of relapses in patients with quiescent ulcerative colitis, and is tolerated by most patients intolerant of sulphasalazine (9). In the present paper we report a prospective, double-blind, randomized multicentre trial in which the relapse preventing properties and the safety of sulphasalazine and olsalazine in patients with ulcerative colitis in remission are compared.

PATIENTS AND METHODS

Patient selection

Thirteen physicians from 10 Dutch hospitals, listed in the Appendix, participated in this study. Inclusion lasted from december 1985 until january 1989. Patients with active ulcerative colitis in the past, proven by endoscopy with biopsies, being in remission for not longer than two years, were elegible. Remission was defined as the absence of clinical signs of inflammation, i.e. three stools or less per day without blood and a normal mucous membrane on sigmoidoscopy. Patients with a normal endoscopic appearance but histological signs of inflammation were included. Patients were recruited from two groups. The first group consisted of patients who had participated in a trial comparing sulphasalazine and olsalazine in active colitis and had achieved a remission after 6 or 12 weeks of treatment. Patients from the second group had not participated in this trial but met the inclusion criteria. Exclusion criteria are mentioned in Table 1.

Protocol review

The study protocol was reviewed and approved by the ethics committee of the

Table 1. *Criteria for exclusion of patients.*

1. Uncooperativeness.
2. Colitis with a specific cause (infectious colitis, pseudomembranous colitis, radiation-induced colitis).
3. Presence of features of Crohn's disease.
4. Proven hypersensitivity to sulpha drugs or salicylates.
5. Pregnancy or desire to become pregnant.
6. Need (for whatever reason) for antibiotics or corticosteroids.
7. Presence of colostomy or ileo-rectal anastomosis.
8. Two or more abnormal liver function tests (bilirubin, alkaline phosphatase, ALAT or ASAT more than twice the upper limit of normal), or signs of cirrhosis of the liver.
9. Clearly impaired kidney function (endogenous creatinine clearance <30 ml/min).
10. Acute intermittent porphyria.

University Hospital Nijmegen, and by the local ethics committees of the participating hospitals. Patients were fully informed and their written consent was obtained in accordance with the declarations of Helsinki and Tokyo.

Study design and randomization

Patients meeting the inclusion criteria, lacking the exclusion criteria and having given their written informed consent were randomly assigned to receive either sulphasalazine or olsalazine daily. Patients were allocated to treatment groups with a modification of the standardized variance allocation method as described by Begg and Iglewicz (10), in order to ensure equal distribution of prognostic factors among both treatments. The modification consisted of standardazation of the variance method. The following factors were taken into account: duration of disease (two years or less, more than two years), sex, age (40 years or less, more than 40 years), extent of last exacerbation (not beyond splenic flexure, beyond splenic flexure, unknown), attending physician, and, if the patient had participated in the active disease trial: time to achieve remission (6 or 12 weeks) and medication in that trial (sulphasalazine or olsalazine).

The treatment lasted 48 weeks, or until the time of relapse. The dose of sulphasalazine was 4 g daily and of olsalazine 2 g daily, divided in two doses, to be taken on top of a meal. In case of adverse effects dose reduction to 3 and 1.5 g daily respectively was allowed. Sulphasalazine and olsalazine were given in externally indistinguishable capsules, containing 333 mg of sulfasalazine or 167 mg of olsalazine, provided by Pharmacia AB, Uppsala, Sweden, in sealed plastic containers. On day 1 and 2 the dosage was one-third, and on day 3 and 4 two-thirds of the full dose.

Control visits were performed after 4, 12, 24, 36 and 48 weeks. At the inclusion visit and each control visit a medical history was taken, patients were questioned about the intake of capsules and the occurrence of possible adverse effects, and a physical examination was made. Blood was drawn for the determination of haemoglobin, leucocytes, platelets, glucose, creatinine, liver function parameters (bilirubin, alkaline phosphatase, ALAT, ASAT and lactate

dehydrogenase) and haptoglobin, in order to recognize possible adverse effects. Urine was analyzed for the presence of protein and glucose.

All patients recorded their complaints on a diary card during each week preceeding a control visit. At the inclusion visit and the 48 week visit a sigmoidoscopy with biopsies was performed to check whether the colitis was in remission indeed.

Criteria for premature discontinuation of treatment

Patients were withdrawn from the trial if a relapse occurred before the end of the 48 weeks period. A relapse was defined as a recurrence of colitis symptoms (blood in stools, with or without diarrhea) and signs of inflammation at endoscopy. A patient was also regarded as having a relapse if he had only endoscopic signs of inflammation at the 48 week assessment, without the presence of complaints.

Patients dropped out if they were uncooperative or wished to discontinue the trial for any reason, if pregnancy occurred, if hypersensitivity to the study drug occurred and if the dosage was lowered to less than 75% for more than 4 weeks, due to adverse effects or other reasons. These patients were not counted a relapse in the statistical evaluation.

Statistical analysis

Both the overall relapse rate and the relapse-free survival in the two treatment groups were compared. Differences between overall relapse rates (numbers of relapses at any time during treatment) and between incidence rates of adverse effects were tested with Fisher's exact test. Relapse-free survival curves were constructed according to the Kaplan-Meier method and differences between the two curves were tested with the log-rank test. When a patient had dropped out for other reasons than a relapse, he or she was deducted from the number of patients at risk. Only two-sided test results were used, and p-values of less than 0.05 were considered significant.

RESULTS

Fourty-nine patients were randomized for the trial. Three of them appeared uncooperative from the very beginning and were not included in the analysis. Of the 46 remaining patients 23 were assigned to sulphasalazine and 23 to olsalazine. The main characteristics of both groups are shown in Table 2.

In the sulphasalazine group 7 patients (30.4%) relapsed and in the olsalazine group 6 patients (26.1%). The 95% confidence interval for the difference in overall relapse rate is - 22.2 to 30.3%. Four patients assigned to sulphasalazine and eight assigned to olsalazine dropped out for other reasons than a relapse, as mentioned in Table 3. The relapse-free survival in both treatment groups is shown in Figure 1. Their was no significant difference at any time during the trial. After 24 weeks of treatment the survival was 81.8% in the sulphasalazine group and 73.7% in the olsalazine group, with a 95% confidence interval of the differerence of -19 to 35%, and after 48 weeks the survival rate was

Table 2. *Main characteristics of both treatment groups.*

	Patients treated with	
	sulfasalazine (n = 23)	olsalazine (n = 23)
median age and range (years)	44 (22 - 78)	36 (16 - 76)
male : female	13 : 10	14 : 9
duration of disease		
less than 2 years	9	10
2 years or more	14	13
extent of colitis at last exacerbation		
not beyond splenic flexure	9	10
beyond splenic flexure	9	9
unknown*	5	4
Patients coming from		
active disease trial	12	12
remission achieved in 6 weeks	7	9
remission achieved in 12 weeks	5	3

* splenic flexure not reached at endoscopy

None of the differences between the two treatment groups was significant.

Table 3. *Reasons for drop out of patients.*

sulphasalazine group		olsalazine group	
adverse effects:		adverse effects:	
upper abdominal complaints	2	loose stools	3
rash	1		
uncooperativeness	1	uncooperativeness	4
		shipwrecked	1

69.7% and and 65.5% respectively, 95% confidence interval -28 to 36%. The minus sign denotes a difference in favour of olsalazine.

No patient had endoscopic signs of inflammation at entry, but in in the biopsies of 4 patients treated with sulphasalazine and 7 patients treated with olsalazine active inflammation was present. There was a trend towards a higher relapse rate in patients with histological evidence of inflammation at entry (5 relapses in 11 patients, and 8 relapses in 35 patients without histological inflammation), but the level of significance was not reached ($p = 0.15$). At the end of the study histological inflammation was present in 9 of 17 assessable biopsies from the sulphasalazine group and in 10 of 18 biopsies from the olsalazine group ($p = 1.0$).

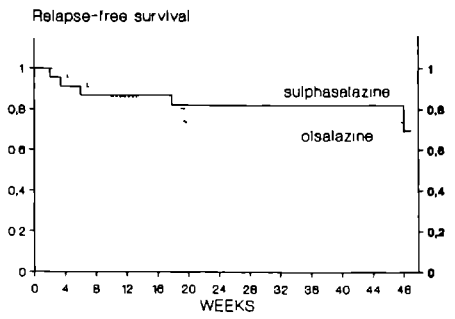

Figure 1. *Relapse-free survival rate in patients with ulcerative colitis in remission, treated with sulphasalazine (n = 23) or olsalazine (n = 23)*

Of the 24 patients who had achieved a remission just before entry six relapsed, as opposed to seven of 22 patients with a longer lasting remission.

Eight patients treated with sulphasalazine (34.8%) reported an adverse effect and nine patients treated with olsalazine (39.1%). The adverse effects resulting in a drop out

are included in Table 3 and the minor adverse effects disappearing spontaneously or after lowering the dose by less than 25% are mentioned in Table 4.

In one patient mild leucopenia (2.8 10^9/l) developed on sulphasalazine. In four patients treated with sulphasalazine and two patients treated with olsalazine serum haptoglobin levels dropped below the lower limit of normal, probably indicating low grade haemolysis.

The drug intake was not significantly different at any time during treatment. The mean intake of sulphasalazine and olsalazine was 97% and 89% of the full dose after 24 weeks and 90% and 84% respectivly after 48 weeks.

DISCUSSION

We found no significant difference between the relapse preventing potentials of sulphasalazine and olsalazine. While the present study was in progress, Ireland et al reported a trial comparing 1 g olsalazine and 2 g sulphasalazine daily for six months in 164 patients with ulcerative colitis in remission (11). They found no difference in relapse rate, being 12.2% for sulphasalazine and 19.5% for olsalazine. Also in the trial of Ireland et al there was a trend to have a higher relapse rate for patients with histological evidence of disease.

In studies comparing controlled release mesalazine with sulphasalazine in quiescent ulcerative colitis relapse rates higher than or comparable to ours were encountered. In one study 54% of patients taking 1.5 g Pentasa^R daily and 46% of patients taking 3 g sulphasalazine daily were in remission after 12 months (12),

Table 4. *Incidence of minor adverse effects.*

sulphasalazine group		olsalazine group	
upper abdominal complaints	3	upper abdominal complaints	2
mild, transient rash	1	fatigue	2
		loose stools	1
		mild itching	1

and in another trial, comparing 0.8-1.6 g Asacol^{R} with 2-4 g sulphasalazine, 37.5% of patients on Asacol^{R} and 38.6% of patients on sulphasalazine had suffered a relapse (13). These figures are roughly comparable with the results from the present study.

Adverse effects were not absent in patients taking olsalazine. Upper abdominal discomfort was more common during sulphasalazine treatment, but the occurrence of loose stools were the most frequent side effect of olsalazine in this study. Four out of 23 patients (17.3%) suffered from this untoward effect, and on three occasions it was a reason to stop the medication. The same problem has been encountered in other studies, where incidence rates of loose stools range from 2.2 to 12.5% (9,14-17). Whereas it was mentioned initially that its incidence was related to the extent of inflammation (9), others were not able to confirm this (11). In patients with active colitis we found an incidence of 7%, lower than in the present remission-phase study.

In accordance with the study of Ireland et al we found no significant difference between the total numbers of adverse effects in both treatments groups. It has to be borne in mind that the majority of patients in the present trial had taken sulphasalazine in the past, so a part of the study population is selected on its tolerance of sulphasalazine.

We did not pay attention to a "hidden" but important adverse effect of sulphasalazine, being infertility in man at reproductive age, due to impaired seminal quality (18,19). It has been demonstrated that this effect is reversible after withdrawal of the sulphapyridine part and that men remain fertile after institution of mesalazine (20) or olsalazine (9). It is therefore a good reason not to start sulphasalazine in this catagory of patients.

It is concluded that sulphasalazine and olsalazine are equally
effective in maintaining remission in patients with ulcerative colitis and that both treatments are accompanied by a similar incidence of adverse effects, that are different of character.

ACKNOWLEDGEMENTS

Marno C.M. Rijk received a grant from Pharmacia AB, Uppsala, Sweden, who also kindley gave further financial support and supplied the study drugs. The authors wish to thank Hans Bakker, hospital pharmacist, who excellently took care for the distribution and dispense of the study drugs.

REFERENCES

1. Dissanayake AS, Truelove SC. A controlled therapeutic trial of long-term maintenance treatment of ulcerative colitis with sulphasalazine. Gut, 1973; **14:** 923-26.
2. Khan AKA, Howes DT, Piris J. Truclove SC. Optimum dose of sulphasalazine for maintenance treatment in ulcerative colitis. Gut 1980; **21:** 232-40.
3. Das KM, Eastwood MA, McManus JPA, Sircus W. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. N Eng J Med 1973; **289:** 491-5.
4. Khan AKA, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulfasalazine. Lancet 1977; ii: 892-5.
5. Van Hees PAM, Bakker JH, van Tongeren JHM. Effect of sulphapyridine, 5-aminosalicylic acid and placebo in patients with idiopathic proctitis: a study to determine the active therapeutic moiety of sulphasalazine. Gut 1980; **21:** 632-5.
6. Sandberg-Gertzén H, Ryde H, Järnerot G. Absorption and excretion of a single 1 g dose of azodisal sodium in subjects with ileostomy. Scand J Gastroenterol 1983; **18:** 107 - 11.
7. Peppercorn MA, Goldman P. The role of intestinal bacteria in the metabolism of salicylazosulfapyridine. J Pharmacol Exp Ther 1972; **181:** 555-62.
8. Van Hogezand RA, van Hees PAM, Zwanenberg B, van Rossum JM, van Tongeren JHM. Disposition of disodium azodisalicylate in healthy subjects. A possible new drug for inflammatory bowel disease. Gastroenterology 1985; **88:** 717-22.
9. Sandberg-Gertzén H, Järnerot G, Kraaz W. Azodisal sodium in the treatment of ulcerative colitis. A study of tolerance and relapse-prevention properties. Gastroenterology 1986; **90:** 1024-30.
10. Begg CB, Iglewicz A. A treatment allocation procedure for sequential clinical trials. Biometrics 1980; **36:** 81-90.
11. Ireland A, Mason CH, Jewell DP. Controlled trial comparing olsalazine and sulphasalazine for the maintenance treatment of ulcerative colitis. Gut 1988; **29:** 835-7.
12. Mulder CJJ, Tytgat GN, Weterman IT, Dekker W, Blok P, Schrijver M, Vna der Heide H. Double-blind comparson of slow-release 5-aminosalicylate and sulfasalazine in remission

mainenance in ulcerative colitis. Gastroenterology 1988; **95:** 1449-53.

13. Riley SA, Mani V, Goodman MJ, Herd ME, Dutt S, Turnberg LA. Comparison of delayed release 5-aminosalicylic acid (mesalazine) and sulphasalazine as maintenance treatment of ulcerative colitis. Gastroenterology 1988; **94:** 1383-9.
14. Rao SSC, Dundas SAC, Holdsworth CD, Cann PAN, Palmer KR, Corvett CL. Olsalazine or sulphasalazine in first attacks of ulcerative colitis? A double blind study. Gut 1989; **30:** 675-9.
15. Meyers S, Sachar DB, Present DH, Janowitz HD. Olsalazine sodium in the treatment of ulcerative colitis among patients intolerant of sulfasalazine. A prospective, randomized, placebo-controlled, double-blind, dose-ranging clinical trial. Gastroenterology 1987; **93:** 1255-62.
16. Feurle GE, Theuer D, Velasco S, et al. Olsalazine versus placebo in the treatment of mild to moderate active colitis: a randomized double blind trial. Gut 1989; **30:** 1354-61.
17. Ireland A, Jewell DP. Olsalazine in patients intolerant of sulphasalazine. Scand J Gastroenterol 1987; **22:** 1038-40.
18. Toovey S. Hudson E, Hendry WF, Levi AJ. Sulphasalazine and male infertility: reversibility and possible mechanisms. Gut 1981; **22:** 445-51.
19. O'Morain C, Smethurst P, Doré CJ, Levi AJ. Reversible amle infertility due to sulphasalazine: studies in man and rat. Gut 1984; **25:** 1078-84.
20. Riley SA, Lecarpentier J, Goodman MJ, Mandal BK, Turnberg LA. Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. Gut 1987; **28:** 1008-12.

SUMMARY

As mentioned in **Chapter 1**, the aim of this study was to investigate some unexplored areas in the medical treatment of chronic inflammatory bowel disease, in particular the advantage, if any, of the addition of prednisone to sulphasalazine in the treatment of patients with active Crohn's disease, the disposition of sulphasalazine, olsalazine and slow release mesalazine formulations and finally the efficacy and safety of sulphasalazine and olsalazine in patients with active ulcerative colitis and their relapse preventing effect and safety in patients with quiescent ulcerative colitis.

In **Chapter 2** a survey of the present knowledge of the epidemiology, etiology, and prognosis of ulcerative colitis and Crohn's disease is presented, the modes of measurement of disease activity are discussed and available data on pharmacokinetics and the therapeutic effect of drugs used in the treatment of inflammatory bowel diseases are brought together.

In the study decribed in **Chapter 3** the effects of sulphasalazine plus prednisone and sulphasalazine plus placebo are compared in 60 patients with active Crohn's disease. In the first six weeks of a 16-week study period the Van Hees Activity Index decreased significantly more in the 30 patients treated with sulphasalazine plus prednisone (to a median of 70% of the initial value, interquartile range 57 - 84%) than in the 30 patients treated with sulphasalazine plus placebo (median 87%, interquartile range 70 - 94%; $p = 0.001$). In the last four weeks of treatment the difference appeared still in favour of the combination of sulphasalazine plus prednisone but failed to reach the level of significance. By means of the Crohn's Disease Activity Index no statistical difference at all between the two treatment groups could be demonstrated, although the trends had the same direction as the Van Hees Activity Index. The combination of sulphasalazine and prednisone appeared to be especially beneficial in the initial phase of treatment in patients with disease located in the colon, with or without involvement of the small bowel. In the end phase of treatment the only significant difference between both treatment regimens was found in patients with a high

initial Van Hees Activity Index. In patients assigned to treatment with sulphasalazine and placebo, the therapeutic effect was negatively correlated with the severity of diarrhea. Response to treatment did not correlate with the severity of diarrhea in patients who received sulphasalazine and prednisone. The main conclusion of this study is that addition of prednisone to sulphasalazine, in the dosages prescribed in this study, results in a faster initial improvement but not in a significantly better result in the end. In patients with a high initial Van Hees Activity Index or with diarrhea, or both, treatment with sulphasalazine plus prednisone is definitely preferable.

In **Chapter 4** the possible value of the measurement of serum levels of the acute phase proteins orosomucoid and C-reactive protein, as an adjunct to or a substitute for the clinical activity indices, is described. For this purpose, data obtained in patients participating in the study described in Chapter 3 and in patients excluded from that study, mainly because of a too low Van Hees Activity Index, were analyzed. The correlations between the levels of the acute phase reactants on the one hand and the clinical activity indices on the other hand appeared to be rather poor, as none of the r-values exceeded 0.57. Patients with a high initial orosomucoid level (>175mg/100 ml) showed a better response with regard to the van Hees Activity Index to treatment with sulphasalazine and prednisone (median 40.8% of initial value, interquartile range 34.9-66.2%) as compared with sulphasalazine alone (median 62.6%, interquartile range 47.1-85.7%; p=0.07). The changes of the acute phase reactants after 2 and 4 weeks of treatment did not distinguish patients with a good or a bad response. It was concluded from this study that the acute phase reactants cannot serve as a substitute for clinical activity indices and that they are of limited value in predicting the response to therapy.

In **Chapters 5, 6 and 7** the disposition of the 5-aminosalicylic acid delivering drugs sulphasalazine (Salazopyrin^{R}), olsalazine (Dipentum^{R}) and mesalazine (Pentasa^{R}, Asacol^{R} and Salofalk^{R}) is compared in healthy volunteers, in healthy volunteers

with induced diarrhoea, and in patients with inflammatory bowel disease with and without diarrhoea. In all these studies two basic assumptions were made, based on our former findings and on those of other investigators. First it was assumed that 5-aminosalicylic acid, early released in the proximal part of the intestine is rapidly absorbed and excreted into the urine. The second assumption was that 5-aminosalicylic acid released in the colon is acetylated by intestinal bacteria and mucosa. As opposed to unacetylated 5-aminosalicylic acid, acetyl-5-aminosalicylic acid is poorly absorbed from the bowel lumen. Therefore, a large amount of 5-aminosalicylic acid excreted in urine early after ingestion correlates with early release, and the proportion of acetylated 5-aminosalicylic acid in faeces is a measure of with exposure of 5-aminosalicylic acid to the colon.

A study comparing the disposition of 5-aminosalicylic acid from a single dose of the 5-aminosalicylic acid delivering drugs in eight healthy volunteers is described in **Chapter 5**. In these subjects, the early urinary excretion (in the first eight hours after ingestion) of 5-aminosalicylic acid was significantly lower after intake of the azo-compounds sulphasalazine and olsalazine (mean 2.6%) than after intake of the slow-release compounds Pentasa^R, Asacol^R and Salofalk^R (mean 7.3%). The proportion of acetylated 5-aminosalicylic acid in the faeces was significantly higher after ingestion of the azo-compounds (42.3 ± 2.7%, mean ± SEM) as compared with the slow-release compounds (34.6 ± 2.1%). The proportion of unacetylated 5-aminosalicylic acid in faeces was rather small, varying from 5.2 ± 1.3% for Salofalk^R to 12.8 ± 2.2% for sulphasalazine. Little azo-compound was recovered unsplit in faeces: 6.6 ± 1.8% after ingestion of sulphasalazine and 4.1 ± 1.1% after ingestion of olsalazine. It was concluded that in healthy subjects the azo-compounds have the most favourable disposition release profile for disposition in the colon. Individual drugs, however, have different properties and cannot be simply lumped together in an azo-group and a slow-release group. An additional analysis was performed on data obtained for each drug separately, showing that sulphasalazine and olsalazine are preferentially released in the colon, that Pentasa^R and Salofalk^R have a considerably larger proportion released in the small

bowel and that Asacol[R] takes an intermediate position.

The presence of diarrhoea is one of the differences between patients with active inflammatory bowel disease and healthy volunteers. In order to obtain a situation resembling that in patients with active disease, a study similar to the one described in Chapter 5 was performed in healthy subjects after induction of diarrhoea with bisacodyl, the results of which are presented in **Chapter 6**. In the eight subjects participating in this study the use of bisacodyl resulted in a two to threefold reduction of the intestinal transit time. Under these circumstances, the urinary excretion of acetyl-5-ASA was 4.5 ± 1.5% (mean ± SEM) after ingestion of sulphasalazine and 4.9 ± 1.5% after ingestion of olsalazine. The proportions of acetylated 5-aminosalicylic acid in faeces were 6.6 ± 2.1% and 8.4 ± 2.7%, respectively. These very low figures indicate poor disposition of 5-aminosalicylic acid to both small bowel and colon. This appeared to be the result of impaired splitting of the azo-bond in these drugs, as approximately half of the ingested dose was recovered unsplit in the faeces. Ingestion of Pentasa[R] and Salofalk[R] was associated with the largest proportion of acetylated 5-aminosalicylic acid in faeces (21.2 ± 3.4% and 18.6 ± 6.0%, respectively) and in urine (14.5 ± 2.5% and 26.7 ± 4.9%, respectively), indicating more favourable release patterns. The figures for Asacol[R] were intermediate. When the results of this study are compared with the results of the study described in Chapter 5, the disposition of 5-aminosalicylic acid from all drugs is impaired during accelerated intestinal transit time, but most pronounced so in the case of sulphasalazine, olsalazine and Asacol[R].

In **Chapter 7** the disposition of 5-aminosalicylic acid from the 5-aminosalicylic acid delivering drugs is studied during maintenance treatment in 20 patients with inflammatory bowel disease, 10 of whom suffered from diarrhoea. The figures obtained appeared very well comparable to the figures in healthy volunteers with and without induced diarrhoea. The presence of diarrhoea was associated with a less favourable release pattern of all drugs, as the proportion of acetylated 5-aminosalicylic acid in faeces and of acetylated 5-aminosalicylic acid in urine

decreased substantially. The disposition from Pentasa^R was the less influenced. Similar to the findings in healthy volunteers, diarrhoea resulted in a very substantial decrease of the splitting of the azo-bond. In patients with diarrhoea, 42.9 ± 12.2% of sulphasalazine and 47.2 ± 10.0% of olsalazine was recovered unsplit in the faeces.

On the basis of the findings in Chapters 5, 6 and 7 it is concluded that in the absence of diarrhoea the differences in the disposition patterns of the drugs studied are slightly in favour of the azo-compounds if the colon is the intended site of drug delivery. Pentasa^R and Salofalk^R are more fit for delivery of 5-aminosalicylic acid to the small bowel. In case of diarrhoea, however, the timely release of 5-aminosalicylic acid from sulphasalazine, olsalazine and Asacol^R is substantially impaired. In patients with diarrhoea Pentasa^R appears to be the best, and Salofalk^R the second best choice, also for patients with only colonic involvement.
The definite proof of the validity of the conclusions drawn above can only be given in controlled therapeutic trials, comparing the efficacy and safety of the available 5-aminosalicylic acid delivering drugs in patients with quiescent and active inflammatory bowel disease.

In **Chapter 8** the efficacy and safety of sulphasalazine and olsalazine is compared in 55 patients with active ulcerative colitis who were treated in a prospective, double-blind, multicentre trial with 6 g sulphasalazine or 3 g olsalazine daily for six weeks, to be continued for another six weeks if no remission had been achieved. After 6 weeks 6 of 27 evaluable patients (22.2%) had achieved a remission on sulphasalazine, and 9 of 28 patients (32.1%) on olsalazine. The 95% confidence limits are -33.3 and 13.4%. After 12 weeks 11 of 27 patients (40.7%) on sulphasalazine and 14 of 26 still evaluable patients (53.8%) on olsalazine were in remission, the 95% confidence interval of the difference being -39.8 and 13.6%. Substantial endoscopic improvement was eventually achieved in 48.2% of patients on sulphasalazine and 65.4% of patients on olsalazine (95% confidence interval of

the difference -43.4 to 9.0%). Six patients from each group were withdrawn because of adverse effects or increasing severity of disease. By means of a newly developed numerical Ulcerative Colitis Activity Index no significant difference between both treatment groups could be demonstrated. Eleven patients on sulphasalazine (40.7%) and six on olsalazine (21.4%) experienced minor side effects (95%- confidence interval of the difference -5 to 43%). It is concluded that olsalazine is at least as effective and at least as well tolerated as sulphasalazine in patients with active ulcerative colitis.

In the study described in **Chapter 9**, 49 patients with ulcerative colitis in remission entered a prospective, double-blind, multicentre trial comparing the relapse preventing effect and safety of 4 g sulphasalazine and 2 g olsalazine daily during 48 weeks. Of the 46 evaluable patients 23 were assigned to sulphasalazine and 23 to olsalazine. Seven of 23 patients (30.4%) relapsed on sulphasalazine and six of 23 patients (26.1%) on olsalazine (95% confidence limits of the difference -22.0% and 30.3%). The relapse-free survival curves did not differ significantly at any time during the trial period. Three patients assigned to treatment with sulphasalazine dropped out because of adverse effects; two patients because of upper abdominal complaints and one patient because of a skin rash. The occurence of loose stools was an adverse effect leading to the drop out of three patients treated with olsalazine. Four patients on sulphasalazine and six patients on olsalazine experienced minor adverse effects. Moreover, one patient on sulphasalazine had mild leucopenia, and four patients on sulphasalazine and one patient on olsalazine had decreased levels of haptoglobin. Thus, sulphasalazine and olsalazine are equally effective in maintaining remission of ulcerative colitis and are accompanied by a similar incidence of adverse effects.

On the basis of the results obtained in the studies described in the Chapters 8 and 9 it is concluded that olsalazine and sulphasalazine are equally effective and safe, both in patients with active and with quiescent ulcerative colitis. Olsalazine is therefore a good alternative for patients intolerant of sulphasalazine. Starting from the results of the pharmacokinetic studies described in the Chapters 5, 6

and 7 it can be speculated that other 5-aminosalicylic acid delivering drugs, especially Pentasa^{R}, are preferable to olsalazine and sulphasalazine in patients with active disease and diarrhoea. Up to the present this remains to be proven in a controlled clinical trial.

SAMENVATTING

Het doel van deze studie was, zoals vermeld in **hoofdstuk 1**, het onderzoeken van enkele "witte vlekken" op het gebied van de behandeling van chronische idiopathische darmontstekingen. Met name werd onderzoek verricht naar het mogelijke voordeel van het toevoegen van prednison aan salazosulfapyridine bij patienten met een actieve ziekte van Crohn, naar de beschikbaarheid van 5-aminosalicylzuur (mesalazine) uit salazosulfapyridine, olsalazine en slow-release mesalazine preparaten, en tenslotte werden de effectiviteit en veiligheid van salazosulfapyridine en olsalazine vergeleken bij patienten met een actieve colitis ulcerosa en bij patienten met colitis ulcerosa in remissie.

In **hoofdstuk 2** wordt een overzicht gegeven van de huidige kennis op het gebied van epidemiologie, etiologie en prognose van colitis ulcerosa en de ziekte van Crohn en worden de methoden voor het meten van de ziekteactiviteit besproken. Verder wordt een overzicht gegeven van de op dit moment beschikbare gegevens over de farmacokinetiek en het therapeutisch effect van de geneesmiddelen, die gebruikt worden bij de behandeling van deze ziekten.

In het onderzoek dat beschreven wordt in **hoofdstuk 3** wordt het therapeutisch effect van salazosulfapyridine plus prednison vergeleken met dat van salazosulfapyridien plus placebo bij 60 patienten met een actieve ziekte van Crohn. In de eerste 6 weken van een 16 weken durende onderzoeksperiode daalde de activiteitsindex volgens van Hees significant meer bij de 30 patienten die behandeld werden met salazosulfapyridine plus prednison (tot een mediane waarde van 70% van de uitgangswaarde, met een interquartiel bereik van 57 tot 84%) dan bij de 30 patienten die behandeld werden met salazosulfapyridine plus placebo (tot een mediane waarde van 87%, interquartiel bereik 70 tot 94%; $p = 0{,}001$). In de laatste 4 weken van de behandeling was het verschil tussen beide groepen patienten nog steeds in het voordeel van de combinatie salazosulfapyridine plus prednison, zij het niet significant. Door middel van de Crohn's Disease Activity Index kon geen enkel significant verschil tussen beide behandelingsgroepen worden aangetoond, al tendeerden de verschillen in dezelfde richting als

gemeten met de activiteitsindex volgens van Hees. De combinatie van salazosulfapyridine met prednison bleek met name van voordeel in de beginfase van de behandeling bij patienten met de ziekte van Crohn in het colon, al dan niet met gelijktijdige localisaties in de dunne darm. In de eindfase van de behandeling werd het enige significante verschil tussen beide behandelingen gevonden bij die patienten, die een hoge uitgangswaarde hadden van de activiteitsindex volgens van Hees. Bij patienten die aan behandeling met salazosulfapyridine en placebo waren toegewezen was het therapeutisch effect negatief gecorreleeerd met de ernst van de diarree. De reactie op de behandeling hing niet samen met de ernst van de diarree bij patienten die behandeld werden met salazosulfapyridine en prednison. De belangrijkste conclusie van dit onderzoek is dat het toevoegen van prednison aan salazosulfapyridine, althans in de doseringen zoals in deze studie gebruikt, leidt tot een snellere verbetering in het begin van de behandeling, maar niet tot een significant beter uiteindelijk resultaat. Bij patienten met een hoge uitgangswaarde van de activiteitsindex volgens van Hees of met ernstige diarree, of met beide, moet zeker de voorkeur gegeven worden aan behandeling met salazosulfapyridine plus prednison.

In **hoofdstuk 4** wordt de mogelijke waarde van het meten van de serum spiegels van de acute fase eiwitten orosomucoid en C-reactive protein, als aanvulling op of vervanging van de activiteitsindices beschreven. Hiertoe werden gegevens geanalyseerd die verkregen werden bij de patienten die beschreven zijn in hoofdstuk 3, en bovendien bij patienten met de ziekte van Crohn die van dat onderzoek waren uitgesloten, meestal vanwege een te lage activiteitsindex volgens van Hees. De correlaties tussen de serum spiegels van de acute fase eiwitten enerzijds en de hoogte van de activiteitsindices anderzijds bleken nogal mager te zijn, waarbij geen van de correlatie coëfficienten hoger was dan 0,57. Patienten met een hoge uitgangswaarde van het serum orosomucoid gehalte (>175 mg/100 ml) reageerden beter op behandeling met salazosulfapyridine plus prednison, althans gemeten met de activiteitsindex volgens van Hees (die bij hen daalde tot mediaan 40,8% van de uitgangswaarde in de laatste 4 weken van de

behandelingsperiode, interquartiel bereik 34,9 tot 66,2%) dan patienten die met alleen salazosulfapyridine behandeld werden (daling tot mediaan 62,6%, interquartiel bereik 47,1 tot 85,7%; p = 0,07). Op grond van de veranderingen van de acute fase eiwitten na 2 en 4 weken behandeling was het niet mogelijk een onderscheid te maken tussen patienten met een goede of minder goede reactie op de therapie op het einde van de behandelingsperiode. Op grond van deze resultaten wordt geconcludeerd dat acute fase eiwitten de activiteitsindices niet kunnen vervangen en dat hun voorspellende waarde wat betreft de reactie op de behandeling beperkt is.

In de **hoofdstukken 5, 6 en 7** worden vergelijkende onderzoeken beschreven naar de beschikbaarheid van de 5-aminosalicylzuur bevattende geneesmiddelen salazosulfapyridine (Salazopyrine^{R}), olsalazine (Dipentum^{R}) en slow-release mesalazine (Pentasa^{R}, Asacol^{R} en Salofalk^{R}) bij gezonde vrijwilligers, bij gezonde vrijwilligers bij wie diarree is opgewekt en bij patienten met chronische darmontstekingen, met en zonder diarree. Bij al deze onderzoeken werd uitgegaan van twee vooronderstellingen, gebaseerd op eerder onderzoek van onszelf en van andere onderzoekers. Op de eerste plaats werd aangenomen dat 5-aminosalicylzuur dat proximaal in de dunne darm vrijkomt snel wordt opgenomen en in de urine wordt uitgescheiden. Een grote hoeveelheid in de urine uitgescheiden 5-aminosalicylzuur betekent dan een vroege afgifte van 5-aminosalicylzuur uit het betreffende geneesmiddel en een geringere beschikbaarheid voor het distale deel van de darm. De tweede aanname was dat 5-aminosalicylzuur, dat vrijkomt in het colon, geacetyleerd wordt door darmbacteriën en darmslijmvlies. In tegenstelling tot ongeacetyleerd 5-aminosalicylzuur wordt geacetyleerd 5-aminosalicylzuur slecht uit het darmlumen opgenomen. De hoeveelheid geacetyleerd 5-aminosalicylzuur in de feces is dus een maat voor de beschikbaarheid in het colon.

Een vergelijkend onderzoek naar de beschikbaarheid van 5-aminosalicylzuur na een éénmalige toediening van de 5-aminosalicylzuur bevattende geneesmiddelen

bij gezonde vrijwilligers wordt beschreven in **hoofdstuk 5**. Bij deze personen was de vroege uitscheiding (in de eerste 8 uur na inname) van 5-aminosalicylzuur in urine significant minder na inname van de azo-verbindingen salazosulfapyridine en olsalazine (gemiddeld 2,6% van de ingenomen dosis) dan na inname van de slow-release preparaten Pentasa^R, Asacol^R en Salofalk^R (gemiddeld 7,3%). Het percentage geacetyleerd 5-aminosalicylzuur in de feces was significant hoger na inname van de azo-verbindingen (42,4% ± 2,7%, gemiddelde ± S.E.M.) dan na inname van de slow-release preparaten (34,6 ± 2,1%). Het percentage ongeacetetyleerd 5-aminosalicylzuur in de feces was vrij gering, varierend van 5,2 ± 1,3% voor Salofalk^R tot 12,8 ± 2,2% voor salicylazosulfapyridine. Slechts een klein gedeelte van de azo-verbindingen werd ongesplitst in de feces teruggevonden: 6,6 ± 1,8% na inname van salicylazosulfapyridine en 4,1 ± 1,1 % na inname van olsalazine. De conclusie luidde dat bij gezonde proefpersonen de azo-verbindingen het meest gunstige afgifte profiel hebben met betrekking tot beschikbaarheid in het colon. Ieder geneesmiddel op zich heeft echter eigen kenmerken, en een indeling in azo-verbindingen en slow-release preparaten is daarom niet zonder meer gerechtvaardigd. Daarom werden nog aanvullende analyses verricht met de gegevens die voor elk geneesmiddel apart waren verkregen. Hieruit bleek dat de afgifte van 5-aminosalicylzuur uit salicylazosulfapyridine en olsalazine met name in het colon plaatsvond, uit Pentasa^R en Salofalk^R in aanzienlijke mate in de dunne darm, en dat Asacol^R een tussenpositie innam.

Eén van de aspecten waarin patienten met een actieve darmontsteking vaak van gezonde vrijwilligers verschillen is de aanwezigheid van diarree. Teneinde de situatie bij patienten met een actieve ziekte na te bootsen werd een onderzoek als beschreven in hoofdstuk 4 uitgevoerd bij vrijwilligers, bij wie diarree was opgewekt door middel van bisacodyl. De resultaten hiervan zijn beschreven in **hoofdstuk 6**. Bij de acht deelnemers aan deze studie resulteerde de toediening van bisacodyl in een twee- tot drievoudige afname van de darmpassagetijd. Onder deze omstandigheden bedroeg de uitscheiding van acetyl-5-aminosalicylzuur in de

urine 4,5 ± 1,5% (gemiddelde ± S.E.M.) van de ingenomen dosis na inname van salicylazosulfapyridine en 4,9 ± 1,5% na inname van olsalazine. De percentages in de feces uitgescheiden acetyl-5-aminosalicylzuur na inname van deze geneesmiddelen waren respecievelijk 6,6 ±2,1 % en 8,4 ± 2,7%. Deze zeer lage percentages zijn een aanwijzing voor geringe beschikbaarheid van 5-aminosalicylzuur uit deze twee geneesmiddelen voor dunne en dikke darm onder deze omstandigheden. Dit bleek veroorzaakt te worden door een verminderde splitsing van de azo-binding in beide stoffen, aangezien ongeveer de helft van de ingenomen hoeveelheid ongesplitst werd teruggevonden in de feces. Gebruik van Pentasa^{R} en Salofalk^{R} gaf het grootste percentage geacetyleerd 5-aminosalicylzuur in de feces (respectievelijk 21.2 ± 3,4 en 18,6 ± 6,0%) en in urine (respectievelijk 14,5 ± 2,5% en 26,7 ± 4,9%), hetgeen wijst op een gunstiger afgifte profiel. Asacol^{R} nam wederom een tussenpositie in. Bij vergelijking van de resultaten van deze studie met de resultaten van de studie die beschreven is in hoofdstuk 5 blijkt de beschikbaarheid van 5-aminosalicylzuur uit alle geneesmiddelen te zijn afgenomen tijdens versnelde darmpassage, maar het meest uitgesproken in het geval van salicylazosulfapyridine, olsalazine en Asacol^{R}.

In **hoofdstuk 7** wordt de beschikbaarheid van 5-aminosalicylzuur uit de 5-aminosalicylzuur bevattende geneesmiddelen beschreven tijdens een onderhoudsbehandeling bij 20 patienten met chronische darmontstekingen, van wie er 10 diarree hadden. De uitkomsten die hierbij werden verkregen bleken zeer goed vergelijkbaar met de gegevens afkomstig van gezonde vrijwilligers, met of zonder geinduceerde diarree. De aanwezigheid van diarree ging gepaard met een minder gunstig afgifte patroon van alle geneesmiddelen, blijkens een aanzienlijke afname van de hoeveelheid geacetyleerd 5-aminosalicylzuur in feces en in urine. De beschikbaarheid van 5-aminosalicylzuur uit Pentasa^{R} werd het minst beinvloed. Zoals het geval was bij gezonde proefpersonen had diarree tot gevolg dat de splitsing van de azo-binding in salicylazosulfapyridine en olsalazine aanzienlijk verminderde. Bij patienten met diarree werd 42,9 ± 12,2% van salicylazosulfapyridine en 47,2 ± 10,0% van olsalazine ongesplitst in de feces

teruggevonden.

Op grond van de gegevens uit de hoofdstukken 5, 6 en 7 wordt geconcludeerd dat bij afwezigheid van diarree de verschillen in het afgifte patroon van 5-aminosalicylzuur uit de verschillende geneesmiddelen enigszins in het voordeel van de azo-verbindingen zijn, wanneer het gaat om de afgifte van 5-aminosalicylzuur in het colon. Pentasa^{R} en Salofalk^{R} hebben meer afgifte in de dunne darm. Echter, een tijdige afgifte van 5-aminosalicylzuur uit salicylazosulfapyridine, olsalazine, en Asacol^{R} neemt duidelijk af wanneer er sprake is van diarree. Voor patienten met diarree lijken Pentasa^{R} en Salofalk^{R} de beste keus, ook wanneer alleen het colon is aangedaan. Het definitieve bewijs van de geldigheid van de hierboven getrokken conclusies kan alleen geleverd worden in gecontroleerde onderzoeken, waarbij de werkzaamheid en veiligheid van de beschikbare 5-amino-salicylzuur bevattende geneesmiddelen worden vergeleken bij patienten met chronische darmontstekingen, zowel in de actieve als in de rustige fase.

In **hoofdstuk 8** worden de werkzaamheid en veiligheid van salicylazosulfapyridine en olsalazine vergeleken bij 55 patienten met een actieve colitis ulcerosa, die in een prospectief, dubbelblind multicenter onderzoek werden behandeld met 6 gram salicylazosulfapyridine of 3 gram olsalazine per dag gedurende 6 weken. Dit werd nog eens 6 weken voortgezet indien na de eerste 6 weken de ziekte nog niet in remissie was gekomen. Na 6 weken hadden 6 van de 27 met salicylazosulfapyridine behandelde patienten (22,2%) een remissie bereikt, en 9 van de 28 met olsalazine behandelde patienten (32,1%). De 95% betrouwbaarheidsgrenzen van het verschil waren -33,3 en 13,4%. Na 12 weken waren 11 van de 27 met salicylazosulfapyridine behandelde patienten (40,7%) in remissie en 14 van de 26 op dat moment nog evalueerbare patienten (53,8%) die met olsalazine waren behandeld. Het 95% betrouwbaarheidsinterval van het verschil was -39,8 tot 13,6%. Een aanzienlijke endoscopische verbetering op het einde van de behandelingsperiode werd gezien bij 48,2% van de met salicylazosulfapyridine behandelde patienten en bij 65,4% van de met olsalazine behandelde patienten

(95% betrouwbaarheidsinterval van het verschil -43,4 tot 9,0%). Bij zes patienten uit beide groepen werd de behandeling gestaakt wegens bijwerkingen of toename van de ernst van de ontsteking. Door middel van een nieuw ontwikkelde numerieke activiteitsindex voor colitis ulcerosa kon geen significant verschil tussen beide behandelingen worden aangetoond. Bij elf patienten die met salicylazosulfapyridine behandeld werden (40,7%) en zes patienten die met olsalazine behandeld werden (21,4%) traden minder ernstige bijwerkingen op (95% betrouwbaarheidsinteval van het verschil -5 tot 43%). De conclusie van dit onderzoek is dat olsalzine minstens even effectief is en minstens even goed verdragen wordt als salicylazosulfapyridine bij patienten met een actieve colitis ulcerosa.

In de studie die in **hoofdstuk 9** wordt beschreven namen 49 patienten met colitis ulcerosa in remissie deel aan een prospectief, dubbelblind multicenter onderzoek, waarin het effect op het voorkómen van recidieven en de veiligheid van een dagelijkse dosis van 4 gram salicylazosulfapyridine of 2 gram olsalazine gedurende 48 weken worden vergeleken. Van de 46 evalueerbare patienten werden er 23 behandeld met salicylazosulfapyridine en 23 met olsalazine. Zeven van de 23 met salicylazosulfapyridine behandelde patienten (30,4%) kregen een recidief tegenover 6 van de 23 met olsalazine behandelde patienten (26,1%). De 95% betrouwbaarheidsgrenzen van het verschil waren -22,0 en 30,3%. De recidiefvrije overlevingscurven verschilden op geen enkel moment tijdens de behandeling significant van elkaar. Drie patienten, die behandeld werden met salicylazosulfapyridine, vielen uit vanwege bijwerkingen: twee wegens bovenbuiksklachten en één wegens huiduitslag. Het ontstaan van dunne ontlasting was een bijwerking die het uitvallen van drie met olsalazine behandelde patienten tot gevolg had. Vier patienten hadden geringe bijwerkingen van salicylazosulfapyridine, en zes van olsalazine. Bovendien trad bij één patient op salicylazosulfapyridine een geringe leucopenie op, en zes met salicylazosulfapyridine behandelde patienten en één met olsalazine behandelde patient hadden verlaagde serumspiegels van haptoglobine, hetgeen wijst op enige hemolyse.

Salicylazosulfapyridine en olsalazine zijn dus even effectief voor het handhaven van een remissie en gaan in vergelijkbare mate gepaard met het optreden van bijwerkingen.

Op grond van de in de hoofdstukken 8 en 9 verkregen uitkomsten wordt geconcludeerd dat olsalazine en salicylazosulfapyridine gelijkwaardig aan elkaar zijn wat betreft werkzaamheid en veiligheid, zowel bij patienten met een actieve als met een inactieve colitis ulcerosa. Olsalazine is daarom een goed alternatief voor patienten die salicylazosulfapyridine niet goed kunnen verdragen. Uitgaande van de pharmacokinetische studies die beschreven zijn in de hoofdstukken 5, 6 en 7 zou men kunnen stellen dat andere 5-aminosalicylzuur bevattende preparaten, met name Pentasa^{R}, en in wat mindere mate Salofalk^{R}, de voorkeur verdienen boven olsalazine bij patienten met een actieve ontsteking en diarree. Dit dient echter in een gecontroleerd klinisch onderzoek nog bewezen te worden.

WOORDEN VAN DANK

Het schrijven van dit proefschrift is, zoals meestal, slechts mogelijk geweest dankzij de hulp en steun van velen.

Mijn dank gaat in de eerste plaats uit naar alle patienten die enthousiast en nauwgezet aan de verschillende onderzoeken hebben meegewerkt.

De vele collega's in het Sint Radboudziekenhuis en elders in den lande die patienten hebben aangemeld en behandeld in het kader van de "multi centre studies" ben ik zeer erkentelijk. Met name dr. W.M.M. Driessen uit het Sint Josephziekenhuis te Eindhoven (inmiddels Veldhoven) heeft hiervoor zich steeds bijzonder ingespannen.

Dr. R.A. van Hogezand, nu gastroenteroloog in het Medisch Spectrum Twente te Enschede, heeft aan de basis gestaan van de onderzoeken beschreven in de hoofdstukken 3 en 4 en ook een aanzienlijk deel van de praktische uitvoering ervan voor zijn rekening genomen.

Zonder de hulp van de Medisch Statistische Adviesafdeling was dit werk zeker niet tot stand gekomen. Drs. Ph. van Elteren en Ir. H.J.J. van Lier hebben veel energie gestoken in het ontwerpen en uitvoeren van de meeste studies en nog meer energie in het analyseren en publicatie-rijp maken van de resultaten.

Dr. P.A.M. van Hees, gastroenteroloog in het Sint Antoniusziekenhuis te Nieuwegein heeft meegedacht bij de opzet en uitvoering van enkele in dit proefschrift beschreven onderzoeken.

Annie van Schaik, laborante op het laboratorium voor maag-, darm- en leverziekten was een immer vriendelijke en enthousiaste steunpilaar die zeer accuraat de vele bepalingen van 5-aminosalicylzuur en zijn derivaten uitvoerde en ook behulpzaam was bij de nodige distributie- en inzamelingswerkzaamheden.

De firma Kabi Pharmacia stelde gedurende drie jaar een volledige beurs ter beschikking en leverde ook uitgebreide logistieke steun voor de onderzoeken, beschreven in de hoofdstukken 8 en 9. Met name de heer S. Ljungberg van Kabi Pharmacia Sweden en de heren H. Krommendam, drs. H. Looman en P. Ooijevaar van Kabi Pharmacia Nederland ben ik veel dank verschuldigd.

Mijn collega's op de afdeling maag-, darm- en leverziekten ben ik dankbaar voor al het meedenken, de morele steun en de zeer prettige en collegiale sfeer waarin het werk verricht kon worden dat tot dit proefschrift heeft geleid.

Ik ben mijn voorganger in Breda, T.M.J. Ottenhoff, internist, zeer erkentelijk voor het feit dat hij zijn praktijk nog drie maanden langer dan gepland heeft voortgezet waardoor ik in staat was het proefschrift vóór mijn komst naar Breda vrijwel af te ronden.

Herlin, je voelde je vaak als de atleet die steeds vlak voor de finish opnieuw de bel voor de laatste ronde hoorde. Ik dank je voor je uithoudingsvermogen. Bij alle transpiratie waren jij en Martijn mijn inspiratie.

CURRICULUM VITAE

De schrijver van dit proefschrift werd op 26 januari 1953 geboren te Eindhoven. Na het behalen van het diploma gymnasium ß aan het Lyceum Augustinianum in Eindhoven in 1971 werd begonnen met de studie geneeskunde aan de Katholieke Universiteit te Nijmegen. Het doctoraalexamen werd in 1976 en het artsexamen in 1979 afgelegd.

Na vervulling van de militaire dienstplicht werd in september 1980 begonnen met de opleiding tot internist in het ziekenhuis De Stadsmaten te Enschede (opleiders: dr. S.G. Hulst en R.J.Th.M. Ypma), hetgeen vanaf maart 1982 werd voortgezet aan de Universiteitskliniek voor Inwendige Ziekten van het Sint Radboudziekenhuis te Nijmegen (opleider: Prof. dr. A. van 't Laar). Op 1 september 1985 werd hij ingeschreven als internist in het register van erkende medische specialisten.

Aansluitend was hij werkzaam op de afdeling maag-, darm- en leverziekten van bovengenoemd ziekenhuis (hoofd: dr. J.H.M. van Tongeren) waar hij werd opgeleid tot gastroenteroloog en de onderzoeken verrichtte die tot dit proefschrift hebben geleid.

Vanaf 1 juli 1990 is hij gevestigd als internist met als speciaal aandachtsgebied de maag-, darm- en leverziekten in het Interconfessioneel Ziekenhuis de Baronie te Breda, in associatie met de internisten mevrouw A.M. van Gent, B.J.V Horák, J.A.M. Hoskam, dr. P.J. Stijnen en G.P. Verburg.

Hij is getrouwd met Herlin Woldberg. Zij hebben een zoon: Martijn.

STELLINGEN

I

Bij patienten met een actieve ziekte van Crohn leidt het toevoegen van prednison aan salazosulfapyridine tot een snellere verbetering in het begin van de behandeling, maar niet tot een duidelijk beter uiteindelijk resultaat, behalve bij patienten met een ernstige activiteit van de ziekte en/of ernstige diarree.
- dit proefschrift -

II

Een versnelde darmpassage heeft een aanzienlijke invloed op de beschikbaarheid van 5-aminosalicylzuur uit zowel azo-verbindigen als preparaten met vertraagde of uitgestelde afgifte, het minst echter op Pentasa^{R}.
- dit proefschrift -

III

Olsalazine is even effectief als salazosulfapyridine bij de behandeling van patienten met een actieve colitis ulcerosa en bij het voorkomen van recidieven bij patienten met colitis ulcerosa in remissie.
- dit proefschrift -

IV

Bijwerkingen treden niet significant minder op tijdens behandeling met olsalazine dan tijdens behandeling met salazosulfapyridine maar zijn anders van karakter, zodat olsalazine toch een goed alternatief kan zijn bij voor salazosulfapyridine overgevoelige patienten.
- dit proefschrift -

V

Bij oudere patienten met een nog aanwezige galblaas, bij wie langs endoscopische weg een papillotomie van de papil van Vater en extractie van choledochusstenen heeft plaatsgevonden, dient niet routinematig later alsnog een cholecystectomie uitgevoerd te worden.
Rijk MCM en Yap SH. Ned Tijdschr Geneeskd 1989; **133:** 1919-1922.

VI

Bij de behandeling van patienten met de ziekte van Wegener is intermitterend intraveneuze toediening van cyclofosfamide minder effectief dan dagelijkse orale toediening.
Hoffmann et al. Am J Med 1990; **89:** 403-411.

VII

Bij patienten met ernstige, door kanker veroorzaakte pijn heeft continue subcutane toediening van morfine de voorkeur boven continue intraveneuze toediening, omdat het technisch eenvoudiger is en even effectief.
Moulin DE et al. Lancet 1991; **337:** 465-468.

VIII

Bij een gram-negatieve sepsis kan toediening van HA-1A humane monoclonale antistoffen tegen endotoxine een effectieve aanvullende behandeling zijn.
Ziegler JE et al. New Engl J Med 1991; **324:** 429-436.

IX

Zoals blijkt uit de levenskansen van de deelnemers aan de Elfstedentourtocht van 1956 hebben mannen met een goede lichamelijke conditie een grotere kans op het bereiken van een hoge leeftijd.
JLCM van Saase et al. Br Med J 1990; **301:** 1409-1411.

X

Het enthousiasme waarmee trialformulieren worden ontworpen wordt zelden gedeeld door degenen die ze moeten invullen.
- eigen waarneming -

XI

Bij de jacht op statistische significantie wordt te vaak vergeten dat het verschil tussen net wel en net niet statistisch significant niet gelijk staat aan het verschil tussen waar en onwaar, of tussen wel en niet relevant.

XII

Het in het buitenland lezen van nederlandse weerberichten kan ook wel eens tot zware depressies leiden.

Breda, 17 maart 1991

Marno Rijk

Printed by ICG Printing, Dordrecht