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Prolonged-Release Mesalazine[1]

A Review of its Therapeutic Potential in Ulcerative Colitis and Crohn's Disease

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Data Selection

Sources: Medical literature published in any language since 1983 on Mesalazine, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand) and Medline. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'Mesalazine' or 'Mesalamine' or '5-ASA' and ('Inflammatory-bowel-disorders' or 'Proctitis') and ('slow-release' or 'prolonged-release'). Medline search terms were 'Mesalazine' or 'Mesalamine' or '5-ASA' and ('Inflammatory-bowel-diseases' or 'Crohn-disease' or 'Ulcerative-colitis' or 'Proctitis') and 'slow-release'. Searches were last updated 20 Mar 2000.

Selection: Studies in patients with ulcerative colitis or Crohn's disease who received oral prolonged-release mesalazine (Pentasa®). Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Mesalazine, mesalamine, Pentasa®, ulcerative colitis, Crohn's disease, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

1 Also known as mesalamine in the US.

Summary

Abstract

Prolonged-release mesalazine (Pentasa®[2]) consists of ethylcellulose-coated microgranules from which mesalazine (known in the US as mesalamine) is released in the small and large intestine in a diffusion-dependent manner.

Dose-dependent improvements in clinical and endoscopic parameters have been reported with prolonged-release mesalazine 2 and 4 g/day in clinical trials in patients with mild to moderately active ulcerative colitis. Induction of clinical and endoscopic remission was achieved in more patients receiving a daily dosage of 4 g/day than in those receiving placebo.

In patients with ulcerative colitis in remission, prolonged-release mesalazine is effective in reducing the rate of relapse. Higher dosages tend to be more effective, and a 12-month remission rate of 64% has been reported for patients treated with a 4g daily dosage of this formulation. Comparative data indicate that prolonged-release mesalazine has similar efficacy in maintaining remission to molar equivalent doses of sulfasalazine.

Data from a study in patients with mild to moderately active Crohn's disease indicates that higher dosages (4 g/day) of prolonged-release mesalazine are more effective than placebo in reducing disease activity. After 16 weeks' treatment, 64% of patients receiving a 4 g/day dosage experienced clinical improvement and 43% attained remission. In studies of patients in remission of Crohn's disease, the formulation appears to be more effective in preventing relapse in patients with isolated small bowel disease than in those with colonic involvement.

The tolerability profile of oral prolonged-release mesalazine is similar to that of placebo and the incidence of adverse events does not appear to be dose-related. Nausea/vomiting, diarrhoea, abdominal pain and dyspepsia occur most frequent-

2 Use of trade names is for product identification purposes only and does not imply endorsement.

ly, although their incidence is low. Reports of nephrotoxicity during prolonged-release mesalazine treatment are rare.

Conclusions: Oral prolonged-release mesalazine is effective for maintenance and induction of remission of mild to moderately active colitis, both in patients with distal disease and in those with pancolitis. The formulation has similar efficacy to that of equimolar concentrations of sulfasalazine. Prolonged-release mesalazine also appears to be effective in the treatment of Crohn's disease, and maintenance therapy is of particular value in patients with isolated small bowel involvement. Evidence suggests that higher dosages (3 to 4 g/day) of prolonged-release mesalazine have additional therapeutic benefits over lower dosages in patients with inflammatory bowel disease without increasing the incidence of adverse events.

Mode of Action

The mechanism by which mesalazine exerts its therapeutic actions remains elusive. However, numerous *in vitro* studies have indicated modulatory actions of mesalazine on the lipid mediators, cytokines and reactive oxygen species involved in the nonspecific inflammation and tissue damage characteristic of ulcerative colitis and Crohn's disease.

In vitro studies have consistently demonstrated inhibitory effects of mesalazine on leukotriene (LT)B_4 synthesis and release from biopsy specimens from individuals with normal colons and from patients with inflammatory bowel disease. Although mesalazine had conflicting effects on prostaglandin (PG)E_2 levels, higher concentrations appeared to considerably reduce PGE_2 production in colonic mucosa from patients with ulcerative colitis. Mesalazine also appears to reduce *in vitro* levels of LTC_4, 5-hydroxyeicosatetraenoic acid (HETE), 11-, 12-, 15-HETE, PGD_2 and platelet-activating factor.

In addition to inhibiting interferon (IFN)-γ binding, mesalazine reduced IFNγ-induced cell permeability and expression of the HLA-DR product of the major histocompatibility complex in colonic epithelial cell lines. Recent evidence suggests that mesalazine reverses the antiproliferative effects of tumour necrosis factor- (TNF)α and inhibits TNFα signalling events in intestinal cells. Mesalazine may also reduce interleukin (IL)-1/1β and IL-2 production.

Mesalazine reduced production of reactive oxygen species and protected against oxidant-induced tissue injury in several *in vitro* models.

Pharmacokinetic Properties

Entry of water into prolonged-release mesalazine microgranules creates a concentration gradient down which mesalazine diffuses, liberating active drug throughout the small bowel and colon.

Prolonged-release mesalazine acts topically in the affected bowel lumen. In volunteers, 18 to 20% of the administered dose was delivered to the jejunoileal segment as solubilised drug, while cumulative colonic delivery was 82% (approximately 75% as intact microgranules) during the first 7 hours after drug administration. Food intake, local pH and diarrhoeal states do not appear to substantially affect the disposition of mesalazine from the prolonged-release formulation.

Mesalazine is primarily metabolised by acetylation in the gut wall and liver, forming acetyl mesalazine. After oral administration, up to 53% of the administered dose is excreted in the urine as mesalazine plus acetyl mesalazine. Faecal excretion accounts for 40% of the administered dose (14 to 19% as unchanged mesalazine, although exact levels of acetylated and nonacetylated mesalazine in different colonic segments are not known).

Therapeutic Efficacy

Prolonged-release mesalazine at dosages up to 4 g/day has been investigated for the maintenance of remission and treatment of mild to moderately active ulcerative colitis and Crohn's disease. Higher doses of prolonged-release mesalazine (3 to 4 g/day) were generally more effective than low doses (1.5 to 2 g/day) for treatment of acute exacerbations and for maintenance of disease remission.

At dosages of 2 or 4 g/day, the formulation improved clinical and endoscopic findings in patients with active ulcerative colitis, and success of treatment was independent of disease location. At a dosage of 1.5 g/day, the prolonged-release formulation was as effective as sulfasalazine 3 g/day in improving clinical and endoscopic parameters.

The estimated 1-year remission rate in patients with quiescent ulcerative colitis receiving prolonged-release mesalazine 1.5 g/day was similar to that with sulfasalazine 3 g/day (54 *vs* 46%). A 4g daily dosage of the mesalazine formulation was more effective than placebo in preventing endoscopic and clinical relapse (1-year remission rates 64 *vs* 38%).

Low dosages (≤2 g/day) of prolonged-release mesalazine had no significant benefits over placebo in patients with mild to moderately active Crohn's disease. However, the formulation showed benefits compared with placebo at a dosage of 4 g/day in 1 study. In another study, prolonged-release mesalazine 4 g/day produced improvement, but was not statistically better than placebo. In addition to increasing the percentage of patients in remission, or experiencing therapeutic benefit, prolonged-release mesalazine reduced the time to remission and the percentage of treatment failures, compared with placebo. In another study, 16-week remission rates were significantly higher in patients receiving oral budesonide 9 mg/day than in those treated with a 4g daily dosage of prolonged-release mesalazine (62 *vs* 36%).

During prolonged-release mesalazine treatment for maintenance of remission of Crohn's disease, dosages of ≤2 g/day were not consistently effective in producing benefits over placebo. However, significantly lower relapse rates were reported in patients treated with a 3g daily dosage than in those receiving placebo over a 48-week period. In a noncomparative study of up to 30 months' duration, dosages of ≤4 g/day (median 3.7 g/day) were effective in maintaining 72% of patients continuously in remission over a 1-year period. Prolonged-release mesalazine showed particular benefit in reducing the rate of relapse in patients with isolated ileal disease. Endoscopic recurrence rates after 1 year in patients with a recent surgical resection of the affected bowel were significantly lower in those receiving prolonged-release mesalazine 3 g/day than in placebo recipients.

Improvements in disease status have been reported in children (aged 9 to 18 years) receiving prolonged-release mesalazine (22 to 53 mg/kg/day) for the treatment of active Crohn's disease.

Tolerability

There is no evidence of a dose relationship in the adverse events profile of prolonged-release mesalazine and the tolerability profile is similar to that of placebo. The most common adverse events considered related to treatment with the mesalazine formulation at dosages up to 4 g/day were nausea and/or vomiting, headache, abdominal pain, diarrhoea and dyspepsia. Treatment-related adverse events necessitating study withdrawal occurred less commonly in patients receiving a 4g daily dosage of prolonged-release mesalazine than in those receiving placebo.

Although nephrotoxicity has been associated with the use of other mesalazine-containing preparations, impaired renal function does not appear to be asso-

ciated with use of the prolonged-release formulation. However, as with other mesalazine preparations, precautionary monitoring of serum creatinine levels has been advocated.

Prolonged-release mesalazine appears to be well tolerated in patients intolerant of sulfasalazine. In patients who had experienced infertility as a result of sulfasalazine treatment, sperm quality was improved or normalised after switching to prolonged-release mesalazine treatment.

Dosage and Administration

Oral prolonged-release mesalazine at dosages up to 4 g/day is indicated for the induction of remission and treatment of mild to moderate ulcerative colitis in adults. For patients with quiescent disease, the recommended starting dosage is 1.5 g/day in 2 or 3 divided doses. However, evidence from clinical trials of dosages up to 4 g/day indicates a dose-dependent increase in efficacy.

No US or UK dosage recommendations are available for the use of prolonged-release mesalazine in the management of Crohn's disease. However, individualised dosage of up to 4 g/day in divided doses is generally recommended for the treatment of active disease and maintenance of remission in other countries.

Prolonged-release mesalazine should not be used in patients with known sensitivity to salicylates or in those with severe renal and/or liver impairment, and is not recommended for use in children. The formulation should be used with caution during pregnancy.

1. Introduction

Sulfasalazine has been successfully used for acute and maintenance treatment of inflammatory bowel diseases (IBD, encompassing ulcerative colitis and Crohn's disease) for many years. However, its use is frequently associated with the occurrence of adverse events which may be dose- or treatment-limiting in 15 to 20% of patients.[1] A study of the therapeutic properties of sulfasalazine and its constituents [mesalazine (5-amino salicylic acid, 5-ASA) and sulfapyridine] indicated that mesalazine is the therapeutically active component, while sulfapyridine acts as an inert carrier molecule to facilitate delivery to the colon.[2] This discovery, coupled with the implication of sulfapyridine in most of the adverse events associated with sulfasalazine treatment,[3] led to the development of mesalazine as a pure therapeutic entity.

1.1 Mesalazine Delivery Formulations

Mesalazine (fig. 1) is believed to exert its effects via topical actions in the gut lumen. However, orally administered unconjugated mesalazine is extensively absorbed from the proximal small bowel,[4] and alternative oral dosage formulations have been developed to facilitate the delivery of mesalazine to more distal sites of inflammation (table I). These include microgranules of mesalazine coated with a semipermeable ethylcellulose membrane (Pentasa®), mesalazine encased within a pH-dependent acrylic resin (pH-dependent delayed-release preparations: Salofalk®, Claversal®, Mesasal®, Asacol®), or conjugation of mesalazine via an azo bond to an inert carrier (balsalazide) or to another mesalazine molecule (olsalazine). In each case the properties of the delivery system dictate the site of mesalazine release. As with sulfasalazine, the release of mesalazine from the azo-bound prodrugs is dependent on azoreductase activity by intestinal bacteria that reside in the colon. Resin-coated preparations are resistant to low intestinal pH, but dissolve once exposed to the higher pHs encountered in more distal

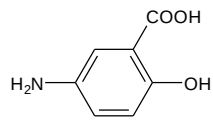

Fig. 1. Structural formula of mesalazine.

Table I. Properties of oral non-sulfa mesalazine-containing formulations[5-8]

Generic name	Trade name	Formulation	Mechanism of release	Site of release
Coated preparations				
Mesalazine	Pentasa®	Individual microgranules of mesalazine coated with an ethylcellulose membrane	Diffusion-dependent prolonged release through a semipermeable membrane	Duodenum, jejunum, ileum, colon
	Salofalk®	Eudragit® L 100[a] resin	pH-dependent delayed release (≥6)	Ileum, colon
	Claversal®			
	Mesasal®			
	Asacol®	Eudragit® S[b] resin	pH-dependent delayed release (≥7)	Terminal ileum, colon
Azo-bound prodrugs				
Balsalazide	Colazide®	Conjugation of mesalazine to an inert carrier molecule[c]	Colonic bacterial azoreduction	Colon
Olsalazine	Dipentum®	Mesalazine dimer	Colonic bacterial azoreduction	Colon

a Eudragit® L 100 = methacrylic acid:methyl methacrylic acid 1:2.
b Eudragit® S = methacrylic acid:methyl methacrylic acid 1:1.
c 4-aminobenzoyl-β-alanine.

regions of the gastrointestinal tract. In contrast, release of mesalazine from ethylcellulose-coated microgranules is diffusion-dependent and begins immediately following ingestion (sections 3 and 3.1).

This review focuses on the properties and clinical effects of the ethylcellulose-coated microgranule preparation (Pentasa®), referred to as prolonged-release mesalazine, which allows continuous delivery of mesalazine throughout the small bowel and colon.

2. Mode of Action

The pathogenesis of IBD and hence the mechanism by which mesalazine exerts its therapeutic effects in this disease remain elusive. However, lipid mediators [leukotrienes (LT), prostaglandins (PG), platelet-activating factor (PAF)], cytokines [including interleukins (IL), interferon-(IFN)γ and tumour necrosis factor-(TNF)α] and reactive oxygen species have been implicated in the nonspecific inflammation and tissue damage characteristic of IBD.[9-11] The modulation of these molecules by mesalazine may underlie the therapeutic effects of the drug.[12-17]

Numerous *in vitro* studies have investigated the effects of mesalazine on inflammatory processes in colonic epithelial cell lines or biopsy specimens from patients with active ulcerative colitis or with normal colons. Additional studies were conducted using peripheral blood cells isolated from healthy volunteers. The findings of these studies are summarised in table II.

2.1. Lipid Mediators

2.1.1 Lipoxygenase and Cyclo-Oxygenase Products

Products of the lipoxygenase pathway of arachidonic acid metabolism [including LTB_4, 5-hydroxyeicosatetraenoic acid (5-HETE) and 11-, 12- and 15-HETE] exhibit leucocyte chemotactic properties and may increase vascular permeability. These mediators and other eicosanoids such as PGD_2 and PGE_2 are thought to be important inflammatory agents in IBD.[12,18,21,28] LTB_4 is particularly implicated, and elevated levels of this mediator have been reported in colonic tissue from patients with ulcerative colitis.[19,20,29] Moreover, rectal dialysate levels of LTB_4 have been positively correlated with disease activity in ulcerative colitis.[30]

In vitro studies in colonic biopsy specimens and mononuclear leucocytes have consistently demonstrated inhibitory effects of mesalazine on the synthesis and release of LTB_4 (table II).[12,18,19] Moreover, treatment of active colitis with a single mesalazine

enema (1g) reduced elevated LTB_4 levels towards normal in patients responding to therapy.[30]

Data regarding the effects of mesalazine on PGE_2 levels are conflicting. Mesalazine did not affect PGE_2 levels in specimens of normal colonic mucosa[12] and had no effect on stimulated PGE_2 release from rectal biopsies from patients with ulcerative colitis.[19] However, in a study of patients with ulcerative colitis treated with mesalazine (administered as a single 1g enema), PGE_2 levels were reduced towards normal in rectal dialysates.[30] In another study in colonic epithelial cells from patients with active ulcerative colitis, mesalazine inhibited PGE_2 production by up to 70%.[20]

Inhibitory effects of mesalazine on the synthesis and/or release of LTC_4,[20] 5-HETE and 11-,12-,15-HETE,[18] and PGD_2[21] have also been demonstrated (table II).

2.1.2 Platelet-Activating Factor

The membrane phospholipid-derived mediator PAF is an inducer of gastrointestinal mucosal damage in animal models,[31] and elevated tissue levels have been demonstrated in colonic mucosa from patients with ulcerative colitis[22,32,33] and Crohn's dis-

Table II. *In vitro* effects of mesalazine in human colonic epithelium[a] and peripheral blood cells

Mediator	Variable	Cell type or tissue	Mesalazine concentration (mmol/L)	Observed effect (% inhibition)	Reference
Lipid mediators					
LTB_4	Synthesis	MNL	10	44	Horn et al.[18]
	Synthesis	Biopsy specimens[b]	0.1	30[c]	Schmidt et al.[12]
	Release	Biopsy specimens[d]	1.3	28	Gertner et al.[19]
LTC_4	Synthesis	Biopsy specimens[d]	1.635	32[c]	Eliakim et al.[20]
5-HETE	Synthesis	PML	10	75	Horn et al.[18]
11-, 12-, 15-HETE	Synthesis	PML	10	83	Horn et al.[18]
PGE_2	Synthesis	Biopsy specimens[d]	1.635, 3.27	42, 71	Eliakim et al.[20]
	Release	Biopsy specimens[d]	1.3	No effect	Gertner et al.[19]
PGD_2	Release	Mast cells	0.01 to 1	60[e]	Fox et al.[21]
PAF	Release	Biopsy specimens[b]	0.05, 0.1	49, 100	Capasso et al.[13]
	Release	Biopsy specimens[d]	0.025 to 0.1	97[e]	Rachmilewitz et al.[22]
Cytokines					
IL-1	Synthesis	Monocytes	0.00065	23	Bruin et al.[23]
	Release	Biopsy specimens[d]	0.65	52	Rachmilewitz et al.[14]
IL-1β	Levels	Biopsy specimens[f]	0.065 to 0.65	62[e]	Mahida et al.[24]
IL-2	Synthesis	Monocytes	0.625	92	Stevens et al.[25]
IL-6	Synthesis	Monocytes	0.625	No effect	Bruin et al.[23]
	Release	Monocytes	0.625	No effect	Mazlam et al.[26]
Reactive oxygen species					
$ONOO^-$	Levels	T84 cells	0.65	68 to 71[c]	Sandoval et al.[17]
HOCl	Levels	Neutrophils	0.05 to 0.2	100[e]	Dallegri et al.[27]
$O_2\bullet-$	Levels	PML	0.01 to 0.2	>50[e]	Gionchetti et al.[16]

a Cultured human colonic epithelial cell lines (T84) and biopsy specimens from individuals with normal colons or with inflammatory bowel disease.

b From individuals with normal colons.

c Calculated values.

d From patients with ulcerative colitis.

e Concentration-dependent; maximum effect reported.

f From patients with inflammatory bowel disease.

HETE = hydroxyeicosatetraenoic acid; **HOCl** = hyperchlorous acid; **IL** = interleukin; **LT** = leukotriene; **MNL** = mononuclear leucocyte; **$O_2\bullet-$** = superoxide anion; **$ONOO^-$** = peroxynitrite anion; **PAF** = platelet activating factor; **PG** = prostaglandin; **PML** = polymorphonuclear leucocyte.

ease.[34] Moreover, increased *in vivo* production of PAF has been correlated with local injury and inflammation in ulcerative colitis. In mucosal samples from individuals with normal colons and from patients with ulcerative colitis, mesalazine at concentrations up to 0.1 mmol/L almost completely inhibited release of PAF (table II).[13,22]

2.2 Cytokines

2.2.1 IFNγ- and TNFα-Induced Effects

The HLA-DR product of the major histocompatibility complex is involved in antigen presentation to T lymphocytes and is expressed primarily on cells of the immune system.[15,35-37] In contrast to normal colon, gastrointestinal epithelial cells in active IBD express HLA-DR.[38-41] *In vitro*, expression of HLA-DR can be induced in intestinal epithelial cell lines by the inflammatory cytokine IFNγ.[15,35-37]

In a human colonic carcinoma cell line (HT29), mesalazine 10 mmol/L significantly ($p < 0.005$) reduced IFNγ-induced HLA-DR expression (29 *vs* 62% in control cells).[35] The inhibitory effects of IFNγ on HT29:19a cell permeability were partially attenuated by basolateral application of mesalazine 50 μmol/L.[15] Additionally, the inhibitory effects of mesalazine on ^{125}I-IFNγ binding to HT29 cells suggests that this agent may act by impairing IFNγ binding to its receptor in colonic epithelial cells.[36]

Recent evidence has indicated that mesalazine reverses the antiproliferative effects of TNFα and inhibits TNFα signalling events in intestinal cells. The effects of TNFα on the activity of mitogen-activated protein (MAP) kinase and nuclear factor (NF)-κB were inhibited by mesalazine at a concentration of 20 mmol/L in a murine colonic cell line.[42]

2.2.2 Interleukins

Human colonic IL-1β levels are elevated in biopsy specimens of inflamed mucosa from patients with active IBD.[24] *In vitro* studies have demonstrated that mesalazine decreases the content, synthesis and release of IL-1/1β in colonic epithelial cells (table II).[14,23,24] Inhibitory effects of mesalazine on IL-2 production have also been reported,[25] although mesalazine does not appear to affect IL-6 levels.[23,26]

In addition to the actions of IL-1/1β and other chemotactic agents, infiltration of leucocytes into the inflamed mucosa is dependent on expression of leucocyte cell surface adhesion molecules that bind to receptors on the vascular endothelium.[10] Expression of the cluster of differentiation (CD)11b and CD18 glycoprotein constituents of the LeuCAM family of leucocyte adhesion molecules is increased in the presence of TNFα.[43] TNFα-induced CD11b expression was completely inhibited in the presence of mesalazine 1 mmol/L, and was reduced by 64% at a concentration of 0.1 mmol/L. Up-regulation of CD18 was significantly ($p < 0.01$) inhibited by the higher concentration of mesalazine. These results suggest that mesalazine may prevent the leucocyte adhesion and migration into gastrointestinal parenchymal tissue that is characteristic of IBD.[43]

2.3 Reactive Oxygen Species

Evidence from experimental and clinical studies indicates that chronic gastrointestinal inflammation is associated with enhanced levels of reactive oxygen species derived from leucocytic infiltrates into the mucosa.[44,45] These reactive molecules are capable of causing oxidising effects and tissue injury,[10] and the protective effects of mesalazine have been suggested to involve free radical scavenging and prevention of oxidant-induced tissue damage.[16,17,27,46,47]

In addition to reducing *in vitro* levels of peroxynitrite anions ($ONOO^-$), hyperchlorous acid (HOCl), superoxide anions ($O_2^{\bullet -}$) and hydroxyl radicals (table II),[16,17,27,46] mesalazine has powerful antioxidant effects[48] and protects against tissue injury. In colonic epithelial cell lines, mesalazine 0.05 to 0.2 mmol/L inhibited peroxynitrite-induced apoptosis and protected against the increase in cell permeability induced by $ONOO^-$ anions. Neutrophil (HOCl)-induced cytolysis of B lymphoblasts was almost completely inhibited by mesalazine 20 mmol/L.[27] Additionally, mesalazine concentration dependently inhibited the peroxidation of red blood cell membrane lipids by up to 65% of control values.[47]

3. Pharmacokinetic Properties

As mesalazine is believed to act topically, sufficient delivery of active drug to the affected site is an important determinant of therapeutic efficacy, while its systemic absorption profile may influence tolerability.

Unmodified oral mesalazine is rapidly absorbed from the small bowel; hence high concentrations of unprotected drug do not reach the colon.[8] To ensure delivery to the affected mucosa, prolonged-release ethylcellulose-coated microgranules (0.7 to 1mm in diameter) of mesalazine have been developed. This oral prolonged-release mesalazine formulation (Pentasa®) is available in 3 dosage forms (tablets, capsules and free microgranules in sachets), the availability of which differs between countries. Most pharmacokinetic studies have been performed using the original tablet form, although single studies have investigated the local bioavailability of mesalazine from prolonged-release capsules[49] or sachets.[50]

When dispersed in gastric juices, prolonged-release mesalazine microgranules (ingested directly from sachets or following disintegration of tablet or capsule forms) behave as a liquid and pass through the pylorus into the small intestine. Ethylcellulose is largely undigested during gastrointestinal transit and thus acts as a semipermeable membrane. Absorption of water through this ethylcellulose membrane initiates dissolution of the drug, forming a concentration gradient between the inside and the outside of the microgranule, down which mesalazine diffuses at a constant rate. Thus, release of mesalazine is diffusion-dependent[51] and, in contrast to that of resin-coated mesalazine formulations (table I), is largely unaffected by pH.[52,53]

3.1 Local Mesalazine Disposition

Disintegration of radiolabelled prolonged-release mesalazine tablets (250mg) occurred in the stomach of volunteers (n = 9) and tablets were completely dispersed within 20 minutes after administration. Radioactivity was undetectable in the stomach of all individuals by the 2.5-hour time-point. Microgranules were present in the small intestine of 8 volunteers (4 of whom also had microgranules remaining in the stomach) 60 minutes after ingestion. Microgranules reached the ascending, transverse and descending colon by 2.5 to 4.5 hours, 4 to 10 hours and 24 hours, respectively, in 8 of 9 volunteers.[6] A similar pattern of intestinal distribution of microgranules was observed after administration of prolonged-release mesalazine 250mg to patients with Crohn's disease.[54] Gastrointestinal transit of the prolonged-release formulation was unaffected by the presence of food.[6,55] In contrast, the gastric residence time of pH-dependent delayed-release mesalazine (Asacol®) was prolonged when administered in the fed state (median values 3.2 *vs* 0.6 hours in the fasted state).[55]

A crossover study in volunteers (n = 8) compared the gastrointestinal spread of a single dose of oral prolonged-release mesalazine administered as tablets (2 × 0.5g) or as a sachet (1g unit dose). Gastric emptying properties and small bowel transit time were similar for both dosage forms.[50]

Measurement of small intestinal luminal aspirates from volunteers given prolonged-release mesalazine indicated that 18 to 20% of the administered dose (0.5g) was delivered to the jejunoileal segment as solubilised mesalazine (7 to 8%) or its principal [therapeutically inert (see section 3.2.3)] metabolite acetyl mesalazine (11 to 12%) during the first 7 hours after drug administration (fig. 2). Cumulative colonic delivery of mesalazine was 82% of the administered dose, comprising solubilised mesalazine that passed the ileal measurement site (7%) and intact microgranules (approximately 75%).[56]

Delivery of mesalazine to the proximal colon by the prolonged-release formulation has been estimated from mesalazine concentrations in stomal effluents. In 6 ileostomy patients (with intact small intestines), 45 to 86% (mean 65%) of a single dose of prolonged-release mesalazine (0.5g) was detected in stomal effluents, most being excreted within 8 hours after ingestion. Approximately 19%

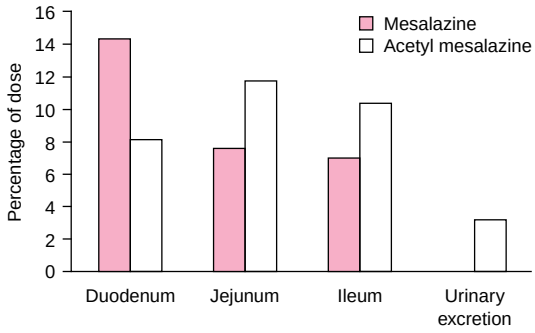

Fig. 2. Small intestinal disposition and urinary excretion of solubilised mesalazine. Mean cumulative delivery to the small intestine and urinary excretion of solubilised mesalazine and acetyl mesalazine from a single dose of prolonged-release mesalazine (2 × 0.25g tablets) during 7 hours postdose in 6 volunteers.[56]

of the ingested dose was retained as microgranules in the ileostomy fluid.[52]

Following 6 days' administration of prolonged-release mesalazine 2 g/day to 12 volunteers and 8 ileostomy patients, faecal recovery of mesalazine accounted for 27% and 49%, respectively, of the daily dose. A small percentage was accounted for by free mesalazine or intact microgranules (4% and 10 to 12%, respectively), with the remainder (20% and 30% of the administered dose) accounted for by acetyl mesalazine. Recovery of acetyl mesalazine was generally higher in patients treated with prolonged-release mesalazine than in those receiving pH-dependent delayed-release mesalazine formulations (Asacol® or Claversal®, both 2 g/day). These findings are indicative of a slow release of drug throughout the small and large intestine from the prolonged-release formulation.[57]

A single study in 24 volunteers has investigated the local bioavailability of mesalazine from the capsule form of prolonged-release mesalazine. After a single 1g dose, at least 91% of the administered drug was released within the gut, and hence was locally available. Based on faecal elimination, 40% of the capsule dose was unabsorbed (9% remained formulation bound), indicating efficient delivery of mesalazine throughout the gastrointestinal tract.[49]

Concentrations of mesalazine in faecal water increased dose-dependently after administration of the prolonged-release formulation. Mesalazine concentrations in faecal water samples were 9.2, 19.0 and 24.4 mmol/L, respectively, in volunteers (n = 13) receiving oral prolonged-release mesalazine 2, 4 or 6 g/day for 7 days. Acetyl mesalazine concentrations (27 to 29 mmol/L, approximate values from graph) were unaffected by dose. Concentrations of both mesalazine and acetyl mesalazine were significantly ($p < 0.01$) higher after administration of prolonged-release mesalazine (at any dose) than after oral olsalazine 2 g/day.[58]

3.1.1 Patients with Diarrhoea

Theoretically, diarrhoea and hence accelerated intestinal transit time, may affect the delivery of mesalazine to the intestinal mucosa. However, systemic absorption of prolonged-release mesalazine was relatively unaltered by laxative-induced accelerated intestinal transit. In a study of 7 volunteers with normal (mean 24 hours) and accelerated (mean 5 hours) intestinal transit times, total recovery of drug after oral administration of prolonged-release mesalazine 1.5 g/day for 14 days was relatively unchanged (87 *vs* 81% of administered dose).[59] However, under accelerated conditions, urinary excretion of mesalazine plus acetyl mesalazine was reduced (23% compared with 34% under normal conditions) and faecal excretion of solubilised mesalazine (17 *vs* 12%) and mesalazine retained in microgranules (12 *vs* 4%) was slightly increased. Almost complete release of mesalazine from microgranules occurred during normal intestinal transit, while approximately 88% was released under accelerated conditions.[59]

After 7 days' oral administration of prolonged-release mesalazine 1.5 g/day in 20 patients with IBD, faecal excretion of mesalazine was higher in the 10 patients with diarrhoea (≥4 bowel movements per day, 29%) than in those without diarrhoea (≤3 bowel movements per day, 16%). However, the percentage of drug present in faeces as acetyl mesalazine was unaffected by the presence of diarrhoea. Similarly, urinary excretion of mesalazine and acetyl mesalazine was not affected by acceler-

ated intestinal transit.[60] These data suggest that the disposition of mesalazine is not substantially influenced by accelerated intestinal transit, and they support the prolonged-release formulation as an acceptable source of mesalazine in diarrhoeal states.

3.1.2 Patients with Ileorectal Anastomosis

Some patients requiring surgery for colonic IBD may undergo ileorectal anastomosis. In this condition of altered gastrointestinal anatomy, delivery of mesalazine for the treatment of residual lesions may be altered. However, in a study of drug disposition following 1 week's treatment with prolonged-release mesalazine 1.5 g/day in 9 patients with an ileorectal anastomosis, mesalazine was effectively delivered to the gastrointestinal lumen. Based on faecal and urinary excretion, at least 47% of the administered dose was available at the target area.[61]

3.2 Systemic Mesalazine Disposition

3.2.1 Absorption

After a single oral dose of prolonged-release mesalazine 250mg to volunteers, the median lag time (t_{lag}) to the first detectable plasma concentration of mesalazine was 45 minutes (range 15 to 150). A maximum plasma concentration (C_{max}) of 0.6 μmol/L (range 0.4 to 1.4) was recorded 240 minutes (t_{max}; 90 to 300) after dose administration. Corresponding values for acetyl mesalazine were: t_{lag} 22 minutes (15 to 45), C_{max} 2.9 μmol/L (1.6 to 3.4) and t_{max} 105 minutes (60 to 300).[62] The plasma concentration-time profile following a single oral dose of prolonged-release mesalazine 1g to healthy volunteers was consistent with a continuous release of drug throughout the gastrointestinal tract. Plasma concentrations peaked at 0.53 mg/L 4 hours after administration, declined rapidly to 0.03 mg/L at 12 hours, then remained fairly constant over the next 24 hours before resuming the final decline, becoming undetectable 60 hours after administration. The area under the plasma concentration-time curve (AUC) for mesalazine was 4.37 mg/L · h. The plasma concentration-time profile of acetyl mesalazine followed a similar pattern to that of mesalazine, and had a C_{max} of 1.33 mg/L and an AUC of 24.23 mg/L · h.[49] Results of a 7-day study in healthy volunteers suggest a dose-dependent increase in systemic mesalazine absorption: mean steady-state plasma concentrations of mesalazine were 3.4, 7.7 and 12.4 μmol/L after oral prolonged-release mesalazine 2, 4 and 6 g/day, respectively, and corresponding acetyl mesalazine concentrations were 7.2, 21.7 and 16.0 μmol/L.[58]

After 6 days' treatment with a 2g daily dosage of mesalazine-containing preparation, plasma concentrations of both mesalazine and acetyl mesalazine were significantly lower in volunteers receiving prolonged-release mesalazine (Pentasa®) than in those receiving pH-dependent delayed-release preparations (Asacol® and Claversal®).[57] A similar trend towards lower serum concentrations in volunteers receiving the prolonged-release preparation than in those treated with Asacol® was reported in another study.[63] Serum levels of mesalazine and acetyl mesalazine were consistently higher following administration of prolonged-release mesalazine than after equimolar doses of the azo-bound formulations olsalazine and sulfasalazine.[63,64]

3.2.2 Distribution

Little is known about the distribution of prolonged-release mesalazine. In 9 pregnant women with IBD who were receiving prolonged-release mesalazine 0.5 to 3 g/day, low concentrations (approximate values from graph) of mesalazine and acetyl mesalazine were measured in maternal (≤0.5 and ≤7.5 μmol/L) and fetal plasma (≤0.25 and ≤18 μmol/L). In 2 patients, low concentrations of mesalazine were detected in breast milk. Mean acetyl mesalazine concentrations in breast milk were 4.4 to 47.5 μmol/L.[65]

3.2.3 Metabolism and Elimination

Mesalazine is primarily metabolised by acetylation in the gut wall and the liver, forming the therapeutically inert metabolite acetyl mesalazine. Both the parent compound and the metabolite are excreted in the urine.[66] After a single oral administration of prolonged-release mesalazine 0.25g in 6 volunteers, the apparent mean elimination half-life of acetyl mesalazine was 802 minutes (range

608 to 993). Determination of the terminal half-life of mesalazine was not possible because of low plasma concentrations.[62]

After oral administration of prolonged-release mesalazine 1.5 to 4 g/day to volunteers, excretion of unchanged mesalazine accounted for 8 to 12% of the daily dose. Total urinary excretion of mesalazine plus acetyl mesalazine was 29 to 53%.[52,57,58] In volunteers, renal clearance of acetyl mesalazine was 12 L/h (201 ml/min) at steady state.[52] In a 7-day study of 15 patients with ulcerative colitis, daily urinary excretion of mesalazine and acetyl mesalazine was higher with prolonged-release mesalazine (1.5 g/day) and pH-dependent delayed-release mesalazine (Asacol ®, 1.2 g/day) than with olsalazine (1 g/day).[63]

In volunteers, faecal recovery of mesalazine and acetyl mesalazine accounted for 40% of the dose after a single administration of prolonged-release mesalazine 1g and after 6 days' treatment with a 1.5g daily dosage. Acetyl mesalazine (26 to 27%) accounted for a higher percentage of faecal salicylates than did the unchanged parent compound (14 to 19%).[49,52] Released and nonreleased mesalazine represented approximately equal proportions of faecal mesalazine recovery.[49,57] Higher faecal recovery of released mesalazine and acetyl mesalazine was found after 6 days' treatment with prolonged-release mesalazine (Pentasa®; 4.4% and 20.1%, respectively) than after Claversal® treatment (3.2% and 10.7%). There was no difference in the faecal excretion pattern between Pentasa® and Asacol® treatment.[57]

4. Therapeutic Efficacy

4.1 Ulcerative Colitis

Aminosalicylates such as mesalazine and sulfasalazine are the agents of choice for the treatment of mild to moderately active ulcerative colitis and for prevention of relapse.[67-69] In the absence of a universally accepted measure of disease activity, treatment efficacy (indicating improvement and/or remission) in the reviewed studies was generally assessed using clinical and endoscopic indices (see tables III and IV).

Table III. Randomised double-blind multicentre studies of oral once daily prolonged-release mesalazine (MES) in the treatment of mild to moderate active ulcerative colitis

Reference	Duration	Dosage (g/day) [no. of patients enrolled]	Clinical improvement[a] at end-point (% of patients)	Endoscopic index[b]		Efficacy
				baseline	change at endpoint	
MES capsules						
Hanauer et al.[70]	8wk	MES 1 [92]	45*[c]	9.9	–3.4	MES 2,4 > PL
		MES 2 [97]	57*[c]	10.2	–4.3*	
		MES 4 [95]	59*[c]	10.3	–5.0*	
		PL [90]	36[c]	10.3	–2.5	
MES tablets						
Munakata et al.[71]	4wk	MES 1.5 [48]	63[d]	NR	–2.49	MES ≡ SUL
		SUL 3 [52]	62[d]	NR	–2.84	

a Clinical symptoms were evaluated by physician assessments, conducted according to a 5-[72] or 6-point[71] scale. With the exception of the inclusion of an additional component (complete relief) in 1 study[71] the scales were identical (marked, moderate or slight improvement, no change or worsening).

b Endoscopic findings were graded according to a 15-point index score [composed of five 0- to 3-point (0 = normal; 1 = slight/mild; 2 = moderate; 3 = severe) categories]. In one study,[71] variables were erythema, friability, granularity/ulceration, mucopus and appearance of mucosal vascular pattern. In the other study,[72] erosion, bleeding, contact bleeding, redness and oedema were assessed.

c Improvement defined as complete relief or marked improvement.

d Marked or moderate improvement.

NR = not reported; **PL** = placebo; **SUL** = sulfasalazine; ≡ indicates similar efficacy to comparator; > indicates significantly greater efficacy than comparator; * $p < 0.05$ *vs* PL.

4.1.1 Active Disease

Data regarding the efficacy of prolonged-release mesalazine as treatment for active ulcerative colitis are limited. Results from an 8-week dose-ranging placebo comparison[70] and a 4-week comparison with sulfasalazine[71] show the formulation to be effective in this indication according to symptomatic (physician assessment) and endoscopic measures (table III). These studies enrolled adults (age >16 or >18 years) with mild to moderately active ulcerative colitis. Disease was left-sided in 35%[71] and 69%[70] of patients. Prolonged-release mesalazine was administered 3 times daily at various fixed dosages (1.5[71] and 1, 2 or 4[70] g/day).

Prolonged-release mesalazine reduced endoscopic index scores versus baseline in both studies, although neither presented statistical analysis of this result. The effects of prolonged-release mesalazine 1.5 g/day on this parameter were similar to those of sulfasalazine 3 g/day.[71] The prolonged-release formulation, at a dosage of 2 or 4 g/day (but not 1 g/day) improved endoscopic findings to a significantly greater extent than placebo.[70] The dose-response relationship seen with prolonged-release mesalazine in this study was statistically significant ($p = 0.011$).

According to physician assessments, prolonged-release mesalazine was also effective in improving clinical symptoms in a significantly ($p < 0.05$) dose-dependent manner (table III). Moreover, disease location did not affect the response to therapy. In patients with pancolitis, 61, 52 and 32% of active- (2 or 4 g/day) or placebo-treated patients, respectively, were successfully treated in comparison with 55, 62 and 37% of patients with distal disease.[70]

Stringent criteria were used to assess the induction of remission (as distinct from clinical improvement) by prolonged-release mesalazine. Compared with placebo, the 4 g/day dosage was significantly ($p < 0.05$) more effective in inducing clinical and endoscopic remission, while the 2 g/day dosage was effective for the endoscopic parameter (fig. 3).[70] Prolonged-release mesalazine tablets (1.5 g/day) were also as effective as sulfasalazine (3 g/day) in 109 patients with ulcerative colitis. Improvements in clinical (62 *vs* 63%) and endoscopic (79 *vs* 71%) findings were similar in patients treated with the mesalazine formulation and sulfasalazine, respectively.[71]

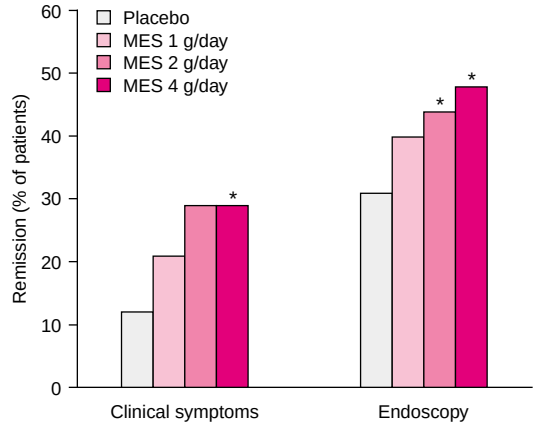

Fig. 3. Effect of oral prolonged-release mesalazine (MES) capsules in patients with mild to moderately active ulcerative colitis. A total of 374 patients were treated with MES 1, 2 or 4 g/day or placebo in a randomised double-blind study of 8 weeks' duration. Clinical symptoms were evaluated using the 6-point Physicians' Global Assessment scale (complete relief; marked, moderate or mild improvement; no change or worsening of symptoms). Clinical remission was defined as complete relief of symptoms. Endoscopic findings were graded according to a 15-point index score composed of five 3-point (0 = normal; 1 = mild; 2 = moderate; 3 = severe) categories (erythema, friability, granularity/ulceration, mucopus, appearance of the mucosal vascular pattern). Remission was defined as a score of ≤5 (maximum possible score 15 points).[70] * $p < 0.05$ *vs* placebo.

A recent study (published as an abstract) compared the efficacy of daily 4g administration of prolonged-release mesalazine in tablet or granule form in 147 patients with mild to moderately active ulcerative colitis. Both dosage forms were effective in improving clinical and endoscopic parameters, and there were no differences in efficacy between treatment groups.[72]

4.1.2 Maintenance of Remission

Three randomised double-blind multicentre 12-month trials have investigated the efficacy of prolonged-release mesalazine (3[73,74] or 4[75] times daily) in the maintenance of remission of ulcerative colitis. One study[75] was placebo-controlled,

Table IV. Randomised double-blind placebo-controlled 12-month trials of prolonged-release mesalazine (MES) in the maintenance of remission of ulcerative colitis

Reference	Dosage form	Dosage (g/day)	No. of patients evaluated	Remission rate[a] at end-point (% of patients)	Efficacy
Miner et al.[75]	Capsule	MES 4	103	64*[b]	MES > PL
		PL	102	38[b]	
Fockens et al.[73]	Tablet	MES 1.5	72	50[c]	MES 3 ≡ MES 1.5
		MES 3	69	67[c]	
Mulder et al.[74]	Tablet	MES 1.5	41	54[d]	MES ≡ SUL
		SUL 3	31	46[d]	

a 1-year remission rates estimated from life table analysis.

b Recurrence was defined as an endoscopic index of ≥5 and/or a mean of ≥5 trips to the toilet or rectal bleeding for 3 of 7 continuous days. The 15-point endoscopic scale was composed of five 0 to 3 point (0 = normal; 1 = mild; 2 = moderate; 3 = severe) categories (erythema, friability, granularity/ulceration, mucopus and appearance of mucosal vascular pattern).

c Clinical (spontaneous blood loss, mucoid discharge, faecal consistency, stool frequency) and endoscopic (colour, vascular pattern, friability, granularity, appearance of rectal valves, distensibility, ulceration, spontaneous bleeding, mucopurulent exudate) symptoms were scored using a 3-grade scale (0, 1 and 2, according to increasing severity) to a maximum of 8 and 18 points, respectively. Scores of ≥2 for clinical and endoscopic symptoms were considered to denote exacerbation of ulcerative colitis.

d Endoscopic variables (mucosal colour, vessel pattern, granularity, presence of valves, distension, polypoid structures, ulcers, spontaneous haemorrhage, mucopurulent covering, friability) were scored as normal, mild, moderate, severe or very severe. Histological appearance was scored as normal, little, medium, severe inflammation, or in remission based on oedema and haemorrhage in the mucosa/submucosa, cellular infiltrate and crypt architecture. The method of clinical evaluation was not specified. Patients were considered to have experienced relapse if all the variables (clinical, endoscopic, histological) were not considered normal or in remission.

PL = placebo; **SUL** = sulfasalazine; ≡ indicates similar efficacy to comparator; > indicates significantly greater efficacy than comparator; * $p < 0.001$ *vs* PL.

1 was dose ranging,[73] and the third compared prolonged-release mesalazine with sulfasalazine.[74] These studies involved 72 to 205 patients, of whom 70 to 84% (calculated values) had disease limited to below the splenic flexure. Recurrence of disease was assessed using symptomatic and endoscopic parameters, although the rating scales and parameters used differed in each study (table IV). All studies used life table analysis to estimate 1-year remission rates.

Prolonged-release mesalazine capsules (4 g/day) showed greater benefits than placebo in maintaining remission.[75] Moreover, treatment response was unaffected by disease location. At the study end-point, 63% of patients in the active group with left-sided disease were in remission, compared with 67% of patients with pancolitis. Remission rates were 41% and 31%, respectively, in placebo-treated patients.[75] A 1.5 g/day dosage of the mesalazine formulation was as effective as sulfasalazine 3 g/day in maintaining remission.[74] Although prolonged-release mesalazine 3 g/day appeared to increase the estimated 1-year remission rate compared with a 1.5g daily dosage in another study, this difference was not statistically significant ($p = 0.057$).[73]

4.2 Crohn's Disease

Mild to moderately active Crohn's disease is generally treated with oral aminosalicylates (eg. mesalazine or sulfasalazine) or glucocorticoids although antibiotics may also be effective. Mesalazine also provides benefits in maintaining remission in patients responding to acute intervention, and in preventing relapses after surgical resection.[67,76]

In clinical trials, the severity of disease activity, and thus the efficacy of the intervention, may be quantified using the Crohn's Disease Activity Index (CDAI). This index integrates clinical variables (stool frequency, abdominal pain ratings, well-being scale ratings, use of loperamide or codeine to control diarrhoea, body weight, haematocrit, presence of abdominal masses) together with symptoms and complications during the 7

days before visit, to give a single score of disease activity.[8] Scores can range from 0 to 700 points; mild to moderate disease activity is indicated by a score of 150 to 400 points, while ≤150 points has been interpreted as disease in remission.

4.2.1 Active Disease

Three large trials (1 noncomparative, 2 placebo-controlled) have investigated the efficacy of prolonged-release mesalazine 1 to 4 g/day (2 and 4 g/day in 1 study[77]) in improving the symptoms of mild to moderately active Crohn's disease.[77-79] Two further studies were conducted with active comparator treatments.[80,81] Patients were generally aged ≥18 years although patients ≥13 years were included in the noncomparative study. The percentage of patients with isolated ileal disease ranged from 35 to 58%. The range of CDAI scores for inclusion was 150 (200 points in 1 study[81]) to 300[80] or 400[78,81] points (upper limit not specified in one study[79]).

Effects of Dosage

Prolonged-release mesalazine capsules at a dosage of 4 g/day were significantly ($p < 0.01$) more effective than placebo in reducing disease activity (table V). Although the 1 and 2 g/day dosages did not produce significant improvements compared with placebo, a significant ($p < 0.001$) dose-response relationship was apparent across the 4 groups. At the highest dosage, compared with placebo, prolonged-release mesalazine significantly reduced the time to remission (defined as a >50-point decrease in CDAI combined with a final visit CDAI of <151) and the percentage of treatment failures (11 *vs* 35%), while increasing the percentage of patients in remission (43 *vs* 18%) or showing a therapeutic benefit (64 *vs* 40%) at the final visit (fig. 4). Treatment effects were not statistically different from placebo in the 1 and 2 g/day dosage groups. However, the 4-dose trend achieved significance ($p < 0.05$) for all 3 parameters.[78]

These results are supported by those of a long term noncomparative study of up to 30 (median 14) months' duration. Prolonged-release mesalazine capsules at dosages ≤4 g/day (mean 3.7 g/day at baseline and 3.4 g/day at the study end) induced remission in 42% of patients at their final study visit.[79] In another 16-week study in 232 patients (reported in a letter), although dosages of 2 and 4 g/day tended to reduce CDAI scores, improvements were not significantly different from placebo treatment.[77] In smaller studies, prolonged-release mesalazine administered at 1.5 g/day in tablet form did not demonstrate benefits over placebo during 6- or 16-week treatment periods.[82,83]

Comparisons with Active Treatment

In a 16-week multicentre (n = 25) double-blind study involving 182 patients, slow-release budesonide 9 mg/day was more effective than prolonged-release mesalazine 4 g/day. Remission rates were higher in the budesonide group than in the prolonged-release mesalazine group at study end (62 *vs* 36% $p < 0.001$). Additionally, the median time to remission was shorter in budesonide-

Table V. Efficacy of prolonged-release mesalazine (MES) capsules in mild to moderately active[a] Crohn's disease

Reference	Study design [duration]	Dosage (g/day)	No. of patients evaluated	CDAI		Efficacy
				baseline	change at end-point	
Singleton et al.[78]	db, pc, mc, pg [16wk]	MES 1	75	271	–8	MES 4 > PL
		MES 2	75	265	–29	
		MES 4	80	260	–72*	
		PL	80	278	–21	
Hanauer et al.[79]	nc, mc [<30mo]	MES ≤4[b]	289	269	–77	✓

a Mild to moderate disease defined as CDAI within the range 150 to 400.

b Some patients were receiving prednisone at baseline and concomitant treatment was allowed during the study period.

CDAI = Crohn's Disease Activity Index; **db** = double-blind; **mc** = multicentre; **nc** = noncomparative; **pc** = placebo-controlled; **pg** = parallel group; **PL** placebo; > indicates significantly greater efficacy than placebo; ✓ indicates effective; * $p < 0.01$ *vs* PL.

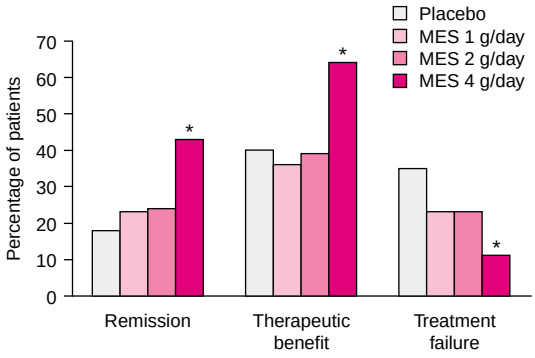

Fig. 4. Effect of oral prolonged-release mesalazine (MES) capsules in patients with mild to moderately active Crohn's disease. Patients were randomised to receive MES 1 (n = 75), 2 (n = 75) or 4 (n = 80) g/day or placebo (n = 80) for 16 weeks.[78] Remission was defined as a >50-point decrease in the Crohn's Disease Activity Index (CDAI) with a final score of <151; therapeutic benefit was defined as >50-point reduction in CDAI; treatment failure was evaluated by defined criteria which varied according to the time the patient remained in the study. Significant ($p < 0.05$) 4-dose trends were reported for each variable. * $p < 0.005$ *vs* placebo.

treated patients than in those receiving prolonged-release mesalazine (28 *vs* 84 days; $p < 0.05$).[81]

The efficacy of twice daily prolonged-release mesalazine tablets (4 g/day) was compared with that of ciprofloxacin 1 g/day in a small nonblind study involving 40 patients (although ciprofloxacin is not an accepted or approved monotherapy for Crohn's disease). After 6 weeks' treatment, both agents were effective in inducing remission (55% of prolonged-release mesalazine-treated patients, *vs* 56% in the ciprofloxacin group). However, the authors acknowledged the small size and methodological limitations of this study.[80]

4.2.2 Maintenance of Remission

Six placebo-controlled studies and 1 noncomparative trial were conducted in patients with Crohn's disease in remission. Study entry criteria were highly variable, being based on CDAI scores,[79,84,85] duration of remission[84,85] or number of exacerbations during a defined time period.[86] Patients with surgically induced remission were specifically enrolled in 2 studies.[87,88] Generally, patients on concomitant glucocorticoid treatment were excluded, although some patients received prednisone during the noncomparative study.[79] Most studies reported clinical outcome in terms of relapse rates, although in 2 studies the outcome measure was the percentage of patients who remained in remission.[79,85] While relapse was usually defined by CDAI scores, criteria varied considerably between studies (table VI).

Noncomparative Study

During ≤30 months' treatment with prolonged-release mesalazine capsules (≤4 g/day), 79% of patients in remission at baseline were in remission at their final visit. Moreover, 72% of patients were maintained continuously in remission from baseline to 1 year. Although 29% of patients also received prednisone during the study period, concomitant treatment did not influence the time to relapse, according to life-table analysis. In this subgroup, prolonged-release mesalazine treatment was associated with a reduction in the mean prednisone dose from 20 to 15 mg/day.[79]

Placebo-Controlled Studies

The results of placebo-controlled studies of the efficacy of various dosages (1.5 to 4 g/day) of prolonged-release mesalazine in the maintenance therapy for Crohn's disease are variable (table VI). Of the 6 trials conducted, only 2 demonstrated overall statistically significant clinical benefits of prolonged-release mesalazine compared with placebo.[84,86]

Although overall benefits compared with placebo were not reported in a 4-month study involving 44 patients considered to be at elevated risk of relapse, there was a trend towards favourable effects of active treatment in patients with isolated ileal disease. In this subgroup, 30% of patients receiving prolonged-release mesalazine relapsed within 4 months, compared with 67% of placebo-treated patients.[85]

In another study, patients were stratified at entry as being at presumed high or low risk of relapse (<3 months or >3 months of remission, respectively). Demographic variables were generally comparable between strata, although the proportion of patients who had previously undergone abdominal surgery

Table VI. Randomised double-blind placebo-controlled multicentre studies[a] of the efficacy of once daily oral prolonged-release mesalazine (MES) in the maintenance of remission[b] of Crohn's disease

Reference	Duration	MES dosage form	Dosage (g/day) [no. of patients evaluated]	Clinical outcome at end-point (% of patients)		Efficacy
				remission rate	relapse rate	
Bondesen et al.[89]c	12–18mo	Tablet	MES 1.5 [101]		29[d]	MES ≡ PL
			PL [101]		29[d]	
Gendre et al.[84]	2y	Tablet	MES 2 [113]	45[e]	55**[e,f]	MES > PL
			PL [81]	29[e]	71[e,f]	
Brignola et al.[85]	4mo	Tablet	MES 2 [22]	50[g]		MES ≡ PL[h]
			PL [22]	59[g]		
Sutherland et al.[86]c	48wk	Capsule	MES 3 [246][i]		31*[j]	MES > PL
			PL		46[j]	
Hanauer et al.[79]k	<30mo	Capsule	MES ≤4 [120]	79[j]		✓
Post-resection patients						
Brignola et al.[87]	12mo	Tablet	MES 3 [43]	72[g]	16[g]	MES ≥ PL[l]
			PL [42]	79[g]	23[g]	
Lochs et al.[88]	18mo	Tablet	MES 4 [152]		25[m]	MES ≡ PL[n]
			PL [166]		31[m]	

a One study had an noncomparative design,[79] and 1 study was conducted in a single centre.[85]

b Remission defined as a Crohn's Disease Activity Index (CDAI) <150. In 2 studies, patients were enrolled on the basis of recent (within 10 days[88] or 1 month[87]) resective surgery.

c Abstract.

d Relapse defined as a worsening of clinical symptoms (bowel frequency and/or abdominal pain).

e Subgroup of patients at high risk of relapse.

f Relapse defined as CDAI >250, or between 150 and 250 but over baseline by >50 points, confirmed 2 weeks later.

g Relapse defined as an increase in CDAI by >100 and a CDAI above 150 for >2 weeks.

h A marked improvement compared with PL was found in the subgroup of patients with isolated ileal disease.

i Total number of patients.

j Relapse defined as CDAI >150 and a 60-point increase over baseline.

k Some patients received concomitant treatment with prednisone.

l A significant ($p < 0.002$) improvement was reported in the endoscopic relapse rate for patients treated with prolonged-release mesalazine compared with those receiving PL.

m Relapse defined as a single increase in CDAI above 250 or a CDAI score of 200 to 250 for 2 consecutive weeks.

n A significant ($p < 0.05$) improvement compared with PL was found in patients with isolated small bowel disease.

PL = placebo; ≡ =indicatessimilar efficacy to comparator; > indicates significantly greater efficacy than comparator; ≥ indicates significantly greater efficacy than comparator in endoscopic parameters but similar efficacy in clinical parameters; ✓ indicates effective; * $p < 0.05$, ** $p < 0.005$ *vs* PL.

for Crohn's disease was considerably higher in the low risk stratum. In this group, the cumulative likelihood of relapse was similar for active and placebo groups (47 *vs* 42%). However, in high risk patients, the cumulative likelihood of relapse was lower in prolonged-release mesalazine-treated patients than in those receiving placebo.[84]

Neither of the 2 studies that exclusively enrolled patients who had undergone resective surgery demonstrated overall benefits for prolonged-release mesalazine over placebo in preventing relapse as determined by CDAI scores.[87,88] However, the rate of severe endoscopic recurrence (defined as diffuse aphthous ileitis with diffusely inflamed mucosa, or diffuse inflammation with large ulcers, nodules and/or narrowing) in all patients after 1 year was 14% in patients receiving prolonged-release mesalazine tablets (3 g/day), compared with 50% in those receiving placebo ($p < 0.002$).[87] In another study, active treatment (4

g/day) significantly reduced the rate of relapse (determined by CDAI scores) compared with placebo, in patients with isolated small bowel disease (22% *vs* 40%; p = 0.02).[88]

4.2.3 Glucocorticoid Withdrawal

The efficacy of mesalazine in reducing glucocorticoid dependence and delaying relapse after glucocorticoid discontinuation has also been investigated. A total of 150 patients with active Crohn's disease (CDAI >200) were treated with oral prednisolone 1 mg/kg/day for 3 to 7 weeks. Patients in remission (n = 129) were subsequently randomised to receive tablets of prolonged-release mesalazine 4 g/day or placebo, administered until discontinuation of glucocorticoid treatment and for 1 year thereafter.[90] The prednisolone dose was tapered in steps of 10mg per 10 days to a dosage of 0.5 mg/kg/day, and subsequently in steps of 5mg per 10 days until complete discontinuation. Glucocorticoid withdrawal was facilitated in 74% and 58% (p = 0.054) of patients receiving prolonged-release mesalazine and placebo, respectively. At the study end, more patients in the placebo group were unable to discontinue prednisolone treatment than those in the prolonged-release mesalazine group (30% *vs* 12%; p < 0.05). In the year after prednisolone withdrawal, the actuarial relapse rates were 64% and 62% in the placebo and active groups, respectively. Likewise, there was no difference between groups in time to relapse. The investigators noted that after adjustment for prognostic factors (high CDAI at weaning, white blood cell count $>9 \times 10^9$/L at weaning, use of mesalazine in the month before preinclusion), the relative risk (RR) of relapse appeared to be lower in the prolonged-release mesalazine group (RR 2, 95% confidence intervals 1.0 to 3.8; p <0.05).[90]

4.3 Studies in Children

A noncomparative pilot study evaluated the use of prolonged-release mesalazine (mean dosage 30.6 mg/kg/day, range 21.8 to 53.8) in children (mean age 14.1 years, range 10.5 to 18.5) with active Crohn's disease (Harvey index ≥4). The mean treatment duration was 8.1 (range 2 to 15) weeks. 6 of the 12 patients experienced improvements in disease status assessed using the Harvey index and 5 remained clinically unchanged. An additional 6 patients with disease in remission (Harvey index 0.6 ± 0.8) received prolonged-release mesalazine as maintenance therapy. Of these, 4 remained in remission during the course of treatment.[91]

In a randomised double-blind placebo-controlled crossover study of 20 weeks' duration (2 × 8 week treatment periods separated by a 4-week washout), 14 patients (mean age 13.8 years, range 9.3 to 16.1) with active Crohn's disease were treated with oral prolonged-release mesalazine at a dosage of 50 mg/kg/day (maximum 3 g/day). 6 patients completed the protocol: 1 patient with an intra-abdominal abcess was withdrawn before initiation of study medication and 1 deteriorated during the washout period and refused the second study treatment, the remainder withdrew because of lack of efficacy (3 and 2 patients receiving placebo and active treatment, respectively, in phase 1; 2 in the washout period). Improvements in the CDAI and the van Hees index of disease activity were observed during treatment with prolonged-release mesalazine but not placebo. Evaluation using the Lloyd-Still and Harvey indices did not indicate improvements with either treatment.[91]

4.4 Effects on Quality of Life

The effects of treatment on patients' quality of life have been addressed in 2 randomised placebo-controlled studies of prolonged-release mesalazine 1, 2 and 4 g/day. Patients with active ulcerative colitis[92] (n = 375) and Crohn's disease[93] (n = 310) were enrolled in 8- and 16-week studies, respectively. 7 function-based parameters (sleep, sexual relations, outdoor activities, social activities, indoor activities, work/occupation, hobbies/recreation) were evaluated using a 10cm visual analogue scale (0 = no effect, 10 = effect 'as bad as it could be') at baseline and at the study end.[94]

Compared with placebo treatment, significant (p < 0.05) improvements from baseline were observed in all 7 parameters in patients with ulcerative colitis receiving dosages of 2 and 4 g/day.[92]

Similarly, all parameters were significantly improved compared with placebo treatment in patients with Crohn's disease receiving prolonged-release mesalazine 4 g/day. Only hobbies/recreation was significantly improved at the 2g daily dosage, although the 4-dose trend was significant for all variables.[93]

5. Tolerability

In an 8-week randomised trial of prolonged-release mesalazine 1, 2 and 4 g/day or placebo in patients (n = 314) with ulcerative colitis, 16% of patients receiving active drug experienced treatment-related adverse events, compared with 22% of patients in the placebo group. No dose-response relationship was observed (fig. 5). The most commonly occurring treatment-related adverse events are shown in figure 6. In total, 5%, 9% and 7% of patients in the 1, 2 and 4 g/day dosage groups discontinued therapy because of treatment-related or unrelated events, compared with 12% of placebo-treated patients. The most common treatment-limiting adverse events were diarrhoea, abdominal pain, fever and melaena.[70]

These results are similar to those reported in a 16-week dose-ranging study of prolonged-release mesalazine in 310 patients with active Crohn's disease. In total, 21%, 31% and 27% of patients receiving prolonged-release mesalazine 1, 2 and 4 g/day experienced adverse events, compared with 19% in the placebo group. Treatment-related adverse events occurred in 26% of patients receiving active drug versus 19% of patients receiving placebo, but were not thought to be dose-related. The most common adverse events considered to be related to prolonged-release mesalazine treatment were nausea and/or vomiting (7.4 *vs* 3.7% in the placebo group), headache (5.2 *vs* 3.7%) and abdominal pain (4.3 *vs* 5.0%). Fewer patients (12%) receiving the highest dosage (4 g/day) withdrew from treatment because of adverse events than in the 1 (24%) or 2 g/day (19%) and placebo groups (19%).[78]

Oral prolonged-release mesalazine was generally well tolerated during long term therapy and

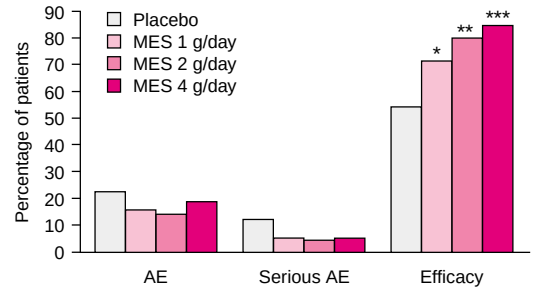

Fig. 5. Dose relationships in treatment-related adverse events (AEs) and efficacy of prolonged-release mesalazine (MES) capsules. Patients with mild to moderately active ulcerative colitis were randomised to receive oral MES 1 (n = 92), 2 (n = 97) or 4 g/day (n = 95) or placebo (n = 90) for 8 weeks.[70] Efficacy was defined as an improvement in symptoms at end-point, compared with baseline. The dose-response relationship in efficacy was significant ($p < 0.05$). * $p = 0.02$; ** $p = 0.0002$; *** $p < 0.0001$ *vs* placebo.

treatment-related adverse events occurred no more frequently than in patients receiving placebo. Most treatment-related events occurred early in therapy (within 9 to 14 weeks of treatment initiation) and were infrequently reported with long term use.[75,79] In a 12-month study involving 205 patients with ulcerative colitis, adverse events necessitating withdrawal occurred in 14% and 33% (2% and 6% considered to be treatment-related) of patients receiving prolonged-release mesalazine 4 g/day and placebo, respectively. Treatment-related adverse events (most commonly nausea 2.9%, abdominal pain 1.9% and dyspepsia 1.9%) were experienced in 6.8% of patients receiving prolonged-release mesalazine. In contrast, 11.8% of patients in the placebo group experienced adverse events related to therapy.[75] In a noncomparative study in 467 patients with Crohn's disease who received prolonged-release mesalazine at dosages up to 4 g/day for a median of 14 months, 12% of patients discontinued because of treatment-related adverse events, of which the most commonly reported were diarrhoea (4.3%), abdominal pain (3.6%) and dyspepsia (3.1%).[79]

Published case reports have described isolated episodes of pancytopenia, hair loss, pneumonitis, pancreatitis, pruritus and exacerbation of ulcera-

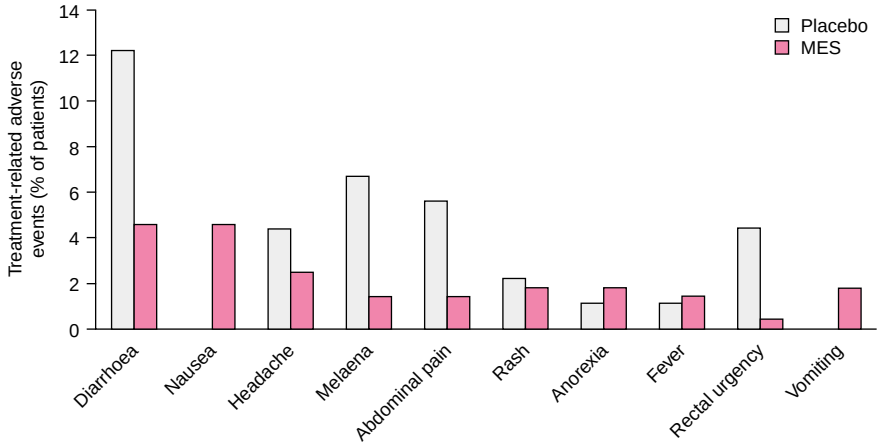

Fig. 6. Tolerability of prolonged-release mesalazine (MES) capsules. Patients with mild to moderately active ulcerative colitis were randomised to receive oral MES 1 (n = 92), 2 (n = 97) or 4 g/day (n = 95) or placebo (n = 90) for 8 weeks.[70] Data for the three MES dosage groups are presented collectively. Treatment-related adverse events reported in ≥1% of patients in either (MES or placebo) treatment group are shown.

tive colitis associated with prolonged-release mesalazine treatment.[95-101] In a pharmacovigilance study in France, concerning patients treated with oral prolonged-release mesalazine, 51 and 79 adverse events were reported to the manufacturer, respectively, in 2 years of surveillance. Each year represented more than 7.7 or 8.7 million days of treatment, and the gross incidence of adverse events was 6.6 or 9.0 per million treatment days. Overall, 44% of events were judged to be possibly or probably related to prolonged-release mesalazine treatment. These included pancreatitis (n = 14), pericarditis/myocarditis (8), elevated liver enzymes (7), leucopenia (5), diarrhoea (5), thrombocytopenia (2), allergic events (2) and renal insufficiency (2).[102]

Prolonged-release mesalazine was well tolerated in the limited number of published studies involving treatment of paediatric patients. Diffuse, mild hair loss, which resolved within 1 week of stopping treatment, was reported by 1 patient.[91]

In a study involving 123 pregnancies in women treated with oral prolonged-release mesalazine, 84% of babies were born at term. Abnormalities (ectopic pregnancy, spontaneous abortion, fetal death, premature delivery, congenital malformation, lethal oxalosia) were reported in 16 women, 8 receiving low (3 g/day) and 8 receiving high (≥3 g/day) dose treatment. None of these events were considered to be related to prolonged-release mesalazine.[103] Another pharmacovigilance study indicated that low doses of prolonged-release mesalazine (≤2 g/day) do not influence the fate of pregnancy.[103] Cessation of treatment with mesalazine-containing preparations during pregnancy did not appear to affect outcome in women (n = 30) with IBD. The outcome of pregnancy was normal in 75% of patients who stopped treatment, compared with 73% in those who did not.[104]

5.1 Renal Toxicity

Episodes of nephrotoxicity have been associated with the use of aminosalicylates, including sulfasalazine, olsalazine and mesalazine-containing preparations.[105,106] Although renal dysfunction has been reported to occur in up to 1% of patients receiving pH-dependent delayed-release mesalazine (Asacol®),[107] there have been few reports of nephrotoxicity during treatment with the prolonged-release formulation. Only 1 episode of impaired renal function has been described in the published accounts of clinical trials of prolonged-release mesalazine reported in this review (involving

>2600 patients with IBD; tables III to VI). This patient was enrolled in a study of maintenance treatment for ulcerative colitis and subsequently left the trial because of an endoscopically confirmed exacerbation of disease activity. The patient continued treatment with prolonged-release mesalazine 1.5 g/day, and at the 3-month follow-up was found to have elevated serum creatinine levels. Renal biopsy revealed an interstitial nephritis, most probably treatment-related, which improved on discontinuation of prolonged-release mesalazine.[73] No other evidence of clinically significant changes in serum creatinine or blood urea and nitrogen levels has been reported in clinical trials of prolonged-release mesalazine.[75,78,84] However, 4 additional case reports of renal toxicity (3 episodes of interstitial nephritis,[108-110] 1 case of renal insufficiency *in utero*[111]) associated with prolonged-release mesalazine treatment have been identified (see section 6).

5.2 Sulfasalazine Intolerance

A 12-month study (published as a letter) was conducted in 71 sulfasalazine-intolerant patients with ulcerative colitis or Crohn's disease to determine whether these patients were able to tolerate treatment with other aminosalicylates. 96% of patients had no recognisable adverse events during prolonged-release mesalazine (1.5 g/day) treatment.[112] In a long term study of prolonged-release mesalazine (≤4 g/day) as treatment for Crohn's disease, 224 of 470 patients had documented intolerance of sulfasalazine at entry. Most of these patients were able to take the prolonged-release preparation without evidence of hypersensitivity or intolerance. The overall occurrence rate for events indicative of aminosalicylate intolerance were similar in patients with (4.5%) and without (2.8%) previous intolerance.[79]

In another study, there was no evidence of cross-sensitivity between prolonged-release mesalazine and sulfasalazine. In 73 patients with ulcerative colitis who had previous sulfasalazine allergy, 6.8% receiving prolonged-release mesalazine (1 to 4 g/day) experienced hypersensitivity reactions (rash, pruritus and/or fever), compared with 5.9% of placebo-treated patients, during the 8-week study period. Overall, treatment-related adverse events were experienced by 19% and 26% of patients with previous sulfasalazine intolerance, in active and placebo groups, respectively.[70]

The impairment of male fertility by sulfasalazine is well documented, and is due mainly to the sulfapyridine moiety.[113,114] In 6 patients who had experienced infertility as a result of sulfasalazine treatment, sperm quality returned to normal in 5 patients and was improved in the remaining individual during 12 months' treatment with prolonged-release mesalazine 1.5 g/day.[112] Significant improvements in sperm motility after 3 months' treatment with the prolonged-release formulation were also reported in men (n = 8) who switched from sulfasalazine therapy.[115] Another study involved 11 patients with IBD in remission for at least 6 months who had been taking sulfasalazine 3 to 6 g/day maintenance therapy for a mean of 7.7 years (range 1 to 22). Patients were switched to prolonged-release mesalazine (1.5 g/day) treatment after a 2-week washout period. During sulfasalazine treatment 8 patients had oligospermia [mean sperm count was $1.138 \pm 0.998 \times 10^7$/ml (normal range 4×10^7/ml to 2×10^8/ml)], a mean of 42% of sperm heads were morphologically normal, 20% of spermatozoa exhibited motility, and only 2 patients had normal sperm motility. Improvements were reported in all these variables after replacement of treatment. Four months after starting prolonged-release mesalazine treatment, only 2 patients had oligospermia, and sperm count increased to $4.18 \pm 2.91 \times 10^7$/ml ($p < 0.01$ *vs* baseline). Moreover, 56% of sperm heads were morphologically normal ($p < 0.02$), 44% of sperm were motile ($p < 0.02$) and motility was normal in 7 patients.[116]

6. Dosage and Administration

Oral prolonged-release mesalazine is available as capsules (250mg) in the US, and in tablet form (250 and 500mg) in other countries in which its use is indicated. Sachets of prolonged-release mesalaz-

ine microgranules (1g unit dose) are available in some European countries. In order to sustain external pressure, the ethylcellulose microgranules in the sachet form also contain microcrystalline cellulose. Consequently, these microgranules do not 'collapse' and may be visibly excreted in the faeces, despite the fact that practically no mesalazine is retained (section 3).

Oral prolonged-release mesalazine is indicated for the induction of remission and treatment of mild to moderately active ulcerative colitis. Individualised dosages are recommended, to a maximum of 4 g/day in divided doses,[117,118] and evidence from clinical trials indicates a dose-dependent increase in efficacy (section 4.1.1). For the maintenance of remission of colitis, the recommended starting dosage is 1.5 g/day in 2 or 3 divided doses.[118] In the US and UK, no dosage recommendations are available for the use of oral prolonged-release mesalazine in patients with Crohn's disease. In other countries, individualised dosage of up to 4 g/day in divided doses is generally recommended for the treatment of active disease and for maintenance of remission (manufacturer's data on file).

Rare cases of renal dysfunction have been reported with prolonged-release mesalazine treatment (section 5.1) and administration should proceed with caution in patients with renal impairment. Monitoring of renal function (serum creatinine levels) should be performed regularly, especially during the initial phase of treatment.[106] The use of prolonged-release mesalazine is contraindicated in patients with severe renal and/or liver impairment and in those with known sensitivity to salicylates, and is not recommended for use in children.[117,118]

Mesalazine from prolonged-release mesalazine preparations crosses the placenta but fetal concentrations are lower than in maternal plasma (section 3.2.2). Negligible amounts of mesalazine are excreted into breast milk.[65] Low doses of prolonged-release mesalazine (≤2 g/day) do not influence the fate of pregnancy, and higher doses do not appear to pose a risk to the fetus.[102,103] However, prolonged-release mesalazine should be used with caution in pregnancy and lactation and only if the potential benefit outweighs the possible hazards.

7. Place of Prolonged-Release Mesalazine in the Management of Ulcerative Colitis and Crohn's Disease

IBD encompasses a number of chronic, relapsing gastrointestinal inflammatory disorders, of which ulcerative colitis and Crohn's disease are classical examples. The incidence rates of these diseases vary by geographic region, and in Western Europe and the US range from 5 to 18 per 100 000 individuals for ulcerative colitis, and 1 to 10 per 100 000 individuals for Crohn's disease.[119] Both diseases share an unpredictable clinical course characterised by periods of exacerbation and remission and may have symptoms in common, making differential diagnosis difficult in some cases.[120]

Crohn's disease is characterised by transmural, mainly submucosal, inflammation which is discontinuous in nature and often associated with epithelioid granulomas. While any part of the gastrointestinal tract may be affected, inflammation is localised in the ileum, colon and perianal region in most patients. In contrast to the segmental, transmural inflammation of Crohn's disease, ulcerative colitis is primarily a mucosal disease in which inflammation extends proximally from the rectum in a continuous manner, and may affect the entire colon. Most patients with ulcerative colitis have distal colonic involvement, with 40 to 50% experiencing proctosigmoiditis and 30 to 40% with left-sided disease. Approximately 10% of patients have pancolitis. In practice, ulcerative colitis is distinguished by its anatomic extent: distal disease is limited to below the splenic flexure and may be treated by rectal formulations, while extensive disease extends more proximally and requires oral therapy.[68]

In accordance with the unknown aetiology of IBD, treatment is aimed at reducing or eliminating symptoms (inducing remission) and preventing episodes of relapse. In patients with ulcerative colitis who fail to respond to intensive medical management, colectomy is indicated. Whereas this proce-

dure is curative in ulcerative colitis, surgical resection of the small or large intestine is associated with a high rate of recurrence in patients with Crohn's disease. In patients with ileal resection, recurrence rates of 50 to 75% have been reported over a 5-year period, compared with 10 to 30% in patients with no small bowel involvement. Additional medical management is indicated in the case of recurrence.[121]

Sulfasalazine, a conjugate of mesalazine and sulfapyridine, is well established for the oral treatment of IBD, although its use is associated with frequent adverse events which occur in 10 to 40% of patients.[122] However, the implication of sulfapyridine in the genesis of sulfasalazine-associated adverse events[3] and the identification of mesalazine as the active moiety[2] highlighted the latter agent as having therapeutic potential. In view of the extensive absorption of unconjugated mesalazine from the upper gastrointestinal tract,[4,8] alternative oral formulations have been developed to improve mesalazine delivery to more distal sites of inflammation. The mesalazine prodrugs balsalazide and olsalazine rely on bacterial azoreductase activity for the release of the active compound and are effective only in colonic disease, while the delayed-release preparations are dependent on local ileal/colonic pH for liberation of mesalazine. In contrast to the site-dependent release profiles of these formulations, the prolonged-release mesalazine formulation reviewed in this article ensures a constant delivery of mesalazine throughout the gastrointestinal tract (duodenum to colon).[56,59,123] The efficient release of mesalazine in the small bowel may be particularly desirable in Crohn's disease, and the continued delivery of active drug in diarrhoeal states or under conditions of accelerated intestinal transit suggests additional therapeutic benefits of prolonged-release mesalazine.

In patients with mild to moderately active ulcerative colitis, oral prolonged-release mesalazine at dosages of ≥2 g/day is effective in achieving therapeutic benefits over an 8-week treatment period. At these dosages, the formulation was effective in inducing clinical and endoscopic remission in 29% and 44 to 48% of patients, respectively, compared with 12% and 31% of patients receiving placebo. Successful treatment of clinical signs and symptoms occurred in 59% of patients at a dosage of 4 g/day. Therapeutic benefits were independent of disease location. While improvements were dose-dependent, there was no related increase in frequency of treatment-related adverse events.[70] Prolonged-release mesalazine has similar clinical efficacy to sulfasalazine, but is associated with an improved tolerability profile.[71]

The chronic relapsing nature of IBD demands maintenance therapy to prolong the period of remission or to delay the onset of an acute exacerbation of the inflammatory process. In keeping with its effects in active disease, prolonged-release mesalazine is more effective than placebo, and has comparable efficacy to sulfasalazine, in preventing relapse in patients in remission of ulcerative colitis. Estimated 1-year remission rates for prolonged-release mesalazine range from 50 to 54% at a dosage of 1.5 g/day, in comparison with 46% in patients receiving equimolar (3 g/day) dosages of sulfasalazine. When treated with higher dosages of prolonged-release mesalazine (3 and 4 g/day), approximately two-thirds of patients remain in remission at 1 year.[73-75]

Previous studies have indicated that sulfasalazine has therapeutic effects in Crohn's disease, being effective in patients with colonic involvement but not for disease limited to the small intestine.[124] Consequently, medical therapy has been unsatisfactory for many patients with ileal Crohn's disease. Initial studies using low dose prolonged-release mesalazine did not support a therapeutic role in active Crohn's disease.[82,83] However, at a higher dosage (4 g/day), the formulation is more effective than placebo in inducing remission. Overall, 43% of patients were in remission after 16 weeks' treatment and 64% of patients experienced therapeutic benefit (compared with 18% and 40%, respectively, for placebo-treated patients). Effects were independent of disease location.[78] A limited number of studies have demonstrated therapeutic

benefits of prolonged-release mesalazine in children with active Crohn's disease.

Although oral glucocorticoids may be used in the management of Crohn's disease, the high incidence of treatment-related adverse events (occurring in >50% of patients on high dose therapy and approximately one-third of those receiving maintenance doses[125]) precludes long term treatment, and glucocorticoid reduction or withdrawal is often associated with symptomatic relapse. In patients with prednisolone-induced remission, addition of prolonged-release mesalazine (4 g/day) to the treatment regimen facilitated withdrawal from glucocorticoid therapy in 74%,[90] suggesting that this formulation of mesalazine has promise as a glucocorticoid-sparing agent.[79,90]

Prevention of symptomatic relapse, which occurs in 40 to 70% of patients over a 2-year period, is a major issue in the long term management of Crohn's disease. Although no comparative studies of mesalazine preparations have been published, a recent meta-analysis involving >2000 patients in 15 randomised controlled trials of several formulations suggests that mesalazine reduces the risk of symptomatic relapse in patients with quiescent Crohn's disease. In particular, patients with ileal disease and those with prolonged disease duration or surgically induced remission were found to experience treatment benefits.[126] In accordance, overall results in studies of prolonged-release mesalazine with mixed patient populations have been inconclusive. Clinical relapse rates with dosages of 1.5 to 4 g/day ranged from 16 to 55% (compared with 23 to 71% with placebo) in trials of 4 to 30 months' duration. However, the formulation has demonstrated considerable benefits over placebo in reducing the relapse rate in patients with isolated small bowel disease, particularly when administered at higher dosages (4 g/day).[85,88]

Although surgical resection is often indicated in patients with Crohn's disease,[121] the reappearance of endoscopic lesions is well documented.[127,128] In a study involving patients with recent resections, prolonged-release mesalazine 4 g/day reduced the rate of recurrence and severity of endoscopic lesions during a 12-month period.[87] Consequently, the formulation may have the potential to improve the clinical course of Crohn's disease by delaying the appearance of inflammatory lesions.

Prolonged-release mesalazine is generally well tolerated by patients with IBD, and the incidence of treatment-related adverse events is similar to that reported during placebo treatment. There is no evidence of a dose relationship in the adverse events profile. In contrast to observations with other mesalazine-containing preparations,[105,107] nephrotoxicity does not appear to be an issue with the prolonged-release formulation. Nevertheless, precautionary monitoring of serum creatinine levels has been advocated in patients receiving mesalazine-containing preparations.[106,107] Although adverse events associated with sulfasalazine are dose- or treatment-limiting in 15 to 20% of treated patients,[1] a prior history of intolerance to sulfasalazine does not appear to predispose patients to adverse reactions to prolonged-release mesalazine. During long term studies (12 to 30 months), fewer than 5% of sulfasalazine-intolerant patients experienced adverse events related to prolonged-release mesalazine treatment.[70,112] Moreover, patients with infertility associated with sulfasalazine treatment experienced improvements in sperm quality after switching to prolonged-release mesalazine.[112,115,116]

For maintenance treatment of ulcerative colitis and Crohn's disease (in countries in which this is indicated) the recommended dose of oral prolonged-release mesalazine is 1.5 g/day. However, treatment guidelines indicate that dosages of mesalazine up to 4 g/day may be used in ulcerative colitis[68] and that dosages above 3 g/day may be required to prevent relapse in Crohn's disease.[76] Results from clinical trials with this formulation appear to support this. Higher dosages (3 to 4 g/day) tended to be more effective in prolonging remission than 1.5 g/day, although conclusive information from dose-ranging studies is not available. However, clear dose-response relationships for treatment benefits were observed in active disease.[70,78] As prolonged-release mesalazine is well

tolerated and adverse events do not appear to be dose-related, higher dosages such as those commonly used in active disease may provide additional benefits in maintenance treatment.

In summary, oral prolonged-release mesalazine is effective for maintenance and induction of remission of mild to moderately active colitis, both in patients with distal disease and in those with pancolitis. The formulation has similar efficacy to that of equimolar concentrations of sulfasalazine. Prolonged-release mesalazine also appears to be effective in the treatment of Crohn's disease, and maintenance therapy is of particular value in patients with isolated small bowel involvement. Evidence suggests that higher dosages (3 to 4 g/day) of prolonged-release mesalazine have additional therapeutic benefits over lower dosages in patients with inflammatory bowel disease without increasing the incidence of adverse events.

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