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World J Gastroenterol 2006 October 14; 12(38): 6115-6123
World Journal of Gastroenterology ISSN 1007-9327

REVIEW

Indications for 5-aminosalicylate in inflammatory bowel disease: Is the body of evidence complete?

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Supported by research grants from Astrazeneca (Zoetermeer, The Netherlands), Ferring BV (Hoofddorp, The Netherlands), P and G Pharmaceuticals (Cincinnati, United States), ALTANA Pharma BV (Hoofddorp, The Netherlands), and Tramedico BV (Weesp, The Netherlands), Falk Company (Freiburg, Germany), and Ferring International (Copenhagen, Denmark)
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Received: 2005-11-08 Accepted: 2006-02-20

Abstract

Mesalazine is a safe drug, although adverse events may be seen in a minority of patients. This applies also to pregnant women and children. The role of mesalazine in combination therapy to improve efficacy and concomitant drug pharmacokinetics, or in chemoprevention against inflammatory bowel disease (IBD)-related colonic carcinoma has not yet been completely elucidated. Therapeutic success of mesalazine may be optimized by a combination of high dose and low frequency of dosage to improve compliance. Therefore, due to its superior safety profile and pharmacokinetic characteristics, mesalazine is preferable to sulphasalazine. This paper reviews the literature concerning mechanisms of action, indications and off-label use, pharmacokinetic properties and formulations, therapeutic efficacy, compliance, paediatric indications, chemoprevention, and safety issues and adverse event profile of mesalazine treatment *versus* sulphasalazine. It also highlights these controversies in order to clarify the potential benefits of mesalazines in IBD therapy and evidence for its use.

Key words: Mesalazine; Sulphasalazine; Review; Ulcerative colitis; Crohn's disease; Treatment; Chemoprevention; Pregnancy; Adverse events

van Bodegraven AA, Mulder CJJ. Indications for 5-aminosalicylate in inflammatory bowel disease: Is the body of evidence complete? *World J Gastroenterol* 2006; 12(38): 6115-6123

http://www.wjgnet.com/1007-9327/12/6115.asp

INTRODUCTION

In the late 1970s, elegant studies revealed that 5-aminosalicylate is the active moiety of sulphasalazine in patients suffering from ulcerative colitis (UC) and Crohn's disease (CD)[1,2]. Since then, 5-aminosalicylate has become the gold standard first line therapy for patients with UC, although its use in CD remains controversial. After 25 years, discussion of monocomponent 5-aminosalicylate with regard to its efficacy in comparison with sulphasalazine[3,4], drug profile[5,6], precise indications[7,8], and adverse events[9,10] continues to be ongoing and lively. This review highlights these controversies in order to clarify the potential benefits of mesalazines in inflammatory bowel disease (IBD) therapy and evidence for its use.

CONSIDERATIONS 1 AND 2

How efficacious is mesalazine in comparison with sulphasalazine in patients with ulcerative colitis and which is the most effective mesalazine?

The therapeutic efficacy of salicylazosulphapyridine (SASP) in inducing and maintaining remission in patients with UC has been recognized for over 60 years[11]. SASP is a conjugate of 5-aminosalicylate and sulfapyridine. 5-aminosalicylate was identified as the principal effective component of this conjugate in the 1970s[1,2], and remains the starting point for the clinical use of monocomponent 5-aminosalicylate or mesalazine. Although the exact mechanism of action of mesalazine/SASP has still to be elucidated[12,13], several potential mechanisms have been suggested, including 5-aminosalicylate-induced inhibition of inflammation by interfering with the metabolism of arachidonic acid, prevention of mucosal generation of leukotrienes and prostaglandins[14], scavenging of free radicals[14,15] and mechanisms only recently identified involving inhibition of nuclear factor-kappaB (NFκB) and induction of apoptosis[16-20]. Further properties include changes in the production of immune globulins and diminished production of interleukin-1 and partial inhibition of platelet activating factor (PAF) expression, resulting in a decrease in leucocyte trafficking[21].

5-aminosalicylate is believed to act in the damaged epithelial intestinal layer, where it is transformed into the inactive acetylated 5-aminosalicylate, which is subsequently filtered and excreted by the kidneys. As a result, the therapeutic activity and efficacy of 5-aminosalicylate are related to its intraluminal concentration[6,13,22,23]. It has been argued that increasing dosages of oral mesalazine are

not correlated with enhanced efficacy. Although this has never been the subject of an extensive study[3], a double-blind study in 321 patients has found no significant dose response between mesalazine (1.5 g/d, 3.0 g/d and 4.5 g/d)[24]. Theoretically, however, dosing of mesalazine above the enzymatic (acetylating) capacity of the epithelial layer increases the subepithelial concentration of mesalazine[25], thereby increasing its potential efficacy[14], a finding that is corroborated by studies demonstrating a dose-response relationship of oral formulations[26-29]. These findings have been recently corroborated by a post-hoc analysis of 423 patients out of the original 687 patients from the ASCEND I and Ⅱ studies, in which daily oral use of 4.8 g mesalazine (Asacol®) was compared to 2.4 g mesalazine, showing that the higher dosage is superior in patients with moderately active UC[30]. There is little doubt that registered doses of oral mesalazine are effective in treatment of active UC[31]. Indeed, the recent (2004) British Society of Gastroenterology (BSG) guidelines[32], recommend a combination of topical and oral mesalazine as first line therapy in the treatment of distal mild to moderate UC.

More contentiously, recent Cochrane meta-analyses of the capacity of mesalazine to induce or to maintain remission[3] in UC patients are not in favour of mesalazine over SASP, particularly in maintaining remission. However, SASP is not as well tolerated as 5-aminosalicylate[3]. Therefore, these authors question whether there is a clinical advantage of monocomponent preparations. However, it should be noted that mesalazine and SASP are equally effective in the 12-mo trials. It is only the 6-mo data that differ. The conclusions made from this meta-analysis are further flawed due to the following reasons. Although the authors have made considerable efforts to group studies with the same patients and outcome variables, these meta-analyses are based on different patient groups from various hospital settings. Moreover, meta-analyses may lead to incorrect conclusions, in particular when smaller studies are added to perform the analysis, as has been shown by the challenging and controversial findings of LeLorier *et al*[33]. They showed that performing well-conducted meta-analyses with available data from small-scale studies leads to incorrect conclusions as exemplified by contradictory findings in properly designed and statistically powered prospective trials, performed to verify the conclusions from these prior meta-analyses. In addition, there is a lack of trials using high-dose mesalazine, with intention-to-treat analysis, and including registered compliance rates. Notwithstanding these limitations, and others posed by the authors (such as lack of standard UC-index of severity and different, partly obscured, treatment strategies), it could be concluded that these Cochrane-analyses showed that efficacy of oral SASP or mesalazine in induction and maintenance treatment in UC is more or less equivalent[3,4]. Therefore, a final decision as to the choice of therapy depends largely on other factors such as adverse events and drug profile, patient's preference, and costs. Knowledge of drug profile and pharmacokinetic characteristics may be helpful in determining the correct choice in oral therapy for UC, although all compounds have proven their efficacy in colonic disease[31,34]. In the early trials, somewhat surprisingly, oral balsalazide therapy was shown to be superior over mesalazine[35,36], in addition to more expected results such as better tolerability than SASP[37,38]. However, it has since been contested that the interpretation and clinical implications of these findings are ambiguous[34,39-41]. Direct comparative studies with well-defined clinical presentations (pancolitis versus left-sided colitis), and well-defined consistent primary study goals, such as number of patients in remission after 8 or 12 wk, are necessary to prove the therapeutic superiority primarily and secondarily, to justify preferences[31,40].

Another important issue relates to the use of topical therapy. Where possible, topical therapy, either as an enema or a suppository, can be an excellent alternative to oral therapy, both for active[42-44] and quiescent disease[45,46]. To adequately cover the extent of the diseased distal colon, enema volume has to be varied[47], whereas all rectal dosages above 1 gram seem equipotent[48]. In addition, new entities such as gels and foams may be a patient friendly alternative[49-51]. Furthermore, regarding combination therapy, it has recently been reported that the combination of oral (4 g/d) and rectal (1 g/d) mesalazine therapy significantly improves remission and improvement rates in extensive mild to moderate active UC[52]. Combination therapy may, in addition, protect against progressive extension of distal disease[53].

The ideal dosage for maintenance treatment of UC has never been studied, and most studies included in the most recent Cochrane analysis have used relatively low dosages of mesalazine[4]. The authors concur that the ability to make general conclusions is limited due to the lack of standard indices, and treatment specifications. A dose-response rate could not be found, probably due to the small number of patients included in this subanalysis. However, it should be noted that the use of olsalazine (Dipentum®) may be limited owing to its diarrhoea-inducing capacity[4]. Nowadays many clinicians believe that the same dose of mesalazine required to induce remission should be continued as maintenance therapy, particularly if higher doses are required to induce remission[34].

CONSIDERATIONS 3 AND 4

Is mesalazine effective in Crohn's disease and is the pharmacokinetic (mesalazine release) profile of importance?

The use of 5-aminosalicylates in patients with CD is more controversial than its use in UC. The landmark study of Singleton *et al* in 1993[54], has demonstrated a dose-response relationship with high dose (4 g/d) mesalazine. However, mesalazine therapy appears clinically beneficial only in specific subgroups, such as patients who have recently undergone ileocoecal resection to prevent relapses[55,56]. The efficacy of mesalazine in the overall heterozygous CD population is inconsistent, both in literature and in practice. Several authors advocate the use of mesalazines in mildly active CD[8,57], although a more critical approach, namely mesalazine is not efficacious in CD, is equally contested by others[7,58]. One meta-analysis, including data from unpublished studies, has shown a significant effect of mesalazine (4 g/d) compared to placebo in reducing CDAI

score 63 *vs* 45 (ITT) ($P = 0.04$) and 83 *vs* 57 per protocol, ($P = 0.02$)[8]. The clinical relevance of these differences has been questioned[58]. Nevertheless, in early studies of mesalazine use in CD, beneficial effects have been observed, which could not be reproduced in larger studies in referral centres[8,54,55,59,60].

The therapeutic effects of mesalazine (1 g t.i.d), 6-mercaptopurine (50 mg/d), and placebo were studied for 2 years following surgery, which revealed that the relapse rate in the 6-mercaptopurine group was 50% compared with 58% and 77% in the mesalazine and placebo groups, respectively, showing a statistical significance only for 6-mercaptopurine[61]. In another open randomized study, comparing properly dosed azathioprine and mesalazine (1 g t.i.d), no statistically significant difference was observed in the cumulative risk of clinical relapse between the two treatment regimens ($P = 0.2$), which may be due to a type 2 error[62]. A potential role of mesalazine in maintenance therapy of CD following medically induced remission is questioned[63].

Others believe that only SASP and not mesalazine, may be indicated for but strictly limited to mildly active colonic CD[7]. This may reflect the colonic release profile of SASP, which clearly differs from the release profile of mesalazine delivered in microgranules, which has been shown to reduce postoperative recurrence in CD patients with small bowel involvement only (mesalazine 22% *vs* placebo 40%, $P = 0.002$)[56,64]. Localization of the disease differs considerably between patients. This clinical heterogeneity may lead to differences in efficacy between mesalazine formulations. Drug release profiles of mesalazine moieties noticeably vary[6]. Mesalazine incorporated in ethylcellulose microgranules (Pentasa®) releases mesalazine from the duodenum through the colon in a gradual manner at all pH levels[6,22,65]. Conversely, mesalazine with a Eudragit-L-coating (Salofalk®) releases mesalazine exposed to a pH level of 6 to 6.5, limiting its action to the mid small intestine and onwards, whereas a similar formulation with Eudragit-S-coating (Asacol®), releases when exposed to pH levels of 7, corresponding approximately to the last part of the small intestine. The prodrugs sulphasalazine (Azulfidine®), balsalazide (Colazal®) and olsalazine (Dipentum®) release 5-aminosalicylate in the azo-reductase containing bacteria-rich colon. Thus, there exist formulations which release 5-aminosalicylates in specific regions of the intestine, while others continuously release 5-aminosalicylates in both the small and large intestine[6,65]. Regionalization of mesalazine delivery is further influenced by enteral motility and anatomy, as exemplified by various recurrence rates after mesalazine use in Crohn's disease patients with different anastomotic configurations following resection[66]. The pharmacokinetics of various mesalazine moieties has recently been reviewed more extensively[5,67].

Since intraluminal concentrations of mesalazine appears to determine therapeutic efficacy, regional targeting of mesalazine is considered to be important[6,60,64]. Remarkably, several generic oral formulations of mesalazine-containing preparations have been approved based on bibliographic files, without conductance of thorough bio-equivalence studies[6]. Clearly, generic preparations with undocumented release profiles cannot be compared with well-documented formulations[5,6]. Nevertheless, "it is as yet unclear whether any specific formulation has shown site specificity for Crohn's disease"[8], and this pharmacokinetic issue has yet to be the subject of a clinical trial. Aside from these pharmacokinetic considerations, the potential of mesalazine in CD has yet to be fully determined although the recent BSG guidelines stated that high-dose (4 g/d) mesalazines could be used as an initial therapy for mild-ileocolonic CD[32]. However, a critical approach is warranted, as concluded by the authors of a Cochrane review concerning any use of 5-aminosalicylates in Crohn's disease patients[63].

CONSIDERATION 5

Does non-compliance contribute to insufficient efficacy of mesalazine in maintenance therapy?

Another often overlooked issue in therapeutic efficacy is lack of compliance with therapeutic regimens. This problem has been recognized as a pitfall in conducting IBD maintenance therapy trials as early as 1982[68]. Although reported compliance in clinical trials is usually in excess of 90%, such high levels of compliance are not necessarily continued in everyday practice. Indeed, a high rate of non-compliance up to 50%, has been reported in IBD-patients[68-70] with a significant impact on treatment outcome which in UC at least is the most important predictor for relapse[71]. Although medication compliance is generally good in acute disease, compliance rates in maintenance therapy decrease considerably once remission is achieved. The interpretation of maintenance studies without measurements of drug levels may therefore be difficult[68]. One of the key risk factors for non-compliance is the number of pills and multiple medications, a risk factor that is common in IBD patients, and in particular in those taking high dosages of mesalazine in multiple dosing regimens[70]. Reduction of the number of dosages, preferably with patient friendly formulations such as granules, without decreasing the dosage would be expected to improve the outcome of mesalazine therapy, particularly during maintenance therapy[72].

CONSIDERATION 6

What are the safety considerations for mesalazine versus SASP?

The short-term use of mesalazine is perceived to be relatively safe[73]. However, specifically olsalazine has been shown to induce diarrhoea in up to 17% of treated patients, probably induced by the release-profile modifying azo-bond which is also used in balsalazide and SASP, the latter two showing similar prosecretory effects in elegant *in vitro* studies[74]. To estimate the more severe potential risks of mesalazine, most data are obtained from case reports concerning adverse events that have been published, especially relating to renal damage[75-79] and pancreatitis[76,80-84], both are idiosyncratic phenomena[85]. Interestingly, 4-ASA enemas may be used when 5-ASA-induced pancreatitis occurs[86]. Predictably, SASP containing 5-aminosalicylate, has also been associated with pancreatitis[83,87], nephrotic syndrome[88,89], and many other

detrimental events. The latter is reportedly associated with the sulfa component of SASP[90,91]. In a recent report on the usage of SASP and mesalazine for ⩾ 5 years in nearly 700 patients, side effects are reported most frequent in SASP-treated patients (20% *vs* 6.5%)[92]. Evaluation of the number of prescriptions *versus* the number of central adverse events has ascribed superior safety to SASP[9]. The methodology of this observation remains controversial[93-95]. For short term therapy, mesalazine is widely perceived to be better tolerated than SASP, as has been measured by several methods[73,92]. Moreover, mesalazine is a good alternative when SASP has to be withdrawn due to adverse events[96]. In addition, other adverse events occur less commonly, or are less reported, a known flaw in epidemiological data obtained from spontaneous reporting. Therefore, many of the well-known adverse events ascribed to SASP are expected to be underreported[95]. Overall, mesalazine is a safe drug, but its use bears a small risk for idiosyncratic renal damage and pancreatitis[10,97-99].

CONSIDERATION 7

Should off-label use of mesalazine be considered?

Fertility, pregnancy and nursery: Conception and pregnancy are common events in the cohort of IBD patients, owing to the fact that many patients with IBD are of child-bearing age without diminished fertility, although SASP and anecdotically mesalazine have been associated with reversible, decreased male fertility[100,101]. Ideally, conception and pregnancy take place during periods of IBD remission, without use of medication[100,102,103]. However, this is not always feasible. Of note is that the progression of pregnancy and foetal development are more endangered by active, insufficiently treated IBD, than by the majority of pharmacological agents[102,104]. Many drugs including mesalazine, that are used for IBD may cross the placenta[65,105]. Therefore, toxicity and teratogenicity cannot be ruled out completely. However, the safety of mesalazine is very well documented[103,105-110], although the safety of oral dosages above 3 g mesalazine per day during gestation has not been documented[105]. In addition, concerns about the rate of stillbirth remain, although this may be due to activity of the disease[110]. One incidence of renal affection in uteri in a foetus where the mother received 4 g mesalazine/day has been reported[111]. In addition, the topical use of mesalazine in enemas appears to be safe[112]. In contrast, SASP is associated with several congenital abnormalities. Although causality has not been proven, the concomitant use of folic acid is recommended[113-115]. Pregnancy outcome in patients using mesalazine is equivalent to that in the non-IBD population[102,103,105,109].

Lactation is not considered to be a contraindication for mesalazine use, although minor concentrations of mesalazine have been detected in breast milk[116]. One case of diarrhoea in a breast-fed child of a 5-aminosalicylate treated mother has been reported[117] and cerebral thrombosis has been recently reported in the child of a breast-feeding mother on mesalazine therapy[118]. However, it is uncertain whether mesalazine contributes to the latter condition.

Paediatric use of mesalazine: The incidence of IBD in children appears to rise in Eastern and Western countries[119-122]. However, not all authors agree[123]. Although the medical approach to IBD in children is largely similar to that of adults, its treatment aims differ from the adult population[124,125]. Mesalazine may be used in mild to moderate or severe UC, alone or in combination with steroids[125] and dosages in children above 12 years of age are similar to those of adults. Therapy for younger children is usually 20-50 mg mesalazine per kilogram bodyweight given in two to three separate dosages per day[126]. The pharmacokinetic profile of mesalazine pellets is comparable to that for adults in these young patients[127]. Maintenance therapy is habitually half that dose with a minimum of 750 mg mesalazine daily. The incidence of adverse events in children is similar to that observed in adults, although rare observations such as IBD-mimicking[128] and pericarditis[129] have been reported. In a paediatric study comparing SASP with mesalazine, the majority of patients prefer mesalazine, due to its superior properties regarding ease and frequency of administration and its better safety profile[130]. The problems regarding acceptance of the disease and its treatment in this patient group supports mesalazine use over SASP[130,131]. In contrast to treatment in adults, paediatricians tend to use mesalazine in non-stenotizing CD and if necessary, concomitant enteral nutritional therapy can be used in active disease or as a maintenance therapy[127,132]. However, none of these indications has been subjected to large controlled trials in children.

Chemoprevention of IBD-related colonic cancer: Traditionally UC and more recently CD have been associated with enteral adenocarcinoma, although the risk appears to be limited to patients with chronic inflammation[133,134]. Interestingly, several studies and reviews refer to potential chemoprotective properties of mesalazine moieties in prevention of this type of cancer[18,19,135-139], similar to the alleged chemoprotective properties of acetylsalicylic acid, although the latter remains contraindicated in patients with IBD. Laboratory and other findings support the hypothesis of mesalazine as a chemoprotective agent[138]. These chemopreventive properties include selectively inducing apoptosis in colorectal cancer (CRC) cells and stabilising effects on micro-satellites[19]. In addition, the incidence of CRC has been demonstrated to be reduced in a case-control study (odds ratio 0.19, 95% confidence interval: 0.06%-0.61%) if patients use mesalazine doses above 1.2 g daily[137]. Nevertheless, it could be argued that the decreasing relative risk for development of colonic carcinoma in patients with IBD is related to successful therapy of chronic active disease *per se*, and is thus unrelated to mesalazine therapy[27,138]. In short, prospective and comparative data are lacking, but the indication for mesalazine as a chemopreventive agent looks promising, as recently concluded in a meta-analysis[140].

CONSIDERATION 8

Does mesalazine have a role in combination therapy?

Concomitant use of mesalazine formulations may be beneficial, as its efficacy seems related to intraluminal

concentrations. Combination therapy of oral and rectal mesalazine has been investigated. Interestingly, higher mucosal concentrations of mesalazine[27] have been associated with the decreased relapse rates but not with higher remission rates[141]. Prior studies have reported that earlier remission can be achieved using combination therapy in left-sided UC[142], and that a longer duration of remission has been observed when enemas are combined with low oral dosages of mesalazine[143]. In addition, recent studies have also demonstrated the benefits of combining high-dose oral mesalazine with topical therapy in terms of remission and improvement rates in patients with UC[52], and protection against increase of disease extent[53]. Again, extensive well-designed dose-response trials are lacking and no final conclusion can be drawn from these sparse data.

Another interesting approach to the treatment of UC patients may be dual therapy with a combination of mesalazine and another inflammation-modifying drug such as butyrate[144,145], fraxiparin[146], or allopurinol[147]. Also, preliminary studies investigating combination therapy with mesalazine and probiotics support their use[148]. It should be noted, however, that as these reports are open-label studies, conclusions may not be as valid as those obtained from studies using classical approaches such as increasing mesalazine dosage or switching of type of drugs. Although the combination of mesalazine and steroids may, theoretically, have synergistic effects, this concept has yet to be substantiated by clinical trials, although for topical therapy, the combination of beclomethasone and mesalazine has been proved beneficial in a small open-label study of patients with mesalazine-refractory ulcerative proctitis[149]. The combination of azathioprine (a potent immunosuppressive drug) with mesalazine (a milder agent) seems counter-intuitive. Proper studies are lacking once again, although one study has suggested that mesalazine may interfere with azathioprine metabolism, inducing a higher concentration of supposedly active metabolites, such as 6-thioguaninenucleotides[150]. After 25 years of mesalazine use, it is clear that the value of combination therapy, whether beneficial or detrimental, remains to be fully elucidated.

SUMMARY

Decisions regarding treatment options for IBD must be carefully weighed following a careful benefit-risk analysis. The immediate goal of controlling active diseases must be balanced against the long-term goal of keeping patients asymptomatic on a therapy with acceptable toxicity. Large prospective and retrospective cohorts demonstrate that mesalazine is a safe drug, although adverse events may be seen in a minority of patients. Overall, in *UC*, mesalazine is beneficial in mild to moderate active diseases[31,151-153]. Maintenance therapy with mesalazine is also well documented[151], although it remains contentious as to which dosage and dosing frequency are optimal. With respect to a high compliance and good therapeutic success, the combination of high dose and low frequency is ideal and mesalazine preparations which can provide this are optimal. Indeed, preliminary studies support this type of therapeutic regimen although further studies are needed to confirm these findings[154,155]. Topical therapy is safe and effective and can be used to reduce systemic concentrations of mesalazine or its methylated metabolite, particularly in those prone to develop adverse events[43]. The alleged potential of mesalazine therapy in CD requires further clarification, but the use of mesalazine delivered in microgranules postoperatively including small bowel CD only, and SASP in colonic disease, is scientifically corroborated[56,58,61]. The limited data available support the use of the low toxicity mesalazine agents in children. The use of mesalazine in pregnancy and during breast-feeding, indicates that mesalazine is very likely to be safe. Preliminary studies suggest that 5-aminosalicylate also plays a role as a chemoprotective agent in reducing the risk of developing colorectal cancer, although further studies are needed to confirm this effect. The combination of various inflammation-modifying drugs with mesalazine is a sparsely investigated field, but initial data are encouraging.

Overall, mesalazine is a safe and effective drug with a pivotal role in UC patients and a limited role in CD patients. Although clinical superiority in comparison with SASP has yet to be proven, the superior safety profile and pharmacokinetic characteristics of mesalazines definitely advocate their use as the treatment of choice when treatment with 5-ASAs is indicated.

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