Gut

Leading article

What dose of 5-aminosalicylic acid (mesalazine) in ulcerative colitis?

Sulphasalazine was developed in the 1930s, initially for use in patients with rheumatic polyarthritis. However, its modest effects in arthritis were soon overshadowed by the striking benefits seen when the drug was given to patients with active colitis.[1] Controlled clinical trials confirmed the early favourable impressions and established a role for sulphasalazine in the treatment of active disease and in the maintenance of disease remission.[2–5] Long term benefit was shown and lifelong treatment is usually recommended.[6]

Although sulphasalazine has had undoubted benefits for many patients with ulcerative colitis, it has two major limitations. Firstly, it has limited efficacy. In active disease, little more than half the patients treated with oral sulphasalazine will achieve symptomatic remission and, even with optimal maintenance treatment, annual relapse rates may be 30% or more. Secondly, side effects and allergic reactions are common, occurring in up to one third of patients taking standard maintenance doses and up to half of those taking therapeutic doses.[7] Although many of these reactions are minor, some are serious and in about 10% they are sufficient to require discontinuation of treatment.

In 1977, Azad Khan *et al* studied the therapeutic activity of the component parts of sulphasalazine and found that 5-aminosalicylic acid (5-ASA; mesalazine) was the active ingredient and that sulphapyridine was therapeutically inert.[8] As most of the adverse reactions to sulphasalazine were thought to be caused by sulphapyridine, the results of this landmark study suggested that new formulations should be developed to deliver 5-ASA to the colon without the toxic sulphapyridine carrier. Such drugs were to offer two potential advantages over conventional sulphasalazine. Firstly, they would be less toxic, better tolerated agents for either first-line use or for the treatment of patients intolerant of sulphasalazine. Secondly, reduced toxicity would permit the use of higher doses which may improve clinical efficacy.

Twenty years on, we have seen the emergence of a range of 5-ASA based formulations. These seem to be as effective as sulphasalazine and have a much reduced toxicity.[9] However, the value of high dose treatment is not well established and the optimal route of 5-ASA administration in different stages of disease remains far from clear.

Clinical dose-ranging studies

In the 1940s and 1950s sulphasalazine was used to treat active disease in doses of 6–8 g daily and in patients with resistant disease up to 16 g daily were occasionally given[10] (1 g sulphasalazine is equivalent to 400 mg 5-ASA). With the introduction of steroid treatment and the realisation that much of the toxicity of sulphasalazine was dose related more modest doses were used.

As maintenance therapy, however, low dose sulphasalazine was the initial choice. Misiewicz *et al*, the first to demonstrate the prophylactic value of sulphasalazine, opted for a dose of 2 g daily, based on previous experience and a perception that asymptomatic patients were unlikely to take large numbers of tablets.[2] Fortuitously, Azad Khan *et al* found that sulphasalazine 2 g daily was the optimal maintenance dose, as relapse rates were higher in patients taking 1 g daily and although numerically fewer in patients taking 4 g daily the benefits were marginal and more than offset by an increase in side effects.[11]

Despite the availability of a range of new agents, relatively few, well designed studies have assessed the value of high dose 5-ASA treatment. Furthermore, the results to date are either conflicting or suggest that the benefits are modest.

The results of high dose maintenance treatment have been particularly disappointing. One of the earliest studies reported no better results with a threefold greater dose of Asacol than with standard doses of sulphasalazine.[12] More recently, the benefits of Pentasa 3 g daily over 1.5 g daily were found to be marginal and fell short of statistical significance.[13] Balsalazide at 4 g daily was found to be better than 2 g daily but 3 and 6 g daily seem to be equivalent[14 15] and two dose-ranging studies with olsalazine have reached somewhat different conclusions.[16 17] Not surprisingly, a meta-analysis of 10 maintenance studies show no clear evidence of a dose response effect.[18]

Studies of unselected patients, however, may miss the potential benefits of high dose treatment in selected subgroups. Ulcerative colitis runs a variable course with some patients enjoying prolonged remission and others relapsing frequently. As poor response to maintenance drug treatment is one possible explanation for frequent relapse, studies of high dose oral treatment would be particularly useful in this subgroup. In this respect it is worth noting that a recent study found that patients with a past history of frequent relapse, relapsed less when given a combination of oral mesalazine 1.6 g daily and 4 g mesalazine enemas twice weekly than when given oral mesalazine alone.[19] How such patients would fare with higher dose oral treatment merits further study.

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Although rectal formulations are often less acceptable to patients as maintenance therapy a number of studies have demonstrated their benefit. A dose response effect may explain why Miner *et al* found that 4 g 5-ASA enemas given daily or on alternate days were equally effective in maintaining remission whereas enemas given every third day were less effective.[20] Dose-ranging comparisons of oral and rectal therapy would be of particular interest as Mantzaris *et al* found that 4 g 5-ASA enemas every third night were more efficacious in maintaining remission of distal colitis than oral 5-ASA 1.5 g daily.[21]

In mild and moderately active disease the data are somewhat more supportive of high dose oral treatment. A meta-analysis of eight placebo controlled trials reports pooled odds ratios for remission of 1.52, 1.86 and 2.68 in patients treated with less than 2 g, 2–3 g and more than 3 g daily, respectively. Surprisingly, a meta-analysis of 5-ASA/sulphasalazine trials did not confirm this dose response effect.[18] The value of increasing the oral dose of 5-ASA much in excess of 3 g daily is not clear. A preliminary report suggests some benefit of 4.8 g over 2.4 g daily.[22] However, many patients with active colitis will not settle on oral 5-ASA alone and require additional treatment with either rectal 5-ASA or steroid or oral steroid to achieve remission.

The development of topical 5-ASA preparations during the 1980s was an important advance in the treatment of active distal colitis. Suppositories, foams and liquid formulations are available. Many trials show favourable comparison with topical steroid therapy and a recent meta-analysis supports the superiority of rectal 5-ASA.[23] There have been few dose-ranging studies but a small pilot study was unable to find a difference between 1 and 2 g 5-ASA enemas and a larger study by Campieri *et al* found that 1, 2 and 4 g enemas were equally efficacious.[24 25] A 1 g 5-ASA enema therefore seems sufficient for patients with mild to moderately active distal colitis.

Combinations of oral and rectal 5-ASA may be the most effective treatment for active disease[25a] but systematic dose-ranging comparisons are not available.

Optimising drug concentrations in tissue

Despite considerable research effort, the precise mode of action of 5-ASA remains unknown. The drug probably acts locally as systemic concentrations are low after oral sulphasalazine and rectal 5-ASA administration. Its fluorescent properties enable it to be localised and following both oral and rectal dosing fluorescence is seen in colonic epithelial cells and throughout the lamina propria. Cells with the morphological characteristics of macrophages seem to take up the drug avidly.[26]

5-ASA has a multitude of actions, any or several of which may relate to its beneficial clinical effect. 5-ASA is known to influence epithelial permeability and cellular metabolism, it modulates eicosanoid metabolism and has a number of immunological effects, including effects on antibody and cytokine secretion, alterations in interleukin 1 release, HLA-DR expression, and lymphocyte function. It also acts as a free radical scavenger. As some of these actions seem to be dose related, tissue drug concentration may be an important determinant of therapeutic response.[27]

The new salicylate formulations use either coat dissolution or azo cleavage mechanisms to effect colonic 5-ASA release. Both delivery systems may be impaired by changes in the luminal mileu[9] and the recent suggestion that balsalazide is more effective than coated mesalazine in active colitis is likely to stimulate more interest in the comparative pharmacokinetics of these products.[27a]

After delivery of 5-ASA into the colon, some is absorbed but most remains within the lumen and is passed in the stool, some in acetylated form. The principal site of acetylation and its relevance to the drug's mode of action are not clear. Colonic epithelial cells absorb and acetylate 5-ASA rapidly[28] but the amount of drug excreted in the stool in acetylated form correlates with transit time[29] suggesting a role for luminal metabolism. N-acetyl-5-ASA is poorly absorbed by epithelial cells and this may explain its apparent lack of therapeutic efficacy.[30]

De Vos *et al* were the first to measure tissue 5-ASA concentrations. Surprisingly, despite comparable clinical efficacy, they found that patients taking delayed release 5-ASA had much higher tissue concentrations than did those taking azo-linked 5-ASA. We have not been able to confirm these findings and believe that surface contamination of the biopsy samples with faeces containing high concentrations of drug and differences in bowel preparation may account for this discrepancy.[31]

Our own studies have shown that, under steady state conditions, rectal tissue concentrations do not correlate well with plasma concentrations (Hussain *et al*, submitted for publication). This is somewhat unusual as most drugs gain access to their site of action through the systemic circulation. However, tissue 5-ASA is likely to be principally derived from the colonic lumen where concentrations of drug in stool and free faecal water are 100 times greater than in the tissues, rather than from plasma where concentrations, following oral dosing, are 10 times less. Variability in tissue concentrations is notable. Factors that influence absorption, such as luminal concentration, transit time, luminal pH, and epithelial permeability, are likely to be important determinants of this variability.

Of particular interest is that patients with quiescent disease who subsequently relapse have lower tissue drug concentrations and higher urinary excretion during quiescence than patients who stay in remission.[32] Whether this reflects an inherent or disease related difference in drug absorption, metabolism, or excretion is unknown. Clearly, lower tissue concentrations may predispose to relapse. Simply increasing the oral dose, however, may not be sufficient. Oral dose-loading, in healthy volunteers, results in a progressive increase in serum, urine, and faecal 5-ASA concentrations. Rectal tissue concentrations, however, increase when the oral dose is increased from 1.2 to 2.4 g daily but do not increase further when the dose is increased to 4.8 g daily.[33] Whether even higher oral doses or rectal delivery would increase tissue concentrations remains to be determined.

Rectal tissue drug concentrations fall very appreciably at times of relapse (10- or 20-fold).[32] Disease related factors such as changes in regional transit, reducing mucosal contact time, and acidification of the luminal contents (the absorption of 5-ASA from acidic enemas is less than from neutral enemas[34]) are probably important. Manipulating such factors, to facilitate absorption, is worthy of further study as it may bring clinical benefit

Dose related toxicity

It is important to consider toxicity when choosing the dose of any drug. The dose related side effects of sulphasalazine were particularly troublesome. However, 80% of patients unable to tolerate sulphasalazine can tolerate one of the new salicylates[35] and in controlled clinical trials, the prevalence of side effects with 5-ASA is comparable to placebo and much lower than with sulphasalazine. Allergic reactions, exacerbations of colitis, pancreatitis, and blood dyscrasias are important but rare, and are probably independent of dose.

The secretory diarrhoea associated with olsalazine, which often limits patients acceptance of the drug, seems to be one of the few truly dose related phenomena.[36] This effect seems to be unique to olsalazine and is a result of the actions of the intact molecule on small intestinal electrolyte transport.

Most concern has focused on the possibility of dose related nephrotoxicity. 5-ASA has structural similarities to aspirin and phenacetin, and in rats and dogs chronic high dose treatment may induce acute tubular and papillary necrosis.[37] In humans a number of cases of acute nephrotoxicity have been reported but there is little to indicate that these reactions are dose related.[38]

Several groups have found evidence of minor abnormalities of renal function in patients with chronic colitis but none has been able to distinguish clearly between a drug and disease related effect.[39 40] Abnormalities are also seen in patients who have not received 5-ASA.[41] Some have suggested that the 5-ASA formulations associated with the higher systemic concentrations are more prone to induce nephrotoxicity. However, when urinary sediment, creatinine clearance, and the urinary excretion of markers of glomerular and tubular toxicity were examined in 34 patients taking high dose Asacol and a comparable group taking sulphasalazine no differences were found.[42]

Although idiosyncratic nephrotoxic reactions undoubtedly occur, the risks of dose related nephrotoxicity, within current dosing recommendations, have probably been overstated.

Conclusions

At present we have limited data to guide us when we choose a dose of mesalazine for an individual with ulcerative colitis. On present evidence, patients with infrequent relapse are probably best treated with low dose maintenance treatment. In those with frequent relapse and mild or moderately active disease the situation is less clear. Higher doses may be of benefit. Large scale, dose-ranging studies, by route of administration and extent of disease, assessing efficacy, patient preference, and cost effectiveness would clearly be of value but this would require a huge research effort. As tissue drug concentrations are likely to be important determinants of response to treatment, an understanding of the factors that determine these concentrations may help us focus on the most relevant clinical issues.

S A RILEY
Department of Gastroenterology, Northern General Hospital, Sheffield S5 7AU, UK

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