Gut, 1991, 32, 462–463

Leading article

Sulphasalazine in ulcerative colitis: in memoriam?

While the aetiology of ulcerative colitis remains unknown, treatment is empirical. Sulphasalazine is effective in controlling moderately active disease[1] and in prolonging remission.[2] Speculation about the drug's mode of action has continued since its introduction in the 1940s for use in patients with rheumatoid arthritis. Received wisdom holds that in ulcerative colitis the reduction of the azo bond by colonic bacteria releases the active moiety of sulphasalazine, 5 aminosalicylic acid (5ASA) which acts topically, and sulphapyridine which is rapidly absorbed causing side effects. Various pharmacological means have been developed for delivering pure 5ASA to the colon since uncoated 5ASA is rapidly absorbed and is thus ineffective. Three formulations are currently licenced in the United Kingdom for use in ulcerative colitis, mesalazine (Asacol, a pH sensitive polyacrylic resin coating of 5ASA, and Pentasa, which contains ethylcellulose coated 1 mm granules of 5ASA) and olsalazine (Dipentum, two 5ASA molecules joined by an azo bond); mesalazine may have captured as much as 30% of the market from sulphasalazine.

Several assumptions underly these new agents. Firstly, that the side effects of sulphasalazine are due to the sulphapyridine molecule alone. Secondly, that unmetabolised sulphasalazine and sulphapyridine have no activity in ulcerative colitis. Thirdly, that sulphasalazine is simply a pro-drug, a means of delivering 5ASA which overcomes the rapid absorption of 5ASA from the small intestine. Fourthly, that where sulphasalazine is ineffective this is due to insufficient concentrations of 5ASA reaching the site of disease activity.

The side effects of sulphasalazine (incidence 15–30%) are dose dependent (dyspepsia, nausea and vomiting, headache, and reversible oligospermia) or idiosyncratic (fever and neutropenia, inflammatory reactions affecting lung, liver, myocardium, and pancreas).[3] Pure 5ASA preparations by eliminating sulphapyridine should prevent these unwanted effects. Adverse responses to sulphasalazine, however, have also been seen with 5ASA products, although at least 70% of sulphasalazine intolerant patients will find 5ASA products acceptable.[4]

Changing the delivery system from an azo bond to mechanical or pH dependent release has two important implications. Firstly, it reduces the effectiveness of colonic 5ASA delivery from 80–98% to 40–95% and, secondly, it alters 5ASA pharmacokinetics. The ethylcellulose coating of Pentasa granules dissolves gradually during passage through the small bowel[5] while the resin coating of Asacol may allow for rapid release of free 5ASA (at an appropriate pH). Free 5ASA is acetylated both in the small bowel[6] and colonic epithelium.[7] In the small bowel this process can be overloaded by rapid release of 5ASA. This allows appreciable amounts of non-acetylated 5ASA to be absorbed, which is clearly nephrotoxic in experimental animals, while acetylated 5ASA is not.[8] 4 Aminosalicylic acid (para aminosalicylic acid previously used in the treatment of tuberculosis) and phenacetin were important causes of crystalluria, haematuria, and nephritis; the structure and metabolism of these drugs are closely similar to non-acetylated 5ASA. Recent reports of interstitial nephritis,[9] including three biopsy proved cases (Committee on Safety of Medicines, R R Shah, personal communication), nephrotic syndrome,[10] pyuria,[11] and rises in urea and creatinine[12] after mesalazine treatment are therefore particularly worrying. A recent bulletin from the Committee on Safety of Medicines highlights nine reports of serious nephrotoxic reactions associated with the use of mesalazine[13] and concludes that the drug is best avoided in patients with established renal impairment. Greater recognition of these side effects (avoided with sulphasalazine or olsalazine because of the completeness of 5ASA acetylation in the colon) prompted one group to suggest monitoring renal function during mesalazine treatment.[12]

Early studies showed a dose-response relation between sulphasalazine and its efficacy in moderately active disease[14] and in maintaining remission[2] with daily doses of between 1 and 18 g.[17] Because of dose dependent side effects a compromise of giving 4 g daily for active disease and 2 g for maintenance treatment is common, providing 1600 mg and 800 mg 5ASA respectively. If sulphasalazine is merely delivering 5ASA to its site of action it should follow that the higher the local concentration of 5ASA the more effective the treatment. While, however, studies have shown 5ASA compounds to be as effective as therapeutic doses (3–4 g) of sulphasalazine none has been superior even with doses of 5ASA equivalent to 12 g sulphasalazine, suggesting there is more to the action of sulphasalazine than 5ASA.

In rheumatoid arthritis the sulphapyridine component of sulphasalazine has been shown to have disease modifying (immunomodulatory) activity,[15] requiring at least six weeks to take effect; nevertheless, it is precisely the systemic and delayed onset of action of sulphapyridine that has not been studied in patients with ulcerative colitis in contrast to its documented inefficacy when given topically in the short term.[16]

It is interesting to compare the actions in vitro of sulphasalazine and 5ASA on the inflammatory cascade. After tissue damage there is disruption of cell membranes with release of arachidonic acid, the fate of which is determined by the relative activity of cyclo- and lipoxygenase. The former generates prostaglandins, which may promote healing, the latter produces leucotrienes, which are potent neutrophil chemoattractants and vasoconstrictors and may cause further damage. There is appreciable overproduction of leucotrienes in active disease and some increase in concentrations of prostaglandins.[18] Work in vitro suggests that therapeutic concentrations of sulphasalazine inhibit lipoxygenase more potently than 5ASA.[19] In contrast, both agents block cyclooxygenase (a potentially serious effect seen in exacerbations of inflammatory bowel disease after ingestion of non-steroidal anti-inflammatory drugs).[20] Sulphasalazine mediated inhibition of prostaglandin degradation, however, causes a net increase in tissue prostaglandin level concentrations[21] and thus promotes healing.

Neutrophils are the chief effector cell in tissue destruction in ulcerative colitis, causing damage by lysosome release and the generation of damaging oxygen free radical species.[22] Sulphasalazine, 5ASA, and sulphapyridine are all effective free radical scavengers.[23] Sulphasalazine, however, alters neutrophil function in ways distinct from ASA and sulphapyridine.[24] Sulphasalazine, but neither of its metabolites, has appreciable inhibitory effects on B lymphocytes in vitro reducing immunoglobulin synthesis at pharmacological doses.[25] Again in contrast to 5ASA, sulphapyridine and

sulphasalazine inhibit natural killer cell activity,[26] while at high doses sulphasalazine has profound suppressive effects on T and B cell mitogen induced lymphocyte transformation of murine spleen cells.[27] Thus many observations show that sulphasalazine, sulphapyridine and 5ASA have different and potentially beneficial actions in ulcerative colitis in controlling inflammation.

The use of steroids delayed the widespread adoption of sulphasalazine in rheumatoid arthritis for over 30 years.[28] Before sulphasalazine is discarded as an outmoded treatment for ulcerative colitis in favour of more modern 5ASA compounds, a greater understanding is needed of the ways in which these drugs work, lest in throwing out the bathwater we lose rather more of the baby than expected.

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