LETTERS TO THE EDITOR

An alternative view of 5-ASA formulations

EDITOR,—While most of the leading article by Gunnar Järnerot is factual, the personal conclusions contain assumptions that are difficult to substantiate (*Gut* 1994 **35:** 1155–8).

All the formulations that deliver 5-aminosalicylic acid (5-ASA) to the colon are of clinical value as maintenance treatment and in disease of mild to moderate activity. Comparison of their relative merits is fraught with difficulty because none of the systems for colonic delivery is ideal – problems may occur in the presence of severe diarrhoea and after surgical resection because of inadequate release to produce a topical mucosal effect. The propensity of olsalazine (Dipentum) to provoke diarrhoea in about 20% of patients with up to 50% appearing intact in the stools of patients with diarrhoea, limits both patient acceptance and colonic availability.[1] The highest mucosal concentrations of 5-ASA have been with mesalazine (Asacol).[2]

Sulphasalazine should no longer be used as first choice. Even patients who appear to take it without problems often feel better when changed to mesalazine – we suspect they tolerate reduced 'well being' with sulphasalazine, which improves when the drug is discontinued.[3] Furthermore, increased doses of sulphasalazine with greater disease activity are associated with dose related side effects caused by the sulphonamide – undesirable in the face of current alternatives.

The controversy that surrounds renal problems with 5-ASA is whether they are 'idiosyncratic' or 'dose related'. Idiosyncratic lesions are uncommon, independent of dose, and occur with a frequency that reflects prescribing patterns for the different preparations. Dose related lesions may occur in those given high doses or formulations that produce high plasma concentrations. Patients have been reported with interstitial nephritis, glomerulonephritis, nephrotic syndrome, raised plasma creatinine, and renal failure. In general clinical practice a wide range of drugs is known to cause interstitial nephritis, resulting from a hypersensitivity rather than a dose related effect.[4] The formulations to deliver 5-ASA that have been associated with renal problems included Asacol, Dipentum, Pentasa, and Salofalk as well as sulphasalazine itself.

Adverse drug reactions reported in the UK for sulphasalazine include nephrotic syndrome (10 reactions), interstitial nephritis (2), glomerulonephritis (4), and renal impairment or failure (12) (Medicines Control Agency, personal communication); the renal safety of this drug is perhaps less than is implied in the article. Most cases reported in the UK, associated with new formulations of 5-ASA have been linked with Asacol, which holds about 90% of the market for these preparations. One case of interstitial nephritis associated with Dipentum has been identified in the UK with other renal cases in the USA and on the Continent. Absolute numbers reported with each formulation have little significance – but the occurrence of renal problems with each formulation identifies a general problem.

The clinical details of reported renal cases have varied, but concurrent use of other drugs with limited information about previous renal function have often made it difficult to draw firm conclusions. Groups of patients who have taken high doses of Asacol for prolonged periods are reported without renal lesions. Comparatively high plasma concentrations and high intestinal absorption have been noted with Salofalk[5] but renal problems have been few with this preparation. There is little to support the suggestion that renal lesions are dose related in patients treated for inflammatory bowel disease.

In conclusion, all the 'new alternatives' for administration of 5-ASA to patients with inflammatory bowel disease are preferable to sulphasalazine. but clinicians should be aware of the potential for renal problems with any formulation of 5-ASA.

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1 Rijk MCM, Van Schaik A, Van Tongeren JHM. Disposition of mesalazine from mesalazine-delivering drugs in patients with inflammatory bowel disease, and without diarrhoea. *Scand J Gastroenterol* 1992; **27:** 863–8.
2 De Vos M, Verdievel H, Schoonjans R, Praet M, Bogaert M, Barbier F. Concentrations of 5-ASA and Ac-5-ASA in human ileocolonic biopsy homogenates after oral 5-ASA preparations. *Gut* 1992; **33:** 1338–42.
3 Riley SA, Mani V, Goodman MJ, Herd ME, Dutt S, Turnberg LA. Comparison of delayed-release 5-aminosalicylic acid (mesalazine) and sulfasalazine as maintenance treatment for patients with ulcerative colitis. *Gastroenterology* 1988; **94:** 1383–9.
4 Schrier RW, Gottschalk MD. In: *Disease of the Kidney.* Boston: Little, Brown 1988: 1861.
5 Laursen Staerk L, Stokholm M, Bukhave K, Rask-Madsen J, Lauritsen K. Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations in patients with ulcerative colitis: comparison of intraluminal colonic concentrations, serum values, and urinary excretion. *Gut* 1990; **31:** 1271–6.

Reply

EDITOR,—The title of my leading article was *New salicylates as maintenance treatment in ulcerative colitis*. The paper by Rijk *et al*[1] was a study of 20 patients with inflammatory bowel disease. Fifteen of these patients had Crohn's disease. One of the five patients with ulcerative colitis had moderately severe disease. My leading article does not discuss Crohn's disease or the role of 5-ASA in active ulcerative colitis. The method used by Rijk *et al*, however, does not permit distinction between 5-ASA in the faeces, which has been released from the various mesalazine formulations from that which still remains in the tablets. Therefore, the results are difficult to interpret but it is obvious from his work that the faecal excretion of 5-ASA is increased during a diarrhoeal state and also with the various mesalazine formulations. It seems reasonable to conclude that during diarrhoea the dose of both azo-based and pure 5-ASA must be increased.

The study by De Vos *et al*[2] on mucosal concentrations of 5-ASA and Ac-5-ASA is also difficult or even impossible to evaluate. Certainly they found higher mucosal 5-ASA concentrations after the Asacol than other preparations. The patients were given sodium-picosulfate, however, during day 5–8 of the eight days they were receiving treatment. Furthermore, before colonoscopy and biopsy they were prepared with colonic lavage with Endopeg solution. As the authors point out in their paper 'this washout interferes with the pharmacokinetic profiles of the preparations'. They also remark that 'the acceleration of transit shortens the time available for bacteria to split the azo-bond. The sterilisation of the gut by the washout can even prevent the cleavage'. Finally, they say 'because of the proved clinical efficacy of Salazopyrin, despite very low mucosal concentrations, studies to correlate these concentrations with clinical benefit are necessary'.

The question regarding the possible renal toxicity induced by various 5-ASA based drugs is more problematic. At present we know very little about how often renal manifestations can be one of many extraintestinal manifestations of ulcerative colitis. The results by Sninsky *et al*[3] show that minimal change renal disease can also be a common manifestation in untreated ulcerative colitis. If so, it seems to be of no important clinical significance. If the interstitial nephritis was caused by idiosyncracy it would be reasonable to assume that during more than 50 years sulphasalazine use it should have been reported more frequently. What is puzzling is that this side effect has been more frequently seen after introduction of mesalazine formulations. Therefore it seems reasonable to speculate on the importance of the formulation. The release of 5-ASA dependent drugs depends on intestinal pH and gastric emptying. In my leader I put forward a hypothesis that dose related interstitial nephritis can occur in patients taking snacks between meals postponing the gastric emptying of the total daily dose until night, provided the subject had an unfortunately high small intestinal pH. In such a case serum peaks can be achieved, which at least in animals are nephrotoxic.[4] A similar event might occur in patients taking sulphasalazine or olsalazine if they have a pathological small bowel flora reducing the azo-bond already in the small gut so that 5-ASA is released above the colon. If this hypothesis is correct, study of groups of patients is of little value as only subjects with special dietary habits in combination with an abnormal small intestinal pH will develop side effects.

During 1984–1994, 35 renal side effects of sulphasalazine have been reported world wide to Pharmacia AB, Sweden. One case of interstitial nephritis and eight cases of nephrotic syndromes. Since mesalazine was released in the UK 72 cases are said to have been reported to the Committee on Safety of Medicines. One case has been on olsalazine. That patient had been treated with Asacol for about two years before being switched to olsalazine. After two to three months receiving olsalazine the interstitial nephritis was diagnosed. No laboratory data are available, however, from the time of change of treatment (Pharmacia, personal communication).

As I only have data obtained by personal communication with Pharmacia it seems important to get an objective report from the Committee on Safety of Medicines where the frequency of renal side effects with the various 5-ASA based formulations are described in relation to the number of prescribed daily doses.

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1 Rijk MCM, van Schaik A, van Tongeren JHM. Deposition of mesalazine from mesalazine-delivering drugs in patients with inflammatory bowel disease, with and without diarrhoea. *Scand J Gastroenterol* 1992; **27:** 863–8.
2 De Vos M, Verdievel H, Schroonjans R, Praet M, Bozeart M, Barbier F. Concentrations of 5-ASA and Ac-5-ASA in human ileocolonic biopsy homogenates after oral 5-ASA preparations. *Gut* 1992; **33:** 1338–42.
3 Sninsky C, Hanauer S, Powers B, *et al.* Sensitive markers of renal dysfunction are elevated in chronic ulcerative colitis. 10th World Congress of Gastroenterology 1994; Los Angeles, CA: 1778.
4 Calder JC, Funder CC, Green CR, Ham KN, Tange JD. Nephrotoxic lesions from 5-aminosalicylic acid. *BMJ* 1972; **1:** 152–4.

New salicylates as maintenance treatment in ulcerative colitis

EDITOR,—I read with interest the paper by Järnerot (*Gut* 1994; **35:** 1155–8) in which he reviewed the oral use of the new aminosalicylates in the maintenance treatment of ulcerative colitis. Firstly, I disagree with the author's suggestion that 5-ASA containing compounds should be relegated to solely maintenance treatment. We, and others, have clearly shown efficacy of 5-ASA preparations in mildly to moderately active ulcerative colitis.[1 2] However, we agree it should not be used as sole treatment for severe disease activity. Secondly, the article attempts to provide a synopsis of available sulpha-free aminosalicylic acid preparations with a guideline for the preferred use of specific 5-ASA preparations. I question the author's statements regarding the comparison of Asacol *v* olsalazine and his conclusions on the risk of renal lesions associated with the use of pH dependent formulations of 5-ASA.

In his review, Järnerot presents the results from a study by Courtney *et al*,[3] which compared the efficacy and tolerability of olsalazine and mesalazine in maintenance treatment of ulcerative colitis. Two separate letters to the editor of *Lancet* have criticised this study and suggested that 'there is good reason to suspect the difference found may be due to chance or some methodologic flaw'.[4–5] Hopefully, well controlled studies in the future will directly tackle this issue.

With respect to renal safety, Järnerot's statements about potential risks of nephrotoxicity associated mainly with pH dependent 5-ASA preparations are at best speculative. The mechanism by which 5-ASA causes nephrotoxicity is still undefined and the mechanism, be it hypersensitivity or dose related toxicity, continues to be investigated. Consequently, the potential of 5-ASA to cause nephrotoxicity should be considered a class effect common to all formulations that release 5-ASA or are converted to 5-ASA, as is the case with olsalazine. This position is reflected in the labelling for all 'new aminosalicylates' available in the US, including Asacol, Dipentum, Pentasa, and Rowasa. In a poster presentation at the 10th Congress of Gastroenterology,[6] we showed that sensitive markers of renal function (alanine aminopeptidase and *N*-acetyl-β-D-glucosaminidase) are increased in the absence of clinically significant renal dysfunction in a substantial subgroup of patients maintained with mesalamine containing formulations (including sulphasalazine) and patients receiving placebo for six months. Further research should clarify whether these changes are: (a) drug effects of mesalamine, (b) clinically relevant, or (c) result from intrinsic renal processes in patients with ulcerative colitis. At present, published works support our recommendation that 5-ASA preparations be used for mildly to moderately active ulcerative colitis and for maintenance of remission. Furthermore, the 5-ASA preparation of choice should be the least expensive, best tolerated preparation with a reported safety profile. We suggest avoiding speculation of toxicity until claims can be substantiated with scientific evidence.

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1 Sninsky CA, Cort DH, Shannahan F, Powers FJ, Sessions JT, Pruitt RE, *et al.* Oral mesalamine (Asacol) for mildly to moderately active ulcerative colitis. *Ann Intern Med* 1991; **115:** 350–5.
2 Sutherland LR, May GR, Shaffer EA. Sulfasalazine revisited: a meta-analysis of 5-aminosalicylic acid in the treatment of ulcerative colitis. *Ann Intern Med* 1993; **118:** 540–9.
3 Courtney MG, Nunes DP, Bergin CF, O'Driscoll M, Trimble V, Keeling PWN, *et al.* Randomized comparison of olsalazine and mesalazine in prevention of relapses in ulcerative colitis. *Lancet* 1992; **339:** 1279–81.
4 Gait JE, Simerl NA. Comparison of olsalazine and mesalazine in prevention of relapses in ulcerative colitis. *Lancet* 1992; **340:** 486–7.
5 Record CO, MaCrae K. Mesalazine versus olsalazine for prophylaxis of ulcerative colitis. *Lancet* 1992; **340:** 1468.
6 Sninsky C, Hanauer S, Powers B, Robinson M, Mayle J, Elson C, *et al.* Sensitive markers of renal dysfunction are elevated in chronic ulcerative colitis. *10th Congress of Gastroenterology*, October 2–7, 1994. Los Angeles, CA: 1778.

Reply

EDITOR,—My leading article was on new salicylates as maintenance treatment in ulcerative colitis and thus I did not discuss the treatment of mildly to moderately active ulcerative colitis with 5-ASA based formulations. I am aware of the fact that they can be used for that condition. What I pointed out was that they are not as effective as corticosteroids. In my opinion it is important to treat active ulcerative colitis aggressively to reduce the risk of developing a state of chronic continuous or refractory disease.

With regard to the study by Courtney *et al*[1] comparing olsalazine and Asacol, I also remarked that this study was only observer blind. Future studies are needed to discover if the results were caused by chance.

I refer to my reply to Drs Rhodes and Coles with regard to the question of nephrotoxicity.

GUNNAR JÄRNEROT

1 Courtney MG, Nunes DP, Bergin CF, O'Driscoll M, Trimble V, Keeling PWN, *et al.* Randomized comparison of olsalazine and mesalazine in prevention of relapses in ulcerative colitis. *Lancet* 1992; **332:** 1279–81.

NOTES

Coloproctology

The annual scientific meeting of the Association of Coloproctology of Great Britain and Ireland will take place at University College Cork on 2-4 July 1995. Enquiries to Professor W O Kirwan, Department of Surgery, Cork University Hospital, Cork, Ireland. Tel: 010 353 21546400 ext 2385.

Liver disease

The XXth International Update on Liver Disease will be held at the Royal Free Hospital School of Medicine, London on 6 to 8 July 1995. Further information from: Professor Neil McIntyre, University Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG. Tel: 0171 794 0500 ext 3969; fax: 0171 794 4688.

Liver studies

The 30th annual meeting of the European Association for the Study of the Liver will be held in Copenhagen, Denmark on 21–23 August 1995. Further information from: Local secretary, Helmer Ring-Larsen, Rigshospitalet, DK–2100 Copenhagen, Denmark. Tel: 45 3545 2451; fax: 45 3545 2913.

Digestive endoscopy

The European Postgraduate Gastro-Surgical School is organising a course on digestive endoscopy in Amsterdam, the Netherlands on 7/8 September 1995. Further information from: Helma Stockmann, Managing Director European Postgraduate Gastro-Surgical School, Room G4–109.3, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. Tel: 31 20 5663926; fax: 31 20 6914858.

Pancreatic Society Travelling Fellowship

The Pancreatic Society awards a fellowship annually to allow a young researcher to travel to obtain experience and visit centres of excellence abroad. The award is made on the basis of applicants' *curricula vitae* and proposed itinerary, and applications are requested in the autumn of each year. An award of £3000 will be made in November 1995, for travel during 1996. Potential applicants should contact the Secretary: Mr C D Johnson, University Surgical Unit, F Level, Centre Block, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD. Tel: 0703 706146; fax: 0703 794020.