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Leading article

New salicylates as maintenance treatment in ulcerative colitis

For decades sulphasalazine has been the only valuable non-corticosteroid drug in the treatment of ulcerative colitis. Then Truelove *et al* showed that the pharmacologically active moiety in sulphasalazine for the treatment of this disease was 5-aminosalicylic acid (5-ASA).[1] This resulted in new 5-ASA formulations for topical and oral use. 5-ASA enemas and suppositories seem to have the same efficacy as topical corticosteroids in active distal ulcerative colitis.[2 3]

Sulphasalazine is not as effective as corticosteroids for the treatment of widespread active disease, and there is no evidence that any of the newer salicylates is better in this respect.[4] Because extensive, active ulcerative colitis must be treated aggressively so that it does not become severe and require surgery, systemic corticosteroids are always the first alternative in these cases. Maintenance treatment is therefore the main indication for oral use of sulphasalazine and the new salicylates in ulcerative colitis. A meta-analysis was unable to show that any of the new salicylates was more efficient than sulphasalazine.[4] There are three factors to consider when choosing which drug to use: (1) effectiveness; (2) which formulation delivers 5-ASA to the colon with the fewest systemic effects; and (3) safety. The formulations and sites of 5-ASA release of various new 5-ASA based drugs are shown in the Table.

New salicylates *v* placebo

Two studies have compared one of the new salicylates with placebo.[5 6] One study showed that 1 g olsalazine (Dipentum) was better than placebo in the maintenance treatment of ulcerative colitis.[5] The other compared 2 g olsalazine with placebo over a 12 month period. Thirty nine per cent of 49 patients given olsalazine relapsed compared with 60% of the 52 patients given placebo. However, 16% of the olsalazine patients withdrew because of diarrhoea compared with only 2% of the placebo group. Thus, only 37% and 31% in the olsalazine and placebo groups respectively completed the trial in remission using an intention to treat analysis.[6]

New salicylates *v* sulphasalazine

There are several studies that compare new salicylates such as Asacol, Pentasa, Claversal, balsalazide (Colazide), and olsalazine (Dipentum) with sulphasalazine.

ASACOL

Asacol, given in doses more or less equivalent to the sulphasalazine doses used, had an effect similar to sulphasalazine.[7 8] A third study comparing Asacol (in a mean dose of 2·7 g/d) with sulphasalazine (in a mean dose of 2·3 g/d: equivalent to 0·9 g 5-ASA) gave no evidence that such an increase in the 5-ASA dose gave better effect.[9]

PENTASA

Pentasa, given as an oral dose of 1·5 g/d, maintained 41 patients in remission to the same extent as 34 patients treated with sulphasalazine 3 g/d.[10] Further studies exist as abstracts, but not as full reports.

Formulations and sites of aminosalicylic acid (5-ASA) release with various new 5-ASA based drugs

Generic name	*Trade name*	*Formulation*	*Thickness of coating*	*Solubility*	*Sites of release*
Mesalazine	Pentasa	Individually coated micro-granules compressed into tablets. Ethylcellulose coating	Probably not relevant	Little influenced by pH	Duodenum, jejunum, ileum, colon
Mesalazine	Claversal Mesasal Salofalk	Eudragit L 100 coated	?	pH≥6	Jejunum, ileum, colon
Mesalazine	Asacol	Eudragit S coating	80–130 μm	pH≥7	Terminal ileum, colon
Olsalazine	Dipentum	Gelatine capsules	Not relevant	Not influenced by pH	Colon
Balsalazine	Colazide	Tablets	Not relevant	Not influenced by pH	Colon

CLAVERSAL
A multinational study compared Claversal (0·75 g/d) with sulphasalazine (1·5–2 g/d) in 344 patients. Why only 273 patients could be evaluated for efficacy is not adequately described.[11] No differences were found between treatment groups but this study was unlike the others in that sigmoidoscopy was not required to confirm remission or recurrence and disease activity was based on a clinical activity index with a wide range which meant that patients with mild-moderately active disease might be classified as being in remission. In addition, a report from the Israeli subgroup of this study said that sulphasalazine was used in a dose of 2·0–3·0 g/d.[12] Hence, Claversal has not yet been shown convincingly to be of value as maintenance treatment for ulcerative colitis.

OLSALAZINE
Olsalazine (Dipentum) (1 g/d) was compared with sulphasalazine (2 g/d) in 164 patients,[13] and the same dosages were used in 227 patients in a Danish study.[14] The efficacy was the same for both drugs. A third study, comprising 329 patients reported in abstract form only, but showed the same result.

BALSALAZIDE
A study of balsalazide (Colazide) (2 g/d in 41 patients) and sulphasalazine (in 38 patients) showed remission rates after six months of 51% and 63% respectively,[15] which were not significantly different.

Olsalazine *v* Asacol
Only one study has compared two of the new salicylates with each other.[16] One hundred patients were randomised to receive either 1 g olsalazine or 1·2 g Asacol. Olsalazine was shown to be significantly better, particularly in patients with distal ulcerative colitis, but this study can be criticised for being observer-blind only.

Dose ranging studies
The first study of this kind compared 1, 2, and 4 g sulphasalazine, corresponding to 0·4, 0·8 and 1·6 g 5-ASA.[17] The 2, and 4 g doses were better than the 1 g dose, and there was a statistically non-significant trend in favour of the 4 g dose compared with the 2 g dose. The number of patients in the 4 g group who completed the trial was sharply reduced, however, because of an increased frequency of side effects with this dosage. These findings were the basis for the conclusion that 2 g sulphasalazine (0·8 g 5-ASA) was the optimal maintenance dose. As mentioned, 2·7 g Asacol was not better than 2·3 g sulphasalazine.[9]

A further study compared 0·5, 1·0, and 2·0 g olsalazine in 198 patients.[18] Remission rates after 12 months were 48%, 60%, and 60% and 60%, 70%, and 78% respectively in the intention to treat analysis and the per protocol analysis. The 2 g dose was more effective in patients with proctitis limited to 15 cm from the anal verge. For patients in remission for less than 12 months before the trial, the remission rates in the per protocol analysis were 21% (0·5 g), 73% (1 g), and 88% (2 g). Thus, with the exception of proctitis patients, a 2 g dose gave little more benefit than a 1 g dose. On the contrary, it increased the withdrawal rate from 9% to 19% because of diarrhoea.

Another dose ranging study that compared balsalazine 2 g (0·7 g 5-ASA) with 4 g (1·4 g 5-ASA)[19] found that the 4 g dose (68 patients) was significantly better than the 2 g dose (65 patients). The intention to treat analysis showed remission rates after 12 months of 45% (2 g dose) and 64% (4 g dose) respectively. Another comparison, of 54 patients who received 3 g/d balsalazide with 54 patients given 6 g/d, showed relapse rates of 18·5% and 27·8% respectively after 12 months.[20] The remission rate with 2 g/d balsalazide (0·7 g 5-ASA) was very similar to that with 0·5 g/d olsalazine (0·5 g 5-ASA). Similarly, the remission rate with 3 or 4 g balsalazide (1·4 g 5-ASA) is similar to that for 1 and 2 g olsalazine.

From the available data it seems probable that for maintenance of remission at least 0·8 g/d of 5-ASA must be delivered to the colon and that the optimal dose may be closer to 1–1·5 g/d. A higher dose may be worthwhile to prevent proctitis and in patients with a recent relapse, provided they can tolerate this.

Which oral doses are needed with various formulations to deliver >0·8 g 5-ASA to the colon?
In subjects with a permanent ileostomy, sulphasalazine and olsalazine pass through the small gut with negligible absorption,[21 22] and this also seems to be the case with balsalazide.[23] Provided that the azo-bonds in these compounds are efficiently split by colonic bacteria, 5-ASA will be delivered exclusively to the colon. In someone whose gut transit time is reduced, however, the azo-bond is less efficiently split, so that more of the parent molecule passes unchanged through the large bowel. This seems to be more evident with olsalazine than sulphasalazine,[24] as the azo-bond in olsalazine is reduced somewhat more slowly (Thomas Berglindh, personal communication). However, for maintenance treatment this is probably not of clinical importance. Asacol is a pH dependent tablet which releases 5-ASA at pH≥7. The faecal water 5-ASA concentration after 2 g Asacol was similar to that with 2 g olsalazine, but there was a wider intersubject variation.[25] The serum concentration was also higher during Asacol treatment than with olsalazine. This is probably because Asacol depends on the pH for the release of 5-ASA, and the considerable intersubject differences in pH in the small gut[26] may induce an earlier release of 5-ASA in the small intestine in some subjects and in others a fairly late release in the colon. The recommended dose for maintenance treatment is 800–1600 mg/d. A dose of 400 mg three times daily seems necessary to achieve colonic delivery of at least 800 mg/d of 5-ASA.

Claversal is also pH dependent, and is released at pH ≥6. In a dose of 2 g/d it gave a considerably lower faecal water concentration than 2 g olsalazine (mean (SEM) 15·0 (2·0) mmol/l and 23·7 (1·9) respectively.[25] The 5-ASA serum concentration was more than fivefold higher after Claversal than olsalazine, and twice as high as during Asacol administration. This indicates that approximately two thirds of the oral dose of Claversal reach the colon and consequently the dose for maintenance treatment should be 1·5–1·75 g/d, divided in three doses.

Pentasa consists of mesalazine in microcapsules mainly released time dependently at pH >6 but at a faster rate at ≥7·5. However, pH 7·5 rarely exists in the gut. About 65% of the oral dose reaches the colon.[27] A dose of 2 g of Pentasa gave a faecal water concentration of mean (SEM) 12·6 (2·2) mmol/l in comparison to 2 g olsalazine, 23·7 (1·9).[25] The 5-ASA serum concentration was similar to the one with olsalazine, however, which reflects the gradual release of 5-ASA from Pentasa with its rapid small gut absorption and urinary elimination. A suitable daily dose for maintenance treatment of ulcerative colitis seems to be 1·5–1·75 g/d in divided doses.

Effect of decreased intestinal transit time

It is well known that in diarrhoeal states azo-compounds are less completely split and that the dose should be increased. Rijk *et al*[24] analysed 5-ASA and acetylated 5-ASA in the faeces during administration of different 5-ASA based drugs in patients with decreased intestinal transit time. Their method, however, did not allow any distinction between released 5-ASA and 5-ASA still retained in the tablet. Furthermore, 5-ASA is already acetylated in the small bowel,[27] from where it is poorly absorbed. Only about 30–35% of an oral dose of acetylated 5-ASA is absorbed, while the remainder is excreted in the faeces.[28] Discussion of the various 5-ASA based formulations[24] is therefore very hypothetical. It seems reasonable, however, that in patients with short intestinal transit time the dosage of any 5-ASA based drug should be increased.

Tolerance and safety

Sulphasalazine often causes side effects. Most of these are unpleasant rather than serious, but they do affect the quality of life. Some of the adverse events, such as fever and rash are serious, however, and occasionally life threatening side effects can occur such as agranulocytosis. Fortunately this is rare.

The patients' tolerance of all the new salicylates is better than that of sulphasalazine, but there are very few direct comparisons of the tolerance of the various new salicylates. One showed that the withdrawal rates in clinical trials because of side effects were similar in olsalazine and Asacol studies.[19] One study compared olsalazine, balsalazide, and Asacol in sulphasalazine intolerant patients. Ninety one per cent of these patients tolerated at least one of the preparations, 42% all three, and 70% two of three.[30] The clinical tolerances for each individual drug were – Asacol 63%, olsalazine 70%, and balsalazide 70%. Nine per cent of the patients experienced an adverse reaction to all preparations indicating that 5-ASA and not the sulpha moiety in sulphasalazine was the cause of intolerance.

The main concern with the mesalazine preparations has been nephrotoxicity, which mainly becomes manifest as interstitial nephritis.[31] Animal studies have shown that 5-ASA is nephrotoxic.[32] This problem seems to be restricted to the formulations that depend on pH for release. Only two cases have been reported during the 50 years that sulphasalazine has been used.[33] I am not aware of any report with Pentasa, so far. It is assumed that this is an idiosyncratic reaction. If so, one would have expected that many more cases would be reported over the years that sulphasalazine has been in use. This also makes it unlikely that the nephritis is caused by a high renal load over the years. It therefore seems more plausible that the reaction is caused by high serum peaks of 5-ASA. Such peaks can only be reached with the pH dependent drugs provided that the patient has an unsuitable small gut pH environment that allows early release of the 5-ASA.

The risk is probably also increased if the patient takes snacks between meals. Snacks can prevent these gastric juice resistant tablets leaving the stomach until night time.[34] If this happens, and the total daily dose is emptied at night in a patient whose intestinal environment allows early release of the tablets, serum peaks that could be nephrotoxic may be reached. If this hypothesis is correct this side effect, although rare, is avoidable.

The diarrhoea which can occur during olsalazine treatment is definitely a concern. In the initial study, 12·5% of patients treated with 1 g/d olsalazine had to be withdrawn because of diarrhoea[5] and in the other placebo controlled study using 2 g/d olsalazine, 15·6% had to quit.[6] In neither study was olsalazine given directly after meals or introduced gradually, which seems to reduce the risk of diarrhoea. There also seems to be a dose related risk. In the dose ranging study, 9% of patients using 0·5 g or 1·0 g olsalazine withdrew because of diarrhoea compared with 19% of those taking the 2·0 g dose.[18] Furthermore, the risk might be greater in patients with extensive disease,[5 6] although this could not be confirmed in two other studies.[13 18] In practice, and considering all kinds of patients, the withdrawal rate because of diarrhoea was 6·3%.[29] This is definitely a clinical problem, but this side effect is easily recognised compared with the nephrotoxicity, which can develop more insidiously.

In conclusion

Maintenance treatment of ulcerative colitis is long lasting – often life long. A drug should be prescribed which most reliably delivers 5-ASA to the colon. It must be given in an optimal dose so that side effects can be avoided.

If a patient is being treated with sulphasalazine and suffers no adverse effects, there is no need to switch to another compound, except in cases of male infertility. In new cases, a sulpha free compound should be chosen to avoid the rare, but very serious, sulpha related side effects of agranulocytosis and sulphonamide induced hepatotoxicity. The pH release dependent formulations should not be used routinely in order to minimise the risk of renal lesions.

The most reliable deliverers of 5-ASA to the colon among the new drugs are olsalazine and balsalazide. Thus far, the clinical trials and experience are more extensive for olsalazine than balsalazide. To achieve optimal colonic delivery of 5-ASA, the maintenance dose for olsalazine seems to be 1 g/d and for balsalazide 2·5–3 g/d.

In a patient who does not tolerate either of these two compounds a mesalazine formulation can be tried. Of these, Pentasa seems the most appropriate as it does not cause high serum peak concentrations of 5-ASA. The optimal dose is probably 1·5–1·75 g/d.

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