Overview of 5-ASA in therapy of inflammatory bowel disease

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SULFASALAZINE (SAS) was developed in the early 1940s (1) as an anti-inflammatory, antibiotic for use in rheumatoid arthritis, then thought to have an infectious etiology. 5-aminosalicylic acid (5-ASA) is the active principal of SAS. 5-ASA is available in carrier-mediated form. Here, the pro-drug is delivered to the large intestine, where bacterial action breaks an azo bond (2) and releases the active principal. For SAS, the release is of the active principal, 5-ASA, and inactive sulfapyridine (3,4). For olsalazine (Dipentum; Pharmacia), splitting the azo bond releases two molecules of 5-ASA. Other pro-drugs, balsalazine and 5-ASA, are not available in Canada (5). Enteric-coated, slow-release, pH-dependent forms of 5-ASA are available in North America: Asacol (Procter and Gamble), Salofalk (Axcan), Rowasa (Solvay Pharmaceuticals; Georgia) (Table 1). These preparations avoid excessive upper intestinal absorption and theoretical renal damage (6). Salofalk and Rowasa are released in the distal ileum, Asacol in the right colon (7). Another preparation, Pentasa (Nordic), is a formulation of 5-ASA granules covered with ethyl cellulose. This allows slow release starting in the proximal small bowel (8).

While SAS inhibits both the lipoygenase and cyclooxygenase arachidonic acid pathways, 5-ASA inhibits leukotriene production by inhibiting 5-lipoxygenase in the cyclooxygenase pathway (9). 5-ASA acts on soluble mediator production. It modulates leukocyte function. It is an inhibitor of prostaglandins, thromboxanes, platelet-activating factor, tumour necrosis
factor, interleukin-1, intestinal mast cell and basophil-stimulated histamine release. It is an effective scavenger of free oxygen radicals (10). The relative importance of these actions is not known.

5-ASA is metabolized to one end product only in humans, N-acetyl-5-ASA (11), and is independent of acetylation phenotype (12). This probably occurs by bacterial action in the colonic lumen as well as in the mucosal cell (13) and the hepatocyte (14). N-acetyl-5-ASA is believed to have no biological action (15) and is excreted by the kidney. Factors affecting oral 5-ASA disposition include food intake, omeprazole, free oxygen radicals (10). The relative action (15) and is excreted by the kidney. The luminal pH, intestinal transit time, coexistent towards normal after effective treatment (16). There are few available studies of intestinal pH in patients with inflammatory bowel disease (IBD). However, using serum, urine and stool measurements, increasing proportions of nonmetabolized 5-ASA reach the colon from the slow release (Pentasa) through the enterico-coated (Salofalk, Asacol) to the pro-drugs (olsalazine, SAS). Topical formulations of 5-ASA are available as enemas, suppositories and foams.

The pro-drug SAS is associated with an approximate 30% incidence of side effects, predominantly related to the salicylic acid component (17). Desensitization is helpful for some, but not for hypersensitivity reactions such as agranulocytosis, hemolysis or aplastic anemia. Other rare side effects include male infertility and folate deficiency. Side effects associated with 5-ASA tend to be dose-related and infrequent in number; headache, nausea, epigastric distress and diarrhea are common (18). Rare complications of 5-ASA include acute pancreatitis (19), pericarditis (20), myocarditis (21), thrombocytopenia (22) and renal tubular damage (23). Rarely, both drugs may exacerbate the IBD (24,25).

5-ASA is recommended for the treatment of patients with mild to moderate IBD. The type of 5-ASA used depends on the type of disease (Crohn's disease or ulcerative colitis), and the site and extent of disease. Oral 5-ASA drugs, including the pro-drugs, are probably equally effective when universal ulcerative colitis is present. Suppositories are the treatment of choice for distal disease of 20 cm or less; enemas are used when there is 20 to 40 cm of disease. Enemas are particularly effective in universal colitis, together with an oral 5-ASA, when rectal symptoms predominate. 5-ASA is particularly useful in Crohn's disease with colonic involvement with or without limited ileal disease. Pentasa is probably the theoretical drug of choice in more proximal small bowel disease because of its mechanism, but this remains to be shown by clinical trial. 5-ASA appears to induce remission more slowly than corticosteroids and is more expensive. However, patient tolerability, especially for the topical formulations, is high and there is less toxicity.

5-ASA is effective in treating IBD (26). Its exact efficacy is difficult to ascertain from careful literature review due to: lack of accurate definitions of remission versus improvement; failure to define the exact type or extent of IBD; whether placebo or active drugs are used for controls; different end-points—

### TABLE 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Coating</th>
<th>Delivery mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salofalk 250, 500, 750 mg</td>
<td>Axcan</td>
<td>Eudragit L</td>
<td>pH &gt;6.0</td>
</tr>
<tr>
<td>Messeal 250, 500 mg</td>
<td>SmithKline Beecham</td>
<td>Eudragit L</td>
<td>pH &gt;6.0</td>
</tr>
<tr>
<td>Asacol 400 mg</td>
<td>Procter &amp; Gamble</td>
<td>Eudragit S</td>
<td>pH &gt;7.0</td>
</tr>
<tr>
<td>Rowasa* 250, 500 mg</td>
<td>Solvay Pharmaceuticals</td>
<td>Eudragit LH</td>
<td>pH &gt;6.0</td>
</tr>
<tr>
<td>Pentasa 250 mg</td>
<td>Nordic</td>
<td>Ethyl cellulose</td>
<td>Slow release</td>
</tr>
<tr>
<td>Dipentum (olsalazine) 250 mg capsule, 500 mg tablet</td>
<td>Pharmacia</td>
<td>Gelatin capsule, Ec tablet</td>
<td>Bacterial cleavage</td>
</tr>
<tr>
<td>Salazopyrin (sulfasalazine) 500 mg</td>
<td>Pharmacia</td>
<td>Regular and Ec tablet</td>
<td>Bacterial cleavage</td>
</tr>
</tbody>
</table>

*Not available in Canada
clinical, endoscopic or histological; use of different scoring systems; varying acute ulcerative colitis range from 5 to 12-month period reveals a therapeutic gain of 43 to 50% (32,33), with a therapeutic gain of 24% using increasing doses of SAS (34). There are many studies showing equal efficacy in maintaining remission between SAS and another pro-drug, Dipentum (35), as well as between SAS and enterico-coated 5-ASA (36). Meta-analyses have shown that 5-ASA is equivalent to SAS in mild to moderate acute ulcerative colitis and in maintenance therapy (37,38). Similarly, the use of topical 5-ASA in ulcerative colitis is very effective for enemas: 85 to 90% using 4 g at nighttime for four to 12 weeks (39,40); for suppositories, similar efficacy was noted using either 500 mg twice or three times a day for six weeks (41,42). For maintenance therapy, a 1 g at nighttime for enemas, and 0.5 g every second night for suppositories are effective treatments. Recent meta-analysis of topical 5-ASA in ulcerative colitis confirms significant benefits over placebo for both active disease and maintenance therapy (43).

5-ASA is effective in active Crohn's disease. There is a 32% therapeutic gain when SAS, 3 g/day, is compared with placebo over a four-month period (44). This was later confirmed in the National Cooperative Crohn's Disease Study where a subgroup with colitis responded better (45). In a recent study, a 25% therapeutic gain with Pentasa versus placebo was seen in 310 patients randomized to various doses over a 16-week period (46). There was no difference between placebo, 1 g or 2 g recipients in this study. In maintenance therapy, Pentasa is beneficial, compared with placebo in a subgroup of patients who had relapsed within three months prior to enrolment (47). Other studies have shown no effect when either Pentasa (48) or SAS (49) was compared with placebo. However, in a large group of patients treated with SAS followed for up to two years, there was a therapeutic gain of 25% (50), and in another study of 12 months' duration, patients randomized to Claversal (SmithKline Beecham) experienced a 24% therapeutic gain over those randomized to placebo (51). Patients with Crohn's disease had remission rates on placebo varying from 35 to 54%, compared with 60% on SAS and 78% on Claversal over 12 months. These findings were confirmed in a recent meta-analysis which found that maintenance therapy with 5-ASA or SAS reduces the likelihood of clinical relapse at one year (52).

5-ASA is a well tolerated medication with few side effects, allowing increase in effective dosage. It is recommended that 4 g 5-ASA be given orally for active IBD, with increases as necessary. It is uncertain whether continuous active treatment should be advised for maintenance therapy, ie, 4 g/day or the standard 2 g/day. Different preparations can be used to target the site of disease, and when given orally, appear to be equally as effective in maintaining remission as SAS. However SAS is much cheaper, and when tolerated, is effective therapy. 5-ASA given to SAS-intolerant patients is of therapeutic benefit in most with the caveat of occasional allergic reaction to 5-ASA.

REFERENCES

volunteers when given intravenously or released for absorption at different sites in the gastrointestinal tract. Gut 1987;28:196-200.


