Therapy of inflammatory bowel disease using 5-aminosalicylic acid, 4-aminosalicylic acid and olsalazine retention enemas: Review of clinical trials

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ABSTRACT: The knowledge that 5-aminosalicylic acid (5-ASA) is the active compound of sulphasalazine and that it acts topically has stimulated the use of 5-ASA containing enemas and other similar compounds such as olsalazine and 4-aminosalicylic acid (4-ASA). 5-ASA enemas have been shown to be effective in controlling active disease in clinical trials and have also been shown to be of benefit in prevention of relapses. Olsalazine enemas have not demonstrated significantly better results than placebo. 4-ASA enemas are effective but the results obtained have differed as to effective dose. *Can J Gastroenterol* 1989;3(2):85-87

Key Words: 4-ASA, 5-ASA, Enemas, Olsalazine

Les thérapies utilisant l'acide 5-ASA, 4-ASA et les lavements de rétention à l'olsalazine: Aperçu des études cliniques

RESUME: Le fait que l'acide amino-5 salicylique (5-ASA) soit le composé actif de la sulphasalazine et qu'il agisse localement encourage l'usage de lavement contenant du 5-ASA et des substances similaires telles l'olsalazine et l'acide amino-4 salicylique (4-ASA). Les lavements de 5-ASA se sont avérés efficaces dans le traitement de la maladie en évolution et se sont également montrés bénéfiques dans la prévention des rechutes. Les lavements l'olsalazine n'ont pas donné une amélioration significative des résultats obtenus avec un placebo. Les lavements de 4-ASA sont efficaces mais les résultats varient quant au dosage.

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IN ADDITION TO THE USUAL ROUTE of administering drugs to patients with ulcerative colitis, (oral or parenteral for corticosteroids, oral for sulphasalazine), topical administration of corticosteroids as rectal enemas have been suggested for years (1). This approach appeared to favour a therapeutic response in the inflamed rectal area while minimizing the risk of systemic side effects.

Interest in the use of topical treatment has increased enormously in recent years due mainly to a more detailed knowledge of sulphasalazine metabolism. It is given orally but acts mainly topically; in fact, when the drug is ingested it reaches the colon almost intact to be split into its two components, 5-aminosalicylic acid (5-ASA) and sulphapyridine. The latter is absorbed and does not play any major therapeutic role, being mainly a carrier. 5-ASA, to the contrary, is poorly absorbed, acts topically and is the active moiety (2,3). Since 5-ASA is effective in the colon it seemed reasonable to employ this active metabolite directly using the rectal route.

RECTAL 5-ASA ENEMAS

5-ASA was first used as a rectal enema in Oxford as part of an experiment to establish the active therapeutic moiety of sulphasalazine. Enemas containing 700 mg of 5-ASA were compared with 2 g of sulphasalazine and 1.3 g of sulphapyridine. Favourable results were achieved after two weeks of treatment in 73% (clinical), 71% (sigmoidoscopic) of the patients treated with 5-ASA; in 75% (clinical), 64% (sigmoidoscopic) of those treated with sulphasalazine; and only in 38% (clinical) and 37% (sigmoidoscopic) of patients treated with sulphapyridine. The same difference was observed histologically (2).

Because both efficacy (4) and side effects (5) of sulphasalazine can be dose dependent, it was important to know whether administration of enemas containing a high concentration of 5-ASA could provide positive results without producing the side effects expected by the same dose of 5-ASA as sulphasalazine. A two week trial compared 4 g in 100 mL 5-ASA enemas with 100 mg hydrocortisone enemas in 86 patients. Of patients receiving 5-ASA enemas, 93% improved, compared with 57% in the hydrocortisone group. In addition to clinical efficacy, no appreciable side effects were noted in the 5-ASA treated group, suggesting an important therapeutic role for 5-ASA enemas (6).

Recently, using the same dose, a multicentre trial was carried out in Canada and the United States to compare 5-ASA enemas with placebo. Seventy-six patients received the active preparation while 77 received placebo. After six weeks of treatment 48 out of 76 (63%) of 5-ASA treated patients were considered to be much improved compared to 22 out of 77 (29%) in the placebo group. Disease activity declined 55% in the 5-ASA treated group compared to 24% in the placebo group ($P < 0.001$). Efficacy was almost immediate, with reduction of bleeding observed within three days of treatment, confirming the value of 5-ASA rectal enemas (7).

In addition to studies in which 5-ASA was used in high doses, other trials have been carried out using lower doses of 5-ASA. In a British-Italian study, 1 g of 5-ASA administered for two weeks was

compared with a placebo. The 5-ASA treated group had significant improvement compared to the placebo group (8). Other investigators compared 2 g and 1 g 5-ASA enemas given for a four week period. No substantial difference was detected using these two regimens. The authors suggested using the lowest dose with the maximum of efficacy, ie, 1 g (9).

A large multicentre study has been carried out in Denmark comparing 1 g 5-ASA enemas with 25 mg of prednisolone. Fifty-three patients completed the study taking 5-ASA enemas and 61 patients received prednisolone enemas. After one month of treatment, improvement or remission was documented in 77% of the 5-ASA group and 72% of the prednisolone group. The 1 g 5-ASA enemas appear to be at least as effective as corticosteroids in acute disease (10).

Another indication for 5-ASA enemas suggested by various American investigators is management of patients refractory to other treatments. Barber and colleagues (11) reported six patients refractory to sulphasalazine, steroid enemas and oral prednisolone who improved after using 5-ASA enemas. After this report a formal trial of 4 g 5-ASA enemas was carried out by Friedman and colleagues (12) in 18 patients with persistent active ulcerative colitis in spite of hydrocortisone enemas. At the end of the study seven of the eight patients who completed the 5-ASA trial improved

clinically while only two who continued in the hydrocortisone group improved. Both studies confirmed the efficacy of 5-ASA and its value in patients who did not respond to standard medical therapy.

The present authors, between 1981 and 1985, treated 183 patients with 420 cycles of 5-ASA, ranging from 2 to 4 g enemas daily for a period of 15, 30 and 45 days. The overall success rate was 84% for clinical evaluation and 80% in sigmoidoscopy assessment. Significant side effects were documented in only six of the 58 patients previously unable to take sulphasalazine (13). The authors have also shown that 5-ASA enemas are poorly absorbed (14) and have sufficient retrograde spread to reach the splenic flexure and a more extensive area in patients with more extensive colitis (15).

Another possible indication for 5-ASA enemas lies in their use in maintenance therapy. A Canadian study carried out over six months compared 2 g (15 patients) and 4 g (14 patients) 5-ASA nightly retention enemas. The relapse rate was 15% after three months and 22% after six months, a rate very similar to sulphasalazine, suggesting the possibility of long term maintenance treatment by rectal route (16).

As summarized in Tables 1 and 2, 5-ASA enemas are effective in controlling active and refractory disease. Further work is necessary to establish the optimum therapeutic dose.

TABLE 1
Clinical trials with 5-ASA enemas

Reference	Number of patients	Dose (g)	Duration (weeks)	Improvement (%)		
				C	S	H
Azad Khan <i>et al</i> (1977)	21	0.7	2	73	71	29
Campieri <i>et al</i> (1981)	44	4	2	93	93	77
Willoughby <i>et al</i> (1986)	19	1	2	61	61	56
Powell-Tuck <i>et al</i> (1986)	25	1-2	4	62	—	—
Danish group (1987)	61	1	2-4	79	72	—
Sutherland <i>et al</i> (1987)	77	4	6	63	—	—

C Clinical; S Sigmoidoscopic; H Histological

TABLE 2
Response to treatment with 5-ASA enemas in patients refractory to other treatment

Reference	Number of patients	Dose (g)	Duration	Improvement (%)		
				C	S	H
Barber <i>et al</i> (1985)	6	3	1 month	100	83	—
Friedman <i>et al</i> (1986)	9	4	3 weeks	78	78	78
Guarino <i>et al</i> (1987)	20	4	3 weeks	80	70	—

C Clinical; S Sigmoidoscopic; H Histological

OLSALAZINE ENEMAS

Olsalazine is a compound created by linking two molecules of 5-ASA together. From a pharmacokinetic point of view it closely resembles sulphasalazine. The drug was originally designed as an oral substitute for sulphasalazine for maintenance treatment. Olsalazine enemas were assessed in a double-blind study at Oxford, comparing 1 g enemas to placebo over two weeks of therapy. Twenty-nine patients received olsalazine while 28 received a placebo. At the end of the study, no significant differences could be detected between the two groups. It seems there will not be a major role for olsalazine enemas in active colitis (17).

4-AMINOSALICYLIC ACID (4-ASA) ENEMAS

4-ASA is a compound similar to 5-ASA differing only in the position of the nitryl group which is in the meta and para position, respectively. After two weeks of treatment significant clinical and sigmoidoscopic improvement was noted in patients receiving 1 g or 4 g 4-ASA enemas compared to placebo

TABLE 3

Clinical trials with 4-ASA enemas

Reference	Number of patients	Dose (g)	Duration (weeks)	Improvement (%)		
				C	S	H
Selby et al (1984)	25	1/2	2	80	72	—
Campieri et al (1984)	31	2	2	77	77	41
Gandolfo et al (1987)	30	2/4	2	77	—	—
Ginsberg et al (1987)	12	2	8	83	83	83

C Clinical; S Sigmoidoscopic; H Histological

(18). The present authors compared the efficacy of 2 g 4-ASA and 2 g 5-ASA enemas. After two weeks' treatment, similar (clinical, sigmoidoscopic and histologic) results were obtained in both treatment groups (19).

Another trial which compared three treatment regimens (4-ASA, either 1 g or 2 g twice a day and placebo, for two weeks) showed some unusual findings. At the end of the study symptomatic improvement (less blood and mucus in stools, less tenesmus and abdominal pain) was demonstrated in the 1 g group but not in the 2 g group compared to the placebo group. Neither dose of 4-ASA enema was better than placebo in improving the sigmoidoscopic appear-

ance at the end of the trial (20). The authors speculated that the 2 g 4-ASA enemas might have been irritating to the rectal mucosa.

A recent trial assessing three weeks of therapy compared 2 g 4-ASA enemas and placebo. By the end of the study 10 out of 12 patients improved in the 4-ASA group compared to two out of 13 in the placebo group suggesting, therefore, a therapeutic role for 4-ASA enemas (21). These studies (Table 3) seem to confirm the value of 4-ASA enemas in active colitis. Since not all the studies provided the same positive results in terms of objective assessment criteria it is necessary to obtain more information with further controlled trials.

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