Topical treatment of ulcerative colitis using enemas containing 5-aminosalicylic acid and beclomethasone dipropionate

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ABSTRACT: 5-Aminosalicylic acid (5-ASA) enemas constitute a first-line therapy for patients with mild to moderate attacks of ulcerative colitis. To date, based on the results of different studies, 5-ASA enemas appear to be satisfactory in at least two-thirds of patients treated. Beclomethasone is one of the new corticosteroids which appear to have minimal systemic effects. The authors have assessed the efficacy of a four week course of 3 mg beclomethasone enemas compared to 2 g 5-ASA enemas in patients with ulcerative colitis. Preliminary analysis would suggest that both therapies are effective in more than 50% of cases.

Key Words: Beclomethasone, Clinical trial, Enemas, Topical therapy, Ulcerative colitis

Toipical treatment using rectal enemas was proposed almost 40 years ago as a useful approach for patients suffering from mild to moderate attacks of ulcerative colitis. The first attempt in this therapeutic approach was carried out by Truelove (1) who treated patients using enemas containing hydrocortisone (100 mg/day) and obtained very satisfactory results in 80% of treated patients. These enemas had good retrograde spread up to the splenic flexure and apparently no adrenal axis suppression was observed. Patient compliance was good.

In the following years other corticosteroid-containing enemas have been successfully used, such as those prepared with prednisolone 21-phosphate and betamethasone (2-4). These preparations have also been shown to be effective in the majority of patients, but adrenal axis suppression was observed in some instances.

In the same period other clinical trials with more acceptable corticosteroid...
preparations such as disposable enemas and later, foams have been carried out. Generally these studies have confirmed the value of topical corticosteroids administered by the rectal route (5-6).

**TOPICAL 5-ASA**

An important advance in the topical treatment of ulcerative colitis developed by the end of the 1970s through a better knowledge of the metabolism of sulphasalazine (7). Sulphasalazine had been used as an oral drug for many years for maintaining ulcerative colitis patients in remission, with almost no knowledge of its metabolism or which of its two components – sulfapyridine or 5-aminosalicylic acid (5-ASA) – was responsible for its therapeutic efficacy. Several studies have shown that sulphasalazine by mouth reaches the colon intact and only there is divided by bacteria into two components, of which 5-ASA is the active compound, acting topically (8-10).

The demonstration that 5-ASA is the active ingredient of sulphasalazine and that it works mainly locally in the colon stimulated many clinical investigators to carry out clinical studies employing this metabolite directly by the rectal route. Clinical trials have therefore been performed using enemas at different concentrations ranging from 1 to 4 g/day with successful results in 66 to 90% of treated patients (11-15). Side effects were noted in only a small number of patients. Major side effects appeared mainly as allergic reactions such as fever, cutaneous rashes and diarrhea, which seemed to develop in patients with a previous history of severe allergic reactions (16). Together with studies on the clinical efficacy of 5-ASA enemas, it has been also shown that absorption of 5-ASA through the colon seems to be rather limited, and enemas routinely reach the splenic flexure (17-18).

All of these data have given more complete information on the role, efficacy, safety and pharmacokinetics of 5-ASA rectal enemas and have confirmed its important therapeutic role for patients with left-sided colitis. More recently, topical treatment with 5-ASA has been advanced with the introduction of suppositories, mainly for patients with limited inflammation. Suppositories have been shown to be practical and well tolerated, with negligible systemic absorption. Clinical trials have also provided extremely satisfactory results (19-22).

**TOPICAL CORTICOSTEROIDS AND BECLOMETHASONE DIPROPIONATE ENEMAS**

Together with the great interest in topical treatment with 5-ASA, some interest has been focused on the new poorly absorbed corticosteroids. It is well known that one of the major relevant side effects related to oral or parenteral corticosteroids is adrenal axis suppression. Since rectal absorption of corticosteroids is only one-third of the same oral dosage, adrenal axis suppression has been observed only in certain patients with prednisolone 21-phosphate but seems more frequent with betamethasone or hydrocortisone (23-24).

Trials have assessed the new poorly absorbable corticosteroids in the hope of obtaining clinical results similar to those obtained with the traditional corticosteroids but avoiding side effects. Several corticosteroids have been used by the rectal route (beclomethasone dipropionate, tixocortol pivalate, budesonide, prednisolone metasulphobenzoate, fluticasone and flunisonide). Some of these preparations have been tested clinically and the results have been satisfactory. In terms of pharmacokinetic data, all compounds seem to produce negligible plasma levels and no adrenal axis suppression when assessed by studies measuring plasma cortisol levels, 24 h urinary cortisol collection and cortisol levels after adrenocorticotropic hormone stimulation.

Beclopmethasone dipropionate is one of the first of this second generation of corticosteroids to be studied extensively in ulcerative colitis patients. Beclopmethasone dipropionate was administered as an enema (0.5 mg/day) to patients with ulcerative colitis. Only negligible plasma levels were observed using beclomethasone dipropionate enemas and no adrenal axis suppression was detected (25). In this trial the beclomethasone dipropionate enemas produced satisfactory results in 66% of treated patients suggesting a possible therapeutic role for this preparation.

A subsequent clinical trial was carried out to test the value of 1 mg beclomethasone dipropionate enemas versus 25 mg prednisolone 21-phosphate enemas for a one month period (a common therapeutic protocol) (26). By the end of the study, 50% of patients taking beclomethasone dipropionate showed good response and two-thirds of patients given prednisolone 21-phosphate responded. In the authors' opinion this partly unsatisfactory result could have been related to the small dosage employed.

A second clinical trial was carried out using 2 and 3 mg of beclomethasone dipropionate versus 25 mg prednisolone 21-phosphate (27). From the results of this study it appeared that both beclomethasone dipropionate dosages were effective and did not produce adrenal axis suppression. These data in terms of clinical, sigmoidoscopic, and histologic results were not inferior to those obtained using prednisolone 21-phosphate enemas.

On this basis the authors decided to carry out a clinical trial to compare the efficacy of 3 mg beclomethasone dipropionate enemas in 100 mL to 2 g 5-ASA enemas. The trial has been conducted as a double-blind trial for a one month period. Clinical and sigmoidoscopic assessments were performed at the beginning, at 15 days, and after one month of treatment. Only preliminary data are available and show that both drugs seem to possess healing properties superior to 50%, but the authors cannot yet give information regarding which is the best form of treatment.

**CONCLUSIONS**

During the 1980s, an interesting new model of topical therapy has been proposed for 5-ASA which has been claimed to be very satisfactory. Now it is time to obtain more clinical data regarding the new corticosteroids and, if their promise is maintained, there will soon be another option for the clinical management of patients with inflammatory bowel disease.
REFERENCES