Beclomethasone dipropionate (3mg) versus 5-aminosalicylic acid (2g) versus the combination of both (3mg/2g) as retention enemas in active ulcerative proctitis

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Sixty patients with active distal ulcerative colitis participated in a multicentre randomized double-blind trial to compare the effect of a beclomethasone dipropionate (BDP) enema (3 mg/100 ml) with 5-aminosalicylic acid (5-ASA) enemas (2 g/100 ml) and enemas with a combination of BDP/5-ASA (3 mg/2 g/100 ml). The patients were treated for 4 weeks and the efficacy of the drugs was evaluated by sigmoidoscopy, histology and subjective symptoms after that time. The overall results after 28 days of treatment were: clinical improvement 100% (BDP/5-ASA) vs. 70% (BDP) and 76% (5-ASA); endoscopic improvement 100% (BDP/5-ASA) vs. 75% (BDP) and 71% (5-ASA); histological improvement 95% (BDP/5-ASA) vs. 50% (BDP) and 48% (5-ASA). After 4 weeks of treatment seven of 19 patients (37%) receiving BDP/5-ASA had healed endoscopically, compared with six of 20 receiving BDP (30%) and two of 21 receiving 5-ASA (10%). Two patients on 5-ASA and three on BDP had a marked deterioration during treatment. The combination of BDP and 5-ASA was significantly superior to single-agent therapy in terms of both improved sigmoidoscopic and improved histological score. No differences in improvement between the 5-ASA vs. BDP-treated patients were noticed. No side effects were seen. The results of the study show that topical treatment of active distal ulcerative colitis with either 5-ASA or BDP is equally efficacious. So far, no data on topical combination therapy have been described. However, combination therapy with BDP/5-ASA seems superior to single-agent therapy and causes no adverse reactions.

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Introduction

Steroids and mesalazine administered as enemas or suppositories are effective in the treatment of distal ulcerative colitis [1–3]. Earlier results from our group and others seem to indicate that the usually rapid improvement seen with prednisolone enemas can also be obtained with beclomethasone dipropionate (BDP) in the treatment of distal ulcerative colitis if given in an adequate dosage [4,5]. Reports comparing mesalazine (5-ASA) with prednisolone or topical steroids are abundant [4–9]. However, so far no data on topical combination therapy with mesalazine and corticosteroids have been described. The lack of evidence in published trials to show that BDP enemas interfere with adrenocortical function indicates that the absorption of this drug is insignificant, or that metabolism to metabolites of minimal biological activity is very rapid [9]. Those studies confirm and amplify the view that rectally administered steroids exert their efffect mainly by local action.

Most studies concerning topical treatment with 5-ASA, prednisolone or topical steroids reveal equal efficacy [3–9]. Major attention has been directed to the problem of hypothalamic–pituitary–adrenal suppression of the systemically acting steroids. However, the clinical importance of

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biochemical suppression of adrenocortical function after short-term corticosteroid administration is controversial, because tests of pituitary–adrenal function do not consistently correlate with responses to stress [10].

The aim of the present investigation was to compare the efficacy of a BDP enema (3 mg/100 ml) with a 5-ASA enema (2 g/100 ml) and a combination of both (3 mg/2 g/100 ml) administered once daily in patients with active distal ulcerative colitis. The objective was to study whether combination therapy is superior to single-agent therapy, and this has consequences for future clinical trials and treatment in daily clinical practice.

Patients and methods

Eligible patients were older than 18 years, outpatients, and suffering from an acute relapse or a first attack of idiopathic ulcerative colitis or proctitis which was limited to the distal 20 cm of the colon. Chronic continuous or refractory distal colitis was a contraindication for this trial [11]. The diagnosis was based on characteristic endoscopic and histological features, together with negative stool cultures. Patients had not been taking corticosteroid medication orally or topically, nor any other topical rectal medication, for at least 1 month before entering the trial.

Patients using sulphasalazopyrine (SASP) or one of the slow-release 5-ASA preparations before entering the trial continued to use these drugs during the trial, but only if they had already been taking these drugs for 4 weeks; the daily doses had to be kept constant during the study period. Patient compliance was checked after the study by counting the remaining medications.

Clinical, endoscopic and histological disease activity was assessed before the start of therapy and after 28 ±2 days (Tables 1 and 2) as previously described [4,5,12].

A biopsy was taken 6–10 cm from the anal verge on the dorsal side of the rectum at entry to the study, and after 28 ±2 days of treatment.

Allocation of patients

This was a randomized double-blind trial with three parallel groups of patients enrolled in three centres. Treatment allocation was carried out by a central randomization list using blocks of six. The scheduled period of treatment was 4 weeks. Patients were assessed at entry and after 28 ± 2 days of treatment. Endoscopy, with biopsy and laboratory analysis, was performed at each visit. Patient compliance was checked through active questioning and counting the number of enemas returned on day 28 ±2.

The study protocol was approved by the Ethics Committee of the Academic Medical Center, Amsterdam, and Rijnstate Arnhem. Each patient gave informed consent before enrolment.

The study medication consisted of either 3 mg BDP or 2 g 5-ASA, or a combination of both BDP 3 mg and 5-ASA 2 g/100 ml. The medications were identical in appearance. Enemas were prepared by Henning Berlin (Marion Merrell Dow, Berlin). Each patient received 30 enemas of 100 ml each. These were dispensed in easily compressible bottles with a rectal nozzle, with appropiate labels and instructions for preparation and use.

The enemas were administered rectally in a volume of 100 ml with the patient lying on the left side, before retiring, to be retained overnight.

Conduct of the trial and assessment of the treatment results

Patients were treated in a double-blind fashion for 28 days and were then reassessed clinically, rectoscopically and histologically, according to the same grading system (Tables 1 and 2). A decrease in endoscopic score of 3 or more and in clinical score of 2 or more was considered indicative of endoscopic or clinical improvement. The histological scoring of the biopsy specimens was performed double-blinded: the pathologist had no clinical information about the patients, the sequence of the specimens or the treatment regimen. Afterwards, the 'before and after' treatment scores were compared and a decrease in histological score of 2 or more was considered to be histological evidence of improvement.

The safety of the treatment was investigated by monitoring adverse events and by laboratory analysis at each clinic visit. Laboratory analysis included haematology, with cell count, electrolytes, liver and renal function tests, total protein and albumin, and urinalysis.

Statistical analysis

The Wilcoxon matched pairs signed-ranks test was used for paired data. Dichotomized data were compared with Fisher's exact test. Probability (P) values were derived from two-tailed tests with 0.05 being taken as the significant level. The primary analysis included all patients treated ('intent-to-treat' analysis). Statistical analysis was performed using the SPSS/PC package (SPSS Inc., Chicago, Illinois, USA). Differences between the groups were compared using the one-way ANOVA. To enhance the statistical power we used the least significant difference (LSD).

Results

Of the 60 patients admitted to the trial, 19 received BDP/5-ASA enemas (group A), 20 patients BDP (group B) and 21 patients 5-ASA (group C). The groups were comparable for sex, age, duration of disease and number of exacerbations (Table 3). The composition of these groups is shown in Table 4. Patient compliance was good and all used 95% or more of the number of enemas required for the study period. Laboratory analysis revealed no abnormalities at entry or at the end of the study. The clinical, endoscopic and histological results of this study are shown in Table 4.

After 4 weeks of treatment seven of 19 patients (37%) receiving BDP/5-ASA had healed endoscopically, compared to six of 20 receiving BDP (30%) and two of 21 receiving 5-ASA (10%). Clinical improvement after 4 weeks was seen in 100% of the BDP/5-ASA combinations, compared to 70% for BDP and 76% for 5-ASA. The difference between the clinical scores before and after therapy was not significant comparing BDP/5-ASA against both single-agent therapies ($P=0.09$). However, the differences between BDP/5-ASA and BDP were significant ($P=0.031$). Endoscopic improvement was seen in 100% of the BDP/5-ASA patients, compared to 75% for BDP alone

Table 1. Assessment of clinical and endoscopic activity.

Score	0	1	2
Assessment of clinical activity			
Stool frequency	<2/d	2–4/d	>4/d
Faecal consistency	normal	semiliquid	liquid
Mucoid discharge	none	sometimes	always
Blood loss	none	sometimes	always
Maximum	0	4	8
Endoscopic assessment			
Colour	normal	red	deep red
Vascular pattern	normal	partially absent	totally absent
Friability (wipe test)	normal	slight	severe
Granularity	absent	fine	coarse
Rectal valves	sharp	swollen	absent
Ulcers	absent	few	multiple
Spontaneous bleeding	absent	discrete	severe
Mucopurulent exudate	absent	little	much
Maximum	0	8	16

A decrease in clinical score >2 was considered clinical improvement, a decrease in endoscopic score >3 was considered endoscopic improvement.

Table 2. Histological assessment.

	0	1	2	3
Ulceration	none	mild	moderate	severe
Erosion	none	mild	moderate	severe
Crypt – abscesses	none	mild	moderate	severe
Cryptitis	none	mild	moderate	severe
Score	0	4	8	12

Each of the parameters was scored 0–3. A decrease of >2 was considered histological improvement.

and 71% for 5-ASA alone. The difference between the endoscopic scores before and after therapy was significant comparing BDP/5-ASA against single-agent therapy ($P=0.021$). Histological improvement was noted in 100% of patients for BDP/5-ASA, as against 50% for BDP and 48% for 5-ASA. The difference between the histological scores before and after therapy was significant comparing BDP/5-ASA against single-agent therapy ($P=0.009$).

Two patients on 5-ASA and three on BDP experienced a marked deterioration during the trial period.

The combination of BDP and 5-ASA was superior to single-agent therapy in overall improvement for the three items ($P<0.01$). In contrast, no significant differences in improvement were seen between the 5-ASA- and the BDP-treated patients. No side effects were noted.

Discussion

The results of this trial with respect to the efficacy of topical 5-ASA and BDP are consistent with those observed in previous studies [5,13–17]. However, our results with the combination of BDP and 5-ASA are remarkable. So far, no data on the combination of topical therapy have been described. In this study combination therapy with BDP/5-ASA appeared clearly superior to single-agent therapy.

Three main endpoints were evaluated: clinical, endoscopic and histological score. The three scores are considered equally important, as each represents a different aspect of the expected efficacy of the enemas: the clinical score is expected to represent the immediate palliative effect of the enema, the endoscopic score will probably reveal the early, and the histological score the longer-lasting, healing effects of the enemas. BDP/5-ASA was superior for every one of these endpoints.

The 5-ASA study of Biddle clearly showed the differences between the different scores [18]. Endoscopic improvement for proctitis is quite different compared to remission for the three factors (clinical, endoscopic, histological) [4,5,12].

We have shown that the goal of therapy – a high local therapeutic efficacy with the lowest degree of systemic side effects – can be realized by a combination of topically active drugs.

Maintenance treatment with topical steroids such as BDP, budesonide and tixocortol has the same side effects as prolonged oral use of corticosteroids, but probably with a much lower incidence [3,9,19–21].

All the newer compounds seem to produce negligible plasma levels and no adrenal axis suppression when assessed by studies measuring plasma cortisol levels and cortisol levels after adrenocorticotrophic hormone stimulation after 4 weeks of treatment [19–21].

Data concerning ACTH, synacthen test and 24 h urinary cortisol collection after longer periods (6 months–1 year) are necessary to discuss its systemic side

Table 3. Details of patients at entry.

Group	n	Sex		Age (years)	Duration of disease (years)			Number of exacerbations
		M	F	Mean	Median	Mean	(Range)	
A	19	9	10	36.3±12.5	4.5	4.9	0.5–15	6 (2–>10)
B	20	11	9	39.8±14.4	5.5	6.2	0.5–17	4 (2–>10)
C	21	9	11	42.95±13.6	6.0	5.4	0.5–20	5 (2–>10)

Table 4. Clinical, endoscopic and histological scores before and after treatment.

	Clinical			Endoscopical			Histological		
	Before	After	Impr	Before	After	Impr	Before	After	Impr
A BDP/5-ASA	4.63±0.35	0.47±0.19	100%	7.31±1.83	0.95±0.91	100%	4.16±0.41	0.32±0.22	95%
B BDP	5.00±0.30	2.40±0.63	70%	6.75±1.5	3.30±3.75	75%	3.58±0.38	1.63±0.50	50%
C 5-ASA	4.52±0.34	1.76±0.54	76%	7.57±2.2	3.14±2.53	71%	3.62±0.30	1.48±0.35	48%

BDP/5-ASA vs. BDP, $P=0.03$. BDP/5-ASA vs. BDP and 5-ASA, $P=0.021$. BDP/5-ASA vs. BDP and 5-ASA, $P=0.009$. Impr, improvement.

effects. We must realize that the majority of information has only been published in abstracts and reviews [3,9,15,19,21,22].

Maintenance treatment with combination therapy might be promising, especially in refractory ulcerative proctocolitis [11]. BDP enemas have been shown to be equally effective as prednisolone enemas and hydrocortisones and equally effective as mesalazine enemas [4,5,13–17]. Furthermore, no common steroid-associated systemic adverse effects have been observed in these studies. The beneficial effects of steroids as prednisolone salts, betamethasone, phosphate, tixocortol pivalate and budesonide have been established.

Tixocortol pivalate and budesonide are commercially available, but Glaxo has no interest in a commercial BDP enema because the drug is out of patent [3]. The reference list of BDP appears to be somewhat outdated. Pharmaceutical companies are not very enthusiastic about supporting BDP trials because of this lack of patent.

In most countries in Europe this combination of BDP and 5-ASA can be prepared in every pharmacy at very low prices [3,23]. Because pharmaceutical industries are only interested in 4-week enema studies for registration purposes there is a lack of adequate therapeutic and endocrinological data about longer periods of administration. Maintenance trials for 2–6 months of enema therapy including endocrinological data are needed. Oral studies with topical steroids over a longer period (8 weeks) are only available for budesonide, and show that 9 mg of budesonide gives plasma cortisol values below the reference limit in almost 70% of patients [24].

We hope that more combination enemas will be studied, for example 5-ASA with prednisolone, and budesonide with 5-ASA and lidocaine or both [25]. Combination therapy with topical steroids in lower dosages than is usual as a single-agent therapy might give better results without systemic side effects during maintenance therapy.

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