Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis

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Abstract

***Background*—Clear strategies to optimise the use of corticosteroids in ulcerative colitis are lacking.**

***Aim*—A meta-analysis was undertaken to examine critically the role of rectal corticosteroids in the management of active distal ulcerative colitis.**

***Methods*—All reported randomised controlled trials were retrieved by searching the Medline and EMBASE databases and the bibliographies of relevant studies. Trials which met inclusion criteria were assessed for scientific rigour. Data were extracted by two independent observers according to predetermined criteria.**

***Results*—Of 83 trials retrieved, 33 met inclusion criteria. Pooled odds ratios (POR) showed conventional rectal corticosteroids and rectal budesonide to be clearly superior to placebo. In seven trials, rectal 5-aminosalicylic acid (5-ASA) was significantly better than conventional rectal corticosteroids for inducing remission of symptoms, endoscopy, and histology with POR of 2·42 (95% confidence interval (CI) 1·72–3·41), 1.89 (95% CI 1·29–2·76), and 2·03 (95% CI 1·28–3·20), respectively. Rectal budesonide was of comparable efficacy to conventional corticosteroids but produced less endogenous cortisol suppression. Side effects, although inconsistently reported, were generally minor. A cost comparison of rectal preparations showed 5-ASA to be less expensive than corticosteroids.**

***Conclusions*—Rectal 5-ASA is superior to rectal corticosteroids in the management of distal ulcerative colitis.**

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Keywords: ulcerative colitis, corticosteroids, therapy, topical administration, enema, suppository.

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Oral corticosteroids have been a well-accepted treatment for active ulcerative colitis since Truelove *et al* reported the efficacy of oral hydrocortisone over 40 years ago.[1] However, their long term use may be limited and patient compliance diminished by potential adverse effects. Administration of a corticosteroid liquid enema was first suggested to be efficacious in distal ulcerative colitis in 1956.[2] The proven efficacy of direct drug delivery to the site of inflammation has since led to widespread acceptance of rectal corticosteroid therapy.[3]

The ability of a rectal preparation to achieve a proximal distribution is determined by the type of vehicle. Liquid enemas can deliver medication consistently to the splenic flexure,[4–9] and a larger volume seems to allow more proximal delivery.[10 11] Rectal foam disseminates medication to the rectum and distal descending colon,[12–16] whereas suppositories coat only the rectum.[17 18]

Although studies of rectally administered corticosteroids have reported fewer systemic adverse effects than with oral preparations, plasma concentrations of prednisolone were similar after administration of identical oral or rectal doses.[19 20] Suppression of the hypothalamic-pituitary-adrenal axis in association with rectal therapy has also been shown.[21–26]

Newer topically active corticosteroids such as tixocortol, beclomethasone, prednisolone metasulphabenzoate, and budesonide, with restricted absorption or rapid hepatic metabolism have been developed to reduce the adverse effects associated with conventional corticosteroids.[27 28]

To examine critically the role of rectal corticosteroids in the treatment of active distal ulcerative colitis, we performed a meta-analysis of all reported randomised controlled trials.

Methods

Relevant clinical trials were identified by searching the Medline database from 1966 to 1996 and the EMBASE database from 1985 to 1996, using the MeSH terms "inflammatory bowel disease", "therapy", and "topical administration", "enema", or "suppository". Bibliographies of all relevant studies and recent review articles were scanned to identify further citations. Each paper was assessed by two independent observers (JKM, EJI) according to predetermined inclusion criteria. Studies were accepted if patients had active ulcerative colitis with a documented disease margin distal to the splenic flexure on radiographic studies or less than 60 cm from the anal verge at flexible sigmoidoscopy or colonoscopy. We required that patients had been randomly assigned to two or more treatment groups, with rectal corticosteroids in at least one treatment arm and a symptom score as one of the main outcome criteria. The minimum duration of therapy permitted was two weeks.

Trials which met the inclusion criteria were then evaluated quantitatively for scientific rigour using a 30 point scoring system.[29] Disagreements in scoring between the two observers were settled by consensus.

Data were extracted from each report using a predefined format. Recorded data points included the number of patients enrolled, number completing the study, sex, and disease distribution. The proportion of patients that improved or attained remission, or both, by

symptomatic, endoscopic, and histological criteria were recorded from each trial using an intention to treat principle. The dose, frequency, duration, and formulation (enema, suppository or foam) of treatments were noted, as were any reported adverse effects of therapy.

We anticipated that the definitions of "improvement" and "remission" would vary considerably among the papers accepted. To overcome the problems of standardising endpoints, provided that an adequate definition of improvement or remission was offered, the authors' criteria for these outcomes were respected. All clinical symptom scores included stool frequency and rectal bleeding.

Studies were grouped for analysis according to the type of corticosteroid and control therapies. Corticosteroid doses were also converted to a hydrocortisone dose equivalent to permit testing for a dose response relation.[30] The statistical analysis was conducted using the method of DerSimonian and Laird.[31] An odds ratio for each trial and a common odds ratio for each group with 95% confidence intervals (CI) were calculated according to Mantel-Haenszel. Unless otherwise stated, odds ratios below 1 favoured corticosteroid treatment, whereas odds radios above 1 favoured the alternative treatment. Continuous data points were pooled and compared using a weighted mean difference.[32] Homogeneity within groups of trials was confirmed using the Breslow–Day test.[33] Overall response rates for each drug were calculated by dividing the total number of patients reaching an endpoint by the total number of patients treated.

Results

ACCEPTANCE AND VALIDITY SCORING

In total, 83 relevant trials were identified by the search, of which 33 met our inclusion criteria. Reasons for excluding a trial included: lack of randomisation (36 trials), inclusion of patients with disease proximal to the splenic flexure (29 trials), lack of a predefined symptom score (nine trials), duplicate reporting of data (three trials), and inclusion of patients with Crohn's colitis (one trial).

Table I summarises the characteristics of the 33 trials accepted for analysis. The median validity score (out of 30) was 21 (range 9–26).

RESPONSE RATES

Table II lists the response rates for all treatments and placebo. Among patients receiving conventional rectal corticosteroids (hydrocortisone, prednisolone, or betamethasone), pooled improvement rates by symptomatic, endoscopic, and histological criteria were 77%, 66%, and 52%, whereas remission rates were 45%, 34%, and 29%, respectively. The pooled response rates for the topically active corticosteroids (budesonide, beclomethasone, or prednisolone metasulphobenzoate) were similar: 73% for symptoms, 69% for endoscopy, and 55% for histology, whereas 46%, 31%, and 23%, respectively, attained remission. When corticosteroid doses were converted to their hydrocortisone equivalent,[30] no dose response relation was observed for either conventional or topical formulations. Similarly, no correlation was apparent between duration of treatment and response rate.

Aminosalicylates (4-ASA or 5-ASA), which were used most frequently as a comparative treatment, produced improvement in symptoms, endoscopy, and histology in, respectively, 81%, 75%, and 65% of patients. Remission with these endpoints was induced in 52%, 41%, and 32% of patients, respectively.

Across four trials, 34% of patients taking placebo improved symptomatically, and 38% improved endoscopically. Remission rates by symptomatic and endoscopic criteria were 9% and 17%.

RECTAL CORTICOSTEROIDS VERSUS PLACEBO

Two trials compared conventional rectal corticosteroids with placebo.[34 35] The combined results clearly favoured corticosteroids, with a pooled odds ratios (POR) for symptomatic and endoscopic improvement of 0·21 (95% CI 0·07–0·71) and 0·27 (95% CI 0·10–0·77), respectively. The PORs for symptomatic and endoscopic remission were 0·07 (95% CI 0·02–0·29) and 0·34 (95% CI 0·10–1·20), respectively. Histological endpoints were not reported in these early trials.

One trial reported that 2·3 mg budesonide enemas were superior to placebo for improvement of symptoms, endoscopy, and histology,[36] whereas another found 2·0 mg or 8·0 mg daily superior to placebo in inducing combined symptomatic and endoscopic remission, with higher response rates at the larger dose.[37]

RECTAL VERSUS ORAL CORTICOSTEROIDS

Rectal hydrocortisone 100 mg was compared with oral prednisolone 60 mg daily in one trial which showed oral treatment to be better for symptomatic improvement and remission.[39] A second trial compared low dose oral prednisolone (7·5 mg daily) with rectal prednisolone metasulphobenzoate 20 mg, and found rectal treatment to be more efficacious for inducing symptomatic improvement.[38] Because of substantial differences in oral dose, these results were not pooled.

RECTAL CORTICOSTEROIDS VERSUS RECTAL 5-ASA

Seven accepted trials compared rectal corticosteroids with rectal 5-ASA.[40–46] The total daily dose of 5-ASA ranged from 1 to 4 g, whereas the hydrocortisone equivalent dose of corticosteroids ranged from 100 to 356 mg. One trial compared a hydrocortisone foam with a 5-ASA suppository,[43] whereas another compared hydrocortisone foam with 5-ASA foam.[45] All other trials compared liquid enema preparations of equal volume. Pooled odds ratios for symptomatic, endoscopic, and histological improvement among the trials reporting these data were 1·36 (95% CI 0·88–2·09), 1·06

TABLE I *Characteristics of trials accepted for meta-analysis*

Reference	*Author (year)*	*Medication (dose and frequency)**	*Duration (days)*	*Number of patients*	*Validity score (maximum=30)*
A *Rectal corticosteroids* v *placebo*					
34	Lennard-Jones *et al* (1962)	Prednisolone (5 mg SUPP od) Placebo	21	39	16
35	Watkinson (1958)	Hydrocortisone (100 mg/100 ml od) Placebo	15	19	17
B *Rectal budesonide* v *placebo*					
36	Danielsson *et al* (1992)	Budesonide (2·3 mg/115 ml od) Placebo	28	41	23
37	Hanauer and Robinson (1995)†	Budesonide (0·5 mg or 2·0 mg or 8·0 mg od) Placebo	42	233	12
C *Rectal* v *oral corticosteroids*					
38	Hamilton *et al* (1984)	Prednisolone metasulphoenzoate (20 mg od) Prednisolone (7·5 mg ORAL od)	14	36	17
39	Lennard-Jones *et al* (1960)	Hydrocortisone (100 mg/150 ml) od Prednisone (variable dose ORAL od) Salazopyrin (4 g ORAL od)	21	60	15
D *Rectal corticosteroids* v *rectal 5-ASA*					
40	Bianchi Porro *et al* (1995)	Hydrocortisone (100 mg/60 ml od) 5-ASA (1 g/100 ml od)	21	52	23
41	Campieri *et al* (1981)	Hydrocortisone (100 mg/100 ml od) 5-ASA (4 g/100 ml od)	15	86	19
42	Danish 5-ASA Group (1987)	Prednisolone (25 mg/100 ml od) 5-ASA (1 g/100 ml od)	14	123	25
43	Farup *et al* (1995)	Hydrocortisone (178 mg/60 ml FOAM bid) 5-ASA (0·5 g SUPP bid)	28	79	23
44	Friedman *et al* (1986)	Hydrocortisone (100 mg/100 ml od) 5-ASA (4 g/100 ml od)	21	18	24
45	Lee *et al* (1996)	Prednisolone (20 mg/30 ml FOAM od) 5-ASA (2 g/120 ml FOAM od)	28	295	25
46	Mulder *et al* (1988)	Prednisolone (30 mg/40 ml od) 5-ASA (3 g/40 ml od)	28	29	24
E *Rectal corticosteroids* v *rectal 4-ASA*					
47	O'Donnell *et al* (1992)	Prednisolone (20 mg/50 ml od) 4-ASA (2 g/50 ml od)	42	45	24
48	Sharma *et al* (1992)	Prednisolone (20 mg/60 ml od) 4-ASA (2 g/60 ml od)	28	40	26
F *Rectal corticosteroids* v *rectal budesonide*					
24	Bianchi Porro *et al* (1994)	Methylprednisolone (20 mg/100 ml od) Budesonide (2 mg/100 ml od)	28	88	21
25	Danielsson *et al* (1987)	Prednisolone (31·25 mg/100 ml od) Budesonide (2 mg/100 ml od)	28	64	20
26	Danish Budesonide Study Group (1991)	Prednisolone (25 mg/100 ml od) Budesonide (1 or 2 or 4 mg/100 ml od)	14	139	19
49	Lofberg *et al* (1994)	Prednisolone (31·25 mg/125 ml od) Budesonide (2·3 mg/115 ml od)	56	100	24
50	Tarpila *et al* (1994)	Hydrocortisone (125 mg/125 ml od) Budesonide (2·3 mg/115 ml od)	28	72	20
G *Rectal budesonide* v *rectal 5-ASA*					
51	Lamers *et al* (1991)†	Budesonide (2 mg/100 ml od) 5-ASA (4 g/60 ml od)	28	62	13
52	Lemann *et al* (1995)	Budesonide (2 mg/115 ml od) 5-ASA (1 g/100 ml od)	28	92	22
H *Other*					
53	Cobden *et al* (1991)	Prednisolone metabenzoate (20 mg/100 ml bid) 5-ASA (0·8 g ORAL qid)	28	37	26
54	Grace *et al* (1987)	Prednisolone (20 mg/100 ml od) Sodium cromoglycate (600 mg/100 ml od)	56	70	18
55	Halpern *et al* (1991)‡	Beclomethasone dipropionate (0·5 mg/100 ml od) Betamethasone phosphate (5 mg/100 ml od)	28	40	22
56	Hanauer *et al* (1986)†	Tixocortol pivalate (250 mg od) Hydrocortisone (100 mg od)	21	125	9
57	Lennard-Jones (1971)	Betamethasone valerate (5 mg/100 ml od) Prednisolone (20 mg/100 ml od)	28	105	17
58	Mulder *et al* (1989)	Beclomethasone diproprionate (2 or 3 mg/40 ml od) Prednisolone (30 mg/40 ml od)	28	25	23
59	Mulder *et al* (1994)†	Beclomethasone dipropionate (3 mg/100 ml od) 5-ASA (1 g/100 ml od) Beclomethasone and 5-ASA (3 mg/100 ml and 1 g/100 ml od)	28	60	13
60	Riley *et al* (1989)	Prednisolone metasulphobenzoate (20 mg/100 ml od) Sucralfate (4 g/100 ml od)	28	44	23
61	Ruddell *et al* (1980)	Hydrocortisone (100 mg/60 ml bid) Hydrocortisone (100 mg/5 ml FOAM bid)	14	30	16
62	van der Heide *et al* (1988)	Beclomethasone dipropionate (1 mg/40 ml od) Prednisolone (30 mg/40 ml od)	28	18	24
63	van Outryve *et al* (1996)†	Ridogrel (300 mg/40 ml od) Prednisolone (30 mg/40 ml od)	28	40	17

*Medication in enema format unless otherwise stated. †Abstract only. ‡Total 32 patients with 40 treatment courses.
SUPP=suppository; od=once daily; bid=twice daily; qid=four times daily.

(95% CI 0·61–1·85), and 2·27 (95% CI 1·22–4·27), with results clearly favouring 5-ASA only for histology (Figs 1 and 3). Using the stricter outcome of disease remission, 5-ASA was significantly better for all three criteria with PORs of 2·42 (95% CI 1·72–3·41) for symptoms, 1·89 (1·29–2·76) for endoscopy, and 2·03 (95% CI 1·28–3·20) for histology (Figs 2 and 3). When the two trials using foam preparations[43 45] were excluded from the analysis, recalculated PORs for remission endpoints still favoured 5-ASA significantly, despite wider confidence intervals as a result of the smaller sample size.

A single trial compared 5-ASA and beclomethasone enemas alone versus a combined 5-ASA/beclomethasone enema.[59] The combination surpassed monotherapy in inducing symptomatic or endoscopic improvement ($p<0·05$).

TABLE II *Pooled response rates for rectal preparations (all trials)*

Medication	Response rate across all trials (ratio, percentage)					
	Improvement			Remission		
	Symptomatic	Endoscopic	Histologic	Symptomatic	Endoscopic	Histological
Conventional corticosteroids						
Hydrocortisone	58/94 (62%)	61/109 (56%)	71/137 (52%)	50/119 (42%)	43/96 (45%)	14/51 (27%)
Prednisolone	272/344 (79%)	146/196 (74%)	73/144 (51%)	149/338 (44%)	127/387 (33%)	83/262 (32%)
Methylprednisolone	28/44 (59%)	20/44 (45%)	20/44 (45%)	16/44 (36%)	8/44 (18%)	6/44 (14%)
Betamethasone	61/71 (86%)	18/20 (90%)	16/20 (80%)	40/71 (56%)	6/20 (30%)	10/20 (50%)
Pooled	428/553 (77%)	245/369 (66%)	180/345 (52%)	255/572 (45%)	184/547 (34%)	113/377 (30%)
Topically active corticosteroids						
Prednisolone metasulphobenzoate	33/40 (83%)	15/22 (68%)	15/22 (68%)	15/22 (68%)	17/41 (41%)	10/22 (45%)
Beclomethasone	42/65 (65%)	44/65 (68%)	24/45 (53%)	9/20 (45%)	16/56 (29%)	5/20 (25%)
Budesonide	49/64 (77%)	163/237 (69%)	110/205 (54%)	53/137 (39%)	70/237 (30%)	26/137 (19%)
Pooled	124/169 (73%)	222/324 (69%)	149/272 (55%)	77/169 (46%)	103/334 (31%)	41/179 (23%)
Aminosalicylates						
5-ASA	230/282 (82%)	154/212 (73%)	93/141 (66%)	195/368 (53%)	140/384 (36%)	84/251 (33%)
4-ASA	37/47 (79%)	20/20 (100%)	29/47 (62%)	9/27 (33%)	18/20 (90%)	5/27 (19%)
Pooled	267/329 (81%)	174/232 (75%)	122/188 (65%)	204/395 (52%)	158/404 (39%)	89/278 (32%)
Placebo	18/53 (34%)	12/32 (38%)		3/32 (9%)	5/32 (17%)	

RECTAL CORTICOSTEROIDS VERSUS RECTAL 4-ASA

Rectal corticosteroids were compared with rectal 4-ASA in two trials.[47 48] Each compared 4-ASA 2 g with prednisolone 20 mg (hydrocortisone dose equivalent 80 mg). POR for symptomatic improvement was 3·88 (95% CI 1·29–11·64), favouring 4-ASA.

RECTAL CORTICOSTEROIDS VERSUS RECTAL BUDESONIDE

Five trials compared conventional rectal corticosteroids with rectal budesonide.[24–26 49 50] The budesonide dose ranged from 2·0 to 2·5 mg, whereas the corticosteroid dose ranged from 100 to 125 mg of hydrocortisone equivalent. Data from one trial could not be extracted adequately for meta-analysis.[26] One trial used a hydrocortisone foam.[50] All other medications were given as enemas.

The PORs for improvement by symptomatic, endoscopic, and histological criteria were 2·08 (95% CI 0·84–5·14), 1·40 (95% CI 0·87–2·25), and 1·23 (95% CI 0·80–1·91), respectively (Fig 4). PORs for symptomatic, endoscopic, and histological remission were 0·85 (95% CI 0·44–1·63), 1·14 (95% CI 0·69–1·88), and 0·68 (95% CI 0·28–1·67). All confidence intervals included 1.

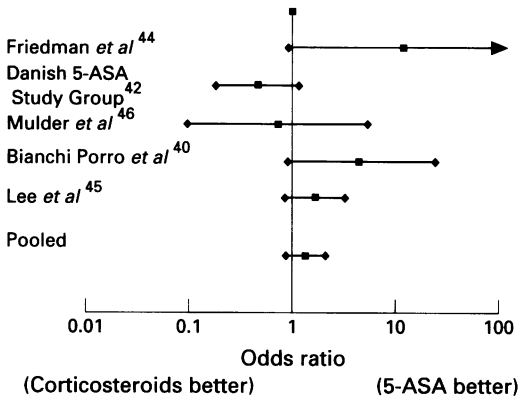

Figure 1: Symptomatic improvement: rectal corticosteroids v *rectal 5-aminosalicylic acid (5-ASA).*

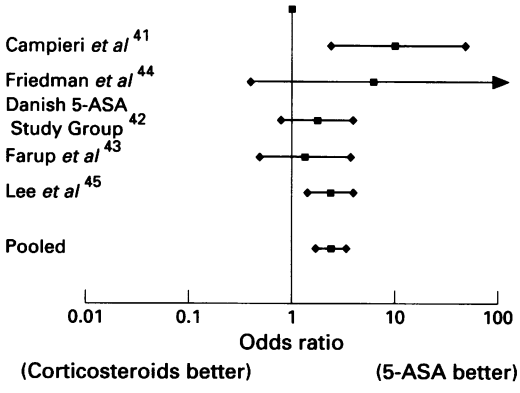

Figure 2: Symptomatic remission: rectal corticosteroids v *rectal 5-aminosalicylic acid (5-ASA).*

RECTAL BUDESONIDE VERSUS RECTAL 5-ASA

Two trials comparing rectal budesonide with rectal 5-ASA were evaluated.[51 52] Endoscopic improvement and remission data were reported in both trials, with a POR of 0·58 (95% CI 0·27–1·22) and 0·95 (95% CI 0·43–2·10), respectively, where an OR <1 favoured 5-ASA. In one of the trials 5-ASA exceeded budesonide for inducing symptomatic remission, with an OR of 0·41 (95% CI 0·18–0·94).[52] The other reported similar symptomatic remission rates in both treatment arms, but the data provided did not permit calculation of an OR.[51]

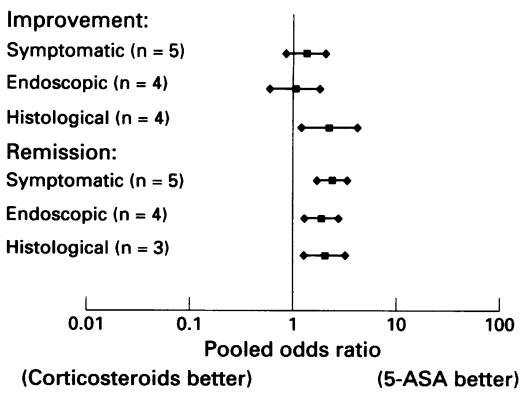

Figure 3: Pooled odds ratios for all outcomes: rectal corticosteroids v *rectal 5-aminosalicylic acid (5-ASA).*

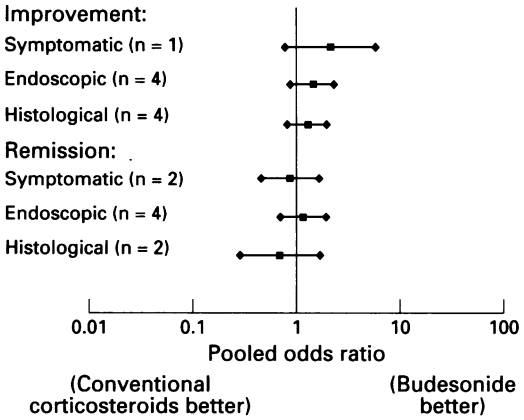

Figure 4: Pooled odds ratios for all outcomes: conventional rectal corticosteroids v *rectal budesonide.*

ADVERSE EFFECTS OF RECTAL CORTICOSTEROIDS

Adverse effects of treatment were inconsistently reported in the accepted trials. Nine of the 33 trials made no reference whatsoever to adverse effects, whereas a further 11 trials reported no drug related adverse effects in any treatment arm. Among the remaining 13 trials, seven dropouts for drug related effects were noted: four on 5-ASA, one on conventional corticosteroids, one on budesonide, and one on 4-ASA. Other drug related adverse effects such as nausea, abdominal distension, fatigue, and perianal irritation were infrequent.

Overall, 10 trials reported hypothalamic-pituitary-adrenal axis function before and after treatment. Three of these compared rectal budesonide with conventional rectal corticosteroids, noting mean cortisol concentrations after four weeks of treatment.[25 49 50] Cortisol concentrations were consistently higher, indicating lesser suppression, in the budesonide group than in the group receiving conventional corticosteroids (Fig 5). The weighted mean difference between pooled treatment arms was 119·1 nmol/l (95% CI 70·3–167·9), confirming that this difference was statistically significant. Another trial reported similar data using an analog scale which could not be pooled.[26]

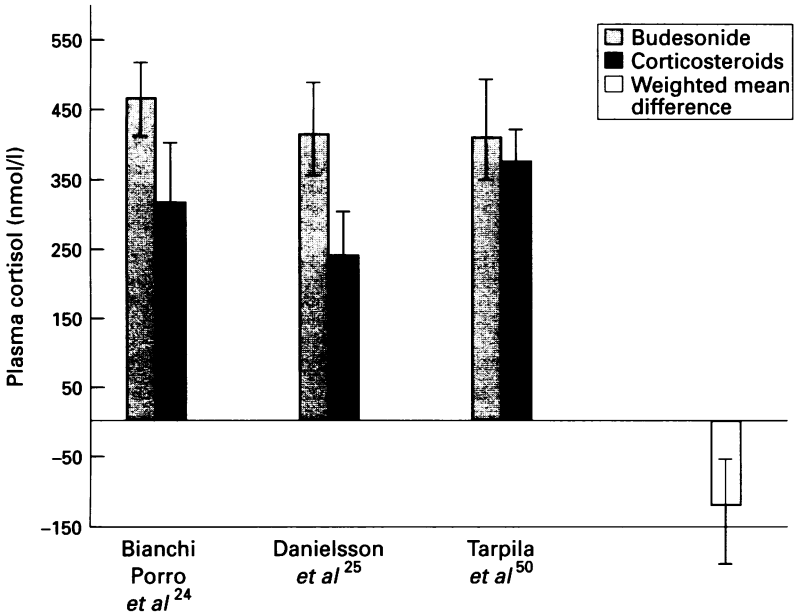

Figure 5: Plasma cortisol concentrations and weighted mean difference (with 95% CI) after four weeks of treatment: conventional rectal corticosteroids v *rectal budesonide.*

TABLE III *Cost of available rectal treatments (Chedoke-McMaster Hospital Pharmacy, July 1996)*

Medication	*Unit cost (Can $; US$; £) excluding dispensing fee*	*Cost of 14 day course (Can $; US$; £) excluding dispensing fee*
Hydrocortisone enema 100 mg (Cortenema)	6·93; 4·89; 3·00	97·02; 68·50; 42·01
Hydrocortisone foam 80 mg (Cortifoam 14 dose cannister)	83·24; 58·77; 36·04	83·24; 58·77; 36·04
Betamethasone enema 5 mg (Betnesol)	8·68; 6·13; 3·76	121·52; 85·79; 52·62
Budesonide enema 2·3 mg (Entocort)	9·00; 6·35; 3·90	126·00; 88·96; 54·56
Tixocortol 250 mg (Rectovalone)	7·95; 5·61; 3·44	111·30; 78·58; 48·19
5-ASA enema 4 g (Salofalk)	7·08; 5·00; 3·07	99·12; 69·98; 42·92
5-ASA enema 2 g (Salofalk)	4·10; 2·89; 1·78	57·40; 40·52; 24·85
5-ASA enema 2 g (Quintasa)	4·35; 3·07; 1·88	60·90; 43·00; 26·37
5-ASA enema 1 g (Quintasa)	3·97; 2·80; 1·72	55·58; 39·24; 24·07

COST COMPARISON

The costs for rectal steroid and 5-ASA enema and foam preparations available in Canada, in Canadian dollars, were obtained from the Chedoke-McMaster hospital pharmacy and are shown in Table III. Hydrocortisone 100 mg and 5-ASA 4 g enemas are comparable in cost, whereas 5-ASA 1 g and 2 g enemas cost considerably less. Budesonide enemas are marginally more expensive than hydrocortisone liquid enema, and hydrocortisone foam costs slightly less. Methylprednisolone enemas currently are not available in Canada.

Discussion

This study confirms that rectal corticosteroids are an effective treatment for active distal ulcerative colitis, with a therapeutic gain over placebo of approximately 30%, but suggests that rectal 5-ASA is significantly more efficacious for inducing disease remission.

Placebo controlled data are becoming increasingly scarce in the recent literature, possibly because of the ethical concerns of treating patients with active ulcerative colitis with placebo. Two early placebo controlled trials[34 63] confirmed the efficacy of conventional rectal corticosteroids for inducing improvement and remission by symptomatic and endoscopic criteria. Two recent trials[36 37] also showed the topically acting corticosteroid budesonide to be superior to placebo using symptomatic, endoscopic, and histological endpoints. Our pooled placebo data demonstrated symptomatic and endoscopic improvement in 34% and 38%, and symptomatic and endoscopic remission in 9% and 17% of patients, respectively. These findings were similar to those of another overview which suggested that placebo benefited 30% of patients and produced remission in 10%.[64]

Our meta-analysis suggests that rectal 5-ASA is as efficacious as rectal corticosteroids for improving disease and is better than rectal corticosteroids for inducing remission. Results were consistent, with similarly narrow confidence intervals, for symptomatic, endoscopic, or histological outcomes. The two trials which

compared rectal 5-ASA with budesonide suggested that 5-ASA is at least as effective in producing disease improvement and remission. However, not all endpoints were noted.

Only two studies compared the role of rectal 4-ASA with corticosteroids, but supported a therapeutic gain in producing symptomatic improvement for 4-ASA.

Budesonide is a new topically active corticosteroid formulation with a high glucocorticoid receptor affinity, and significant first pass hepatic metabolism. The pooled results for accepted trials failed to demonstrate significant therapeutic benefit of either budesonide or conventional corticosteroids. However, budesonide caused significantly less endogenous cortisol suppression, based on pooled mean cortisol concentrations. Although these data are promising, no data have been reported regarding differences in steroid specific adverse effects, such as osteopenia or Cushingoid facies.

Other factors which may influence the efficacy of a treatment formulation include the proximal extent of the disease. Although our pooled data did not permit subgroup analysis, foam and suppositories did produce higher response rates in patients with more distal disease,[43] supporting the findings of radiological and radionuclide studies of a more distal distribution of medication.[12-18] Patient preference for foam or suppository preparations also may augment compliance, and hence the effectiveness of therapy.[61] Similarly, the volume of enema or foam preparations may influence treatment distribution and efficacy.[10] Although most trials used equivalent volumes in both treatment arms, Lee *et al*[45] compared a 30 cc prednisolone foam with a 120 cc 5-ASA foam, a bias which could favour the efficacy of 5-ASA. When these data were excluded from the pooled results, 5-ASA remained superior to corticosteroids in inducing remission, although confidence intervals were wider.

An important feature which potentially could confound results of this meta-analysis was duration of treatment, which ranged from 14 to 56 days among the trials accepted. Although pooled results of trial endpoints did not demonstrate a clear relation, individual trials which reported interim endpoints at different time intervals observed higher endoscopic and histological remission rates with prolonged treatment.[25 36 42 43 49-51] Although longer treatment may potentially increase adverse effects or diminish compliance, treatment requiring endoscopic or histological remission has been associated with a lower relapse rate.[65 66]

Adverse effects for all rectal preparations were under-reported, but seemed comparable. Drug costs using a two week treatment regimen were lower for rectal aminosalicylate products than for most corticosteroid preparations. However, longer term studies may be necessary to evaluate further the median time to remission before it can be concluded that 5-ASA enemas are more cost effective than corticosteroids. To facilitate our analysis, we accepted the authors' definitions of disease response and remission. The ability to pool data effectively from several trials is limited by the variability in outcome criteria. As meta-analyses and overviews are updated, it is essential that methods of diagnosis, definitions of active or inactive disease, and criteria for symptomatic, endoscopic, and histological outcomes are standardised.[67] Increased attention should also be given to the potential confounding influence of proximal disease margin, formulation of delivery vehicle, volume of preparation, and duration of treatment. As the potential for adverse reactions often governs selection among equally effective agents, adverse effects also must be reported more rigorously.

We conclude that treatment with rectal 5-ASA is superior to treatment with rectal corticosteroids in the management of active distal ulcerative colitis. Rectal budesonide seems to be as effective as conventional rectal corticosteroids, but seems to cause less suppression of endogenous cortisol production. Conventional rectal corticosteroids may be regarded as an alternative rectal treatment for active distal ulcerative colitis once aminosalicylates have failed, or in patients allergic to 5-ASA.

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