Therapeutic benefits from a poorly absorbed prednisolone enema in distal colitis

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SUMMARY A double blind controlled trial has been conducted in 40 patients to compare the therapeutic effects of prednisolone metasulphobenzoate enemas with those of prednisolone-21-phosphate enemas. Both enemas brought about improvement in symptoms and sigmoidoscopic appearances in more than 70% of patients treated. The absorption of prednisolone from the metasulphobenzoate enema in three patients was less than from the 21-phosphate enema. In view of the low plasma prednisolone concentrations obtained, there are theoretical advantages in using a poorly absorbed enema to avoid the possibility of systemic steroid effects in patients requiring long term steroid treatment.

Retention enemas containing prednisolone have been a standard treatment for distal ulcerative colitis for many years.¹ Previous work has shown that significant plasma prednisolone concentrations result from the administration of an enema containing 20 mg prednisolone as prednisolone-21-phosphate, in 100 ml water.^{2,3} Although systemic side effects are rarely seen, the possibility exists that long term treatment with prednisolone-21-phosphate enemas may be detrimental. Lee and his colleagues³ reported low plasma levels of prednisolone after administration of an enema containing 20 mg prednisolone as prednisolone metasulphobenzoate and postulated a local site of action. To test the clinical efficacy of these enemas we undertook a double blind controlled trial, comparing prednisolone-21-phosphate and prednisolone metasulphobenzoate enemas, in conjunction with further studies of prednisolone absorption after administration of both types of enema.

Methods

ABSORPTION STUDIES

Enemas containing 20 mg prednisolone as prednisolone-21-phosphate or 20 mg prednisolone as prednisolone metasulphobenzoate in 100 ml water were given to each of three patients on separate days. Three other patients received an enema containing 60 mg prednisolone as prednisolone

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zoate in 100 ml water. Oral or topical steroid preparations were not given for at least 24 hours before the test enema. Blood was removed for plasma prednisolone concentrations before, and 30, 60, 120, 240, and 360, or 480 minutes after, enema administration. A rectal biopsy was taken at 360 or 480 minutes after the enema had been given.

LABORATORY METHODS

Blood samples were placed in lithium heparin tubes, centrifuged and the supernatant stored at -20°C until analysis. Rectal biopsies were taken in the standard way, and washed with saline to remove debris, surface secretion and residual enema fluid before freezing at -20°C until analysis. Plasma and tissue prednisolone concentrations were measured using a radioimmunoassay technique previously reported.⁴ The cross-reactivity of prednisolone metasulphobenzoate with the antiserum was 100% of that with prednisolone.

CLINICAL TRIAL METHODS

Forty outpatients with an exacerbation of previously diagnosed distal ulcerative colitis were admitted to the trial after giving informed consent. Each received a nightly enema for two weeks. Both prednisolone preparations were clear solutions packaged in identical plastic containers holding 100 ml. The identity of the prednisolone salt received by each patient was retained by the hospital pharmacy and remained unknown to the patients and their doctors until after completion of the trial. Patient's

symptoms, and the sigmoidoscopic and histological appearances of the rectal mucosa were documented before and after the treatment period and estimations made of haemoglobin levels and ESR. Sigmoidoscopic appearances were graded as: non-haemorrhagic, score 0; haemorrhagic with bleeding on light contact with the sigmoidoscope, score 1, and haemorrhagic with spontaneous bleeding seen in front of the advancing sigmoidoscope, score 2. Histology was reviewed by a single observer who had no prior knowledge of the patients, or of the timing, relative to treatment, of the biopsies.

Results

ABSORPTION STUDIES

Table 1 shows peak plasma concentrations, area under the absorption curve and tissue levels for each of the three types of enema used. The Figure shows by the absorption curves for the 20 mg prednisolone-21-phosphate and prednisolone metasulphobenzoate enemas. Both the peak plasma concentrations and areas under the curve measured by a linear trapezoidal method were less after prednisolone metasulphobenzoate enemas than after prednisolone-21-phosphate enemas, confirming the findings of Lee *et al.*³ Indeed, comparable peak levels were only obtained after administration of 60 mg prednisolone in the form of prednisolone metasulphobenzoate. Tissue levels showed a reciprocal pattern, being higher after prednisolone metasulphobenzoate than after prednisolone-21-phosphate.

CLINICAL TRIAL

Two patients failed to attend for their follow up appointment, and a third patient was diagnosed as having the solitary rectal ulcer syndrome on review of the histology. All three patients had received prednisolone-21-phosphate enemas. Table 2 shows

Figure Plasma prednisolone absorption curves obtained after the administration of 20 mg prednisolone as either prednisolone-21-phosphate or prednisolone metasulphobenzoate.

the distribution of sex, age, and extent of disease in the two groups. Table 3 gives the results after treatment as judged by patient's symptoms, stool frequency, sigmoidoscopic score and histological appearance. Fourteen patients reported an improvement in their symptoms after prednisolone-21-phosphate, compared with 15 after prednisolone metasulphobenzoate. After treatment with either enema, there was significant improvement, using

Table 1 Levels of prednisolone in plasma and in rectal biopsies after administration of retention enemas containing either prednisolone-21-phosphate or prednisolone metasulphobenzoate.

Patient	Prednisolone-21-phosphate 20mg*			Prednisolone metasulphobenzoate 20 mg*			Prednisolone metasulphobenzoate 60 mg*		
	Peak level (ng/ml)	Area under the curve (ng/ml h)	Tissue level (ng/g)	Peak level (ng/ml)	Area under the curve (ng/ml h)	Tissue level (ng/g)	Peak level (ng/ml)	Area under the curve (ng/ml h)	Tissue level (µg/g)
1	100	341	39	16	45	Not done			
2	235	1051	80	32	107	304			
3	109	406	12	2	11	269			
4							200	1000	1.56
5							184	845	1.48
6							56	51	2.06

* measured as prednisolone.

Table 2 Comparability of the two treatment groups.

	Prednisolone 21-phosphate	Prednisolone metasulphobenzoate
Male:female	14:6	11:9
Age range (years)	22-80	22-72
Age mean $\pm$ SD	45 $\pm$ 16	43 $\pm$ 6
Proctitis	10	10
Proctocolitis	10	10

Student's *t* test for paired data, in stool frequency and sigmoidoscopic score. There was no difference between the two groups.

Discussion

We have shown that a poorly absorbed steroid enema which presumably acts at the site of application is as effective as a well absorbed enema which produces high plasma prednisolone values. These

Table 3 Results of treatment for 2 weeks with retention enemas containing prednisolone, 20 mg, as either the 21-phosphate or metasulphobenzoate ester.

	Prednisolone 21-phosphate	Prednisolone metasulphobenzoate
Symptoms after treatment		
Symptom-free	5	2
Improved	9	13
No change	2	5
Worse	1	0
Withdrawn	3	0
Stool frequency		
Mean $\pm$ SEM		
Before	4.5 $\pm$ 0.6	4.5 $\pm$ 0.5
After	2.6 $\pm$ 0.6*	2.7 $\pm$ 0.3†
Sigmoidoscopy score		
Total (mean)		
Before	25 (1.34)	31 (1.6)
After	13 (0.7)†	11 (0.6)†
Histology		
Improved	6	6
No change	10	11
Worse	1	2
No biopsy	0	1

* $p < 0.01$ † $p < 0.001$

results are interesting, but do not help solve the question of the ultimate site of action of prednisolone in ulcerative colitis. The marked difference in tissue levels is probably explained by the good absorption of prednisolone through the rectal mucosa after a prednisolone-21-phosphate enema, while this does not occur after prednisolone metasulphobenzoate, and the tissue levels rise progressively.

Previous studies⁵ have shown little suppression of the adrenal cortex after chronic treatment with prednisolone enemas though there are a few patients who complain of troublesome fluid retention, weight gain, 'mooning' of the face or acne while receiving long term treatment. Patients whose disease requires such long term treatment to maintain remission of their inflammatory bowel disease or those at particular risk of side effects such as those with a diabetic tendency could avoid the risks of adverse effects by using poorly absorbed enemas.

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References

- 1 Matts SGF. Intra-rectal treatment of 100 cases of ulcerative colitis with prednisolone-21-phosphate enemas. *Br Med J* 1961; **1**: 165-8.
- 2 Powell-Tuck J, Lennard-Jones JE, May CS, Wilson CG, Paterson JW. Plasma prednisolone levels after administration of prednisolone-21-phosphate as a retention enema in colitis. *Br Med J* 1976; **1**: 193-5.
- 3 Lee DAH, Taylor M, James VHT, Walker G. Rectally administered prednisolone - evidence for a predominantly local action. *Gut* 1980; **21**: 215-8.
- 4 Chakraborty J, English J, Marks V, Dumasia MC, Chapman DJ. A radioimmunoassay method for prednisolone: comparison with competitive protein binding method. *Br J Clin Pharmacol* 1976; **3**: 903-6.
- 5 Lee DAH, Taylor GM, James VHT, Walker G. Plasma prednisolone levels and adrenocortical responsiveness after administration of prednisolone-21-phosphate as a retention enema. *Gut* 1979; **20**: 349-55.