Betamethasone 17-Valerate and Prednisolone 21-Phosphate Retention Enemata in Proctocolitis

A Multicentre Trial

British Medical Journal, 1971, 3, 84–86

Summary

The efficacy of betamethasone 17-valerate (5 mg) and prednisolone 21-phosphate (20 mg) retention enemata in the outpatient treatment of distal proctocolitis was compared in a formal clinical trial. The two treatments were equally effective in inducing remissions of the disease, but the betamethasone valerate enema produced less adrenal suppression.

Introduction

The efficacy of local steroid treatment in proctocolitis is well established (Truelove, 1958; Matts, 1960; Lennard-Jones *et al.*, 1962). In recent years betamethasone 17-valerate (Betnovate) has been recognized as a potent topical treatment for inflammatory skin diseases (Williams *et al.*, 1964; Munro *et al.*, 1967). It therefore seemed of interest to investigate the effect of this compound when applied topically to the inflamed colonic mucosa. Because prednisolone 21-phosphate is widely used in steroid enemas and has been claimed not to cause adrenal or pituitary suppression when given rectally in a dose of 20 mg daily (Matts *et al.*, 1963), a comparison was made between it and betamethasone 17-valerate when each was given in retention enemas for the treatment of outpatients with distal colitis.

Patients and Methods

SELECTION OF PATIENTS

The patients who took part in the trial were all outpatients suffering from an acute relapse or a first attack of idiopathic proctitis or left-sided ulcerative colitis. Proctitis was defined as active disease restricted to the rectum with a normal vascular pattern seen above at sigmoidoscopy. Left-sided colitis was defined as active disease in the rectum with no upper limit seen at sigmoidoscopy and with no radiological abnormalities proximal to the splenic flexure.

All the patients had symptoms and abnormal sigmoidoscopic appearances at the time of study. Those with mild systemic upset such as weight loss, fever, or malaise were accepted for treatment provided this was not of a degree which would normally have precluded outpatient treatment with topical corticosteroids alone. Patients were classed as untreated or sulphasalazine-treated. Untreated patients had had no treatment for six weeks before admission into the trial; patients presenting for the first time or those in a fresh relapse were included in this group. Sulphasalazine-treated patients were those who had relapsed while on sulphasalazine maintenance treatment, having had no corticosteroids for six weeks before admission into the trial. The dose of sulphasalazine was continued unchanged throughout the duration of the enema trial.

ALLOCATION OF PATIENTS

Each patient selected for the trial was given a pack containing 28 100-ml bottles of enemas, a 100-ml plastic syringe, a catheter, and a card on which to record daily bowel frequency and length of time for which the enema was retained. The enemas were administered by the patient nightly for four weeks (Jones *et al.*, 1965), each enema containing either 5 mg of betamethasone 17-valerate or 20 mg of prednisolone disodium 21-phosphate formulated in an identical cetomacrogol/liquid paraffin aqueous suspension with appropriate buffers.* The two drugs were allocated according to a random code, and neither the doctor nor the patient knew which treatment was given.

CONDUCT OF TRIAL AND ASSESSMENT OF RESULTS

The patients were seen at the start of treatment and after two and four weeks. At each attendance the patient's symptoms, weight, E.S.R., and haemoglobin were recorded. The frequency and character of the stools and the presence or absence of blood and mucus were noted. Side effects were not specifically inquired after, but were recorded if patients complained of them.

Sigmoidoscopy was performed at each attendance and the appearances were assessed independently by two observers, one of whom was unaware of the patient's symptoms. The mucosal appearances were graded as "severely haemorrhagic," "moderately haemorrhagic," "abnormal but not haemorrhagic," or "normal" when a vascular pattern was visible (Baron *et al.*, 1964). Blood for plasma cortisol estimation was taken as close as possible to 10 a.m. and never outside the range 9.30 a.m. to 12 noon. The plasma was frozen and the cortisol measured by a modified Mattingly method (Black and Friedman, 1965). Plotting of the plasma cortisol results showed a log-normal distribution and statistical analysis was therefore carried out after conversion of the data to logarithms. Student's *t* test was used for paired comparisons at two and four weeks within each group; comparisons between the two treatment groups were performed on the differences between the respective means. Iron preparations were not prescribed during the trial because oral iron sometimes aggravates the symptoms of colitis. Withdrawal of a patient from the trial at any time was left to the clinician's discretion.

The results of treatment were assessed at two weeks and at four weeks, the overall result being categorized as "remission," "improved," "no change," or "worse." A remission was defined as absence of rectal bleeding or discharge (an occasional trace of blood on a normal stool being allowable), minimal bowel disturbance, and a non-haemorrhagic mucosa.

The following physicians took part in the trial:

St. Mark's Hospital, London: J. HYWEL JONES, M.B., M.R.C.P.; J. E. LENNARD-JONES, M.D., F.R.C.P.; J. J. MISIEWICZ, M.B., M.R.C.P.ED.; J. A. PARRISH, M.D., M.R.C.P.

Royal Infirmary, Worcester: M. ATKINSON, M.D., F.R.C.P.

West London Hospital: A. MORTON GILL, M.D., F.R.C.P.; A. T. OTAKI, M.D., M.R.C.P.

Western General Hospital, Edinburgh: W. SIRCUS, M.D., F.R.C.P.(LOND., ED.); K. JALAN, M.B., M.R.C.P.ED., R. WALKER, M.B., M.R.C.P.

Western Infirmary, Glasgow: G. WATKINSON, M.D., F.R.C.P.

* A betamethasone 17-valerate enema will be available commercially in the near future.

Results

COMPARABILITY OF THE TREATMENT GROUPS

Of 110 patients originally admitted into the trial five were excluded—three failed to attend, one was unable to retain the enemas, and another failed to administer the enemas. Of the remaining 105 patients, 51 received betamethasone valerate and 54 received prednisolone 21-phosphate. Table I shows that the composition of the two groups was similar.

CLINICAL RESULTS

The results of clinical assessment of the patients after four weeks' treatment with betamethasone 17-valerate or prednisolone 21-phosphate enemas are summarized in Figs. 1 and 2. In Fig. 1 the results are shown in relation to the extent of the disease, and in Fig. 2 the patients are grouped according to whether or not they were taking sulphasalazine at the time of admission to the trial. It is apparent from Figs. 1 and 2 that the effectiveness of the two corticosteroids in the treatment of left-sided proctocolitis is similar. Of the patients treated with prednisolone 21-phosphate enemas alone, 17 out of 34 went into remission compared with 9 out of 15 who had sulphasalazine in addition. Of the patients treated with betamethasone 17-valerate enemas alone, 18 out of 36 went into remission compared with 10 out of 12 who had sulphasalazine in addition. The results at two weeks are summarized in Table II and show that fewer patients were in remission at this time than at four weeks.

TABLE I—*Composition of the Treatment Groups*

	Betamethasone Valerate	Prednisolone 21-phosphate
Total No. of patients	51	54
Untreated	38	37
Sulphasalazine treated	13	17
Extent of colitis: Proctitis	18	15
Extent of colitis: Left-sided colitis	32	34
Extent of colitis: Unspecified	1	5
Male	16	23
Female	35	31
Mean age (range)	41·5 years (17-77)	41 years (20-78)
Mean duration of disease (range)	5 years 10 months (1 month-33 years)	4 years 9 months (1 month-30 years)
Mean duration of present attack (range)	2·8 months (2 weeks-18 months)	3·4 months (2 weeks-18 months)

TABLE II—*Results of Clinical Assessment at Two Weeks*

Patients	Proctitis		Left-sided Colitis		Not Treated With Sulphasalazine		Treated With Sulphasalazine	
	B.	P.	B.	P.	B.	P.	B.	P.
In remission	2	4	6	7	3	8	5	3
Improved	12	8	23	23	29	22	7	12
No change or worse	2	3	2	3	4	6	0	2

B. = Betamethasone 17-valerate. P. = Prednisolone 21-phosphate.

Side effects were complained of by 13 patients—seven treated with betamethasone 17-valerate and six with prednisolone 21-phosphate enemata—but no patient stopped using the enemas for this reason. The side effects mentioned by patients treated with betamethasone valerate included backache, cramp in legs, malaise, indigestion, nausea, pain on defaecation, and a skin rash; those mentioned by patients treated with prednisolone 21-phosphate included abdominal discomfort, depression, malaise, and perianal irritation. No patient developed moon face or acne.

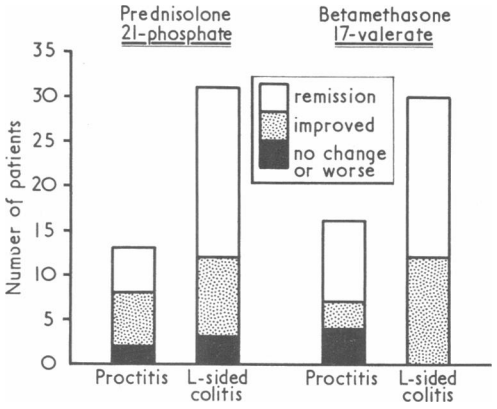

FIG. 1—Results of treatment at four weeks related to the type of treatment and extent of the colitis.

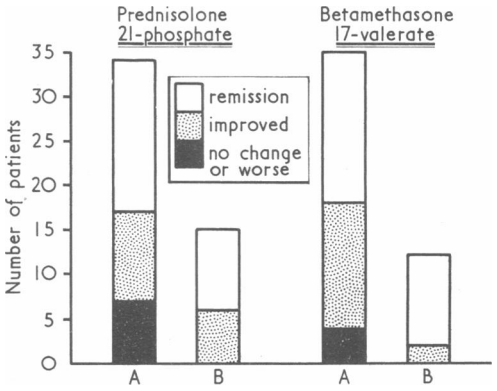

FIG. 2—Results of treatment at four weeks in patients treated with corticosteroid enemas alone (A) compared with results in patients treated also with Sulphasalazine (B).

PLASMA CORTISOL LEVELS

Serial measurement of plasma cortisol were available in 37 patients at two weeks and in 33 patients at four weeks in the betamethasone valerate group; the corresponding figures in the prednisolone group were 40 and 36. Six patients who showed evidence of residual adrenal suppression at entry into the trial (plasma cortisol < 8 μg/100 ml) were excluded from the consideration of effects of the treatments on adrenal function, but are included in the clinical analysis.

The plasma levels are shown in Fig. 3. There was no difference in the mean initial level of plasma cortisol in the two groups ($P > 0{\cdot}1$), but in both groups there was a significant fall in plasma cortisol after the first two weeks of the trial ($P < 0{\cdot}001$), indicating adrenal suppression during treatment. There was no further significant fall of the plasma cortisol levels at four weeks. However, both at two and at four weeks of the trial the mean plasma cortisol level was significantly lower in the patients treated with the prednisolone enemas than in those receiving the betamethasone valerate enemas ($P < 0{\cdot}001$). There was no apparent correlation between the percentage fall of plasma cortisol and the clinical response to treatment.

Discussion

Results of this trial indicate that 5 mg of betamethasone 17-valerate or 20 mg of prednisolone 21-phosphate are equally effective in inducing a remission when used locally in the outpatient treatment of proctocolitis, but the former produces less adrenal suppression. It is of interest that though orally admin-

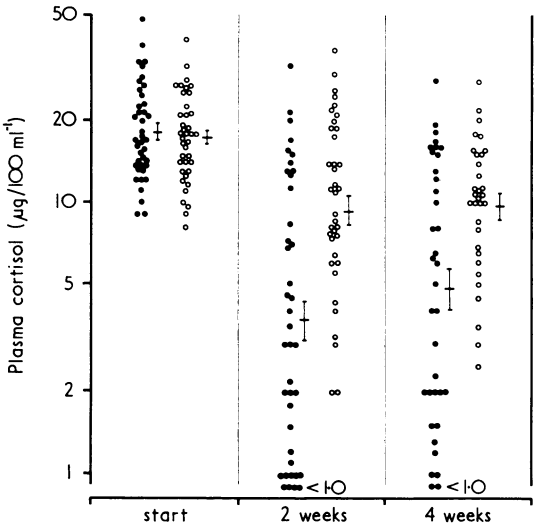

FIG. 3—Plasma cortisol levels before and after treatment for two and four weeks with the two types of retention enema. ● Prednisolone ○ Betamethasone valerate.

istered betamethasone 17-valerate also suppresses adrenal function, there are conflicting reports on its effectiveness in the treatment of colitis (Gill *et al.*, 1965; Friedman *et al.*, 1967). The present results are not helpful in deciding the relative importance of the local, as opposed to the systemic, actions of rectally administered steroids in the treatment of distal colitis. The greater proportion of patients in remission in the sulphasalazine-treated groups suggests that the effectiveness of both the corticosteroid enemas is enhanced by concurrent treatment with sulphasalazine. Betamethasone phosphate in 5-mg enemas has been shown to be effective in the treatment of proctocolitis, but produced moon face in all the patients studied (Matts, 1962). The same treatment resulted in a decreased excretion of 17-hydroxycorticosteroids and in a diminished response to corticotrophin, confirming that the steroid was being absorbed (Matts *et al.*, 1963).

In the present study with 5 mg of betamethasone valerate no clinical side effects of corticosteroid therapy have been noted, though the depression of adrenal cortical function suggests that absorption of this compound from the distal colon does occur. The explanation may be that the valerate is absorbed less readily than the phosphate.

There are conflicting views on the degree of rectal absorption of prednisolone 21-phosphate. Matts *et al.* (1963) found no suppression of adrenal corticol or anterior pituitary function in patients with proctocolitis after treatment with enemas containing 20 mg of prednisolone 21-phosphate. For this purpose they assessed the effect of corticotrophin and metyrapone on plasma and urine 17-hydroxycorticosteroids. This work appeared to be confirmed by the finding that the 24-hour excretion of prednisolone plus metabolites averaged only 3·6% when enemata containing 40 mg of prednisolone 21-phosphate were given to patients with proctocolitis (Wood *et al.*, 1964). On the other hand, 25 mg of rectal prednisolone 21-phosphate produced a significant reduction of plasma cortisol in patients free from intestinal disease, and the radioactivity in the urine collected for 24 hours after rectal administration of ^{14}C-labelled prednisolone averaged 72% of the given dose (Halvorsen *et al.*, 1969). Our findings confirm the reduction of adrenocortical function after rectal administration of prednisolone 21-phosphate and suggest that long-term treatment of this nature might indicate the necessity for corticosteroid cover should the patient subsequently undergo an operation. The lesser degree of adrenal suppression with equal therapeutic effect of betamethasone valerate enemas, if confirmed in further studies, is an advantage of this compound.

We thank Glaxo Laboratories Ltd., Greenford, Middlesex, and Miss L. C. Wilson for generously providing the betamethasone 17-valerate and prednisolone 21-phosphate enemas in the special packs and for help in the running and analysis of this trial.

Requests for reprints should be addressed to Dr. J. E. Lennard-Jones, St. Mark's Hospital, City Road, London EC1V 2PS.

References

Baron, J. H., Connell, A. M., and Lennard-Jones, J. E. (1964). *British Medical Journal*, **1**, 89.
Black, S., and Friedman, M. (1965). *British Medical Journal*, **1**, 562.
Friedman, M. *et al.* (1967). *British Medical Journal*, **1**, 335.
Gill, A. Morton, Otaki, A. T., Daly, J. R., and Spencer-Peet, J. (1965). *British Medical Journal*, **2**, 29.
Halvorsen, S., Myren, J., and Aakvaag, A. (1969). *Scandinavian Journal of Gastroenterology*, **4**, 581.
Jones, J. Howel, Lennard-Jones, J. E., and Misiewicz, J. J. (1965). *Gut*, **6**, 514.
Lennard-Jones, J. E., Baron, J. H., Connell, A. M., and Jones, F. Avery (1962). *Gut*, **3**, 207.
Matts, S. G. Flavell (1960). *Lancet*, **1**, 517.
Matts, S. G., Flavell (1962). *Gut*, **3**, 312.
Matts, S. G., Flavell, Wharton, B. A., Kelleher, J., and Walters, G. (1963). *British Medical Journal*, **2**, 24.
Munro, D. D., Wilson, H. T. H., and Rhodes, Ellen, L. (1967). *British Medical Journal*, **4**, 275.
Truelove, S. C. (1958). *British Medical Journal*, **2**, 1072.
Williams, D. I., *et al.* (1964). *Lancet*, **1**, 1177.
Wood, W. A., Walters, G., and Matts, S. G. Flavell (1964). *British Medical Journal*, **2**, 1045.