Rectally administered prednisolone—evidence for a predominantly local action

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SUMMARY Plasma prednisolone levels have been compared in healthy volunteers and in patients suffering from idiopathic proctocolitis after the administration of standard retention enemata containing either prednisolone-21-phosphate or prednisolone metasulphobenzoate sodium. The levels were significantly lower after the latter, irrespective of the presence or degree of activity of the disease. Prednisolone metasulphobenzoate appeared to be as effective as the 21-phosphate ester for the treatment of proctocolitis in the few patients where the two drugs were compared. It seems possible that the beneficial effect of the form of therapy is exerted predominantly locally, rather than by systemic action.

The effectiveness of rectally administered prednisolone in the treatment of idiopathic proctocolitis has been well established since the early 1960s, although whether its predominant action is local or systemic or a combination of the two has been disputed. In a recent communication, we concluded that the predominant effect was exerted locally but that sufficient prednisolone was absorbed for there also to be some systemic action.

Most of the previous studies of the efficacy of rectally administered prednisolone and its site of action have been of preparations containing prednisolone-21-phosphate. A retention enema containing prednisolone metasulphobenzoate sodium (Predenema; Pharmax) has been available for clinical use for several years, but its efficacy has not been formally tested.

In this study, we have compared plasma prednisolone levels in normal subjects and patients suffering from idiopathic proctocolitis after administration of the two preparations of retention enema. Although not designed as a clinical trial, this study has enabled us to obtain a clinical impression of the efficacy of prednisolone metasulphobenzoate in the treatment of proctocolitis.

Methods

Subjects
Nine subjects each received a standard prednisolone-21-phosphate retention enema which contains the equivalent of 20 mg prednisolone alcohol. Four were suffering from an acute exacerbation of proctocolitis as judged by symptomatology, sigmoidoscopic appearances, and rectal biopsy and another three were entering remission after a variable period of treatment with this form of therapy. The remaining two subjects were healthy volunteers.

Eleven subjects each received a retention enema of prednisolone metasulphobenzoate, which contains the equivalent of 20 mg prednisolone alcohol. Seven had been diagnosed as having proctocolitis, three of whom had suffered a recent relapse. The remaining four subjects were healthy volunteers.

Five of the 11 subjects had also been studied after receiving a prednisolone-21-phosphate enema (see above).

The test enema was administered at 8.30 a.m. Five millilitre blood samples were taken at 20 minute intervals for four hours and then hourly for another three, through an indwelling cannula inserted in a forearm vein. The samples were taken into lithium heparin tubes, and at the end of the test period were centrifuged and the plasma stored at −20°C until assayed. All the subjects remained supine after administration of the enema, which was retained by each of them for at least four hours. The patients who were receiving therapy with prednisolone retention enemata at the time of the study were instructed to administer their last one no later than 24 hours before the start of the test.

Plasma prednisolone levels were measured by a radioimmunosassay technique that has been outlined elsewhere. The samples were assayed using an antiserum to prednisolone which cross-reacted...
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Fig. 1 Mean plasma prednisolone concentration-time profiles after administration of prednisolone-21-phosphate to healthy subjects (■—■) and to patients with colitis (●—●) and prednisolone metasulphobenzoate to healthy subjects (□—□) and to patients with colitis (◇—◇).

slightly in vitro with cortisol (10%) and prednisone (5%). The specificity of the method was checked by assaying several samples with and without separation of the prednisolone by paper chromatography. No significant difference was found between the two sets of results, except at time zero, which was probably due to cross-reaction with cortisol. The plasma cortisol concentration always diminished over the test period.

Results

The mean plasma prednisolone concentration-time profiles after administration of both preparations to normal subjects and patients suffering from proctocolitis are shown in Fig. 1. After prednisolone-21-phosphate, appreciable amounts of prednisolone were detectable in the peripheral circulation, both in patients suffering from colitis and the healthy subjects. Disease activity did not affect plasma levels, but the two healthy subjects did achieve higher concentrations, although the numbers were too small for statistical analysis. After prednisolone metasulphobenzoate, peak plasma prednisolone levels (CMax) were significantly lower (p<0.001), and there was no difference between the patients with colitis and the healthy subjects (0.4<p<0.5). Individual profiles are shown in Fig. 2. Five of the subjects received both types of enema (Fig. 3) and in all of them plasma prednisolone levels were lower after the metasulphobenzoate preparation.

Two of the subjects, and two others not included in this study, were treated for an exacerbation of proctocolitis for up to four weeks with prednisolone metasulphobenzoate enemata. Three of them had received treatment in the past with prednisolone-21-phosphate enemata, and were therefore able to make a subjective comparison between the forms of

Fig. 2 Individual plasma prednisolone concentration-time profiles after administration of prednisolone metasulphobenzoate.
therapy. All four subjects responded to therapy with prednisolone metasulphobenzoate as judged by the improvement in symptoms and sigmoidoscopic appearances. The clinical impression was that the response was as good as that usually seen after treatment with prednisolone-21-phosphate. The three patients who had received both preparations also felt that there was no difference between them in terms of their efficacy.

Discussion

Previous attempts to define the site of action of rectally administered prednisolone have involved the use of enemata containing either the 21-phosphate ester\(^4\)\(^5\)\(^9\)\(^10\)\(^11\) or radio-labelled methyl prednisolone.\(^5\)\(^9\)\(^10\)\(^18\) The amount of prednisolone that was absorbed (and hence conclusions about its predominant site of action) was assessed by measuring either the concentration of the free steroid or the amount of radioactivity in a 24-hour urine collection. The results were inconsistent and opinions divided as to whether the predominant site of action was local, systemic, or a combination of the two. More recently, in 1976, Powell-Tuck et al.\(^5\) compared plasma levels after the rectal administration of prednisolone-21-phosphate with those achieved after a similar dose of the drug had been given by mouth. They concluded that the beneficial effect of this form of therapy was due to a combination of local and systemic action and noted similar plasma prednisolone levels after both modes of administration. By contrast, our own study\(^4\) revealed significantly less rise in plasma prednisolone after the rectal preparation than after an oral dose.

In the present study, we have demonstrated that significantly less prednisolone reached the peripheral circulation after administration of a retention enema containing the steroid as its metasulphobenzoate ester than when the equivalent dose of rectal prednisolone-21-phosphate was given. It is possible that prednisolone metasulphobenzoate reached the circulation intact (the ester itself would not be measured by the assay) but this is unlikely as it has been demonstrated that for absorption to occur, steroid esters are usually hydrolysed in the bowel lumen or mucosal cells.\(^18\) After oral administration, prednisolone metasulphobenzoate is hydrolysed\(^18\) and a possible reason why more prednisolone was detectable in the circulation after the 21-phosphate ester than after the metasulphobenzoate is that the milieu of the rectum and distal colon is inappropriate for the hydrolysis of the latter. This explanation of the possible different behaviour of the two pred-

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**Fig 3** Individual plasma prednisolone concentration-time profiles after administration of prednisolone-21-phosphate (♦ — ♦) and prednisolone metasulphobenzoate (◇ — ◇) in five subjects who received both preparations.
nisolone esters is at present, however, only a hypothesis and could be confirmed by further incubation experiments with faecal homogenates and/or biopsy material. However, some degree of hydrolysis probably occurred because, in most of the subjects, prednisolone was detectable after administration of the metasulphobenzoate ester. Similar observations have been made for several different esters of cortisol which were equally effective in the treatment of proctocolitis. Thus cortisol acetate was not absorbed\(^{14}\) whereas the plasma cortisol concentration rose after rectal administration of the hemisuccinate.\(^{14}\)\(^{16}\)\(^{17}\)

An alternative explanation for the detection of prednisolone in the circulation after metasulphobenzoate is also theoretically possible. The enema may contain up to 4% prednisolone alcohol (personal communication) and some at least of the circulating steroid may have come from this source.

Although this study was not designed to be a formal trial, the clinical impression gained was that prednisolone metasulphobenzoate administered as a retention enema was equally effective in the treatment of proctocolitis as prednisolone-21-phosphate.

The finding of lower plasma prednisolone levels after the former suggests therefore that the predominant site of action of this form of therapy is local.

A formal clinical trial to compare the efficacy of these two preparations would now seem to be indicated. If it is confirmed that prednisolone metasulphobenzoate is equally effective, this might be the treatment of choice, because only small amounts of prednisolone reach the systemic circulation, thereby reducing the risk of side-effects.

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