Prednisolone absorption in acute colitis

P R ELLIOTT,¹ J POWELL-TUCK,² P E GILLESPIE,³ J M LAIDLAW,
J E LENNARD-JONES, J ENGLISH, J CHAKRABORTY, AND V MARKS

From St. Mark's Hospital, London, and the Department of Biochemistry, University of Surrey, Guildford

SUMMARY Peak plasma levels were reduced after an oral dose of 40 mg prednisolone in six patients with severe acute colitis as compared with six normal subjects, though total absorption appeared to be similar; the findings suggest that prednisolone absorption was delayed in acute colitis. A dilutional fall in plasma albumin was observed in normal subjects and in the patients after 40 mg prednisolone by mouth.

In severe acute colitis prednisolone is often given by intravenous infusion rather than by mouth, though there is no direct evidence that intestinal absorption of the drug is impaired. Previous observations have shown that the expected suppression of blood cortisol levels by oral prednisone may not occur in acute colitis, a fact that could indicate poor absorption (Friedman *et al.*, 1969). Plasma prednisolone levels, measured by radioimmunoassay, after a single oral therapeutic dose of prednisolone in patients with severe acute colitis are compared in this study with the levels observed after the same dose in normal subjects.

Methods

CLINICAL METHODS

Six patients with severe acute colitis (Table 1) and six healthy volunteers were studied after obtaining their informed consent. Subjects fasted for 10 hours before, and during the eight hours after, taking 40 mg prednisolone by mouth. Blood samples were withdrawn through an indwelling venous needle, kept patent with sodium citrate, before and 30, 60, 90, 120, 150, 180, 240, 360, and 480 minutes after the dose. Each sample was centrifuged immediately and the plasma stored at -20°C until analysis.

¹Address for reprint requests: P R Elliott, St. Mark's Hospital, City Road, London ECV1 2PS.

²Powell-Tuck, Wellcome Research Fellow, Clinical Nutrition and Metabolism Unit, Hospital for Tropical Disease, St. Pancras Way, London.

³Present address: P E Gillespie, Department of Gastroenterology, Westmead Hospital, Westmead, Sydney, Australia.

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LABORATORY METHODS

Prednisolone assay

Prednisolone was measured by radioimmunoassay of an ethyl acetate extract of the plasma samples using an antiserum with a low cortisol cross-reactivity raised in sheep against prednisolone-21-hemisuccinate (Chakraborty *et al.*, 1976, Henderson *et al.*, 1979). As the dose levels—and therefore the blood levels—were relatively high, it was felt that the thin layer chromatography step, which eliminates cortisol interference, could be omitted. The cortisol cross-reactivity with the antiserum used was 4%. The residue from the ethyl acetate extract of plasma was dissolved in buffer and an aliquot used in the radioimmunoassay.

Free prednisolone

One millilitre of the plasma sample containing a trace amount of 6,7-³H-prednisolone (100 000 dpm; Sp. act 43 Ci/mmol) was dialysed against 1 ml phosphate buffer (pH 7.4, 0.1M) for 16 hours at room temperature. The solutions were contained in Teflon dialysis cells and separated by a Visking membrane. The percentage of the radiolabelled steroid which dialysed into the buffer was taken to be a reflection of the percentage of the non-protein bound prednisolone in the plasma.

Plasma albumin concentration was measured by the bromocresol green method (Hernandez *et al.*, 1967). Prednisolone did not interfere with the assay either by altering the extinction coefficient or by shifting the wavelength of the peak colour formation.

Statistical methods

The statistical significance of the results was estimated using Student's *t* test.

As the drug was administered orally it is not

Table 1 Details of patients studied

Sex, age (yr)	Temperature* (°C)	No. bowel action* (24 h)	Haemoglobin† (g/dl)	ESR* (mm/h)	Baseline albumin† (g/l)	Extent of disease	Sigmoidoscopic appearances	Surgery same admission
M30	37.5	5	13.3	26	35	Extensive	Spontaneous haemorrhage	Yes
M 52	38	5	8.1	88	33	Extensive	Spontaneous haemorrhage	Yes
F58	37.8	7	12.6	77	32	Substantial	Friable	No
F 65	36.2	12	11.7	17	30	L-sided	Spontaneous haemorrhage	Yes
F 31	37.8	6	11.4	40	36	Extensive	Spontaneous haemorrhage	Yes
F 23	37	9	10.1	100	28	Extensive	Minimal abnormality‡	No

*Highest in first 48 hours. †Lowest in first 48 hours. ‡Rectal sparing, probable Crohn's disease.

possible to use the term 'plasma half-life' in its strict sense. The time taken for the plasma concentration of the drug to fall to half its maximal concentration was calculated from the log. concentration of the drug in the plasma against linear time.

The area under the plasma curve from zero to eight hours was calculated by numerical integration using the trapezoidal rule.

Fig. 1 (a) Plasma prednisolone measured in six patients with acute colitis and in six healthy volunteers after taking prednisolone 40 mg orally (mean $\pm$ SEM). (b) Plasma free prednisolone measured in six patients with acute colitis and in six healthy volunteers after taking prednisolone 40 mg orally (mean $\pm$ SEM).

Fig. 2 Plasma albumin measured in six patients with acute colitis and in six healthy volunteers after taking prednisolone 40 mg orally (mean $\pm$ SEM).

Results

PLASMA PREDNISOLONE LEVELS (Fig. 1a and b)

The mean total plasma prednisolone at 60 minutes was less ($P < 0.01$) in the patients ($181 \text{ ng/ml} \pm 47 \text{ SEM}$) than in the control subjects (362 ± 41). At 180 minutes, and thereafter, the mean plasma levels of the patients tended to be higher than the controls. Results for mean plasma free prednisolone paralleled these results.

The area under the curves for total and free prednisolone over the eight hour study period was similar for patients and controls (Table 2). The time taken for the plasma concentration of the drug to fall to half its maximal concentration was markedly longer in the patients ($P < 0.001$).

PLASMA ALBUMIN LEVELS (Fig. 2)

Plasma albumin levels were less ($P < 0.001$) in the patients than in the controls. The levels dropped

Table 2 Mean values ($\pm$ SEM) for total and free prednisolone

Subjects	Total prednisolone				Free prednisolone		
	Peak time (min)	Peak concentration (ng/ml)	Area under curve (ng/ml/h)	T1/2 (min)	Peak time (min)	Peak concentration (ng/ml)	Area under curve (ng/ml/h)
Patients ($\pm$ SEM)	180	206* ± 35	1236 ± 167	300† ± 24	90	47 ± 10	251 ± 36
Controls ($\pm$ SEM)	60	362* ± 44	1305 ± 155	138† ± 36	60	84 ± 11	232 ± 25

* <0.01 , † <0.001 .

($P<0.02$) in the control subjects to a minimum 60 minutes after the dose of prednisolone and a similar trend was seen in the patients from 0–240 minutes after the dose. The reduction in plasma albumin was paralleled by reductions in the plasma concentrations of urea, sodium, and free fatty acids.

Discussion

This study does not show that the total absorption of prednisolone differs between patients with severe acute colitis and normal subjects, but it has suggested a different pattern of absorption. A higher peak level of total prednisolone occurred in normal subjects, and free prednisolone followed the same trend. Later results showed a tendency for the levels in the patients to fall more slowly than in the control subjects. The most likely explanation of this finding is delayed absorption of prednisolone from the gastrointestinal tract of patients with severe acute colitis. Reduced plasma clearance as a major cause of the sustained plasma levels in patients seems unlikely, as peak levels were earlier and higher in normal subjects.

The possible clinical significance of delayed absorption with a low peak and prolonged rise of plasma prednisolone levels in the patients is uncertain. A clinical trial has shown that prednisolone 40 mg given in one oral dose daily appears to be therapeutically equivalent to four doses of 10 mg taken at intervals through the day (Powell-Tuck *et al.*, 1978), a finding which suggests that total absorption is more important than the peak level achieved. As the area under the curve in both normal subjects and patients with acute colitis in this experimental study was similar, it is likely that the total prednisolone absorbed was the same and the results of the controlled trial suggest that delayed absorption should not alter the efficacy of this orally administered prednisolone.

A surprise finding after prednisolone administration in control subjects was the fall of plasma albumin by about 20% of the original value at 60 minutes and which persisted to a lesser degree for three

to four hours after the dose. A similar fall by about 14% occurred in the patients. This change was most likely to be dilutional because the concentration of urea, sodium, and free fatty acids also fell. The observation is analogous to that of Lahdensuu *et al.*, (1975) who found a fall in haematocrit of traumatised rabbits after methyl prednisolone.

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