*Br. J. clin. Pharmac.* (1992), **33**, 495–499

# A pharmacokinetic and pharmacodynamic comparison of plain and enteric-coated prednisolone tablets

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**1** Eight healthy volunteers and eight patients suffering from chronic obstructive pulmonary disease (COPD) received 30 mg prednisolone as plain (P) and enteric-coated tablets (EP) in a randomised, cross-over manner. Plasma prednisolone and cortisol and blood glucose were measured over 24 h.

**2** Although absorption of prednisolone was considerably slower when administered as the enteric-coated form, peak plasma drug concentrations and total AUC (0,24 h) were equivalent for the two formulations. Malabsorption of prednisolone was not observed.

**3** The administration of EP was associated with significantly less adrenal suppression in volunteers than P as judged by measurement of AUC (0,24 h) values for endogenous cortisol. However, this difference did not reach statistical significance in the patient group.

**4** Plasma cortisol concentrations declined more slowly following administration of the enteric-coated form to both groups. The difference in time taken (median and range) to maximum suppression of cortisol was statistically significant ($P < 0.05$) between P (2.5 h; 2–4 h) and EP (4 h; 3–12 h) preparations administered to volunteers. There was a similar significant difference ($P < 0.05$) between P (2.5 h; 1–4 h) and EP (7 h; 2–12 h) in the patients.

**5** Plasma cortisol concentrations were significantly lower at 24 h in patients receiving the enteric-coated product in association with higher terminal prednisolone concentrations.

**6** Blood glucose concentrations increased over an 8 h period in both groups. The mean maximum values were 8.2 mmol $l^{-1}$ (P) and 7.7 mmol $l^{-1}$ (EP) in volunteers and 9.5 mmol $l^{-1}$ (P) and 10.8 mmol $l^{-1}$ (EP) in patients. A lag in the increase of glucose following administration of the enteric-coated form was not observed.

**7** Eosinophil counts were significantly reduced to an equal extent after administration of P and EP in both patients and volunteers.

**Keywords** prednisolone pharmacokinetics pharmacodynamics formulation

## Introduction

It has been shown that gastric irritation associated with oral corticosteroids can be minimised by the use of an enteric-coated formulation (Kammerer *et al.*, 1958). Enteric-coating can, however, lead to changes in steroid bioavailability. For example, incomplete or variable absorption of enteric-coated prednisolone (EP) has been reported in renal transplant patients (Hulme *et al.*, 1975), and in patients with rheumatoid arthritis (Hayes *et al.*, 1983) and pulmonary disease (Mant, 1979). We have recently shown that the extent of absorption for a plain prednisolone tablet and an enteric-coated formulation was equivalent in healthy subjects although absorption was slower with the latter preparation (McCann *et al.*, 1987).

The aim of this investigation was to compare plasma concentrations of prednisolone after administration of these two formulations of prednisolone to normal volunteers and to patients with chronic obstructive

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pulmonary disease (COPD). Plasma cortisol and blood glucose concentrations and eosinophil counts were also measured.

## Methods

### *Study protocol*

The study involved eight COPD patients (4M;4F: age range 63–81 years) and eight normal volunteers (8M: age range 22–44 years) who were randomised to receive 30 mg plain prednisolone (P: Precortisyl tablets 5 mg, Roussel Laboratories) or enteric-coated prednisolone (EP: Deltacortril Enteric tablets 5 mg, Pfizer Ltd), with 100 ml water, at 09.00 h following an overnight fast. Venous blood samples (10 ml) were withdrawn through an indwelling venous catheter before prednisolone administration and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h post-dosing. A light lunch was provided 3 h after drug administration. The blood was collected in heparinised tubes and the separated plasma stored at −20°C prior to assay of prednisolone and cortisol by high-performance liquid-chromatography (h.p.l.c.).

In addition, samples of whole blood were analysed for glucose by a standard laboratory method (YSI, Clandon Instruments, UK) at the biochemistry laboratory of the Royal Victoria Hospital. Samples for eosinophil count were taken before the study and 4 h after drug administration.

The study was carried out in a randomised cross-over manner. After a 7 day wash-out period each subject received the alternative prednisolone preparation. While all patients had received previous steroid therapy, those who had had a course of prednisolone within 1 month of study were excluded. However, all were receiving inhaled steroids (beclomethasone 500 μg four times daily). None of the volunteers had ever received oral or inhaled steroids.

The study was approved by the ethics committee of The Queens University of Belfast and all volunteers and patients gave informed, written consent prior to the investigation.

### *Pharmacokinetic analysis*

AUC (0,24 h) values of prednisolone were calculated using the linear trapezoidal rule and used for subsequent statistical analysis. These values were shown to be greater than 90% of the AUC extrapolated to infinity. Maximum plasma concentrations of prednisolone ($C_{max}$) and the times at which they occurred ($t_{max}$) were determined for each subject as were the times to attain trough concentrations of endogenous cortisol and maximum blood concentrations of glucose. These values were compared statistically using the Wilcoxon signed rank test, while time-paired concentrations and AUC data were compared using analysis of variance with repeated measures.

### *Prednisolone and cortisol analysis*

Prednisolone and cortisol concentrations were determined in plasma using h.p.l.c. (McElnay, 1988). The instrumentation comprised a Shimadzu LC-6A pump, a Shimadzu SPD-6A Spectrophotometer (Shimadzu Corporation, Kyoto, Japan), a Waters Wisp 710b autosampler (Waters Millipore, UK) and a Trio data analyser (Trivector, Bedfordshire, UK).

The mobile phase consisted of dichloromethane (66.45% v/v), water saturated dichloromethane (30% v/v), methanol (2.5% v/v), tetrahydrofuran (1.0% v/v) and glacial acetic acid (0.05% v/v). The column was Hypersil silica (25 cm × 4.6 mm i.d. 5 μm particle size: Shandon, Deeside, UK) through which the mobile phase was pumped at a flow rate of 2 ml $min^{-1}$. Detection was by u.v. absorption at 240 nm. The reagents used were of h.p.l.c. grade and were filtered and degassed prior to use. All analyses were performed in duplicate. The coefficients of variation of the prednisolone and cortisol assays were less than 5%. The limit of determination of the assay for prednisolone and cortisol was 5 ng $ml^{-1}$.

Extraction of the sample involved addition of 0.1 ml internal standard (1 mg $ml^{-1}$ solution of dexamethasone) to 1.9 ml plasma. Prednisolone and cortisol were then extracted into 6 ml 60% ether/40% dichloromethane (v/v) by vortex mixing for one minute followed by centrifugation for a further 5 min at 2000 rev $min^{-1}$. The organic phase (5 ml) was added to 1 ml of 0.1 M NaOH and vortex mixed for 30 s. Following further centrifugation (2000 rev $min^{-1}$) 4 ml of the organic phase were then transferred to a separate tube, evaporated to dryness under warm air and reconstituted using 250 μl of mobile phase. Aliquots (100 μl) of this solution were then injected onto the column.

## Results

The pharmacokinetic parameters describing the fate of prednisolone are summarised in Table 1. Mean plasma concentrations of prednisolone and cortisol and mean blood glucose concentrations for each study group/preparation are shown in Figures 1, 2 and 3, respectively.

A lag in absorption was apparent after administration of the enteric-coated preparation of prednisolone when compared with the plain tablet in normal volunteers and

**Table 1** Pharmacokinetic parameters of prednisolone in eight patients with COPD (Pt) and eight healthy volunteers (Vol) after administration of plain (P) and enteric-coated (EP) prednisolone tablets 30 mg. Data for $C_{max}$ and AUC are mean and 95% confidence interval while data for $t_{max}$ are presented as median and range

| *Prednisolone preparation* | $C_{max}$ *(ng $ml^{-1}$)* | $t_{max}$ *(h)* | AUC(0,24 h) *(ng $ml^{-1}$ h)* |
|---|---|---|---|
| $P_{Pt}$ | 531 (489,574) | 2.5* (1–4) | 4249 (3482,5015) |
| $EP_{Pt}$ | 431 (315,547) | 7.0 (2–12) | 4020 (3359,4681) |
| $P_{vol}$ | 491 (473,509) | 2.5* (2–4) | 3127 (2832,3421) |
| $EP_{vol}$ | 488 (460,516) | 4.0 (3–12) | 3816 (3505,4117) |

* $P < 0.05$ compared with other treatment.

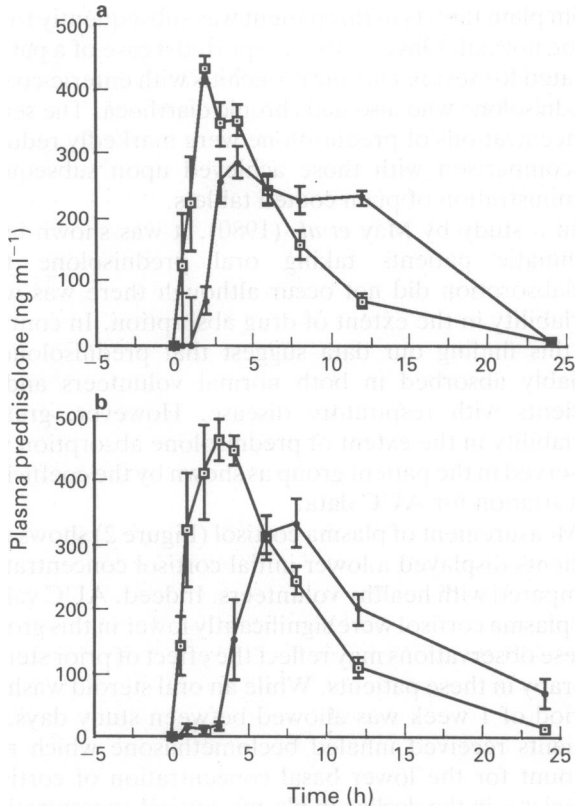


**Figure 1** Mean ± (s.e. mean) plasma prednisolone concentrations in (a) healthy volunteers and (b) patients after administration of enteric-coated (•) and plain tablets (□). The dose of prednisolone administered was 30 mg.

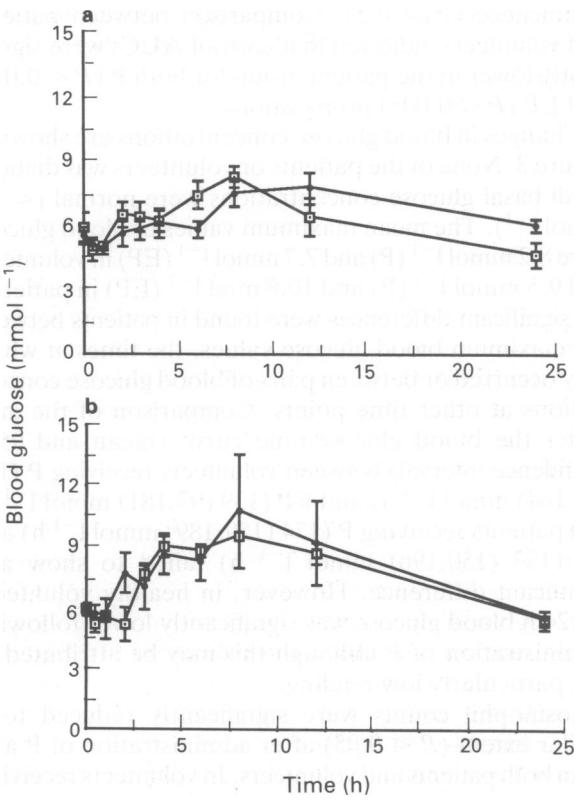


**Figure 3** Mean (± s.e. mean) blood glucose concentrations over the 24 h study period in (a) healthy volunteers and (b) patients after administration of enteric-coated (•) and plain tablets (□).

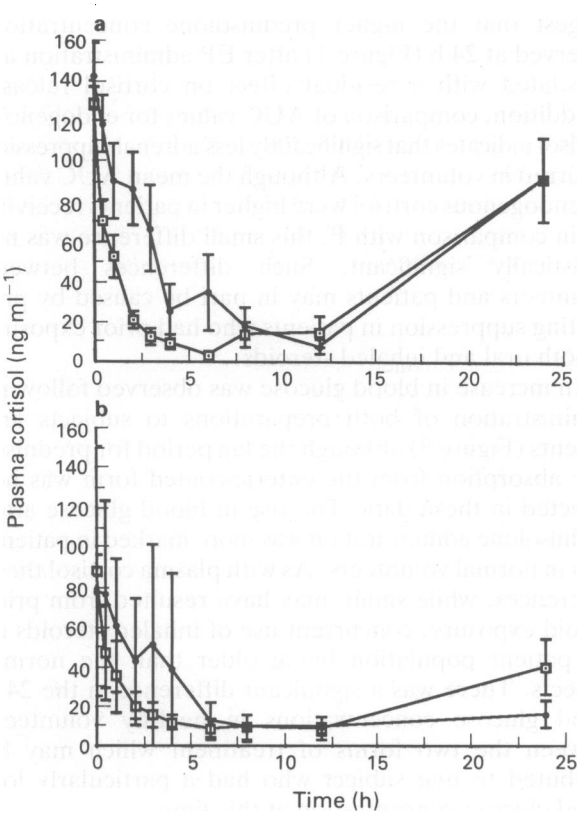


**Figure 2** Mean (± s.e. mean) plasma cortisol concentrations in (a) healthy volunteers and (b) patients after administration of enteric-coated (•) and plain tablets (□).

patients (Figure 3). The value of $t_{max}$ was significantly prolonged in the case of EP for both study groups ($P < 0.05$). In addition, comparison of plasma concentrations at each specified time interval showed significant differences between P and EP at 1, 2, 3, 4 and 8 h in patients and at 1, 2 and 4 h in the volunteer group. However, no significant differences were observed between $C_{max}$ or AUC values for P and EP in either study population. The coefficients of variation of AUC (P) and AUC (EP) were 20.1% and 18.4%, respectively, in patients and in volunteers they were 11.3% (P) and 9.8% (EP).

In patients and volunteers, plasma cortisol concentrations declined more slowly after administration of EP (Figure 2). The difference in time taken (median and range) to reach trough concentrations was statistically significant ($P < 0.05$) between P (2.5 h, 2–4 h) and EP (4 h, 3–12 h) preparations administered to volunteers. There was also a significant difference ($P < 0.05$) in this parameter between P (2.5 h, 1–4 h) and EP (7 h, 2–12 h) in the patients. Significant differences ($P < 0.05$) were noted in cortisol concentrations between P and EP at 24 h in patients and at 2 h in volunteers. No other differences between pairs of data points were observed. The area under the cortisol concentration-time curve (AUC) was measured for each preparation in both patients and volunteers. There was a significant difference ($P < 0.025$) in the cortisol AUC (mean and 95% confidence interval) between volunteers administered P (950 (649,1250) ng ml$^{-1}$ h) and EP (1323 (1024,1622) ng ml$^{-1}$ h). However, the difference in cortisol AUC for patients receiving P (548 (357,738) ng ml$^{-1}$ h) and EP (657 (425,889) ng ml$^{-1}$ h) failed to reach statistical

significance ($P > 0.5$). Comparison between patients and volunteers indicated that cortisol AUCs were significantly lower in the patient group for both P ($P < 0.025$) and EP ($P < 0.005$) preparations.

Changes in blood glucose concentrations are shown in Figure 3. None of the patients or volunteers was diabetic as all basal glucose concentrations were normal (< 7.8 mmol $l^{-1}$). The mean maximum values of blood glucose were 8.2 mmol $l^{-1}$ (P) and 7.7 mmol $l^{-1}$ (EP) in volunteers and 9.5 mmol $l^{-1}$ (P) and 10.8 mml $l^{-1}$ (EP) in patients. No significant differences were found in patients between the maximum blood glucose values, the times at which they occurred or between pairs of blood glucose concentrations at other time points. Comparison of the area under the blood glucose-time curve (mean and 95% confidence interval) between volunteers receiving P (131 (98,164) mmol $l^{-1}$ h) and EP (139 (97,181) mmol $l^{-1}$ h) and patients receiving P (174 (159,189) mmol $l^{-1}$ h) and EP (173 (150,196) mmol $l^{-1}$ h) failed to show any significant difference. However, in healthy volunteers the 24 h blood glucose was significantly lower following administration of P although this may be attributed to one particularly low reading.

Eosinophil counts were significantly reduced to a similar extent ($P < 0.05$) after administration of P and EP in both patients and volunteers. In volunteers receiving P, eosinophils (mean and 95% confidence interval) decreased over 4 h from 160 (66,254) cells $\mu l^{-1}$ to 46 (15,61) cells $\mu l^{-1}$ and for EP from 250 (110,390) cells $\mu l^{-1}$ to 103 (14,191) cells $\mu l^{-1}$. In the patient group these decreases were from 213 (130,296) cells $\mu l^{-1}$ to 106 (64,148) cells $\mu l^{-1}$ and from 408 (301,515) cells $\mu l^{-1}$ to 162 (82,242) cells $\mu l^{-1}$ for plain and enteric-coated preparations respectively.

## Discussion

Kammerer *et al.* (1958) observed peptic ulceration in patients treated for rheumatoid arthritis with oral corticosteroids. These findings suggested that cortisol analogues affect the gastric mucosa by a direct action since the incidence of dyspepsia was much lower in patients receiving corticotrophin who also displayed Cushing's syndrome. These findings led to the development of enteric-coated preparations of glucocorticosteroids which release the active drug in the lower gastrointestinal tract, thereby minimising the incidence of gastric irritation and ulceration (West, 1959).

Our data for patients and volunteers demonstrate that there is a significant lag in the absorption of prednisolone when administered in the enteric-coated form. While the rate of absorption differed between the two preparations, there was no difference in the extent of absorption either in normal volunteers or patients.

Previous authors have reported individual cases of malabsorption of enteric-coated steroids in patients being treated for respiratory disorders. Mant (1979) reported the therapeutic failure of enteric coated prednisolone administered to an asthmatic patient. Malabsorption was confirmed by the demonstration of abnormally low plasma prednisolone concentrations associated with the use of these tablets. The absorption of prednisolone from plain tablets in this patient was subsequently found to be normal. Olivesi (1985) reported a case of a patient treated for severe chronic bronchitis with enteric-coated prednisolone who also had chronic diarrhoea. The serum concentrations of prednisolone were markedly reduced in comparison with those achieved upon subsequent administration of plain coated tablets.

In a study by May *et al.* (1980), it was shown in 12 asthmatic patients taking oral prednisolone that malabsorption did not occur although there was wide variability in the extent of drug absorption. In contrast to this finding our data suggest that prednisolone is reliably absorbed in both normal volunteers and in patients with respiratory disease. However, greater variability in the extent of prednisolone absorption was observed in the patient group as shown by the coefficient of variation for AUC data.

Measurement of plasma cortisol (Figure 2) shows that patients displayed a lower initial cortisol concentration compared with healthy volunteers. Indeed, AUC values for plasma cortisol were significantly lower in this group. These observations may reflect the effect of prior steroid therapy in these patients. While an oral steroid washout period of 1 week was allowed between study days, all patients received inhaled beclomethasone which may account for the lower basal concentration of cortisol. The delay in the decline in plasma cortisol concentrations in both study groups following administration of the EP preparation is consistent with the lag in absorption of prednisolone observed with the enteric-coated preparation. Although cortisol profiles for P and EP were similar there was a significantly prolonged depression in cortisol concentrations at 24 h following administration of the enteric-coated preparation to patients. These data suggest that the higher prednisolone concentrations observed at 24 h (Figure 1) after EP administration are associated with a residual effect on cortisol release. In addition, comparison of AUC values for endogenous cortisol indicates that significantly less adrenal suppression occurred in volunteers. Although the mean AUC values for endogenous cortisol were higher in patients receiving EP in comparison with P, this small difference was not statistically significant. Such differences between volunteers and patients may in part be caused by pre-existing suppression in patients who had prior exposure to both oral and inhaled steroids.

An increase in blood glucose was observed following administration of both preparations to subjects and patients (Figure 3) although the lag period for prednisolone absorption from the enteric-coated form was not reflected in these data. The rise in blood glucose after prednisolone administration was more marked in patients than in normal volunteers. As with plasma cortisol these differences, while small, may have resulted from prior steroid exposure, concurrent use of inhaled steroids or the patient population being older than the normal subjects. There was a significant difference in the 24 h blood glucose concentrations in healthy volunteers between the two forms of treatment which may be attributed to one subject who had a particularly low blood glucose concentration at this time.

In all cases, eosinophil counts were observed to decline rapidly following administration of either prednisolone preparation. Kong *et al.* (1989) have developed a

pharmacokinetic/pharmacodynamic model describing various responses to methylprednisolone including cortisol suppression. They have shown that the time course of the cellular effects of methylprednisolone (basophil histamine decline) may be predicted by this means.

In conclusion, our data indicate that in patients with COPD, although absorption of prednisolone was considerably slower when administered as an enteric-coated tablet, peak plasma drug concentrations and total prednisolone absorption (as measured by AUC) were equivalent for the two formulations. The data suggest that the pharmacokinetic differences between preparations of prednisolone were not reflected in pharmacodynamic changes in blood glucose or eosinophil count. However, administration of the enteric-coated form resulted in a lag in the decline of plasma cortisol and, in volunteers, cortisol suppression was not as marked when EP was used.

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*(Received 14 April 1991, accepted 7 January 1992)*