Cortisol does not inhibit prednisolone clearance

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The disposition of prednisolone has been studied in eight male subjects with and without the concomitant administration of cortisol which produced plasma cortisol concentrations 10-fold higher than endogenous levels. The clearance and steady-state distribution volume of total prednisolone were increased as was the prednisolone free fraction but the clearance of unbound prednisolone was unaltered by cortisol co-administration.

Keywords prednisolone disposition cortisol

Introduction

In two previous studies we found an association between plasma cortisol concentrations and a reduction in unbound prednisolone clearance (Meffin *et al.*, 1984a,b). The reduction in unbound prednisolone clearance occurred in the morning but not in the evening and was only observed with low doses of prednisolone which produced prednisolone plasma concentrations similar in magnitude to endogenous cortisol concentrations (Meffin *et al.*, 1984a). Similarly the inhibition of unbound prednisolone clearance in women taking oral contraceptives, which also increase plasma cortisol concentrations, was greater at a low prednisolone dose than at a higher dose (Meffin *et al.*, 1984b). On the basis of these observations we suggested that cortisol may competitively inhibit the clearance of unbound prednisolone. In the present study we attempt to examine this hypothesis directly by determining prednisolone clearance in the presence and absence of high concentrations of exogenous cortisol.

Methods

Eight healthy male subjects of mean (s.e. mean) age 24.8 (2.4) years and weight 73.6 (5.4) kg took part in this study. Prior to entry into the study, each subject underwent a medical assess-

ment, including a medical history, complete examination, screening haematology and biochemistry tests. The nature and purpose of the study was explained to each subject who gave written consent to participation. The study was approved by the institutional committee for human experimentation and complied with the Australian National Health and Medical Research Council's guidelines on human experimentation.

On two occasions, 1 week apart, each subject received a dose of prednisolone phosphate equivalent to 0.2 mg kg⁻¹ of prednisolone by constant intravenous infusion over 5 min into a peripheral arm vein. On one of these occasions each subject received intravenous hydrocortisone sodium succinate equivalent to 1 mg kg⁻¹ of cortisol 30 min prior to the prednisolone dose and 0.2 mg kg⁻¹ of cortisol, as the sodium succinate ester, each 30 min after the prednisolone dose for 9 h (cortisol administration). On the other occasion an equivalent volume of normal saline was administered at the specified times (control). The order of each treatment was randomized. Blood sampling, the preparation and storage of plasma and the analysis of these samples for prednisolone and cortisol concentrations were carried out as previously described (Meffin *et al.*, 1984a). The free fraction of prednisolone in plasma was measured in all

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samples following each dose using equilibrium dialysis and the unbound prednisolone concentration in each sample and the time average free fraction over the 9 h sampling period were determined as previously reported (Meffin *et al.*, 1984a).

The clearances and distribution volumes at steady-state for both total and unbound prednisolone were calculated from dose-area relationships as previously described (Meffin *et al.*, 1984a). The time average plasma cortisol concentration during each sampling period following prednisolone administration was determined by dividing the area under the plasma cortisol concentration-time curve by the sampling period. The statistical significance of differences between means was determined using the Wilcoxon matched pairs signed-ranks test.

Results

The mean time averaged plasma cortisol concentration over the 9 h sampling period following cortisol administration was approximately 10 fold higher than following the administration of saline (Table 1). During cortisol administration the mean clearance of total prednisolone (bound and unbound) increased to 160% of the control value and mean total steady-state distribution volume increased to 140% of the control mean (Table 1). These increases can be attributed to the rise in prednisolone free fraction which increased during cortisol administration to 140% of the control mean (Table 1). The unbound prednisolone clearance was unaltered by cortisol administration, but mean unbound prednisolone

distribution volume showed an increase to 130% of its control value (Table 1).

Discussion

In a previous study on the circadian variation in prednisolone disposition we reported that, following prednisolone doses of 0.075 mg kg^{-1} , unbound prednisolone clearance was 14% lower and plasma cortisol concentrations approximately two-fold higher when the dose was administered in the morning compared to evening administration (Meffin *et al.*, 1984a). No such circadian variation in unbound prednisolone clearance was apparent following doses of 1.5 mg kg^{-1} . The circadian reduction of unbound prednisolone clearance at low but not at high doses was attributed by us to competitive inhibition of prednisolone clearance by cortisol which occurred when plasma cortisol concentrations were similar or greater than the concomitant prednisolone plasma concentrations (Meffin *et al.*, 1984a). This interpretation also appeared to be consistent with a greater effect of oral contraceptives in inhibiting unbound prednisolone clearance at low compared to high prednisolone doses, as plasma cortisol concentrations were also elevated by oral contraceptive use (Meffin *et al.*, 1984b).

In the present study mean cortisol concentrations, 10-fold higher than control values and approximately five-fold higher than the previous two studies, failed to produce any alteration in unbound prednisolone clearance. Thus our hypothesis of competitive inhibition of prednisolone clearance by cortisol, inferred from elevated

Table 1 Effect of cortisol administration on prednisolone disposition

Parameter	Treatment [mean (s.e. mean)]		
	Control	Cortisol	P value
Total clearance ($\text{l h}^{-1} \text{ kg}^{-1}$)	0.14 (0.01)	0.23 (0.024)	< 0.01
Total distribution volume (l kg^{-1})	0.62 (0.05)	0.89 (0.08)	< 0.01
Time averaged prednisolone free fraction	0.27 (0.01)	0.35 (0.04)	< 0.01
Unbound clearance ($\text{l h}^{-1} \text{ kg}^{-1}$)	0.56 (0.04)	0.61 (0.05)	> 0.05
Unbound distribution volume (l kg^{-1})	1.51 (0.08)	2.00 (0.14)	< 0.01
Time averaged cortisol concentration sample ($\mu\text{g l}^{-1}$)	44.8 (6.6)	453.3 (32.6)	< 0.01

plasma cortisol concentrations in the two previous studies is not supported by direct cortisol administration. The circadian variation in unbound prednisolone clearance reported by us and by others (Meffin *et al.*, 1984a; English *et al.*, 1983) must have some other basis. Similarly the reduction in unbound prednisolone clearance in women taking oestrogen-containing oral contraceptives (Boekenoogen *et al.*, 1983; Meffin *et al.*, 1984b) would appear not to have a component due to elevated plasma cortisol concentrations.

The increases in total prednisolone clearance and steady-state distribution volume and the

elevation in prednisolone free fraction upon cortisol administration (Table 1) are consistent with our previous findings (Meffin *et al.*, 1984a,b) and the report of Rocci *et al.* (1982). Both of these studies demonstrate that cortisol is able to displace prednisolone from transcortin but not from albumin. The increase in unbound prednisolone distribution volume implies that there is increased binding of prednisolone in tissue.

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