ADRENOCORTICAL SUPPRESSION BY SYNTHETIC CORTICOSTEROID DRUGS: A COMPARATIVE STUDY OF PREDNISOLONE AND BETAMETHASONE

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- 1 Single-dose studies were conducted to investigate the relative potency of prednisolone and betamethasone in suppressing adrenocortical function.
- 2 Betamethasone produced more profound suppression of plasma cortisol than an equivalent anti-inflammatory dose of prednisolone.

Introduction

Synthetic oral corticosteroid drugs are commonly used in the treatment of rheumatoid arthritis. In a recent series, 26.4% of patients with rheumatoid arthritis (RA) were found to be receiving steroid drug therapy (Mason, Brooks, Lee, Kennedy & Buchanan, 1975). Although these drugs are potent anti-inflammatory agents, their long-term use is often associated with multi-system toxicity. Pharmacokinetic phenomena associated with the development of Cushingoid features include low plasma albumin (Lewis, Jusko, Burke & Graves, 1971) and a reduced rate of drug metabolism (Kozower, Beatch & Kaplan, 1974). There are several different oral steroid drugs currently available for clinical use and estimates of their relative efficacy have been based essentially on comparative clinical studies (Neustadt, 1959). Prednisolone is the most widely used preparation, but approximately 15% of patients receive an alternative steroid drug (Mason *et al.*, 1975). The most important unwanted effect of long-term treatment is suppression of endogenous adrenocortical activity. If withdrawal of oral corticosteroid drugs is contemplated, it is customary to reduce the dosage by small decrements over a period of time in order to allow reactivation of the adrenal cortex. When prednisolone is used, the wide variety of tablet size available allows for small percentage adjustments in dosage to be made. When other synthetic analogues are used, e.g. betamethasone, small percentage reductions are impossible with currently available tablet sizes. Consequently it is common practice to convert the dosage of the more potent compound to an 'equivalent' dose of prednisolone. The conversion ratios shown in Table 1 illustrate the range of allegedly equivalent dosages currently shown in standard reference textbooks. Such a conversion assumes that the relative potencies of

betamethasone and prednisolone, based on their anti-inflammatory activities, can be applied to their efficacy in adrenocortical suppression. The present study was designed to compare the effects of 'equivalent' doses of these two drugs on adrenocortical function.

Methods

Subjects

Twenty-one patients (six males, fifteen females), with a variety of rheumatic disorders, aged between 35 and 68 years (mean $\pm$ s.d. 53.7 ± 10.8 years) participated in the study. Nine subjects were involved in a single-blind triple crossover using placebo, prednisolone (8 mg) and betamethasone (1 mg) administered in random order in single doses 1 week apart at 22.00 h. A profile of plasma cortisol was constructed between 11 and 17 h after the drug had been administered. In the remaining twelve subjects, a single-blind crossover study was performed using prednisolone and betamethasone, with construction of the cortisol profile until 21 h after drug administration. None of the patients had ever received corticosteroid drugs in the past.

Drug presentation

In this study, the 'placebo' preparation was 2 $\times$ 200 mg ibuprofen (Brufen) since this drug is not known to have any effect on adrenocortical function. Prednisolone was given in a dose of 8 mg (1 $\times$ 5 mg and 3 $\times$ 1 mg tablets) and betamethasone in a dose of 1 mg (4 $\times$ 0.25 mg tablets). The steroid doses were chosen as the most unfavourable of the published figures for the purposes of the present study.

Table 1 Relative potencies of two synthetic corticosteroids

<i>Anti-inflammatory potency ratio</i>	
<i>prednisolone: betamethasone</i>	<i>Source (Textbook)</i>
1:6.25	Burgen & Mitchell (1972)
1:6.25	Goodman & Gilman (1975)
1:6.7	British National Formulary (1976–1978)
1:6.7	Crossland (1970)
1:7.5	Bondy & Rosenberg (1974)
1:8.0	Lawrence (1973)

Plasma cortisol profile

Venous blood was withdrawn from an arm vein at 11, 13, 15, 17 and 21 h after the drug had been given. The plasma was separated on withdrawal and stored at -20°C to await analysis. Plasma cortisol was measured in terms of 11-hydroxycorticosteroids (11-OHCS) by the fluorimetric method of Mattingly (1962).

Ethical considerations

Each subject agreed to participate in the study after a full explanation of the procedure had been given. The protocol was approved by the local hospital committee for ethics in medical research.

Results

Table 2 shows plasma cortisol levels obtained in 9 subjects after exposure to single doses of the 3 test drugs.

Table 2 Plasma cortisol (11-OHCS) levels (mean $\pm$ s.e. mean) after single dose administration of three test drugs ($n = 9$)

<i>Drug</i>	<i>Plasma cortisol (nmol l⁻¹)</i>			
	<i>11 h</i>	<i>13 h</i>	<i>15 h</i>	<i>17 h</i>
Placebo	423.7 $\pm$ 51.3	296.7 $\pm$ 44.7	262.2 $\pm$ 43.6	227.7 $\pm$ 31.7
Prednisolone	176.4 $\pm$ 62.9	122.8 $\pm$ 29.8	163.9 $\pm$ 63.5	161.7 $\pm$ 36.7
Betamethasone	78.1 $\pm$ 23.7	66.2 $\pm$ 22.1	89.2 $\pm$ 34.2	55.5 $\pm$ 14.4

Table 3 Plasma cortisol (11-OHCS) levels (mean $\pm$ s.e. mean) after single dose administration of two synthetic corticosteroid drugs ($n = 21$)

<i>Drug</i>	<i>Plasma cortisol (nmol l⁻¹)</i>				
	<i>11 h</i>	<i>13 h</i>	<i>15 h</i>	<i>17 h</i>	<i>21 h</i>
Prednisolone	154.0 $\pm$ 30.4	147.1 $\pm$ 29.8	184.4 $\pm$ 32.3	159.5 $\pm$ 18.5	114.8 $\pm$ 24.0
Betamethasone	98.5 $\pm$ 19.6	71.8 $\pm$ 12.4	91.1 $\pm$ 17.9	90.3 $\pm$ 17.7	83.1 $\pm$ 16.0

Figure 1 Plasma 11-OHCS levels (mean $\pm$ s.e. mean) after administration of three drugs.

■ after placebo ($n = 9$);
○ after prednisolone ($n = 21$);
● after betamethasone ($n = 21$).

Analysis of variance indicates that the cortisol profiles are significantly different ($F = 20.2$; $F_{01,2,9} = 8.02$) at the 1% level.

Table 3 shows the result of similar analysis in the total of 21 subjects when the plasma cortisol profile was extended up to 21 h after administration of prednisolone and betamethasone. Both profiles are again significantly different ($F = 28.9$; $F_{01,1,8} = 11.26$) at the 1% level.

The results from Table 3 are shown graphically in Figure 1 with the cortisol profile after placebo (Table 2) superimposed for reference purposes.

Discussion

Both corticosteroid analogues suppressed the output of cortisol from the adrenal cortex as shown by the lower values for cortisol after administration of prednisolone and betamethasone, compared with the 'placebo' preparation. However, the suppression of adrenal activity was more profound after betamethasone. In the absence of objective information to the contrary, it is assumed that the bioavailability of and absorption of both steroid compounds is comparable within the subjects involved. This assumption is generally made in clinical practice when dosage conversion is performed. The present

results suggest that, in single dose studies, the published 'equivalent' doses are not valid in respect of adrenocortical suppression. It is not feasible from this investigation to predict that a similar discrepancy will occur during long-term corticosteroid therapy, but studies are currently in progress to investigate this phenomenon. However, the data from the present study suggest that it may not be valid to assume a single fixed relative potency figure for synthetic corticosteroid analogues across the wide spectrum of steroid pharmacodynamic effects.

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Requests for reprints should be sent to M.E.P.

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