Plasma prednisolone studies in rheumatic patients

M. HAYES,¹ A. F. M. S. ALAM,² F. E. BRUCKNER,² S. M. DOHERTY,³
A. MYLES,³ J. ENGLISH,¹ V. MARKS,¹ AND
J. CHAKRABORTY¹

From the ¹Clinical Biochemistry Division, Department of Biochemistry, University of Surrey, Guildford, Surrey; the ²Department of Rheumatology, St George's Hospital, London; and the ³Department of Rheumatology, St Peter's Hospital, Chertsey, Surrey

SUMMARY Prednisolone concentration in plasma after a daily maintenance steroid dose was monitored in 83 patients with rheumatic diseases. Although no restrictions were imposed on the intake of food or drink, plasma drug levels tended to peak at 1 h after the ingestion of the standard tablets, whereas intestinal absorption of the enteric-coated preparation was found to be most unpredictable. A profound individual variation was observed in plasma prednisolone concentrations, and neither total nor unbound drug levels showed any consistent relationship with the size of the prednisolone dose or the control of the disease activity. The basal cortisol production was suppressed in one-third of the patients. There is no support from this study for the concept of an 'optimum therapeutic range' of plasma prednisolone for the treatment of rheumatic disease.

Prednisolone (1 α Δ -cortisol) has an important place in the treatment of several rheumatic diseases. For maintenance therapy 2-10 mg is commonly given either as a single daily dose or in divided doses. The knowledge of plasma drug levels may provide a basis for adjusting the prednisolone dosage and assist in the assessment of clinical response to therapy in the individual patient. This can now be explored with the sensitive methods available for the measurement of prednisolone.¹⁻³

We monitored plasma prednisolone and cortisol levels in 83 rheumatic patients on long-term corticosteroid therapy who were attending 2 rheumatology outpatient clinics. Patients were studied after their usual daily prednisolone dose and the findings are reported here.

Patients and methods

The details of 83 patients admitted into the study are given in Table 1. They were allowed their usual food and drink and other medication, if any. Prednisolone BP (Precortisyl) or enteric-coated prednisolone (Deltacortril) was given orally as a single dose between 10 and 10.30 a.m. Blood samples were taken immediately before and 1 h (in some instances also

0.5 and 1.5 h) after the dose. Plasma was separated and stored frozen until the analyses.

Steroid assay. Ethyl acetate extract (2 $\times$ 3 ml) of plasma (1 ml) was evaporated to dryness under N₂ at 40°C. The residue, redissolved in a small volume of ethyl acetate, was then chromatographed in dichloromethane/ethanol/water (150/10/1, v/v) on silica gel plates (Eastman-Chromatogram, no. 13181). The prednisolone band on the plate was cut out and eluted with 5 ml ethanol. Prednisolone was determined by a radioimmunoassay procedure⁴ using an antiserum raised in the sheep against prednisolone-21-hemisuccinate conjugated to

Table 1 Details of patients investigated

Diagnosis	No. of patients	Mean age in years (range)	Mean body weight in kg (range)
Rheumatoid arthritis (RA)	44	60.1 (33-80)	64.2 (47.6-88)
Polymyalgia rheumatica (PMR)	31	68.4 (51-85)	61.6 (37.5-91.6)
Others*	8	61.7 (34-78)	64.5 (52.1-85.7)

*Temporal arteritis 2, systemic lupus erythematosus 2, frozen shoulder 1, polyarteritis nodosa 1, osteoarthritis 1, psoriatic arthropathy 1.

Accepted for publication 9 February 1982.

Correspondence to Dr F. E. Bruckner, St George's Hospital, Blackshaw Road, London SW17 0QT.

Table 2 Plasma prednisolone levels in patients after standard or enteric-coated tablets given by mouth

Diagnosis	Prednisolone dose (mg)	Tablet	Prednisolone level (nmol/l) following oral dose			
			0 h	0.5 h	1 h	1.5 h
Rheumatoid arthritis	5	Standard	0	77	158	153
Rheumatoid arthritis	5	Standard	27	130	129	118
Rheumatoid arthritis	5	Standard	15	154	185	165
Temporal arteritis	5	Standard	0	ND	119	99
Polymyalgia rheumatica	10	Standard	49	77	111	117
Polymyalgia rheumatica	10	Standard	0	100	191	177
Rheumatoid arthritis	5	Enteric-coated	0	0	0	0
Frozen shoulder	5	Enteric-coated	0	0	0	ND
Rheumatoid arthritis	6	Enteric-coated	31	52	75	ND
Rheumatoid arthritis	7.5	Enteric-coated	15	54	92	ND
Polymyalgia rheumatica	12.5	Enteric-coated	35	40	237	288
Polymyalgia rheumatica	13	Enteric-coated	0	0	0	0

ND = not determined.

bovine serum albumin. The recovery of prednisolone from plasma was checked by adding ^3H -prednisolone (2.5 nCi) to the sample prior to the ethyl acetate extraction step.

Cortisol was measured by a fluorimetric method⁵ and plasma protein binding of prednisolone analysed by a technique based on equilibrium dialysis.⁶

Results

The prednisolone antiserum cross-reacted with prednisone, 20-dihydroprednisolone and cortisol to the extent of 11.1, 20.6, and 3.9% respectively. However, when the plasma from a patient who had received prednisolone was radioimmunoassayed before and after double-dilution with

dexamethasone-suppressed plasma, the plot of percentage binding against prednisolone concentration was superimposable on the prednisolone standard curve. At 27.7–554 nmol/l concentrations the overall recovery of prednisolone from plasma after due corrections ranged between 98 and 100% and the coefficient of variation 6 and 11%.

Plasma prednisolone levels in 12 patients at 0, 0.5, 1, and 1.5 h after a 10 mg dose are given in Table 2. After prednisolone standard tablets peak drug levels in plasma were attained 1 h after the dose. In contrast the plasma drug pattern varied widely after enteric-coated preparations; in some instances prednisolone was not measureable in the plasma until 1.5 h after ingestion. The 1 h time point was therefore chosen for all subsequent analyses of plasma drug concentra-

Plasma Prednisolone levels nmol/l

Fig. 1 Plasma 1 h prednisolone levels after oral dose.

tions, and only those patients receiving the standard tablets were included in the study.

Plasma prednisolone values at 1 h after drug administration, in patients who benefited from steroid therapy, were plotted against prednisolone dose per kg body weight (Fig. 1). No significant correlation was observed, and the same was true when dose was expressed as total dose per patient. Table 3 shows the plasma drug concentrations after similar doses in 7 patients who, unlike the previous group, had a poor response to steroid therapy ('non-responders'), as judged by elevated erythrocyte sedimentation rate and clinical evidence of continuing disease activity. One patient had a very low prednisolone level, but the other 6 had levels of plasma prednisolone, both total and free, that were indistinguishable from the other group.

The protein binding of prednisolone, determined in 60 patients, varied between 86 and 97%. The

amount of free prednisolone depended on the total concentration, with a correlation coefficient of 0.88 (Fig. 2).

The plasma cortisol levels in the morning were below the lower end of the reference range of 200–650 nmol/l in 20 of the 60 patients examined. They were not related to the size of the prednisolone maintenance dose. The magnitude of the suppression of plasma cortisol 1 h after the administered prednisolone (5–12 mg) was between 11 and 67% of the basal values and was not dose-dependent.

Discussion

The present study was undertaken to examine the practicability of single time-point drug analysis in steroid therapy. As it was intended to monitor the plasma drug levels achieved normally during prednisolone therapy, the patients were given their normal daily dose of the steroid, and no restriction was imposed on other medications, food, or drink.

In those patients who had serial plasma drug level estimations after prednisolone standard tablets peak values were reached at 1 h, indicating an intestinal absorption rate similar to that found previously in fasted healthy volunteers.^{4 6–8} However, the prednisolone values were markedly smaller and more widely variable than might have been expected from those found in the normal volunteers. Long-term steroid therapy and concomitant use of other drugs as well as the difference in food intake might have contributed to this.⁹ It was thus not surprising that plasma drug concentrations were not closely related

Table 3 Plasma prednisolone levels in poor responders to steroid therapy

Diagnosis	Dose (mg)	Plasma 1 h prednisolone	
		Total (nmol/l)	Free (%)
Polymyalgia rheumatica	7	105	4.5
Rheumatoid arthritis	7	†	
Rheumatoid arthritis	7.5	405	3.2
Polymyalgia rheumatica	8	28	11.2
Rheumatoid arthritis	10	327	9.4
Polymyalgia rheumatica	10	97	10.1
Polymyalgia rheumatica	12	166	12.4

All patients except * received standard prednisolone tablets.

†Present but not measurable.

Fig. 2 Protein binding of prednisolone in plasma at 1 h after oral dose

to the daily steroid dose.¹⁰ It remains to be established whether these large differences in total and free plasma prednisolone levels after the same dose of the drug may influence the pharmacokinetics of prednisolone in individual patients.⁹

The function of the hypothalamic-pituitary-adrenal axis was suppressed in a large proportion of the patients studied. The peak plasma prednisolone levels, total and free, did not seem to have any bearing on the observed clinical response of the patients to steroid therapy. Thus, while in a majority of the responder subjects the plasma drug levels were between 55.5 and 124.8 nmol/l, in 6 of the 7 'non-responders' the corresponding values were also within or above this range. We conclude that in the latter patients absorption, metabolism, and excretion of prednisolone was normal. In only one of the 7 'nonresponders' was the peak plasma prednisolone level below the normal range, suggesting poor absorption.

The apparent lack of correlation between peak plasma prednisolone levels and the control of disease activity in our patients is in agreement with a previous report.¹¹ The concept of an optimum therapeutic range of plasma prednisolone concentrations for the treatment of rheumatic disease is not supported by our study. Corticosteroids in most chronic inflammatory diseases should be used in the lowest dose that produces symptomatic relief, and each individual has to be treated according to his personal needs.

We thank the Arthritis and Rheumatism Council for financial support.

References

- 1 English J, Chakraborty J, Marks V. A competitive protein binding method for prednisolone assay. *Ann Clin Biochem* 1974; **11**: 11-4.
- 2 Colburn W A, Buller R H. Radioimmunoassay of prednisolone. *Steroid* 1973; **21**: 833-46.
- 3 Scott N R, Chakraborty J, Marks V. Determination of prednisolone, prednisone and cortisol in human plasma by high-performance liquid chromatography. *Anal Biochem* 1980; **108**: 266-8.
- 4 Chakraborty J, Hayes M, English J, Bayliss M, Marks V. Prednisolone concentrations in plasma, saliva and urine. *Eur J Clin Pharmacol* 1981; **19**: 79-81.
- 5 Mattingly D. A simple fluorimetric method for the estimation of free 11-hydroxycorticoids in human plasma. *J Clin Pathol* 1962; **15**: 374-9.
- 6 Elliot P R, Powell-Tuck J, Gillespie P E, *et al.* Prednisolone absorption in acute colitis. *Gut* 1980; **21**: 49-51.
- 7 Uribe M, Schalm S W, Summerskill W H J, Go V L W. Effect of liquid diet on serum protein binding and prednisolone concentrations after oral prednisone. *Gastroenterology* 1976; **71**: 362-4.
- 8 Tembo A V, Hallmark M R, Sakmar E, Bachmann H G, Weidler D J, Wagner J G. Bioavailability of prednisolone tablets. *J Pharmacokin et Biopharm* 1977; **5**: 257-70.
- 9 Pickup M E. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1979; **4**: 111-28.
- 10 Wilson C G, Ssendagire R, May C S, Paterson J W. Measurement of plasma prednisolone in man. *Br J Clin Pharmacol* 1975; **2**: 321-5.
- 11 Bakran I, Korsic M, Durakovic Z, Vrhovac B, Tagic M. The effect of alternate-day prednisolone therapy in cortisol secretion rate in corticosteroid-dependent asthmatics. *Int J Clin Pharmacol* 1977; **15**: 57-60.