Variation in plasma prednisolone concentrations in renal transplant recipients given enteric-coated prednisolone

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Summary and conclusions

Renal transplant recipients receiving intermittent haemodialysis and kept under normal ward conditions showed appreciable differences in plasma prednisolone concentrations after therapeutic doses of enteric-coated prednisolone tablets. This gross day-to-day variation occurred irrespective of the dosage used. Breakfast given before prednisolone tended to reduce the rate of absorption of the drug, the effect being quantitatively most pronounced with large doses. Haemodialysis had no apparent effect on the elimination of prednisolone from plasma.

Such erratic blood concentrations of prednisolone as observed in these patients, possibly resulting from variable absorption, may be potentially hazardous. Hence use of enteric-coated tablets in renal transplant recipients should be viewed with caution.

Introduction

Corticosteroids and azathioprine constitute the mainstay of treatment in preventing rejection after renal transplantation. For the past 10 years patients in Cambridge have received corticosteroids as enteric-coated prednisolone in an effort to reduce the risk of peptic ulceration.[1] Boluses of unabsorbed tablets, however, have commonly been found many hours after ingestion in the gut of patients who have required subsequent abdominal exploration.

To assess the day-to-day variation in intestinal absorption of prednisolone we monitored the plasma drug concentrations on two consecutive days in renal transplant recipients who received enteric-coated prednisolone tablets as part of routine treatment. In two other, separate studies we also examined the effects of haemodialysis on the disappearance of prednisolone from plasma and the way food influences prednisolone absorption.

Patients and methods

Patients from groups 1 and 2 were studied within three weeks after transplantation and while all but one still required intermittent haemodialysis. Patients from group 3 all had functioning grafts. No restrictions were placed on food and drink, and other drug treatment was continued unchanged. Table I gives details of the patients studied.

Study 1—Plasma prednisolone concentrations were measured in three women and five men (group 1) at various times after their respective oral doses (100-200 mg) of the drug, which were given after breakfast. Measurements were made on two consecutive days, the tablets (Deltacortril R, CAP-coated 5 mg tablets) being swallowed with water.

Study 2—The effect of haemodialysis on plasma prednisolone was studied on three occasions in one man and one woman (group 2). Prednisolone 80 mg (Codelsol) was given intravenously on two consecutive days, on one of which haemodialysis was performed. The drug was administered at the start of dialysis. Timed venous specimens were taken for measurement of prednisolone.

Study 3—The effect of food on prednisolone absorption was studied in three men and one woman (group 3). Enteric-coated prednisolone was given as a single dose of 20 or 50 mg on two consecutive mornings. The drug was administered 20 minutes after breakfast on the first day and after a six-hour fast on the second day. Timed venous specimens were collected for prednisolone assay.

Prednisolone measurement—Blood was centrifuged immediately and the plasma stored at −20°C until assayed. The sample (1 ml) was extracted with ethyl acetate (3 ml × 2), the extracts being pooled and dried by evaporation at 40°C under a stream of nitrogen. The residue was reconstituted in 0·5 ml 0·1M phosphate buffer, pH 7·4, and aliquots (0·1 ml, either neat or appropriately diluted) analysed for prednisolone by radioimmunoassay. Table II gives the composition of the incubation mixture. Samples were incubated at 40°C for two hours, the rest of the procedure being as described.[2]

TABLE I—*Details of patients studied*

Case No	Sex	Age (years)	Body weight (kg)	Creatinine clearance (ml/min)
		Group 1		
1	M	38	73·0	0·4
2	M	40	76·5	<1·0
3	M	28	64·7	<1·0
4	F	39	62·5	0·5
5	F	28	70·9	0·8
6	M	28	66·6	1·3
7	M	33	61·8	2·0
8	F	22	62·5	31·0
		Group 2		
9	M	50	66·6	<1·0
10	F	18	53·2	<1·0
		Group 3		
11	M	52	73·1	66·0
12	F	43	55·6	57·0
13	M	35	65·1	36·0
14	M	42	70·0	18·0

TABLE II—*Composition of mixture used for radioimmunoassay. All volumes in μl*

	Total content	Zero standard	Standard	Sample	Non-specific binding
Phosphate buffer (0·1 mol/l, pH 7·4)	600	500	400	400	600
Standard (0·10 ng)			100		
Sample aliquot			—	100	
Label (10 nCi)	100	100	100	100	100
Antibody (1/2250 dilution)	100	100	100	100	

Results

Tables III and IV show the cross-reactivity of the prednisolone antiserum with some other steroids and the accuracy and precision of the radioimmunoassay used. Two of the possible metabolites of prednisolone (prednisone and 20-dihydroprednisolone) showed appreciable cross-reactivities in the absence of prednisolone, but in the presence of prednisolone one of these (20-dihydroprednisolone) showed a reduction in cross-reactivity to under 10%. Hence owing to the normally low concentrations of these steroids in blood, even when large amounts of prednisolone are present,[3 4] they were unlikely to interfere noticeably with the results.

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TABLE III—*Cross-reactivity of various steroids with prednisolone antiserum in absence of prednisolone*

	Cross-reactivity (%)		Cross-reactivity (%)
Prednisolone	100·0	5α-Tetrahydrocortisol	1·8
Prednisone	11·1	5β-Tetrahydrocortisol	1·4
20-Dihydroprednisolone	20·6	Corticosterone	2·1
Cortisol	3·9	Progesterone	0·6
Cortisone	2·8	Testosterone	0·1
6β-Hydroxycortisol	0·9	Cholesterol	<0·1

TABLE IV—*Accuracy and precision of prednisolone radioimmunoassay*

Amount of prednisolone added (ng/ml)	Within-batch: Mean amount measured (ng/ml)	Within-batch: Coefficient of variation (%) (n = 10)	Between-batch: coefficient of variation (%) (n = 10)
1	1·05	5·9	7·3
10	9·98	3·6	5·1
100	99·6	4·9	7·1

Replicate assays were carried out on pooled normal human plasma to which known amounts of prednisolone were added.

Patients in group 1 showed a gross variation in the rate of appearance of prednisolone in the blood and peak values achieved irrespective of the dosage used (table V). After the same dose given to different patients there was a difference in the time required to reach the peak plasma prednisolone concentration and, more strikingly, its magnitude between patients, as well as when the same subject was investigated on two separate occasions. In most instances the plasma concentration either peaked at four hours or continued to rise for another four hours.

TABLE V—*Plasma prednisolone concentrations in group 1 after enteric-coated prednisolone tablets on two successive days*

Case No	Dose (mg)	Day	Plasma prednisolone concentrations (ng/ml) at times after dose: 0	0·5 h	1 h	2 h	4 h	8 h
1	200	1*	67	83		100	83	117
		2	67	900	1067	900	1017	1267
2	200	1	0	90	100	3000	3350	2550
		2*	420	1300	1270	1270	1060	
2	175	1*	1020	930	880	990	2000	2300
		2	630	500	490	1470	4700	3350
3	175	1	955		898	852	943	1057
		2	375	295	227	841	1875	716
4	175	1*	450	388	400	500	2500	2475
		2	400	325	250	188	163	423
5	150	1	933	1067	1333	1367	1400	1017
		2*	600	850	1150	2933	2800	1367
4	125	1*	25	38	25	40	25	75
		2		450	300	250	613	688
6	125	1	267	183	117	183	900	917
		2*	133	67	550	717	1533	833
7	100	1*	160	170	240	200	350	1350
		2	70	1070	570	660	1300	670
8	100	1*	396	281	271		708	979
		2	115	63	73	63	63	406

* Haemodialysis carried out.

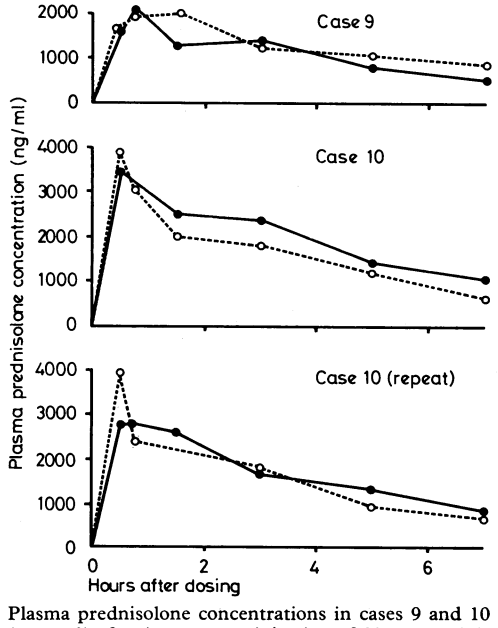
Since in most cases the concentrations had not returned to zero by 24 hours, the values recorded over the eight hours after ingestion probably included the remains of previous doses. The overall peak concentrations ranged from 117 to 3350, 423 to 4700, 688 to 1533, and 406 to 1350 ng/ml after 200, 175, 125, and 100 mg doses respectively. In case 1 after a 200 mg dose on day 1 and in case 4 after 175 mg on day 2 and 125 mg on day 1, the plasma prednisolone concentrations rose only marginally above basal values.

When the drug was given after a six-hour fast (group 3) peak plasma prednisolone concentrations were achieved in almost all cases within four hours (table VI). Breakfast taken before dosing, however, resulted in a delay of 7-10 hours before peak values were reached. Fasting before taking the prednisolone produced up to eightfold higher peak concentrations after 175 and 150 mg doses (case 14), but this effect was not observed after 20 and 50 mg doses (cases 11-13).

The figure shows the plasma prednisolone concentrations after the 80 mg dose given intravenously (group 2). Plasma half lives ranged from 3·3 to 4·2 hours and showed no change that could be clearly attributed to haemodialysis.

TABLE VI—*Effect of food on plasma prednisolone concentrations in group 3*

Case No	Dose (mg)	Break-fast	Plasma prednisolone concentrations (ng/ml) at times: 0	2 h	4 h	7 h	10 h	14 h
11	50	Yes	16	66	93	104	122	128
		Yes	17	47	128	106	108	109
		No	34	53	96	356	178	48
		No	144	200	378	200	189	106
12	50	Yes	56	77	176	163	103	105
		Yes	58	88	95	178	178	120
		No	74	183	173	115	103	88
		No	65	175	175	114	101	92
13	20	Yes	34	27	30	36	88	48
		Yes	25	18	36	118	98	50
		No	18	59	77	136	91	41
		No	20	18	173	127	91	48
14	175	Yes	29	165	157	177	169	
		No	82	936	1068	499	388	
	150	Yes	60	41	43	47	49	
		No	58	870	821	668	412	



Plasma prednisolone concentrations in cases 9 and 10 (group 2) after intravenous injection of 80 mg prednisolone on two consecutive days. —First day. - - - - Second day. On second day patient received haemodialysis and drug was given at start of treatment.

Discussion

Gross day-to-day variation in plasma prednisolone concentrations were observed in patients studied within three weeks after transplantation. The explanation is probably multifactorial: it may be related to the bioavailability of the drug formulation, the influence of haemodialysis on drug disposition in the body, the effect of food on intestinal absorption, and the patient's gastrointestinal activity.

Sherlock and Lerreri,[5] who examined the effect of haemodialysis on 6-methylprednisolone, reported significant dialysance of the drug and suggested that the dosage might require adjustment. We found no evidence to support this, since haemodialysis immediately after an intravenous injection of prednisolone made no noticeable difference to the clearance of the drug.

Enteric coating influences the pharmacokinetics of prednisolone.[6 7] It delays the appearance of prednisolone in the blood but does not alter its bioavailability as compared with the uncoated drug when given in 10-20 mg doses to healthy volunteers and patients with lung disease. In a study of patients who had undergone renal transplantation one to three years before, the peak plasma prednisolone concentration attained after 30 mg of enteric-coated tablets was much lower than after the same dose of the plain preparation.[8] No other investigators have examined the variation in plasma prednisolone concentrations with re-

peated administration of the drug. Although absorption of the preparation we used is reportedly better[9] than other preparations studied, erratic absorption of the large number of 5 mg tablets ingested by our patients—who may have had impaired gastrointestinal function because of recent abdominal surgery—seems most likely to explain the observed wide scatter in plasma prednisolone concentrations. We cannot say whether altered metabolism of the drug in these patients was contributory. Since the patients ate and drank normally during the study we could not assess the extent to which food in the gut influenced drug absorption in group 1. In group 3, however, it appeared that whereas at lower doses the main effect of breakfasting before drug ingestion was to delay prednisolone absorption (which has also been noted with uncoated tablets[10]), at higher doses it also greatly reduced the plasma drug concentrations observed over the period studied.

Such very low plasma prednisolone concentrations as observed in some of our patients might be potentially hazardous, possibly favouring graft rejection. Although administration of the drug to patients who are fasting may improve intestinal absorption, this seems unlikely to be a complete answer. Possibly the enteric coating is responsible for erratic absorption. Since any advantage that has been claimed for the coating in preventing peptic ulceration is questionable,[11] the continued use of this preparation needs reappraisal. Alternatively, it may be that absorption of the drug given as a large number of small tablets is less uniform than if the same dose was administered as one or more larger tablets. Clearly, such implications warrant further study.

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Raised blood pressure and plasma noradrenaline concentrations in teenagers and young adults selected from an open population

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Summary and conclusions

Plasma noradrenaline (PNA) concentrations were measured in 38 subjects aged 13-23, who were followed up for two to four years after an initial blood-pressure (BP) reading of 140/90 mm Hg or over was obtained, and in 39 age-matched controls from the same open population. Subjects who were hypertensive when the PNA concentration was measured had a significantly higher concentration (351 ± SE 26 pg/ml) compared with their controls (248 ± 29 pg/ml). Furthermore, in those subjects in whom the mean arterial pressure decreased by under 5% during the follow-up period the mean concentration was 363 ± 27 pg/ml, compared with 271 ± 29 pg/ml in their controls. PNA concentrations and systolic BP were positively correlated. A positive association between PNA concentrations and age was observed in the controls but not the subjects with hypertension, owing to the higher concentrations in younger hypertensive subjects. These findings support the hypothesis that excessive sympathetic activity is related to early essential hypertension.

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Introduction

Evidence is increasing that essential hypertension has its roots in childhood. Persistently raised blood pressure (BP) is not uncommon in children,[1-3] who tend to keep their relative positions in the distribution of BP over time,[4 5] possibly from the first months of life.[6] The hypothesis has been proposed that overactivity of the sympathetic nervous system plays an important part in the pathogenesis of essential hypertension in its early phase, and that other factors—for example, kidney changes—are more important later.[7] As a reflection of this, plasma catecholamine concentrations would be expected to be increased in young people with raised BP. Until now only studies of plasma catecholamine concentrations in adults[8-13] and a few adolescents[14] have been reported, and the data have been equivocal. We have measured the plasma noradrenaline (PNA) concentration in young people with potential hypertension and matched controls selected from the same population.

Subjects and methods

Blood pressure was measured as part of a tracking study of indicators of cardiovascular risk (EPOZ study) in 3924 children and teenagers initially aged 5-19, representing 82% of the population in that age group living in two districts in a Dutch town. Subjects with an