PAPERS AND ORIGINALS

Serious renal transplant rejection and adrenal hypofunction after gradual withdrawal of prednisolone two years after transplantation

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Summary and conclusions

Ten patients with stable renal function two years after transplantation had their sole immunosuppressive treatment (oral prednisolone 10 mg daily) withdrawn by reducing the daily dose by 1 mg at monthly intervals. Plasma prednisolone concentration, cortisol concentration, creatinine clearance, and serum creatinine concentration were measured in all patients, and the adrenal response to corticotrophin was determined in five by measuring plasma cortisol concentrations before and after tetracosactrin injection. No episodes of rejection occurred in patients taking over 7 mg prednisolone daily. Although three patients apparently required only minimal immunosuppressive treatment (less than 5 mg daily), the remainder suffered episodes of rejection at daily doses below 7 mg. There was a tenuous association between rejection and low plasma cortisol concentration, but neither the pattern of plasma prednisolone concentrations nor the responses to tetracosactrin were related to episodes of rejection.

Reducing the daily dose of oral prednisolone to under 7 mg should not be attempted in patients with renal transplants unless there are extenuating circumstances.

Introduction

A generally accepted immunosuppressive regimen two years after renal transplantation is prednisolone, 10-15 mg daily, and azathioprine. We have shown that azathioprine may be safely

stopped in some renal transplant recipients.¹ Long-term treatment with prednisolone is associated with several undesirable side effects. We therefore reduced the dosage of prednisolone in patients who were not taking any other form of immunosuppressive treatment two years after transplantation to the lowest value compatible with graft survival. A preliminary account of this work has been reported.² We now describe the follow-up of these patients with special reference to their plasma drug concentrations and adrenal function.

Patients and methods

Ten patients with renal transplants who had not taken azathioprine for 3-31 months were included in the study (see table I). Full clinical details have been published elsewhere.² Side effects associated with steroid treatment included hypertension, obesity, Cushingoid facial features, hypertriglyceridaemia, avascular necrosis of bone, and acne. The plasma creatinine concentrations at the beginning of the study were normal (70-140 $\mu\text{mol/l}$; 0.8-1.6 mg/100 ml) in all patients except one (case 3: concentration 170 $\mu\text{mol/l}$; 1.9 mg/100 ml).

All patients were taking 10 mg of prednisolone daily (two 5 mg enteric-coated tablets) at the start of the study. This was reduced by 1 mg at monthly intervals by replacing one of the 5 mg tablets with the appropriate number of 1 mg tablets. Blood was taken at 9 am after an overnight fast and subsequently one, three, and six hours after an oral dose of prednisolone. Plasma was separated immediately and stored at -20°C until assayed. Prednisolone concentration was measured by radioimmunoassay³ and cortisol by a standard fluorometric method, the within-batch and between-batch coefficients of variation for the prednisolone radioimmunoassay being 5.0% and 6.5% respectively. All assays were performed in duplicate, and samples were reassayed if duplicate values differed by more than 10%. The time intervals of one, three, and six hours for measuring prednisolone concentrations were chosen in accordance with the absorption characteristics of the two different prednisolone preparations used: standard nonenteric-coated tablets produce peak plasma concentrations one hour after administration, whereas enteric-coated tablets produced peak concentrations after about three hours. The plasma concentration of the drug remains high for about six hours.⁴

In five patients (cases 1, 2, 3, 8, and 10) the adrenal response to corticotrophin was monitored by measuring plasma cortisol concentrations before and one, three, and six hours after an intramuscular injection of 2 mg tetracosactrin (Synacthen Depot).⁵

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Results

The lowest dose of prednisolone reached in the 10 patients was 1-6 mg daily (table I). Episodes of rejection did not occur when patients were taking over 7 mg prednisolone daily.

In five patients (cases 4-8, table I) rejection occurred when they were taking 3, 6, 5, 4, and 2 mg prednisolone daily respectively, 44, 47, 46, 35, and 51 months respectively after transplantation. In all five patients biopsy showed evidence of cellular and vascular rejection. In only one patient (case 5) was renal function restored easily and maintained by either increasing prednisolone, treating with intravenous pulses of methylprednisolone, or administering subcutaneous heparin.⁶ In cases 7 and 8 the initial deterioration in renal function was controlled by increasing the dose of prednisolone to 30 mg daily. In case 7 once the rejection was controlled the dose was again reduced gradually to 20 mg daily (fig 1). The mean serum creatinine concentra-

FIG 1—Case 7. Mean serum creatinine concentrations and oral prednisolone doses after asymptomatic deterioration in renal function seven months after gradual withdrawal of prednisolone.

Conversion: SI to traditional units—Serum creatinine: 1 $\mu\text{mol/l} \approx 0.011 \text{ mg/100 ml}$.

tion remained steady for over two months while the prednisolone dose was gradually reduced still further to 12.5 mg daily. There was a further progressive deterioration in renal function while the patient was taking the latter dose. Biopsy showed chronic cellular and vascular rejection. The patient was then given methylprednisolone pulse treatment (2 g intravenously on alternate days), 5000 units heparin subcutaneously three times daily, and an increased dose of oral prednisolone (30 mg daily). Mean serum creatinine concentration stabilised at 360 $\mu\text{mol/l}$ (4.1 mg/100 ml). In case 8 (fig 2) the serum creatinine concentration fell to 110 $\mu\text{mol/l}$ (1.2 mg/100 ml). The dose of

FIG 2—Case 8. Mean serum creatinine concentrations and oral prednisolone doses in case 8 after asymptomatic deterioration in renal function 10 months after gradual withdrawal of prednisolone.

Conversion: SI to traditional units—Serum creatinine: 1 $\mu\text{mol/l} \approx 0.011 \text{ mg/100 ml}$.

oral prednisolone was then gradually reduced. Further deterioration in renal function occurred while the patient was taking 17.5 mg prednisolone daily more than one month after the original asymptomatic rise in serum creatinine concentration. This was controlled by two courses of methylprednisolone pulse treatment (2 g intravenously on alternate days). There was a steady fall in mean serum creatinine concentration to 110 $\mu\text{mol/l}$ (1.2 mg/100 ml) at the end of the study. Mean creatinine clearance was then 43.6 ml/min. In case 9 acute deterioration in renal function due to acute pyelonephritis was treated successfully. The dose of prednisolone was not reduced below 5 mg in case 10 because of lethargy and severe weight loss.

In the remaining three patients (cases 1-3) the daily dose of prednisolone was reduced to 1, 1, and 5 mg respectively. Mean serum creatinine concentration remained stable. In cases 2 and 3 there was total compatibility of HLA matching.

After oral prednisolone doses of 7-10 mg the plasma prednisolone concentrations were not proportional to the size of the dose (table II). No clear and consistent pattern of differences in plasma drug concentrations was seen either between groups or between patients to explain the different clinical courses or the plasma cortisol values found at various doses of prednisolone. Most patients had low plasma cortisol concentrations at the beginning of the study, and those patients who showed signs of rejection tended to have cortisol concentrations at the lower limit of the normal range.

Of the five patients who were taking 5 mg or less of prednisolone daily, four produced a subnormal response to intramuscular tetra-

TABLE I—Mean creatinine clearance, mean serum creatinine concentration, lowest dose of prednisolone given, and history in 10 patients with renal transplants in whom prednisolone treatment was gradually withdrawn. (Numbers in parentheses are months after transplantation)

Case No	Creatinine clearance (ml/min)			Serum creatinine ($\mu\text{mol/l}$)			Lowest dose (mg/day)	History
	At start of withdrawal	During rejection	At end of study	At start of withdrawal	During rejection	At end of study		
1	72.7 (32)	—	61.4 (56)	140	—	160	1	Non-rejection group
2	61.5 (31)	—	77.0 (55)	110	—	120	1	
3	64.0 (34)	—	54.9 (56)	170	—	160	5	
4	61.0 (36)	13.3 (44)	27.0 (62)	90	270	220	3	Rejection group
5	72.8 (42)	38.7 (47)	75.2 (66)	130	220	120	6	
6*	79.6 (40)	8.0 (46)	— (54)	120	850	—	5	
7	80.0 (28)	42.0 (35)	19.4 (52)	110	200	470	4	Others
8	80.0 (39)	12.1 (51)	43.6 (63)	90	510	110	2	
9	53.0 (28)	—	60.6 (52)	110	—	120	6	
10	86.6 (43)	—	75.5 (67)	80	—	90	5	

*Patient underwent dialysis after episode of rejection.

MP = Pulses of intravenous methylprednisolone.

Conversion: SI to traditional units—Serum creatinine: 1 $\mu\text{mol/l} \approx 0.011 \text{ mg/100 ml}$.

TABLE II—Mean plasma prednisolone concentrations (ng/ml) in 10 patients with renal transplants after oral administration. Each patient received same dose for one month before study

Case No	Hours after 10 mg				Hours after 9 mg				Hours after 8 mg				Hours after 7 mg			
	0	1	3	6	0	1	3	6	0	1	3	6	0	1	3	6
Non-rejection group																
1	10	30	88	77	0	120	83	101	0	112	96	76	0	88	70	102
2	1	7	11	0	14	53	86	100	19	90	91	88	21	60	96	30
3	9	38	86	76	0	114	120	68	5	94	78	65	5	84	85	64
Rejection group																
4	0	10	140	100	7	0	91	28	1	7	5	12	5	117	98	102
5	2	10	0	0	4	109	92	54	6	32	49	49	12	43	39	16
6	1	105	116	93	4	93	90	74	6	89	92	56	17	87	73	89
7	8	89	91	100	0	21	34	44	13	72	91	93	19	50	78	78
8	0	0	0	1	17	125	129	95	12	25	97	105	12	66	66	24
Others																
9	9	145	192	168	0	129	89	33	0	24	15	11	19	51	62	52
10	0	48	93	130	8	99	86	77	4	100	82	52	15	123	107	73

FIG 3—Mean plasma cortisol concentrations after injection of 2 mg tetracosactrin (Synacthen Depot) in five patients (cases 1, 2, 3, 8, and 10) taking up to 5 mg oral prednisolone daily. Dotted line shows lower limit of normal values.

Conversion: SI to traditional units—Plasma cortisol: 1 nmol/l $\approx$ 0.036 μ g/100 ml.

developed severe rejection while taking 2 mg of prednisolone daily and another (case 10) in whom the gradual withdrawal of prednisolone was stopped when he developed symptoms of hypoadrenalism.

Discussion

Our study shows that in some renal transplant recipients there is sufficient graft-host tolerance to permit almost complete discontinuation of immunosuppressive treatment. Di Padova *et al*⁷ reported a case in which no untoward effects were seen more than two years after a patient had stopped taking immunosuppressive treatment. This, however, must be viewed with caution because we find that even a gradual reduction of the prednisolone dose is likely to precipitate episodes of rejection. Unlike the observations of Owens *et al*,⁸ we found that such episodes of rejection could be catastrophic. One patient (case 6; table I) developed acute rejection then a rapidly progressing chronic rejection, eventually requiring dialysis—a history similar to that described by Lokkegaard *et al*.⁹ In cases 7 and 8 (figs 1 and 2) the initial episode of rejection was easily reversed by increasing the dose of oral prednisolone, but this was followed by a rapid deterioration in renal function that occurred while the patients were taking higher doses of oral prednisolone. In case 8 this deterioration was controlled, but only by intravenous pulses of methylprednisolone. In case 7, however, there was severe and irreversible damage to renal function.

Attempts have been made to define the minimal dose of

steroid below which rejection is likely to occur.¹⁰ Those patients in whom episodes of rejection occurred more than 24 months after renal transplantation were receiving a mean dose of prednisolone at the time of rejection of $130 \pm \text{SD } 30 \mu\text{g/kg}$ body weight. In another series,¹¹ rejection occurred in three patients when they were taking 100, 130, or 160 $\mu\text{g/kg}$. Our findings, however, suggest that the requirements for immunosuppressive drugs vary between patients, so that a standard "minimum-threshold dose" is unlikely to be generally applicable. Thus five of our patients who developed rejection were taking between 30 and 75 μg prednisolone/kg daily, whereas three patients taking similar doses (cases 1-3) remained well and maintained stable renal function.

Subjects vary in their handling of oral prednisolone.^{12, 13} We studied the relation between the dose of prednisolone and the plasma concentration after the oral administration of four small, different doses of either enteric-coated prednisolone or enteric-coated and standard prednisolone. There were no consistent differences in plasma prednisolone concentration among patients at the doses of prednisolone used. This was so even after the 10 mg dose (two 5 mg enteric-coated tablets) was given. The large individual variations in plasma prednisolone concentration after the same dose of prednisolone did not seem to be implicated in the episodes of rejection seen in some patients.

The plasma cortisol concentrations in these patients tended to be below normal or at the lower end of the normal range, which was also apparently inconsistent with the patterns of plasma prednisolone concentrations. Four of the five patients in whom adrenal function was assessed showed moderate to severe impairment (fig 3). The response to tetracosactrin in one of these patients (case 8), who subsequently developed rejection, however, was not distinguishable from that seen in the other three patients (cases 2, 3 and 10; fig 3).

Our findings therefore suggest that, although reduction of the prednisolone dose to 7 mg daily in renal transplant recipients more than two years after transplantation may be relatively safe, any further reduction should be avoided unless there are extenuating circumstances or the patient is receiving adequate immunosuppressive treatment with azathioprine.⁷ Measuring the plasma drug concentration or assessing adrenal function does not provide any clear guideline for predicting which patient will safely tolerate virtually complete withdrawal of all immunosuppressive treatment. Until reliable indices are available patients must be warned about the dangers of stopping prednisolone in the absence of alternative immunosuppressive treatment.

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Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial

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Summary and conclusions

After baseline studies, 21 patients with osteoporosis were treated with human parathyroid hormone fragment (PTH 1-34) given as once-daily subcutaneous injections for 6-24 months. The dose used did not cause hypercalcaemia even in the first few hours after injection. Calcium and phosphate balances improved in some patients, but there was no significant improvement in the group values. There were, however, substantial increases in iliac trabecular bone volume: the mean increase, confirmed by repeat blind measurements, was 70% above mean baseline volume. The new bone was histologically normal. Those patients who had the

largest increases in ⁴⁵Ca-kinetic and histomorphometric indices of new bone formation showed the greatest increases in trabecular bone volume, suggesting that treatment with human parathyroid hormone fragment caused a dissociation between formation and resorption rates that was confined to trabecular bone.

Since vertebrae are four-fifths composed of trabecular bone, this hormone fragment may prove useful in treating patients with the crush fracture syndrome.

Introduction

The rate of renewal of the skeleton in most patients with osteoporosis is about 5% yearly.^{1,2} Thus any treatment aimed at rapidly reversing a typical³ 20% relative deficit in bone mass must increase the rate of formation of new bone. We have reported that giving low doses of synthetic human parathyroid hormone fragment (PTH 1-34) daily for six months roughly doubles the bone formation rate.^{4,5} We report here further results from our multicentre study.

Patients and methods

Sixteen women aged 49 to 78 years (mean 63) and five men aged 52 to 61 years (mean 56) were studied. Each gave informed consent to participation in the trial in the manner approved by his or her local hospital ethical committee. All but one had at least one severe vertebral crush fracture (the mean number being five: the remaining patient had a history of fractures of long bones (table). No patient had received fluoride treatment or a prolonged course of glucocorticoid treatment. The only known precipitating cause for osteoporosis apart from a lack of oestrogen was thyrotoxicosis. This had occurred in one patient and had been successfully treated 35 years before the trial. At the time of acceptance into the study no patient had received pharmacological doses of any vitamin D preparation within two years, although one patient in Boston (case 21) was treated with vitamin D₃ 50 mg (2000 IU) daily for two years before entering the trial, and all the British patients (cases 1-8) were given vitamin D₃ 12.5 mg (500 IU) daily from three months before their baseline values were determined. These doses were maintained throughout the study.

The following indices were normal in all patients: liver function tests, age-corrected and size-corrected glomerular filtration rates, plasma calcium and phosphate concentrations, alkaline phosphatase

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