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INCIDENCE OF SKELETAL COMPLICATIONS IN RENAL GRAFT RECIPIENTS

Effect of Changes in Pharmacotherapy

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The purpose of this study was to examine whether the occurrence of skeletal complications of renal transplantation is affected by a reduction in the steroid dose and avoidance of hypophosphataemia after the operation. A group of 36 patients that had been given smaller steroid doses and where non-phosphate-binding antacid had been given to most of the patients with hypophosphataemia were compared with a group of 144 long-term survivors given the formerly used, higher dose of steroids, and also phosphate-binding antacid agents. The modification of the regimen did not reduce the incidence of spontaneous fractures but none of the patients developed osteonecrosis after this change ($P < 0.1$). Patients in the group receiving non-phosphate-binding antacids displayed a higher serum phosphorus level ($P < 0.1$). Our results suggest that the development of osteonecrosis after renal transplantation may be avoided by reducing the steroid dose and avoiding hypophosphataemia.

Key words: antacid agents; corticosteroids; fracture; osteonecrosis; renal transplantation

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Spontaneous fractures and avascular necrosis are common complications of renal transplantation (Elmstedt & Svahn 1981, Ibels et al. 1978) and are usually ascribed to the steroid therapy. In consequence of the high incidence of osteonecrosis, among other factors, the steroid dose was reduced about 3 years ago. Another factor that might have bearing on the development of skeletal complications is disturbance of the calcium-phosphorus balance. Hypophosphataemia is not uncommon after transplantation (Pieper et al. 1977) and in a study of factors predisposing for avascular necrosis significantly lower serum phosphorus levels 2 months after the transplant operation were found in the group with this complication (Elmstedt 1981). On noticing this we modified the antacid therapy, replacing the phosphate-binding agents previously used in most patients by a non-phosphate-binding variety. The purpose of the present study was to examine the effect of these modifications in regimen on the occurrence of skeletal complications.

MATERIAL AND METHODS

The dose of steroids received by the renal graft patients in Stockholm was reduced in November 1977, and between this date and May 1979 a total of 73 transplantations were carried out in 71 patients. The 36 patients who had not previously undergone a renal transplant operation and whose graft kidney was still functioning after 12 months provided the series for this study. Twenty-two of them were males and 14 females. Two of the patients had two graft operations within the period. Twenty of the grafts were from cadavers and 16 from living relatives. The patients ranged in age from 12 to 68 years. The follow-up period was between 12 and 30 months. This group of patients was compared with the 144 patients (78 males, 66 females) receiving renal grafts between 1972 and 1976 with a graft survival of at least 1 year, reported on previously (Elmstedt

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1981). For each patient in the new series four patients from the old series, all of whom had had at least an equal period of graft function, were selected for comparison. Skeletal complications in the old series of patients were accounted for only if they had occurred within a time limit set by the actual follow-up time in the new series of patients. The mean ages in the two groups were 41 and 40.7 years respectively. The immunosuppressive therapy prior to November 1977 has been reported elsewhere (Elmstedt & Svahn 1981). From November 1977 the initial dose of oral prednisone was reduced to 120 mg/d, intravenous doses were not given and the rejection therapy was reduced to 1-g doses of alpha-methyl prednisolone for 3–5 days.

To avoid gastrointestinal side effects of the steroids the patients were given 10–15 ml of an antacid agent 8–10 times a day for the first few months after the operation. From 1977 a change was made from the phosphate-binding agents given earlier to aluminium phosphate, which is not phosphate-binding. One patient was excluded from analysis because of persistent secondary hyperparathyroidism. At the follow-up examination of the remaining 35 patients it was found that this agent had been given consistently to only 14 patients. In patients whose grafts did not function immediately, aluminium phosphate was not given in the early course after transplantation and 12 patients received it for only a short period before it was replaced by other antacids, usually aluminium hydroxide. The change was made because of side effects of the phosphate, in particular constipation.

All the patients were examined for musculoskeletal diseases. If avascular bone necrosis or spontaneous fracture was suspected, a radiographic examination was performed, sometimes with scintigraphy. A fracture was classed as spontaneous if it had occurred after minimal or no trauma. In only a few cases was there uncertainty as to the classification.

The serum phosphorus and serum creatinine levels were determined 1 and 2 months after the transplant operation. The oral dose of prednisone to each patient was calculated after 1, 2, 3, 6, and 12 months, as was the mean daily consumption in relation to the body weight. The total dose of steroids, oral prednisone and intravenous methyl prednisolone, was determined at the same times, and the mean daily intake of these drugs was calculated in relation to the body weight and body surface area (m^2BSA).

In the statistical analysis the chi-square test and Student's t-test were used.

RESULTS

Of the 36 patients receiving a renal graft after November 1977, spontaneous fractures were found in eight (22 per cent), compared with 27 of

Table 1. Skeletal complications following renal transplantation in patients treated with higher doses of steroids and phosphate-binding antacids (1972–76) and with lower doses of steroids and non-phosphate-binding antacids (1977–79)

Steroid dose	Lower (1977–79)		Higher (1972–76)	
	n	%	*n*	%
Number of patients	36		144	
Number sustaining spontaneous fractures	8	*22*	27	*19*
Number developing avascular necrosis	0	*0*	17	*12*

Table 2. Serum phosphorus and serum creatinine values after renal transplantation in patients with phosphate-binding and non-phosphate-binding antacids

	Phosphate-binding antacids		Non-phosphate-binding antacids	
	Mean	±S.D.	Mean	±S.D.
Number of patients	21		14	
Serum phosphorus (mmol/l)				
1 month after transplantation	0.76	0.58	0.69	0.33
2 months after transplantation	0.68	0.37	0.84	0.24
Difference				
1 month–2 months	–0.14	0.71	0.14	0.29
Serum creatinine (μmol/l)				
1 month after transplantation	128	87	101	46
2 months after transplantation	117	66	97	37

Table 3. The oral prednisone dose and the total steroid dose (oral prednisone plus intravenous methylprednisolone) during the first year after the renal transplant operation in the two series with higher and lower doses of steroids

		1977–1979		1972–76	
		Mean	±S.D.	Mean	±S.D.
Number of patients		36		144	
Oral prednisone					
Total intake, g	1 month	1.8	0.2	3.1	0.9
	3 months	4.1	0.4	6.0	2.1
	12 months	9.8	1.1	11.9	2.9
Mean daily intake					
Related to body	1 month	1.0	0.3	1.9	0.7
weight mg/d/kg	3 months	0.8	0.2	1.1	0.4
	12 months	0.4	0.1	0.5	0.2
Total steroids					
Total intake, g	1 month	4.4	3.3	6.3	2.9
	3 months	9.5	5.6	10.9	4.9
	12 months	15.4	5.9	17.4	6.2
Mean daily intake					
Related to body	1 month	2.5	2.0	3.6	1.8
weight mg/d/kg	3 months	1.8	1.1	2.0	1.0
	12 months	0.7	0.3	0.8	0.3

the 144 (19 per cent) receiving their graft between 1972 and 1976.

Avascular bone necrosis was found in none of the patients transplanted after November 1977 but in 17 (12 per cent) of the patients in the earlier series (Table 1). Because of the low incidence of avascular bone necrosis a large series is required for testing whether an observed change is statistically significant; there was, however, a clear tendency for the number of patients developing avascular bone necrosis to be lower in the group receiving the smaller steroid dose ($P < 0.1$).

The serum phosphorus and serum creatinine values during the first 2 months after the transplant operation were calculated for the groups given phosphate-binding or non-phosphate-binding agents (Table 2). There was a difference in the change in the serum phosphorus level between 1 and 2 months after the operation, the patients receiving non-phosphate-binding agents showing a higher serum phosphorus level ($P < 0.1$).

The reduction in the steroid dose meant that the oral dose of prednisone during the first 2 months after the transplant operation was decreased to about 60 per cent of the earlier dose (Table 3). Though the change from the earlier dose was smaller at the later times, it was still highly significant throughout the first 12 months after the operation ($P < 0.0001$). The total steroid dose – that is, oral prednisone and intravenous methyl prednisolone – was not decreased as much as the oral dose. During the first month after the operation the total dose was about 70 per cent of the earlier value, but the reduction decreased with time, and 3 months after the operation the difference was just significant ($P < 0.05$).

DISCUSSION

The change to a lower steroid dose evidently did not reduce the incidence of spontaneous fracture, possibly because corticosteroids in high doses inhibit the action of parathyroid hormone and thus reduce bone resorption (Elmstedt 1982, Kukreja et al. 1976, Raisz et al. 1971).

In an earlier study no correlation was found

between the patients' individual steroid dose and avascular bone necrosis in the first year after the operation (Elmstedt 1981). In a compilation of several renal transplant series where adequate information on dose could be obtained the critical dose of prednisone that differentiated the treatment groups with high and low incidences of avascular osteonecrosis was found to be about 100 mg/d during the first month after the operation (Ibels et al. 1978). This is supported by the results of the present study, where the complication was avoided when the dose was reduced from about 100 to about 60 mg/d.

The analysis of serum phosphorus in groups treated with phosphate-binding and non-phosphate-binding antacid agents indicates that the former have a bearing on the development of hypophosphataemia after transplantation (Table 2). This is consistent with the results of earlier studies of renal graft patients (Alfrey et al. 1968, Schwartz et al. 1979). In one study, however, it has been questioned whether hypophosphataemia has a dietary causation, since the recipients were normocalcaemic (Kokot et al. 1978). Hypophosphataemia of dietary origin has, however, been reported in association with normocalcaemia (Lotz et al. 1968).

After modification of the pharmacotherapy in the present study avascular osteonecrosis did not develop in any of the renal graft patients. It would thus appear that this skeletal complication can be avoided by limiting the steroid dose and by the avoidance of hypophosphataemia.

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