Parathyroid Supressibility in Renal Osteodystrophy

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Introduction

In patients with chronic renal failure hypocalcaemia is recognized as the most important factor in the aetiology of parathyroid gland hyperactivity. Persistent hypocalcaemia provides a continuous stimulus for hyperparathyroidism. Excessive secretion of parathyroid hormone (PTH) in the presence of normo- or hypercalcaemia probably indicates an autonomous state of the glands, termed tertiary hyperparathyroidism. The therapeutic use of ‘high’ dialysate calcium concentrations, calcium supplements and phosphate binders in patients with tertiary hyperparathyroidism is based on the assumption of the suppressibility of the parathyroid glands (Goldsmith et al, 1971). If, however, the parathyroid glands are in a state of functional autonomy these measures will be inadequate and either total or sub-total parathyroidectomy is indicated. Various forms of calcium infusion tests have been used in the past to test the suppressibility of parathyroid glands (Falls et al, 1966; Reiss and Canterbury, 1971; Berson and Yalow, 1966; Kastagir et al, 1970), but heterogeneity of immunoreactive PTH circulating in plasma places a severe restriction on the use of changes in its concentration during a calcium infusion test (Arnaud, 1973; Berson and Yalow, 1971). Changes in plasma hydroxyproline concentration appear to be a sensitive index of bone collagen turnover and the osteoclastic response to PTH (Hahn and Avioli, 1970; Bishop et al, 1971; Varghese et al, 1973; Moorhead et al, 1974). We have therefore investigated the changes in plasma hydroxyproline concentration in response to an acute intravenous infusion of calcium in patients with chronic renal failure.

PATIENTS AND METHODS

Twelve patients (nine male and three female) with end-stage chronic renal failure were studied. Four of the patients received a calcium infusion immediately before being started on regular dialysis treatment; the other eight patients were on
maintenance haemodialysis treatment (MHT) at the time of the calcium infusion. The age of the patients ranged from 15 to 53 years. A radiological skeletal survey was performed immediately before and six to nine months after the calcium infusion. All patients were dialysed for 25 to 30 hours per week, using a 'Meltec' Kil dialyser. The dialysis fluid contained 7.5 mg calcium/100 ml. The patient's dietary calcium intake ranged from 500 to 800 mg/day. None of the patients was given vitamin D or calcium supplements over the period of study. All foods containing gelatin were excluded from the diet for the five days prior to the infusion. In the patients on MHT the calcium infusion was performed 36 hr after the previous dialysis.

Calcium Infusion

Calcium was infused as calcium gluconate in a dose of 15 mg of calcium/kg body weight diluted in half-normal saline to a final volume of 500 ml. The infusion was over a four-hour period. Venous blood samples were collected without stasis from the arm opposite to the infusion before 0 hr and at 1 hr, 3 hr, 5 hr and 7 hr after starting the infusion. Total plasma calcium, inorganic phosphate, total protein, albumin, and hydroxyproline concentrations were measured by standard biochemical methods (Varghese et al., 1973).

RESULTS

The changes in the plasma concentrations of the variables studied during calcium infusion are summarised in Table I. Despite the administration of calcium in a dose based on body weight, the increases observed in plasma calcium concentration in the individual patients were variable. The mean maximal increase in plasma calcium concentration was 2.15 mg/100 ml. In all of the patients except one (No. 9) the plasma calcium concentration was raised by the infusion to a value which was above the upper limit of the normal range. In none of the patients was there any marked effect on plasma alkaline phosphatase activity, nor were there any changes in either total protein or albumin concentration following the calcium infusion. In eight of the patients there was a slight decrease in plasma phosphate concentration, while there was an increase in 3 (Nos. 4, 7 and 12) and no change in the other patient (No. 9).

In all of the patients the plasma hydroxyproline concentration was above the upper limit of the normal range (0.4 to 2.8 mg/ml) before calcium infusion. During the infusion there was a decrease of 40% or more from the baseline (0 hr) value in plasma hydroxyproline concentration in five patients (Figure 1).

The radiological findings before calcium infusion and after dialysis against a high calcium concentration are shown in Table II. Three of the five patients (Nos. 1, 2 and 5) who showed a reduction in plasma hydroxyproline concentration
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Figure 1. Changes in plasma hydroxyproline concentration during and after calcium infusion expressed as percentages of the base-line values.

TABLE II. Radiological Findings Before Calcium Infusion and After Dialysis against a Calcium Concentration of 7.5 mg/100 ml for 6 to 9 Months

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before Calcium Infusion Test</th>
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<td>Osteitis fibrosa</td>
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<td>Osteitis fibrosa and osteosclerosis</td>
<td>Changes of osteitis fibrosa and osteosclerosis more marked</td>
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<td>Vascular calcification</td>
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<td>12</td>
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</table>

during the calcium infusion test had radiological improvement with high calcium dialysis (Figure 2); in one other (No. 3) there was no change, and in the remaining patient (No. 4) there was an increase in vascular calcification. In the remaining 7 patients, who showed no significant alteration in plasma hydroxyproline concentration during the calcium infusion, the skeletal lesions either remained unchanged or became more marked on high calcium dialysis. Three of these patients subsequently underwent total parathyroidectomy. In all of them the plasma hydroxyproline concentration had decreased into the normal range within five to ten days of the operation, and by six months they all showed marked radiological improvement.

In one patient (No. 5) separate results of the value of changes in plasma hydroxyproline concentration as an index of parathyroid dysfunction were also
Figure 2. Radiographs showing changes in patient No. 2 before calcium infusion (left), 9 months after starting on haemodialysis (right).

Figure 3. Changes in plasma hydroxyproline concentration due to variations in the calcium concentration of the dialysate in patient No. 5.
obtained. In 1972 this patient, who was on home dialysis, inadvertently used a dialysate with a calcium concentration of 5.5 mg/100 ml. Towards the end of that year he complained of bone pain, and on radiological examination was found to have severe renal osteodystrophy with marked osteitis fibrosa and osteosclerosis. His plasma hydroxyproline concentration was 15.8 mg/l (Figure 3). He subsequently used a dialysate calcium concentration of 7.5 mg/100 ml and within fourteen weeks his plasma hydroxyproline fell to 3.4 mg/100 ml. This subsequently fell into the normal range and there was radiological evidence of healing of the osteitis fibrosa and disappearance of the osteosclerosis.

DISCUSSION

In five of 12 patients studied there was a reduction in plasma hydroxyproline concentration during calcium infusion. In four of these five patients there was radiological evidence of hyperactivity of the parathyroid glands as shown by osteitis fibrosa. In three of these four patients after dialysis with a high calcium dialysate there was evidence of healing of the radiological lesions with no change in the other.

In the seven patients who showed no change in plasma hydroxyproline concentration during calcium infusion the radiological lesions of parathyroid hyperactivity either showed no change or increased in severity after dialysis with a high calcium dialysate. These differences in response suggest variations in the suppressibility of parathyroid gland function in response to calcium. In some patients radiological findings improved after high calcium dialysis. These results were in general agreement with the reduction in plasma hydroxyproline after acute calcium infusion.

Hypercalcaemia may be masked by the accompanying hyperphosphataemia in patients with end-stage chronic renal failure. A failure of the feed-back control of parathyroid hormone secretion can occur in hyperplastic glands, because of the sheer increase in the numbers of secreting cells, which may produce more than normal amounts of parathyroid hormone even at their basal secretory rate. In the parathyroidectomised patients, chief cell hyperplasia was very marked. An increase in the number of secreting cells was also found in a different context in the studies of Gittes and Radde (1966) who showed persistent hypercalcaemia and hypophosphataemia in rats after increasing the number of normal parathyroid glands by transplantation.

In the present study, plasma hydroxyproline fell in some patients, remaining elevated in others. In the latter, hydroxyproline probably remained high because the serum calcium was not raised enough to suppress the parathyroid glands. The fall in plasma hydroxyproline obtained after parathyroidectomy supports the view that hydroxyproline is a good biochemical marker for parathyroid gland overactivity (Varghese et al, 1973).
The finding of a significant correlation between i-PTH and plasma hydroxyproline concentration (Wills et al, 1974) strengthens this relationship. However, a non-specific elevation of hydroxyproline due to reduction in catabolism as a consequence of uraemia cannot be excluded. It would seem unlikely, however, that variations in catabolism play any role in the sequential changes in hydroxyproline following calcium infusion. The long-term radiological improvements in those patients who showed a fall in plasma hydroxyproline concentration during calcium infusion suggest that this test is a valuable index in the assessment of functional parathyroid autonomy in patients with chronic renal failure.

References

Arnaud, C D (1973) *Kidney International*, 4, 89
Gittes, R F and Radde, I C (1966) *Journal of Urology*, 95, 595

Open Discussion

S MASSRY (Los Angeles) This is very interesting Dr. Sweatman. You refer to variability in suppressibility, but you show us that the serum calcium after calcium infusion varies between about 9.5 and 14 mg/100 ml. I wonder whether the five patients who showed a reduction in hydroxyproline are those patients who had the higher calcium with calcium infusion?

The degree of suppressibility appears to depend on the mass of the parathyroids, which may become suppressible once you remove some of the tissue.

SWEATMAN That's an interesting point; in fact we found no correlation between the calcium or phosphate levels and the ease of suppressibility in these patients. As regards your point about the actual mass of parathyroid tissue, the glands
removed were very large, but there were no adenomata in our series. We are going
to use longer infusion times to see the effect of prolonged hypercalcaemia or a
higher level of hypercalcaemia.
E SLATAPOLSKY (USA) In your first slide you show that there was roughly
50% decrease in hydroxyproline levels in five patients. I would like to know the
actual concentration levels, not in percentages, and what is the sensitivity of the
method?
SWEATMAN The concentrations varied. The upper limit of normal is 2.8, the
actual levels range from 5.3 to the highest of 97. The method is very sensitive.
SLATAPOLSKY When we talk about suppressibility we have to remember that
the kidney is there to remove PTH, and if we take a patient who has primary
hyperparathyroidism and we do a sub-total parathyroidectomy after 24 hr we
cannot measure PTH in blood. If we take a uraemic patient or a uraemic dog and
we remove the four parathyroid glands there is PTH in the blood for several days.
Although calcium may shut off the parathyroid glands, PTH fragments are present
in blood and may remain there for prolonged periods of time.
VARGHESE (London) May I answer that? We are suggesting that these patients
have got functional autonomy. If you do plasma hydroxyproline levels after a
parathyroidectomy in primary hyperparathyroid patients you will see changes in
hydroxyproline within hours whereas if you do parathyroidectomy in chronic
renal failure it may take between three and five days for plasma hydroxyproline
to return to the normal range. This would fit with the long half-life of PTH in
uraemia. The test is sensitive and does not pick up the hydroxyproline-rich Clq
component of the complements.
A FOURNIER (France) I want to stress the lack of reliability of this acute sup-
pressive test in our hands. In the Mayo Clinic we have found that infusion of
calcium during eight hours did not depress the level of PTH, in spite of which we
achieved regression of the secondary hyperparathyroidism after a month’s treat-
ment. Sometimes it may be useful to dialyse patients up to five times a week. I
would like to ask you how many times you dialysed the patients whose hyper-
parathyroidism got worse?
VARGHESE Well, in general all patients were dialysed 8–10 hr, three times a
week. There were no exceptions. In the initial training period, patients dialyse
four or five times a week, but still may have hyperparathyroidism.