Calcium Infusion Test in Uraemic Osteodystrophy

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The incidence of osteodystrophy in chronic progressive uraemia is now well recognized and the frequency of its incidence increases with the length of duration of uraemia. Osteopathologically, the uraemic osteodystrophy is characterised by a combination of osteomalacia, varying degrees of osteoclastic activity and osteitis fibrosa due to secondary hyperparathyroidism (Stanbury & Lumb, 1966) and mixture of osteoporosis and osteosclerosis (Ball, 1960). It is well known that the diagnosis of hyperparathyroidism can be most difficult in the presence of renal failure, when values of urinary calcium and phosphorus excretion are not reliable, and changes of osteomalacia may mask osteitis fibrosa in the bone biopsy. Unlike primary hyperparathyroidism, absolute hypercalcaemia does not occur until late in the course of the disease, and the actual measurement of parathormone in the plasma is not as yet readily available. In the presence of uraemia, a state of 'autonomous' or irreversible hyperparathyroidism may exist which is manifested by hypercalcaemia when uraemia has been corrected by dialysis or renal transplantation (Kleeman et al, 1967; McPhaul, 1964). In this study, the calcium infusion tests, according to the method of Barter and Pronore (1961) and the results of serum calcium determinations during the test are presented and correlated with the radiological and bone biopsy findings in an attempt to distinguish irreversible hyperparathyroidism in patients with chronic renal failure.

MATERIALS AND METHODS

Eleven patients on the maintenance dialysis programme were found to have uraemic osteodystrophy by X-ray and iliac crest biopsy. Patients were dialysed three days per week as described earlier (Kwan-Gett et al, 1969). A calcium infusion test was performed in these patients in an inter-dialysis steady-state condition, using 15 mg of calcium per kg of body weight infused over a period of four hours.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Duration of CRF (months)</th>
<th>Skeletal X-ray</th>
<th>Bone Biopsy</th>
<th>Calcium Infusion Test</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>DW</td>
<td>22</td>
<td>M</td>
<td>CPN</td>
<td>36</td>
<td>Demin.</td>
<td>OF</td>
<td>10.1  10.3  10.9</td>
<td>Renal Transplantation</td>
</tr>
<tr>
<td>DA</td>
<td>21</td>
<td>M</td>
<td>CGN</td>
<td>39</td>
<td>Subperios Resorp.</td>
<td>OF</td>
<td>9.2   11.4  11.9</td>
<td>Subtotal PTX; Vitamin D and calcium</td>
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<td>DM</td>
<td>21</td>
<td>F</td>
<td>CGN</td>
<td>21</td>
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<td>OF (osteoclastic)</td>
<td>10.5  12.0  12.8</td>
<td>Subtotal PTX; Vitamin D and calcium</td>
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<td>M</td>
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<td>24</td>
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<td>OF (osteoclastic)</td>
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<td>RS</td>
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<td>M</td>
<td>CGN</td>
<td>18</td>
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<td>not done</td>
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<tr>
<td>SR</td>
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<td>F</td>
<td>CGN</td>
<td>18</td>
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<td>CGN</td>
<td>24</td>
<td>Demin.</td>
<td>OF</td>
<td>10.8  12.5  13.0</td>
<td>Vitamin D and calcium</td>
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<tr>
<td>MB</td>
<td>10</td>
<td>M</td>
<td>HIN</td>
<td>28</td>
<td>Demin. Rickets</td>
<td>OF</td>
<td>11.0  12.7  13.2</td>
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<td>RB</td>
<td>21</td>
<td>M</td>
<td>CPN</td>
<td>8</td>
<td>Demin.</td>
<td>No OF</td>
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<td>DW</td>
<td>12</td>
<td>M</td>
<td>HIN</td>
<td>14</td>
<td>Demin. Rickets</td>
<td>No OF</td>
<td>6.9   7.2    6.8</td>
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<td>F</td>
<td>MCD</td>
<td>9</td>
<td>Demin.</td>
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<td>Calcium</td>
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<tr>
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<td>M</td>
<td>HIN</td>
<td>18</td>
<td>Demin. Rickets</td>
<td>No OF</td>
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<tr>
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<td>9.8   10.5  10.8</td>
<td>None</td>
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<td>CGN</td>
<td>8</td>
<td>Normal</td>
<td>No</td>
<td>9.2   9.9    10.3</td>
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**KEY**
- PTX = Parathyroidectomy
- CRF = Chronic Renal Failure
- CGN = Chronic Glomerulonephritis
- CPN = Chronic Pyelonephritis
- HIN = Hereditary Interstitial Nephritis
- MCD = Medullary Cystic Disease
- Demin. = Demineralization
Serum calcium and phosphorus levels were determined before, at the second hour and at the end of the infusion. Since the creatinine clearance in these patients was less than 5 ml/min, urinary excretion values of calcium and phosphorus were not relevant and therefore omitted from this study. Calcium infusion was performed in each patient at the time of admission to the study and again after subtotal parathyroidectomy. The result of the calcium infusion test was correlated with the X-ray and bone biopsy findings and was compared to that in four uraemic patients whose bone biopsy findings were normal. Mode of therapy of uraemic osteodystrophy was evaluated in each patient as a result of these findings. Uraemic patients with osteodystrophy were treated with a large dose of Vitamin D (25,000 to 50,000 units daily) according to the method of Stanbury and Lumb (1966). Subtotal parathyroidectomy (3 3/4 glands) was performed in those patients who developed hypercalcaemia during Vitamin D therapy.

RESULTS

Fifteen patients are divided into three groups according to the X-ray and bone biopsy findings:

1. Eight patients with predominantly osteoclastic activity and/or osteitis fibrosa. One patient (MB) in this group developed irreversible hyperparathyroidism in the course of long-standing rachitic changes due to chronic renal failure.
2. Four patients (including one from Group I) with predominant demineralisation in X-ray and bone biopsy.
3. Four patients with uraemia on maintenance dialysis with normal bones.

Group I: Osteoclastic Activity and Osteitis Fibrosa

Table I summarises the clinical data and the effect of calcium infusion test on the serum calcium values. In all patients, calcium level rises during the four hour infusion period above the normal range (Figure 1) without any significant change in the serum phosphorus values. These patients developed hypercalcaemia during treatment with Vitamin D. Following subtotal parathyroidectomy, serum calcium returned to normal level and Vitamin D therapy could be continued without any risk of hypercalcaemia. Serum alkaline phosphatase level had a tendency to fall following parathyroidectomy, indicating healing of the bone lesions (Figure 2).

The calcium infusion test was repeated in three patients in this group, six months after subtotal parathyroidectomy. Their serum calcium levels during the four hour test period remained unchanged, in contrast to their tendency to rise during the calcium infusion test prior to subtotal parathyroidectomy (Figure 3).
Figure 1. Calcium infusion in eleven patients with uraemic osteodystrophy and four uraemic patients without bone disease. Note rising serum calcium level in patients with osteitis fibrosa in contrast to the other two groups.

Figure 2. Effect of Vitamin D therapy (25,000-50,000 units daily) in patients with osteitis fibrosa. Note hypercalcaemia in all 5 patients which is relieved by sub-total parathyroidectomy (PTX). Note fall in alkaline phosphatase level following PTX. All patients received Vitamin D after PTX.
One patient in this group needs special mention: MB, 10-year-old male was found to have rachitic bone changes (Figure 4) in May, 1968, secondary to chronic renal failure. He also showed diffuse demineralisation in his skeleton. Calcium infusion at this time showed serum calcium level to fall during the test (Figure 1). Oral calcium supplements and Vitamin D (25,000 units daily) was started and the patient maintained on three days per week haemodialysis. After ten months on Vitamin D regime, he developed intermittent hypercalcaemia. A calcium infusion test at this time showed a tendency for serum calcium values to rise during the test. In view of persistent hypercalcaemia, Vitamin D was discontinued and subtotal parathyroidectomy was performed in August 1969. Serum calcium level became normal soon after parathyroidectomy and Vitamin D dosage could be resumed. Calcium infusion test six months after parathyroidectomy showed unchanged serum calcium levels during the test described above (Figure 3). There is radiological evidence of bone healing in October 1969 (Figure 5).

**Group II: Demineralisation**

Four patients in this group had diffuse skeletal demineralisation and obliteration of fine trabeculae radiologically, but no subperiosteal resorption. Bone biopsy did not show any osteoclastic activity or osteitis fibrosa. The calcium infusion test (Figure 1) showed a tendency of the serum calcium to fall during the four hour test period without any significant change in the serum phosphorus levels (Table I).
Figure 4. Rachitic changes in the ulnar bones in a child of 10 (MB) before starting treatment for uraemic osteodystrophy

Figure 5. Healing of uraemic rachitic changes and re-mineralisation of bones after treatment with Vitamin D and subtotal parathyroidectomy
These patients have all been treated with Vitamin D (25,000 units daily) and calcium supplements, with slow healing of the bone disease. Serum calcium has remained within the normal range throughout the period of treatment, ranging from four to sixteen months, except in one patient (MB) who developed hypercalcaemia and has been described above.

Group III: Normal Bone

Four uraemic patients on maintenance haemodialysis with normal radiological and biopsy appearance of bone, showed no change in this normal pre-infusion serum calcium values during the test (Table I).

DISCUSSION

Deminerlisation and osteitis fibrosa are two predominant pathologic entities in the whole spectrum of bone lesions in uraemic osteodystrophy. While the former is caused by failure of intestinal calcium absorption and calcium deposition in the bone, due to Vitamin D resistance (Liu & Chu, 1943; Dent et al, 1961; Harrison, 1966; Stanbury & Lumb, 1966) occurring since early in uraemia (Lichtwitz & Parlier, 1965), the latter is a manifestation of continuous stimulation of the parathyroid glands (Sherwood et al, 1966) with the excessive production of the parathyroid hormone (PTH). It has been proposed that correction of the Vitamin D resistance by large doses of Vitamin D, dialysis or renal transplantation, and restoration of normal serum calcium may entirely correct the process of uraemic osteodystrophy and 'shut off' the hypersecreting parathyroid glands (Kleeman et al, 1967). Normal calcium homeostasis is restored and the calcium salts are then normally deposited in the avid bones under the physiologic influence of thyrocalcitonin. A calcium load at this stage of the disease in Group II by calcium infusion results in temporary inhibition of PTH secretion. A fall in the plasma level of calcium during and after the calcium infusion may be explained by the inhibition of PTH secretion and the direct effect of thyrocalcitonin. In this state of reversible hyperparathyroidism, treatment with Vitamin D, dialysis or renal transplantation may result in healing of bone lesions. On the other hand, in some cases an irreversible so-called 'autonomous' hyperparathyroidism develops. Continuous and excessive secretion of PTH gives rise to osteitis fibrosa, hypercalcaemia and metastatic calcification. Long duration of uraemia increases the incidence of the irreversible hyperparathyroidism as is seen in Table I. Correction of uraemia by dialysis and administration of Vitamin D aggravate the severity of this condition. A calcium load by calcium infusion (Group I patients) fails to 'shut off' the parathyroid glands and a rising serum calcium level is seen, despite marked calcium deficiency in these patients. Subtotal parathyroidectomy restores a euparathyroid state and normal serum calcium level. Large dose Vitamin D therapy should follow to correct osteomalacia.
SUMMARY

Results of the calcium infusion test (15 mg calcium/kg body over four hour period) in eleven patients with uraemic osteodystrophy are presented. Patients with osteitis fibrosa differ from those with predominantly demineralised bone in their response to the calcium infusion test. The former group of patients have normal serum calcium level in presence of hyperphosphataemia and the serum calcium level tends to rise above the normal range, despite marked calcium deficiency, during a four hour calcium infusion test. On the other hand, the patients with demineralised bone had hypocalcaemia before the calcium infusion and their serum calcium level had a tendency to fall during the calcium infusion. The former group of patients developed hypercalcaemia rapidly (weeks) with the Vitamin D therapy. Subtotal parathyroidectomy (3 3/4 glands) was performed with immediate control of hypercalcaemia, and Vitamin D therapy was continued to correct osteomalacia. The patients with radiological demineralised bone and without osteitis fibrosa in the bone biopsy, tolerated Vitamin D in large doses with progressive healing of bone. An exception to this was one patient (MB) who developed osteitis fibrosa in the course of long-standing 'renal tickets'. Subtotal parathyroidectomy was performed in this patient to control hypercalcaemia.

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REFERENCES

Ball, J. (1960) 'Recent Advance in Pathology'. Chapter 9, Churchill, London
Harrison, H. E. (1966) Yale Journal of Biology and Medicine, 38, 393
Page 196
Liu, S. H. and Chu, H. I. (1943) Medicine (Baltimore), 22, 103
Stanbury, S. W. and Lomb, G. A. (1966) Quarterly Journal of Medicine, 35, 1