Postgrad Med J (1990) **66**, 918 - 922

Immobilization-related hypercalcaemia – a possible novel mechanism and response to pamidronate

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Summary: Immobilization-related hypercalcaemia is an uncommon but important condition being associated not infrequently with both urolithiasis and osteoporosis. In this study 5 patients who had been immobilized for a mean of 3 months and had a mean adjusted serum calcium of 3.15 mmol/l were treated with doses of intravenous pamidronate ranging between 10 mg and 45 mg. All patients became normocalcaemic by day 3. Patients 1–3 mobilized shortly after treatment and remained normocalcaemic. In those patients who continued to be immobile hypercalcaemia recurred after an interval of several weeks. Retreatment with pamidronate again resulted in normocalcaemia. No side effects were noted with treatment.

All of the patients studied had increased rates of bone resorption as shown by elevated urinary hydroxyproline/creatinine ratios (median:range) of 0.101:0.045–0.180 (normal <0.033) and elevated calcium/creatinine ratios of 2.50:0.69–3.63 (normal <0.50).

None of the patients in this study had any of the usual risk factors for developing immobilization-related hypercalcaemia though all 5 patients had problems with significant sepsis which we postulate may have lead to cytokine release which in turn contributed to the development of hypercalcaemia.

We conclude that pamidronate (at doses as low as 10 mg) is safe and effective in immobilization-related hypercalcaemia and suggest that sepsis should be added to the list of risk factors for development of this syndrome.

Introduction

Immobilization-related hypercalcaemia was first described by Albright in 1941.[1] Although it is an uncommon condition hypercalciuria and negative calcium balance is common with resulting osteoporosis.[2] Generally immobilization-related hypercalcaemia is associated with conditions where bone turnover is high such as in children, adolescents[3] or in patients with Paget's disease of bone.[4] In the patients described in this study these conditions were not present but rather all cases were associated with sepsis which may be a hitherto unrecognized aetiological factor in this syndrome. We and others have found pamidronate (amino-hydroxypropylidene bisphosphonate) to be of value in the treatment of the accelerated bone resorption associated with hypercalcaemia of malignancy[5] and Paget's disease of bone.[6] Since increased bone resorption is also the major factor in immobilization-related hypercalcaemia[7,8] we looked at the effects of pamidronate on 5 patients with this syndrome.

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Accepted: 2 July 1990

Patients and methods

The details of patients studied are shown in Table I. All were normally hydrated both clinically and biochemically and all gave informed consent prior to treatment. All infusions of pamidronate were given intravenously in 500 ml 0.9% saline over 4 hours. No side effects were noted. The diagnosis of sepsis in each patient was made on the basis of elevated white cell counts, erythrocyte sedimentation rates (ESR) and positive bacterial culture from the sites of infection and in all cases (except patient 3) from blood cultures. At the time of study all patients were receiving appropriate antimicrobial therapy. None of the patients was receiving any therapy thought likely to interfere in their calcium homeostasis except patient 4 who was receiving 50 mg per day of prednisolone, though this had

Table I Patient details

	Dose pamidronate (mg)	Age	Sex	Diagnosis	Duration of immobilization before hypercalcaemia	Adjusted serum Ca	Serum albumin	Serum creatinine	PTH	$25(OH)D_3$	$1,25(OH)_2D_3$
Reference range						2.20–2.60 mmol/l	35–55 g/l	40–130 μmol/l	undetect. –600 ng/l 1.0–5.0 pmol/l	15–100 nmol/l	20–120 pmol/l
Patient 1	10	35	M	Abdominal fistulae and sepsis	4 months	3.20	30	60	<250	12	16
Patient 2	15	19	M	Septic hip joint	3 months	3.10	27	85	480	–	–
Patient 3	30	58	F	Pulmonary tuberculosis Hepatic failure	5 weeks	3.15	31	65	<0.8	12	–
Patient 4	30	46	F	Crohn's disease Fistulae and sepsis	3 months	3.30	34	85	<1.0	13	10
Patient 5	45	62	F	Ruptured oesophagus with mediastinal sepsis	3 months	3.00	30	50	<0.8	71	–

For abbreviations, see text.

been commenced 4 months prior to the development of hypercalcaemia.

Serum calcium, phosphate, creatinine and albumin were measured by standard autoanalyser techniques (Technicon, Tarrytown, USA). Serum total calcium was adjusted for albumin as previously described.[9] In patients 1 and 2 immunoreactive parathyroid hormone (PTH) was measured by a double antibody radioimmunoassay.[10] In patients 3, 4 and 5 intact PTH 1–84 was measured by a two-site immunoradiometric assay.[11] 25-Hydroxycholecalciferol [$25(OH)D_3$] was measured in a competitive protein binding assay and 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$) was measured using a radioreceptor assay.[12] Urinary hydroxyproline (OH-Prol) excretion was measured by resin catalysed hydrolysis[13] followed by autoanalyser quantitation. Both urinary calcium and urinary OH-Prol excretion were expressed as a ratio of urinary creatinine excretion in mmol/mmol. Calcium excretion (CaE) was derived by multiplying the fasting urinary calcium/creatinine ratio by the prevailing serum creatinine[14] and expressed as μmol/l glomerular filtrate (GF). Transiliac bone biopsies were carried out after tetracycline double labelling using a Meunier trephine needle in patients 2 and 4 prior to treatment with pamidronate. Statistical measurement of changes in serum calcium and urinary calcium/creatinine ratios were made using a Mann-Whitney U-test.

Results

The response of serum calcium and urinary calcium/creatinine ratio following pamidronate treatment is shown in Figures 1 and 2. It can be seen that all patients were normocalcaemic by day 3 post-treatment. Patients 1–3 began to mobilize

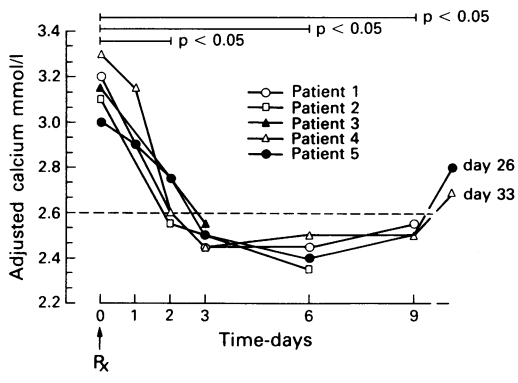

Figure 1 Changes in adjusted serum calcium (dotted line indicates upper limit of reference range).

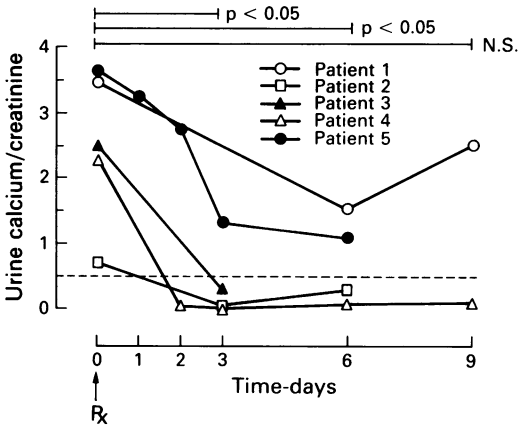

Figure 2 Changes in urinary calcium/creatinine ratio (mmol:mmol). (Dotted line indicates upper limit of reference range).

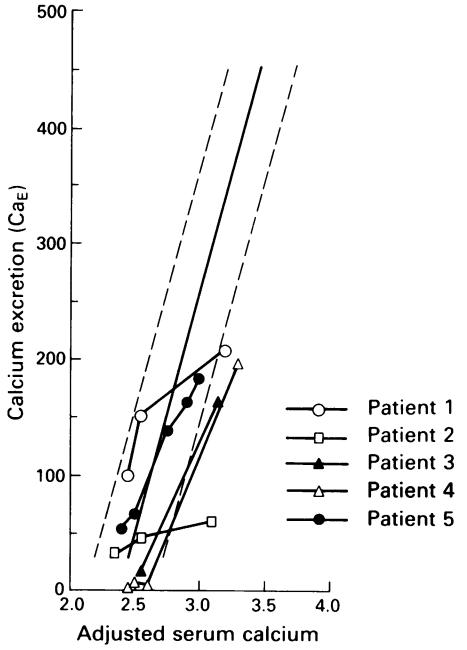

Figure 3 Relationship between adjusted serum calcium and calcium excretion (CaE). (Dotted lines indicate two standard deviations from the mean of the normal relationship – from Peacock *et al.*[14]

soon after treatment and remained normocalcaemic. Patients 4 and 5 remained immobile and recurrence of hypercalcaemia occurred at days 33 and 26 respectively. Calcium/creatinine ratios fell in all patients with a nadir at day 3. Figure 3 shows the relationship between serum calcium and the amount of calcium excreted per unit glomerular filtrate. Though marginal, values tended to lie to the right of the normal reference range described by Peacock *et al.*[14]

From Table I it can be seen that serum PTH was undetectable in all patients except patient 2, where it was measured on two occasions within the reference range. As might be expected $1,25(OH)_2D_3$ levels (where measured) were low and $25(OH)D_3$ levels were low, possibly reflecting poor nutritional state, lack of sunlight exposure or general illness. In patient 5, $25(OH)D_3$ levels were normal, although this patient was receiving total parenteral nutrition which included 200 units/day of vitamin D. OH-Prol/creatinine ratios were markedly elevated in all patients pre-treatment with a median of 0.101; range: 0.045–0.180 (normal <0.033). Similarly urinary calcium/creatinine ratios were markedly elevated pre-treatment with a median of 2.50; range 0.69–3.63 (normal <0.50).

Marked osteopenia was present histologically in patients 2 and 4 with trabecular bone volumes of 21% and 16% respectively (normal in our laboratory $>25\%$). Bone formation rates were normal with osteoid surfaces of 9% and 17% (normal $<24\%$). Bone resorption, however, tended towards the upper limit of normal with resorption surfaces of 6.3% and 5.2% (normal $<7\%$). There was no histological evidence of hyperparathyroidism and mineralization was normal.

Relapse was defined as a rise in serum calcium to 2.80 mmol/l. In the two patients where this occurred further infusions of pamidronate were given at the same dose as the original treatment. On each occasion serum calcium returned again to normal. The duration of normocalcaemia varied considerably after this second infusion (patient 4 = 97 days to relapse, patient 5 = 14 days to relapse). This may be because patient 4 became at least partly mobile. Both patients became fully mobile after they had received a total of 3 infusions each and normocalcaemia was maintained thereafter. After 6 months of hospitalization patient 4 developed a vertebral compression fracture.

Discussion

Immobilization-related hypercalcaemia, though rare, is important in that problems secondary to the hypercalcaemia and hypercalciuria, such as renal stones and osteoporosis, may occur. In one series,[15] over 50% of children immobilized due to spinal cord injury who were hypercalcaemic developed urolithiasis. The prolonged period of negative calcium balance which occurs predisposes to osteoporosis. Work in immobilized monkeys has shown significantly greater loss in axial cancellous bone than in peripheral cortical bone.[16] This pat-

tern of bone loss may be similar in man as suggested by the fact that one of our patients in this study, after prolonged immobilization, developed a vertebral compression fracture.

Previous work using radiolabelled calcium[7] and the incorporation of tetracycline into bone[8] has suggested the mechanism of the hypercalciuria and osteoporosis to be due to increased bone resorption and decreased bone formation. The high urinary OH-Prol/creatinine and calcium/creatinine ratios would be consistent with this hypothesis. However, the data from the bone biopsies suggest that while bone resorption tends to be increased, bone formation rates are normal.

The patients in this study were significantly older than would usually be the case in immobilization-related hypercalcaemia as this condition usually occurs in children or adolescents where bone turnover is high. Further, there was a greater time interval between the onset of immobilization and the development of hypercalcaemia than is usual. The main feature which these patients had in common was major sepsis with elevated white cell counts in all cases. Cytokines such as interleukin-1 (IL-1) and tumour necrosis factor (TNF) are known to stimulate increased bone resorption and the development of hypercalcaemia.[17,18] Furthermore, elevated levels of IL-1 have been described in patients with infection post-surgery.[19] We may postulate therefore that cytokines such as these may be contributory in this syndrome.

Although some calcium excretion (CaE) versus serum calcium values were to the right of normal (Figure 3), these were borderline and not indicative of any major renal calcium reabsorption component to the raised serum calcium and may simply reflect the fact that these patients did not receive intravenous saline rehydration before treatment. In one patient (patient 2) with the most abnormal CaE/serum calcium relationship PTH was measurable albeit within the reference range. This patient developed mesangial IgA disease associated with his infected hip joint which reduced his creatinine clearance to 70 ml/minute though his serum creatinine remained normal. This may explain the measurable PTH and also the apparently abnormal calcium excretion.

Previous work has shown that calcitonin,[20] etidronate[21] and clodronate[22] are of some value in the treatment of immobilization-related hypercalcaemia and hypercalciuria. A recent report[23] on one patient has also demonstrated intravenous pamidronate to be useful in the treatment of this syndrome though, in this case, transient hypocalcaemia was noted. This was not a feature in any of our patients. There was no evidence of a 'dose-response' effect as has been suggested with pamidronate in cancer associated hypercalcaemia[24] as in this study doses as low as 10 mg were effective. This may be because in this syndrome there is no evidence of parathyroid hormone-related-peptide (PTHrP) being present. It has been shown that when this factor is thought to be present in cancer-associated hypercalcaemia the effect of pamidronate is less good.[25,26]

In summary, pamidronate is safe and effective in treating both hypercalcaemia and hypercalciuria which may accompany immobilization. Further it would appear that sepsis, possibly by way of cytokine release, may also contribute to the pathogenesis of this syndrome.

Acknowledgement

We are grateful to Ciba-Geigy Ltd. for providing pamidronate.

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