

test dose while the patients were in the ward under supervision. Propranolol is reputed not to have an immediate lowering effect on blood pressure and we were surprised to find a reduction over the four-hour period with the higher dose. This suggests that the use of low starting doses of propranolol leads to a slower onset of hypotensive action.

Doubling the dose of propranolol in the outpatient study above 120 mg/day did not cause a statistically significant increase in the hypotensive effect. We have observed this lack of an increase in effect in a group of patients given the cardioselective beta-blocker atenolol, and the lack of an increase in effect has

also been shown by others with oxprenolol.²⁻⁴ Within-patient comparisons of the doses used in this study with higher doses—for example, 360 mg—4 g/day—would clearly be of interest.

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Hypophosphataemic osteomalacia in patients receiving haemodialysis

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Summary

Four patients had symptomless osteomalacia at the time of starting regular haemodialysis. After 21-40 months they became hypophosphataemic and developed disabling skeletal symptoms. In each case an exacerbation of histological osteomalacia was shown. Symptoms improved after measures designed to raise serum inorganic phosphate concentrations or vitamin D administration, or both. Patients undergoing maintenance haemodialysis should have their serum phosphate and alkaline phosphatase levels monitored every month. Predialysis phosphate levels below 1 mmol/l (3 mg/100 ml) and rising serum alkaline phosphatase concentrations are danger signals. If the diagnosis is confirmed early aggressive treatment should be started.

Introduction

Phosphate-binding agents (such as aluminium hydroxide) are widely used to reduce serum inorganic phosphate in patients with renal failure.¹⁻² These agents are known to cause phosphate depletion in patients with normal renal function³ and in patients with renal failure.⁴⁻⁵ Hypophosphataemic osteomalacia has been reported.⁶ We have recently seen four patients who became hypophosphataemic and developed severe osteomalacia while receiving maintenance haemodialysis. Our experiences are reported in this paper.

Case 1

A 16-year-old man with familial renal-retinal dystrophy⁷ presented in renal failure in July 1972. The serum calcium concentration was 1.25 mmol/l (5.0 mg/100 ml), serum inorganic phosphate 2.3 mmol/l

(7.0 mg/100 ml), and serum alkaline phosphatase 166 IU/l. Bone x-ray films showed a bone age of 11 years but were otherwise normal. Bone biopsy showed osteomalacia with an osteoid index⁸ of 5.0. Treatment with regular haemodialysis was started in July 1972, and oral aluminium hydroxide (2.4 g daily) was started four months later. The patient received phenytoin in doses ranging from 200-300 mg/day from July 1972 to May 1974. Serum calcium levels returned to normal within three months of the start of dialysis, while predialysis serum inorganic phosphate levels between October 1973 and May 1974 ranged from 0.55 to 1.2 mmol/l (1.7-3.6 mg/100 ml) (mean 0.71 mmol/l (2.2 mg/100 ml)). Serum alkaline phosphatase gradually rose to 1150 IU/l. Serum immunoreactive parathyroid hormone levels ranged from 0.6-2.4 µg/l. On 9 May 1974 he was admitted with severe pain in the limbs and inability to walk. Pelvic x-ray examination showed Looser zones, and a repeat bone biopsy showed severe osteomalacia with an osteoid index of 30.

The patient was treated with 2.5 mg dihydrotachysterol per day, and aluminium hydroxide treatment was discontinued. These measures were followed by complete symptomatic relief in six weeks. Predialysis serum inorganic phosphate levels rose to 1.3 mmol/l (4.0 mg/100 ml) or greater. Serum alkaline phosphatase activities initially rose to 2500 IU/l and fell to 200 IU/l three months later. The patient resumed aluminium hydroxide treatment and continued to take dihydrotachysterol (0.625 mg/day).

Case 2

A 21-year-old man with membranoproliferative glomerulonephritis started regular haemodialysis in March 1970, when he was 17. At that time he also started taking aluminium hydroxide (1.8 g daily) without apparent ill-effect. He received a cadaveric renal allograft in June 1971, but it was removed seven months later because of chronic rejection. Regular haemodialysis and aluminium hydroxide treatment were resumed at that time. Because of intractable hypertension he underwent bilateral nephrectomy in February 1972, and was trained for domiciliary haemodialysis two months later. Skeletal x-ray examination in May 1973 showed a bone age of 16 years and subperiosteal resorption of the phalanges. Skeletal histology showed mild hyperparathyroidism and severe osteomalacia with an osteoid index of 16.2. The mean predialysis serum inorganic phosphate concentration between November 1973 and May 1974 was 0.9 mmol/l (2.8 mg/100 ml), and the mean predialysis calcium level was 2.45 mmol/l (9.8 mg/100 ml). Serum alkaline phosphatase gradually rose to 923 IU/l. The mean predialysis serum immunoreactive parathyroid hormone level was 4.2 µg/l.

In May 1974 he was admitted because of generalised muscle weakness and pain in the limbs which were so severe that he was unable to walk. Skeletal x-ray films showed rachitic changes, and a repeat bone biopsy showed an osteoid index of about 30. Aluminium hydroxide was withdrawn and dihydrotachysterol (0.625 mg/day) was prescribed.

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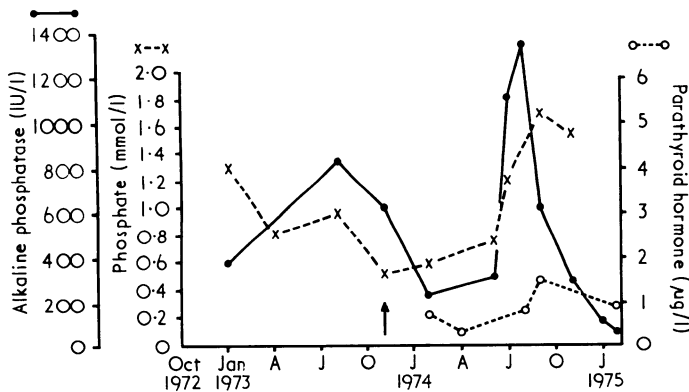
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Within four weeks the patient lost all symptoms. Predialysis serum phosphate levels rose to 1.9 mmol/l (6 mg/100 ml), and serum alkaline phosphatase levels rose to 1315 IU/l after eight weeks and fell to 65 IU/l within 12 months. In December 1974 he incurred a traumatic fracture of his right tibia and fibula which healed spontaneously. Since then he has received 0.6 g of aluminium hydroxide and 0.25 mg of dihydrotachysterol daily.

Case 3

A 24-year-old man with bilateral vesicoureteric reflux started regular domiciliary haemodialysis in April 1971. Aluminium hydroxide (2 g/day) was prescribed then, and the patient took this medication regularly for the next two and a half years. Bone x-ray films were normal in April 1972, but a year later soft tissue calcification was evident. The results of biochemical investigations performed in this patient are shown in the figure. Between 1973 and mid-1974 his mean



Case 3. Predialysis serum inorganic phosphate, serum alkaline phosphatase, and serum immunoreactive parathyroid hormone concentrations during the evolution of hypophosphataemic osteomalacia. Arrow indicates the date of the first bone biopsy. Note rise in serum inorganic phosphate, serum alkaline phosphatase, and serum immunoreactive parathyroid hormone after aggressive treatment in June 1974.

Conversion: SI to traditional units—Phosphate: 1 mmol/l \approx 3.1 mg/100 ml.

predialysis serum inorganic phosphate concentration was 0.74 mmol/l (2.3 mg/100 ml), the mean serum calcium level was 2.6 mmol/l (10.4 mg/100 ml), and serum alkaline phosphatase values ranged between 380 and 835 IU/l. Serum immunoreactive parathyroid hormone ranged from 0.3 to 0.6 μ g/l. A bone biopsy performed in November 1973 showed no evidence of hyperparathyroidism but showed pronounced osteomalacia with an osteoid index of 20. Treatment with 1.25 mg ergocalciferol was started and the daily dose of aluminium hydroxide was reduced from 2 g to 650 mg. In June 1974 he complained of weakness of hand grip, pain on shaking hands, and generalised aches. A repeat bone biopsy again showed osteomalacia with osteoid index of 31.2. Aluminium hydroxide medication was stopped and the ergocalciferol dose was increased to 5 mg daily. After this change in treatment the serum inorganic phosphate rose to 1.6 mmol/l (5 mg/100 ml). The serum alkaline phosphatase rose to 1350 IU/l before falling to within normal limits. Symptoms were completely relieved within four weeks, but hypercalcaemia developed seven months after the start of calciferol treatment.

Case 4

A 20-year-old woman with idiopathic non-obstructive pyelonephritis started peritoneal dialysis in September 1971. At that time she had no musculoskeletal symptoms and bone x-ray pictures were normal except for a bone age four years less than her chronological age. Bone histology showed moderate osteomalacia with an osteoid index of 5. Domiciliary haemodialysis was started in February 1972 but phosphate-binding gels were not required, as predialysis serum phosphate levels were invariably normal. Pain and tenderness in the back, ribs, and pelvis developed in November 1972 and a repeat bone biopsy showed severe osteomalacia with an osteoid index of 16. The administration of ergocalciferol (2.5 mg/day) was followed by relief of symptoms.

In April 1973 she received a cadaveric renal allograft, which was removed three months later because of cytomegalovirus infection

and chronic rejection. Domiciliary haemodialysis was resumed but phosphate binding agents once again were not necessary because the mean predialysis serum inorganic phosphate was 0.68 mmol/l (2.1 mg/100 ml).

In March 1975 bone pain and muscle tenderness recurred. The serum alkaline phosphatase had risen from 151 to 425 IU/l and a third bone biopsy showed more severe osteomalacia with an osteoid index of 20.1. Dihydrotachysterol (0.25 mg/day) was started and subsequently increased to 0.5 mg/daily to relieve symptoms. Within three months of the start of vitamin D treatment the patient's symptoms had disappeared. The serum alkaline phosphatase rose to 500 IU/l and subsequently fell to 165 IU/l.

Methods

Serum calcium was estimated by the method of Zettner and Seligson⁹ or by the Technicon method,¹⁰ serum inorganic phosphate by the method of Young,¹¹ and serum alkaline phosphatase by the method of Morgenstern *et al.*¹² Serum immunoreactive parathyroid hormone was determined by the method of Kleerekoper *et al.*¹³ and the bone age by the method of Greulich and Pyle.¹⁴ Bone biopsies and histological evaluations were performed according to the method of Garrick *et al.*¹⁵

The dialysate calcium concentration ranged from 1.8 to 2.0 mmol/l (7.3-8.0 mg/100 ml), the total phosphate from 0.03 to 0.06 mmol/l (0.1-0.2 mg/100 ml), and the fluoride from 0.95 to 1.0 parts per million. Dialysis regimens ranged from six to 12 hours three times a week.

Discussion

These patients illustrate a therapeutic dilemma relating to maintenance haemodialysis. On the one hand, prolonged hyperphosphataemia leads to hyperparathyroidism, soft tissue calcification, or both.^{1, 2, 16} On the other hand, phosphate-binding agents, which reduce serum inorganic phosphate, cause osteomalacia in experimental animals¹⁷⁻¹⁹ and in man.^{3, 6} Moreover, osteomalacia is present in a third of patients entering a haemodialysis programme,²⁰ and in most cases this lesion becomes worse during the subsequent year.²¹ The question therefore arises whether it is possible to identify those patients who are vulnerable to the development of crippling osteomalacia.

All our patients were young, all had histological osteomalacia before starting haemodialysis, three showed radiological evidence of a reduced bone age, three were treated by domiciliary haemodialysis (24-30 hours/week), and three of them took aluminium hydroxide in doses and frequencies considered desirable by their medical attendants. Only one was taking barbiturates or phenytoin, drugs believed to aggravate osteomalacia in patients on maintenance haemodialysis.²²

It is not clear which, if any, of these features are related to the pathogenesis of severe osteomalacia. Patients on domiciliary haemodialysis probably suffer greater phosphate losses⁵ than hospital patients, whose dialysis periods tend to be shorter. Biochemical checks also tend to be less frequent in the domiciliary group. Phosphate-binding agents, which are known to lower serum inorganic phosphate (and are administered for this purpose), must clearly be regarded as one factor in the development of osteomalacia in this group of patients. Possibly the high prevalence of osteomalacia among patients at some dialysis centres reflects the compliance of the patients and the physician's attitude to "optimal" biochemical control.

Clinicians caring for patients receiving maintenance haemodialysis should prevent the development of hypophosphataemic osteomalacia by monitoring serum inorganic phosphate and alkaline phosphatase levels at monthly intervals. The serum phosphate concentration should range from 1.3 to 1.6 mmol/l (4-5 mg/100 ml) before dialysis with a fall to 0.8-1.2 mmol/l (2.5-3.7 mg/100 ml) after dialysis. Predialysis phosphate levels of 0.97 mmol/l (3 mg/100 ml) or less and a rising serum alkaline phosphatase should be considered as danger signals. Serum parathyroid hormone concentrations tend to be low in this syndrome.¹⁶

When symptoms of malacia become manifest in a hypophosphataemic patient histological confirmation of the diagnosis should be obtained and early aggressive treatment of the condition undertaken to prevent the rapid development of disabling bone disease. Aluminium hydroxide should be temporarily withdrawn and vitamin D should be given. Withdrawal of aluminium hydroxide may, by itself, be sufficient²³ but as these patients are likely to be suffering from abnormalities of vitamin D metabolism also²⁴ some form of vitamin D seems indicated. In addition, Jones¹⁷ showed that hypophosphataemic rickets in rats could be prevented or cured by vitamin D.

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Immediate plasma renin response to propranolol: differentiation between essential and renal hypertension

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Summary

The immediate short-term effect on plasma renin activity of intravenous injection of propranolol was studied in 31 normal subjects and 166 hypertensive patients. In patients with essential hypertension and normal subjects plasma renin activity fell considerably within 15 minutes; the fall was directly proportional to initial plasma renin levels. In contrast, in patients with renal hypertension the fall was much less pronounced or totally absent. These differences in response to propranolol provide, though presently only on a group basis, a biochemical means of differentiating between patients with renal hypertension and those with essential hypertension. The observations also indicate that, unlike normal subjects and patients with essential hypertension, in patients with renal hypertension sympathetic activity plays no part in the control of basal plasma renin levels.

Introduction

Precision in endocrine diagnosis depends on the ability to measure all components of the feedback loops controlling hormone secretion.¹ Nevertheless, renin levels in hypertensive patients are commonly still being interpreted without consideration of renal perfusion pressure, sodium concentration at the macula densa, or sympathetic tone at the juxtaglomerular apparatus, these probably being the main factors controlling renal renin release.² None of the components of the feedback loops by which renin secretion is controlled is easily measurable in clinical practice. In an attempt to quantify sympathetic tone at the juxtaglomerular apparatus we have taken the immediate effect of acute beta-receptor blockade on basal plasma renin activity (PRA) as an indication of the extent to which renin release under basal conditions is mediated by the sympathetic nervous system. A preliminary account of part of this work has been published.³

Patients and methods

We studied (a) 31 normal volunteers (19 female and 12 male hospital employees), (b) 102 patients (61 women) with stable benign essential hypertension (WHO stage 1 and 2), (c) 58 patients (30 women) with well-established renal hypertension of comparable duration and severity caused by chronic parenchymatous renal disease, and (d) six patients (two women) on chronic intermittent haemodialysis with hypertension of terminal renal failure.

Clinical details of the subjects are given in table I. Essential hypertension was diagnosed only after secondary forms of hypertension had been excluded by the usual diagnostic tests, which included urine analysis, blood chemistry, intravenous rapid-sequence

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