SHORT REPORTS

Hypercalcaemia as complication of accelerated chronic granulocytic leukaemia

Hypercalcaemia is a well-recognised, potentially lethal complication of certain non-endocrine neoplasms but rarely occurs in leukaemia. This is especially true in the case of chronic granulocytic leukaemia (CGL), few such instances having been reported.¹⁻³ We therefore describe three patients with CGL who developed hypercalcaemia while in the accelerated phase of the disease. Two also had complicating encephalopathy.

Case reports

Case 1—A 19-year-old girl was diagnosed as a case of Philadelphia-chromosome-positive CGL in October 1972. Treatment with hydroxyurea was initially successful but in February 1973 blastic transformation occurred with 60% myeloblasts in the bone marrow. Blood chemistry was normal. Haematological remission was obtained but in June she relapsed and was found to have a serum calcium concentration of 3.7 mmol/l (14.6 mg/100 ml). Blood urea, serum phosphorus, and alkaline phosphatase concentrations were normal. Radiography showed generalised lytic lesions and extensive blood vessel calcification (see figure). There were no symptoms referable to either bone lesions or hypercalcaemia. Prednisone and intravenous phosphate failed to reduce the serum calcium but a combination of intravenous mithramycin 2 mg and calcitonin 160 MRC units eight-hourly was rapidly effective. Subsequent episodes of hypercalcaemia were treated with mithramycin alone. Antileukaemia treatment proved ineffective, however, and during another hypercalcaemic episode she died. Necropsy showed extensive leukaemic blast-cell infiltration of the bone marrow and reticuloendothelial system. Severe calcification was found in blood vessels, heart, pulmonary alveoli and bronchi, and kidney. Extensive bone lysis was present and osteoclastic activity increased. Parathyroids were normal.

Case 2—A 34-year-old man presented in October 1974 with malaise, left hypochondrial pain, weight loss, and hepatosplenomegaly. Results of investigations were: haemoglobin 7 g/dl; white cell count $6.2 \times 10^9/l$ ($6200/mm^3$) (polymorphs 2.5×10^9 , lymphocytes 3.2×10^9 , and monocytes $0.5 \times 10^9/l$); and platelets $97 \times 10^9/l$. Bone marrow contained 60% lymphoblasts. Cytogenetic analysis showed three cell lines, one normal and two with the Philadelphia chromosome.⁴ The diagnosis was acute lymphoblastic trans-

formation of clinically occult CGL. Serum calcium was 3.25 mmol/l (13 mg/100 ml). Treatment with vincristine, prednisone, and colapsase resulted in a partial haematological remission with return of the serum calcium concentration to normal. In June 1975 an asymptomatic recurrence of hypercalcaemia was treated with prednisone but he subsequently presented with bone pain, confusion, and a fluctuating level of consciousness. Serum calcium was 4 mmol/l (16 mg/100 ml) and radiography showed lytic lesions in several ribs. Intravenous mithramycin 2 mg temporarily restored the calcium concentration and mental state to normal but he was subsequently readmitted in hypercalcaemic coma and died.

Case 3—A 23-year-old man was diagnosed in November 1972 as a case of Philadelphia-chromosome-positive CGL. The disease was controlled with hydroxyurea until November 1976, when severe splenomegaly recurred. Results of extensive investigation, however, were consistent only with the chronic phase of CGL. In January 1977 he was readmitted with malaise, vomiting, and generalised bone pain. Investigations showed: haemoglobin 10.7 g/dl; white cell count $42 \times 10^9/l$ (blast cells $1.6 \times 10^9/l$); platelets $25 \times 10^9/l$; serum calcium 3.9 mmol/l (15.6 mg/100 ml); and normal serum urea and electrolyte concentrations. The serum calcium concentration rose rapidly and he became comatose. Despite intensive resuscitative measures including calcitonin and mithramycin he died.

Comment

As has been noted previously, the occurrence of hypercalcaemia in leukaemia is a grave prognostic sign and in CGL may perhaps partially reflect the usually associated change in the course of the disease. Though in two of our cases hypercalcaemia was not a major factor influencing disease outcome, in one it was the cause of relatively sudden death. The presence of increased osteoclastic activity in case 1 is of aetiological importance as both parathormone and osteoclast stimulating factor production have been described in haemopoietic neoplasms.⁵

The imprecise and variable symptomatology of hypercalcaemia in CGL may result in failure to recognise the presence of a potentially reversible complication.

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³ Licht, A, Many, N, and Rachmilewitz, E A, *Acta Haematologica*, 1973, **49**, 187.

⁴ Ayraud, N, Dujardin, P, and Audoly, P, *Nouvelle Presse Médicale*, 1975, **4**, 3013.

⁵ Libnoch, et al, *American Journal of Medicine*, 1977, **62**, 432.

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Prediction of postdialysis hypophosphataemia

Phosphate retention is a normal accompaniment of chronic renal failure, and phosphate-binding agents (such as aluminium hydroxide) are commonly used to prevent hyperphosphataemia. Patients receiving these binding agents may develop phosphate depletion,¹ which may produce osteomalacia in patients with impaired renal function² and those undergoing maintenance haemodialysis.³ It has also been suggested that phosphate depletion prevents severely osteomalacic renal patients from responding to 1α -hydroxycholecalciferol, a synthetic analogue of 1,25-dihydroxycholecalciferol,⁴ and that phosphate depletion may be a factor in the syndrome of dialysis dementia. It is

Case 1. Radiographic appearances of lytic lesions and calcification in blood vessels and soft tissue (arrowed).

therefore advisable to prevent recurrent or prolonged hypophosphataemia in any patient with chronic renal disease. This is particularly important in patients on maintenance haemodialysis, as the near universal use of phosphate-free dialysate fluid produces a fall in the plasma phosphate concentration, and after dialysis the patient may be hypophosphataemic. The measurement of the postdialysis phosphate concentration is obviously important, but it is more usual to measure the predialysis concentration. This study shows that the predialysis concentration of phosphate is all the clinician needs to know, as it bears a simple and constant relation to the postdialysis value.

Patients, methods, and results

Thirty-eight patients on haemodialysis (Meltec multipoint 1.5 m² for 4 hours or Meltec multipoint 1.0 m² for 6 hours) were dialysed with a dialysate fluid containing 1.5 mmol/l (6 mg/100 ml) of calcium and no phosphate with a blood flow rate of at least 160 ml/minute. Plasma phosphate was measured by the Technicon SMA method immediately before and after each dialysis session. A total of 52 predialysis and postdialysis plasma samples were examined with the patients in the non-fasting state and the mean change in plasma phosphate was 0.93 ± 0.66 mmol/l (2.9 ± 2.0 mg/100 ml).

Relation between initial plasma phosphate concentration and fall in concentration during dialysis.

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

An additional 17 samples were obtained before and after dialysis from patients who had fasted for 12 hours before starting haemodialysis, and then remained fasting throughout the dialysis session. In this fasting group the mean change in plasma phosphate concentration was 1.12 ± 0.66 mmol/l (3.47 ± 2.0 mg/100 ml) (no significant difference between the groups on *t* testing). There was also no significant difference in the change in plasma phosphate that occurred in the patients dialysed with a 1.5 m² or 1.0 m² dialyser.

There was a correlation between the initial plasma phosphate concentration and its fall which occurred during a dialysis session ($r = 0.88$; $P < 0.001$). The mean regression line for these data was $\Delta[\text{PO}_4] = 0.7 \times [\text{PO}_4]_i - 0.4$ (see figure). From this equation it was possible by simple manipulation to be able to predict the postdialysis phosphate concentration from any predialysis phosphate concentration: $[\text{PO}_4]_p = 0.4 + 0.3 \times [\text{PO}_4]_i$.

Comment

The result of this study clearly shows that the reduction in the plasma phosphate concentration during dialysis regimens occurs most predictably. It depends primarily on the initial plasma phosphate concentration, as the two different dialysers used in this study did not seem to influence the fall significantly; nor did the dietary intake of phosphate just before or during haemodialysis. The clinician can therefore safely use the predialysis plasma phosphate concentration to prevent subclinical phosphate depletion developing in patients on dialysis. If the lower limit of the normal range of phosphate is 0.8 mmol/l (2.5 mg/100 ml), as in our own laboratory, it can be calculated that the predialysis concentration should be no lower than 1.33 mmol/l (4.1 mg/100 ml) if postdialysis hypophosphataemia is to be prevented. This accords well with Massry's suggestion that 1.3 mmol/l (4.0 mg/100 ml) was the minimum safe plasma phosphate

concentration necessary to prevent the development of hypophosphataemic osteomalacia.⁵

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⁴ Pierides, A M, et al, *Lancet*, 1976, **1**, 1092.

⁵ Massry, S G, *Dialysis and Transplantation*, 1976, **5**, 38.

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Malabsorption of frusemide caused by phenytoin

Ahmad has reported that epileptics on chronic anticonvulsant treatment have a diminished response to frusemide, possibly owing to renal insensitivity rather than alteration in absorption, although no measurements of frusemide metabolism were made.¹ To investigate this phenomenon further, we performed frusemide absorption studies in normal volunteers both taking and not taking phenytoin. We found that malabsorption of frusemide occurred in the former.

Subjects and methods

Five healthy male volunteers aged between 21 and 30 taking no medication were studied during control conditions and after a ten-day course of phenytoin, 100 mg three times per day, the order being randomised. They were allowed unrestricted fluids and one hour after a normal light breakfast were given frusemide. All subjects had both intravenous and oral ³⁵S-frusemide (10.6 μ Ci aqueous ³⁵S-frusemide (20 mg) kindly supplied by Hoechst

Effects of phenytoin on absorption and clearance of frusemide in normal subjects

	Serum clearance (ml/min)	Absorption (%)	Maximum concentration (μ g/ml)
Control	125.1 ± 11.5	80.9 ± 6.46	2.24 ± 0.34
Phenytoin	116.5 ± 7.5	39.0 ± 5.4	1.22 ± 0.10
P	NS	<0.01	<0.01

NS = Not significant.

Pharmaceuticals Limited). Blood samples were taken at half-hourly intervals for four hours and one four-hour urine specimen collected. Serum and urine samples were counted in a liquid scintillation counter and the concentrations calculated from the specific activity. Thin-layer chromatography (TLC) was performed to identify significant labelling of any metabolites, and also to ensure that the starting product contained no degradation products. Serum concentration (IV) curves were plotted and the areas under curves calculated using an ICL 19045 digital computer.

The following calculations were made:

$$\text{Absorption (\%)} = \frac{\text{Area under oral curve}}{\text{Area under IV curve}} \times 100$$

$$\text{Serum clearance} = \frac{\text{Dose administered}}{\text{Area under IV curve}} \text{ ml/min.}$$

Data are expressed as mean $\pm$ SE of mean. In the statistical analysis values obtained during the control period and after phenytoin administration were compared by paired *t* test as each subject served as his own control.