were first reported by Ryan, but no details of the case were given³; and Rubino and Jackson described a patient who developed confusion and paranoia while receiving tocainide but only after the addition of propranolol to the treatment regimen.⁵

Serum drug concentrations during toxic manifestations may vary widely in different subjects¹ and in our patients the concentrations of tocainide during toxicity were within the peak therapeutic range (5–15 mg/l, mean 10.3 mg/l).³ In each case there was a 48 hour delay between initiating the final tocainide dose regimen and the onset of psychosis. This may be explained by an elimination half life ranging from 10 to 17 hours, which delays the onset of steady state peak drug concentrations and hence toxicity. High peak concentrations and toxicity may be avoided by administering tablets with food⁴ and by careful prescription in the presence of propranolol⁵ and in patients with renal disease, since normally 40% of the unchanged drug is excreted in the urine.¹

We thank Mr M Stapleton for his help and Drs N Coulshed and E J Epstein for permission to report the cases.

¹ Winkle RA, Meffin PJ, Fitzgerald JW, Harrison DC. Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic, tocainide. *Circulation* 1976;54:884-9.

² Turner WM. Lidocaine and psychotic reactions. [Letter.] *Ann Intern Med* 1982;97:149-50.

³ Ryan W. Efficacy of a new oral agent (tocainide) in the acute treatment of refractory ventricular arrhythmias. *Am J Cardiol* 1979;43:285-91.

⁴ Winkle RA, Meffin PJ, Harrison DC. Long-term tocainide therapy for ventricular arrhythmias. *Circulation* 1978;57:1008-16.

⁵ Rubino M, Jackson E. Severe paranoia with concomitant tocainide and propranolol therapy. *Clin Pharm* 1982;1:177-9.

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Hypocalcaemia in pernicious anaemia

We describe a previously unreported association of hypocalcaemia and pernicious anaemia. After an initial observation in an index case, a group of patients who had previously been found to have pernicious anaemia were investigated retrospectively.

Case report, methods, and results

A 32 year old man presented with a six month history of malaise, weakness, and loss of 3.2 kg; he denied abdominal pain and steatorrhoea. On examination he was seen to be pale but had no other physical signs. Haemoglobin concentration was 8.4 g/dl, mean corpuscular volume was 110 fl (110 μm^3), and platelet and white cell counts were normal, although the blood film contained hypersegmented neutrophils. Serum calcium concentration was 2.1 mmol/l (8.6 mg/100 ml) and albumin 38 g/l. Alkaline phosphatase activity and other liver function values, phosphate, iron and iron binding capacity, folate, xylose tolerance, and three day faecal fat excretion, were all within normal ranges. Vitamin B₁₂ concentration was < 50 pg/l with an abnormal Schilling test part I (< 7% of an oral dose of radioactive vitamin B₁₂ alone excreted in the urine in 24 hours) but normal Schilling test part II. Bone marrow aspirate confirmed a megaloblastic picture. After six weeks of treatment with hydroxycobalamin the haematological indices and film were normal and the serum calcium concentration 2.3 mmol/l (9.0 mg/100 ml) and albumin 40 g/l.

Serum calcium concentrations in patients reviewed six months to seven years after diagnosis of pernicious anaemia

	Age and sex matched controls	Group with pernicious anaemia	
		At presentation	After treatment
No of subjects	32	32	22
Mean corrected* calcium concentration (mmol/l)	2.41 (SD 0.13)	2.24 (SD 0.10) [†]	2.30 (SD 0.05) [†]

* Corrected to an albumin concentration of 40 g/l.

[†] Significant at $p < 0.01$.

Conversion: SI to traditional units—Calcium: 1 mmol/l $\approx$ 4 mg/100 ml.

The last 32 consecutive patients with pernicious anaemia were reviewed retrospectively. All had a macrocytosis (mean corpuscular volume 106–142 fl), and the diagnosis was established by low serum values of vitamin B₁₂, confirmatory abnormal Schilling test results and, in those who underwent bone marrow aspiration, a megaloblastic picture. There were 21 women and 11 men with an average age of 64 years (range 18–87), and all were white. Results of multichannel analysis (of electrolytes, urea, creatinine, calcium, phosphate, alkaline phosphatase, bilirubin, globulins, albumin, and transaminases were normal for every variable except calcium. In five patients the concentration was less than 2.2 mmol/l (8.6 mg/100 ml). Twenty two of these patients were contacted (six months to seven years after initial presentation) and a full blood count and multichannel analysis repeated. All 22 patients were haematologically and biochemically normal except for their calcium values (see table).

Comment

Our group of patients with pernicious anaemia had significant hypocalcaemia as compared with an age and sex matched control group, the cause of which was uncertain. Although treatment was associated with a significant rise in serum corrected calcium values, the group was still significantly hypocalcaemic as compared with the control group. The index patient had no signs, symptoms, or biochemical abnormalities of malabsorption or osteomalacia, and all patients studied had normal serum phosphate and alkaline phosphatase activities, making these diagnoses unlikely.

Hypoparathyroidism is a possible explanation, but rare, although an autoimmune aetiology might explain this and the pernicious anaemia. Chronic hypergastrinaemia occurs in pernicious anaemia but the concentration is usually not high enough to affect calcium metabolism by stimulating secretion of calcitonin.^{1,2} Further investigation is necessary, including measurements of vitamin D and its metabolites; parathyroid, calcitonin, and gastrin hormone estimations; and measurements of magnesium and 24 hour urinary calcium excretion. These last two values were normal in our index patient.

We are indebted to Dr A Black for permission to report on his patients.

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² Lamers CBH, Hakeng WH, Thiem TR, Tongren JHM. Serum concentrations of immunoreactive calcitonin in patients with hypergastrinaemia. *Digestion* 1980;20:379-82.

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Disodium etidronate in hypercalcaemia due to immobilisation

Hypercalciuria and hypercalcaemia may occur in prolonged immobilisation, especially in young adults and adolescents. The hypercalcaemia reflects an appreciable increase in osteoclastic activity combined with depressed osteoblastic bone formation.¹ Treatment of the hypercalcaemia should include early mobilisation and adequate fluid intake. When the hypercalcaemic symptoms are severe, however, unspecific treatment—for example, phosphate buffer—or specific treatment of the increased osteoclastic activity—for example, with calcitonin—may be needed. Diphosphonates are potent inhibitors of osteoclastic bone resorption.² To our knowledge no previous reports of the use of disodium etidronate in patients with hypercalcaemia due to prolonged immobilisation have been published. We therefore report on two patients, one of whom had severe symptoms, in whom conventional treatment was unsuccessful and disodium etidronate improved the symptoms and caused the serum calcium concentration to return to normal.

Case reports

CASE 1

The patient was a 19 year old previously healthy man who was injured while ski jumping and sustained complete tetraplegia. X ray examinations disclosed fractures of C4 and C5. On admission to hospital he had normal serum concentrations of calcium, phosphate, creatinine, and parathyroid and thyroid hormones. Repeated chest x ray films were normal, as were x ray films of the skull, lumbar spine, and pelvis.

Case 1. Serum and urinary calcium concentrations and drugs given to lower calcium concentrations. Horizontal broken line indicates upper limit of normal for serum calcium (2.6 mmol/l (10.4 mg/100 ml)). Vertical arrows represent two single injections of salcatonin, 400 MRC units each.

Conversion: SI to traditional units—Calcium: 1 mmol $\approx$ 40 mg. Sodium acid phosphate: 1 mmol phosphorus/24 h $\approx$ 31 mg/24 h.

Two months after the accident the serum calcium concentration increased above 3 mmol/l (12 mg/100 ml) (figure); he developed anorexia, malaise, vomiting, and abdominal pains, and his general condition declined. His daily fluid intake was increased (3 l/day), and frusemide was given; the serum calcium concentration and abdominal complaints remained unchanged. Treatment with salcatonin (Miacalcin), 100-200 MRC units/24 h intramuscularly or subcutaneously, was started, and the serum calcium concentration decreased to 2.5 mmol/l (10 mg/100 ml) but then increased again. Sodium acid phosphate was given by mouth; symptoms resolved, and near normal serum calcium concentrations were established.

Four months after the start of the combined treatment his symptoms and hypercalcaemia recurred, serum calcium concentrations exceeding 3 mmol/l (12 mg/100 ml) being recorded. It was then decided to try disodium etidronate (Didronel) 5 mg/kg/24 h by mouth; salcatonin and sodium acid phosphate were stopped. Within a month he had essentially normal serum calcium concentrations, his gastrointestinal complaints had resolved completely, and he began to gain weight. Two months after disodium etidronate was stopped he still had normal serum calcium concentrations.

CASE 2

The patient was a 17 year old healthy man with normal serum calcium concentrations. Three months after he was immobilised because of a fracture at the level of C6-7 hypercalcaemia of 3.1 mmol/l (12.4 mg/100 ml) was noted. Disodium etidronate 5 mg/kg/24 h was given by mouth. The serum calcium concentration returned to normal in 10 days, and he was mobilised. Fluid intake was 3 l/24 h, but no other measures were undertaken to lower the serum calcium concentration.

OTHER FINDINGS

Urinary hydroxyproline concentrations were raised in both patients and did not change during treatment with disodium etidronate. No side effects of disodium etidronate were noted.

Comment

In both these patients serum calcium concentrations returned to normal within one month after the start of treatment with disodium etidronate. Interestingly, no changes occurred in urinary hydroxyproline excretion, a finding reported previously with treatment with disodium etidronate and of unknown importance.³ The possibility that the doses of the drug used in our patients were too low does not seem likely.

Treatment with disodium etidronate confers a risk of developing osteomalacia, and long term use of high doses should be avoided. Disodium clodronate and disodium aminohydroxypropylidene-

diphosphonate show a lesser tendency to cause osteomalacia.⁴ Disodium clodronate prevents bone mineral loss and hypercalcaemia in paraplegic patients⁵ but has now been abandoned because of potentially cancerigenic effects.

In conclusion, we suggest that disodium etidronate (5 mg/kg/24 h for less than six months) or, preferably, disodium aminohydroxypropylidenediphosphonate be used in hypercalcaemia due to immobilisation when conventional treatment is insufficient.

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Corrections

Potentiation of oral anticoagulants by ketoconazole

We regret that an error occurred in the article by Dr Alastair G Smith (21 January, p 188). In the second line of the second paragraph of the case report "blood clotting ratio" should read "British comparative ratio."

Effects of two antihistamine drugs on actual driving performance

In the paper "Effects of two antihistamine drugs on actual driving performance" by Tim Betts and colleagues (28 January, p 281) the doses of triprolidine were inadvertently stated as 10 mg. The sentence relating to dosage of this drug should, in fact, have read "... 5 mg triprolidine on the Friday, three 5 mg doses on the Saturday, and a final 5 mg dose two hours before testing on the Sunday."