were first reported by Ryan, but no details of the case were given; 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.

Serum drug concentrations during toxic manifestations may vary widely in different subjects 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). 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 food and by careful prescription in the presence of propranolol and in patients with renal disease, since normally 40% of the unchanged drug is excreted in the urine.

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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 µm3), 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, xylene 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

<table>
<thead>
<tr>
<th>Age and sex matched controls</th>
<th>Group with pernicious anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>At presentation</td>
<td>After treatment</td>
</tr>
<tr>
<td>No of subjects</td>
<td>32</td>
</tr>
</tbody>
</table>

Mean corrected* calcium concentration (mmol/l)

| Serum calcium concentration | 2-41 (SD 0.13) | 2-24 (SD 0.010) | 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 = 4 mg/100 ml

The last 32 consecutive patients with pernicious anaemia were reviewed retrospectively. All had a macrocytosis (mean corpuscular volume 106-142 f), 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 phosphate, 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. 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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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. Consequently, 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, but 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.