cholesterol contributes to the metabolism of prostacyclin. These changes together could partly mediate the preventive potential of regular physical exercise against ischaemic heart disease. It has been shown that high density lipoprotein stimulates and low density lipoprotein inhibits synthesis of prostacyclin *in vitro*.²²⁻²⁵ The association between the main metabolite of prostacyclin and HDL₂ cholesterol in the present study also accords with the suggested stimulatory effect of high density lipoprotein production of prostacyclin. We conclude that regular aerobic exercise of only mild intensity has favourable effects, at least for a short time, on some of the biochemical risk factors for ischaemic heart disease in healthy middle aged men. Exercise has its most pronounced effect on serum lipoproteins, especially as an increase in serum HDL₂ concentration and a decrease in HDL₃ and low density lipoprotein cholesterol concentration.

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SHORT REPORTS

Paranoid psychosis induced by tocainide

Tocainide is a primary amine analogue of lignocaine which has a high level of bioavailability after oral administration.¹ Its use is indicated for the control of ventricular tachyarrhythmias after myocardial infarction. Although psychoses occurring in association with lignocaine toxicity are well recognised,² there are no reports of psychosis induced solely by tocainide. We describe two such cases.

Case reports

Case 1—A 58 year old man with an acute myocardial infarction developed recurrent symptomatic ventricular tachycardia the day after admission to hospital. The arrhythmia was initially suppressed by intravenous lignocaine (4 mg/min) followed by oral tocainide 400 mg three times daily. Recurrence of ventricular tachycardia on the fifth and sixth days was treated by increasing tocainide to 400 mg and 600 mg four times daily, respectively. On the eighth day, one hour after administration of tocainide, the patient suddenly became garrulous, irrational, suspicious, agitated, and irritable. He suffered recurrent visual hallucinations including visions of animals. His delusions of persecution concerned fellow patients, nurses, and medical staff, and he was aggressive to anyone who approached him. The symptoms subsided over the subsequent two hours, only to recur again within one hour

after the next dose of tocainide. The serum tocainide concentration was estimated to be 6.7 mg/l. The psychological disturbance disappeared after withdrawing tocainide, and the arrhythmia was successfully controlled by oral disopyramide.

Case 2—A 48 year old man began to suffer recurrent syncope due to ventricular tachycardia five months after myocardial infarction. The arrhythmia was initially suppressed by intravenous lignocaine (4 mg/min), and oral tocainide (400 mg three times daily) was started on the second day. Recurrent ventricular tachycardia the next day necessitated increasing the tocainide to 600 mg three times daily. Two hours after tocainide on the fifth day he suffered sudden dysarthria, nausea, incoordination, paraesthesia, confusion, agitation, and flight of ideas. He became frightened and thought that the nursing staff were persecuting him and trying to harm him. The symptoms disappeared spontaneously over the next hour and he apologised for his behaviour. The serum tocainide concentration was 10.2 mg/l during the psychosis. Withdrawal of tocainide led to further ventricular tachycardia necessitating DC cardioversion and intravenous lignocaine (4 mg/min). The lignocaine induced a similar psychotic behaviour pattern and was therefore replaced by intravenous and oral amiodarone with good effect.

Comment

Adverse effects of tocainide include tremor, dysarthria, nausea, blurred vision, night sweats, and paraesthesia.^{1,3,4} Our two patients developed an acute short lived confusional state with paranoid features after receiving tocainide. Paranoid delusions and mental impairment

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.

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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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Disodium etidronate in hypercalcaemia due to immobilisation

Hypercalcaemia 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.