Ratios of plasma insulin to plasma glucose concentrations before and one and three hours after start of intravenous infusion of quinine in three groups of Malawian children with falciparum malaria. Dotted lines indicate mean values

hours insulin concentrations were similar in all groups (19.8 (11.6), 14.7 (8.4), and 16.2 (8.9) mU/l ($F=0.61$; $df=2,24$; $p>0.5$)).

Changes in the ratio of insulin to-glucose concentration from baseline values in the three groups (figure) were similar to changes in plasma insulin concentration. The increase in the ratio differed significantly among the groups at one hour ($F=6.18$; $df=2,23$; $p<0.01$), being greatest in group 3. The increase at three hours was similar for all groups. Plasma quinine concentrations at one hour correlated significantly with the increases in both plasma insulin concentration ($r=0.550$, $n=28$, $p<0.01$) and the ratio of insulin to glucose concentration ($r=0.548$, $n=23$, $p<0.01$) during the first hour of treatment in all patients.

Comment

The hypoglycaemic effect of quinine was first noted by Hughes, who suggested that quinine stimulates secretion of insulin by the pancreas.³ Various rates of infusion have been recommended for treating malaria. When given over three hours in a constant infusion of 5% glucose quinine did not cause hypoglycaemia in 76 Malawian children with cerebral malaria,⁴ but four of nine Zairean children given one hour infusions developed hypoglycaemia (plasma glucose concentration <2.8 mmol/l).⁵

The results of the present study suggest that the rate of infusion of quinine is an important determinant of the secretion of insulin that is induced by the drug and that a one hour infusion may lead to higher insulin concentrations and a greater risk of hypoglycaemia than a slower infusion.

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Release of atrial natriuretic factor after pericardiocentesis for malignant pericardial effusion

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Atrial natriuretic factor is a 28 amino acid polypeptide hormone which has diuretic, natriuretic, and vaso-relaxant properties. It is secreted by the heart in response to increases in atrial pressure, but the mechanism of this response is poorly understood: the primary stimulus may be an increase in atrial pressure or increased atrial distension. In most clinical circumstances it is difficult to separate the influence of these possible stimuli, but patients with cardiac tamponade have raised atrial pressures without an associated increase in atrial distension. Pericardiocentesis in such patients results in dissociation between atrial pressure (which falls) and atrial distension (which rises)¹ and therefore provides a model for studying the mechanism of atrial natriuretic factor secretion in man.

Patients, methods, and results

Six patients (three men) with malignant pericardial effusion were studied before and after pericardiocentesis. The mean age (range) was 57 (37-74) years. The primary site of malignancy was lung (3 patients),

breast (2 patients), and unknown (1 patient). All patients had a clinical diagnosis of cardiac tamponade confirmed by echocardiography. Blood samples were drawn for measuring the plasma atrial natriuretic factor concentration immediately before, 30 minutes after, and 180 minutes after pericardiocentesis. Samples were collected in chilled tubes containing edetic acid and aprotinin, and plasma was immediately separated by centrifugation at 4°C and assayed for atrial natriuretic factor by radioimmunoassay after extraction in Sep-pak cartridges² (reference range 2-17 pmol/l). Significance levels were determined by Student's paired *t* test.

The mean volume (range) of fluid removed at pericardiocentesis was 725 (400-1100) ml. Plasma atrial natriuretic factor (mean and SD) was slightly raised at baseline before pericardiocentesis, at 19.2 (7.1) pmol/l (figure). There was a further rise to 30.3 (7.7) pmol/l ($p<0.05$) 30 minutes after and to 36.7 (11.9) pmol/l ($p<0.005$) 180 minutes after pericardiocentesis. The mean rise in plasma atrial natriuretic factor concentration at 180 minutes was 17.5 pmol/l, (95% confidence interval 9.7 to 25.3 pmol/l). All patients improved clinically, with a rise in arterial blood pressure, a fall in jugular venous pressure, and diuresis.

Comment

This is the first report of plasma atrial natriuretic factor concentrations in a series of patients with cardiac tamponade of malignant aetiology. We found that peptide levels rise after pericardiocentesis.

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Plasma concentrations of atrial natriuretic factor in six patients before and after pericardiocentesis. Bars represent mean and standard deviation; reference range is shaded

Our results confirm a previous case report in which a sharp rise in plasma atrial natriuretic factor was recorded immediately after pericardiocentesis.³ A similar twofold to threefold increase was also described after pericardiectomy in a patient with chronic constrictive pericarditis.⁴ These findings are in strong contrast to other conditions, such as left ventricular failure, in which cardiac filling pressures are correlated with circulating concentrations of atrial natriuretic factor.⁵ Clinical deterioration is associated with a

further increase in peptide concentrations, while treatments which lower cardiac filling pressures also lower plasma atrial natriuretic factor values.⁵ Our findings suggest that raised atrial pressure does not directly stimulate the release of atrial natriuretic factor. Rather, raised filling pressures increase atrial distension, which in turn increases secretion of the peptide.

Further support for this hypothesis has come from a definitive experiment, conducted in anaesthetised dogs, in which the induction of cardiac tamponade did not increase plasma concentrations of atrial natriuretic factor despite a considerable increase in atrial pressures.¹ In contrast there was a threefold rise in peptide values when atrial pressures were raised to a similar degree by constriction of the great arteries. We conclude that in humans, as in this animal model, the primary stimulus for the release of atrial natriuretic factor is atrial distension.

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Changes in glucose tolerance and development of gall stones during high dose treatment with octreotide for acromegaly

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Octreotide, a longer acting analogue of somatostatin, growth hormone inhibiting hormone, lowers growth hormone concentrations in resistant acromegaly¹ and is well tolerated by most patients. There have been reports of changes in blood glucose values and isolated reports of gall stone formation in people receiving octreotide.¹ Patients with somatostatinomas often have diabetes and gall stones.² We have studied prospectively both glucose tolerance and, by ultrasonography, gall stone formation in 10 acromegalic patients receiving high dose octreotide treatment.

Patients and methods

Ten acromegalic patients (mean age 45, mean duration 11 years) were treated with octreotide. All 10 had undergone surgery or irradiation, and eight had received bromocriptine (four of whom were intolerant). All had a baseline 24 hour profile of growth hormone measured every two hours, followed by a 75 g oral glucose tolerance test starting at 1000. The initial dose of octreotide was 100 µg subcutaneously at 0800, 1600, and 2400 for one month and was increased at monthly intervals by 300 µg a day to a maximum of 1500 µg/day if the mean of the 12 growth hormone measurements remained >5 mU/l. Treatment continued at this dose for a further seven months. The glucose tolerance test was repeated at six months. (One insulin dependent

diabetic patient did not have a glucose tolerance test.) Seven patients had a baseline gall bladder ultrasound examination (Diasonics 400R with a 3.5 MHz probe), which was repeated at six months and one year.

One patient was withdrawn from the study because of persistent diarrhoea and another because of insulin resistant diabetes. Six were maintained on 1500 µg daily, one on 1200 µg daily, and one on 600 µg daily. Mean serum growth hormone fell from 36 (SE 10) mU/l at the onset of the study to 8 (1) mU/l and 8 (2) mU/l (n=8, p<0.05) after six and 12 months respectively. Of three patients with normal glucose tolerance initially, one remained normal, one developed impaired glucose tolerance, and one became diabetic (by World Health Organisation criteria). Of four patients who had impaired glucose tolerance initially, two remained unchanged, one developed diabetes, and the other returned to normal glucose tolerance. One of the seven patients who had normal baseline ultrasonographic appearances of the gall bladder had developed multiple small gall stones after six months of treatment, and another two developed similar findings after one year (fig). One patient did not have an initial examination but after four months of therapy had four gall stones, which remained unchanged at each assessment.

Comment

Octreotide successfully lowered growth hormone concentrations and was generally well tolerated. It had a heterogeneous effect on glucose tolerance. Three patients became more glucose intolerant, three showed no change, and one had improved glucose tolerance. As growth hormone induces insulin resistance and octreotide reduces both insulin and growth hormone secretion the relative change of each will influence glucose tolerance.³

The high incidence of new gall stones found in our prospective study is a cause for concern. Previously