Details of implantation treatment in 12 women with supraphysiological oestradiol concentrations

Case No	Duration of treatment (years)	Interval between insertion of penultimate and last implants (months)	Type of implant last inserted	Interval between insertion of last implant and recurrence (weeks)	Oestradiol when symptoms recurred (pmol/l)
1	2·5	3	Oestradiol 75 mg, testosterone 50 mg	9	2325
2	3	3	Oestradiol 75 mg	12	2000
3	7	4	Oestradiol 50 mg, testosterone 100 mg	3	1500
4	3	2	Oestradiol 200 mg	<4	2995
5	0·75	4	Oestradiol 50 mg, testosterone 100 mg	8	2400
6	2	2·5	Oestradiol 50 mg, testosterone 100 mg	<4	1450
7	4	4	Oestradiol 100 mg, testosterone 100 mg	12	2500
8	7	4	Oestradiol 100 mg, testosterone 100 mg	16	1600
9	7	7	Oestradiol 100 mg	<4	>3500
10	7	5	Oestradiol 50 mg, testosterone 100 mg	16	1900
11	5	4	Oestradiol 100 mg	6	1800
12	3	3	Oestradiol 75 mg, testosterone 100 mg	6	1865

doctor into inserting higher doses more frequently because symptoms recurred early.

The table shows the total duration of treatment, the interval between insertion of the penultimate and last implants, the type of implant last inserted, the interval between insertion of the last implant and recurrence of symptoms, and the plasma oestradiol concentrations when symptoms recurred.

Comment

Troublesome symptoms of oestrogen deficiency (flushes, sweats, mood swings, and irritability) in patients with supraphysiological plasma oestradiol concentrations (above 1200 pmol/l, the periovulatory peak) have not been reported previously. We suspect that this phenomenon is a form of tachyphylaxis, with successive implants relieving symptoms for ever diminishing periods. The mechanism of action is unknown. In adult lower mammals supraphysiological oestradiol concentrations cause major functional changes, possibly due to perineuronal gliosis and glial thickening within the hypothalamus[5]; similar anatomical changes that disturb function in the vasomotor centre might occur in postmenopausal women.

Irrespective of the mechanism, the clinical importance of these data is clear: doctors should not rely solely on the recurrence of symptoms to time reimplantation. Some of our patients (cases 1, 2, 4, 12) received implants too frequently (after three months or less). Other patients treated with implants of only 50 mg oestradiol (for example, case 5) received a new implant when symptoms recurred every four months, and yet plasma oestradiol concentrations of 2400 pmol/l were eventually achieved. Because of these and previous reports of accumulation[4] we wonder whether plasma oestradiol concentrations should be measured routinely before reimplantation if there is any risk of accumulation.

Optimal management in the cases described here is not known. There are no data to indicate that supraphysiological oestradiol concentrations cause harm. We suspect, however, that further implantation relieves symptoms for ever shorter periods. Our approach has been to withhold all forms of oestrogen until the plasma oestradiol concentration has returned to less than 200 pmol/l. This may take many months, during which the patients suffer intense vasomotor and psychological symptoms, are miserable, and need much support. We then start giving oestrogens in a form that does not cause accumulation.

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Effect of rate of infusion of quinine on insulin and glucose responses in Malawian children with falciparum malaria

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Quinine given intravenously is the treatment of choice for severe falciparum malaria; hypoglycaemia due to hyperinsulinaemia is a potential complication when quinine is given parenterally.[1] To find out whether the rate of infusion of quinine is an important determinant of the glycaemic response to it we measured changes in plasma insulin and glucose concentrations in Malawian children with severe falciparum malaria given intravenous quinine in three different regimens.

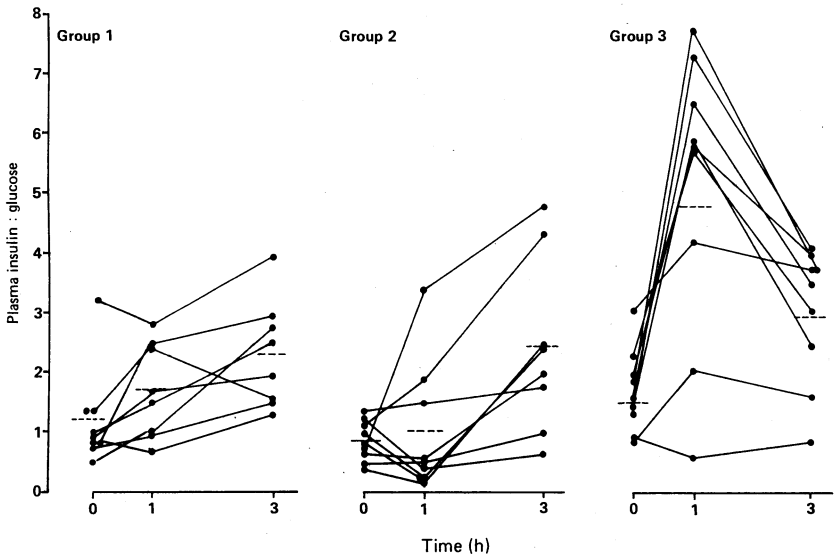
Patients, methods, and results

Twenty nine children (10 girls and 19 boys aged 2-9) were studied prospectively in the Queen Elizabeth Central Hospital, Malawi. All presented with a fever and coma. Asexual *Plasmodium falciparum* was detected in their blood, but no other cause of their symptoms was identified.[2] All were normoglycaemic (glucose concentration >2·2 mmol/l) at admission.

We measured their plasma glucose (by the glucose oxidase method with an autoanalyser), insulin (by solid phase radioimmunoassay), and quinine (by high performance liquid chromatography) concentrations at zero, one, and three hours after the start of the first infusion of quinine dihydrochloride, which was given intravenously according to the following three regimens: nine patients received 10 mg/kg infused over three hours (group 1); 10 received 20 mg/kg infused over three hours (group 2); and 10 received 10 mg/kg infused over one hour (group 3). Quinine was given in 5% (50 g/l) glucose in half strength Darrow's solution at 80 ml/kg/24 h in all groups.

The patients in group 2 had a significantly lower mean packed cell volume than those in groups 1 and 3 (0·19 compared with 0·29 and 0·32 respectively). There were no significant differences among the three groups in any other variables, including age, duration or pattern of symptoms, physical signs, and additional treatment. At the end of the first hour of treatment the mean (SD) plasma quinine concentrations were 4·6 (2·4), 10·1 (2·4), and 13·0 (3·1) mg/l in groups 1, 2, and 3, respectively ($F=20·1$; $df=2,21$; $p<0·0001$ by analysis of variance). At three hours they were 10·1 (3·4), 17·4 (3·1), and 10·3 (3·3) mg/l ($F=16·9$; $df=2,24$; $p<0·001$).

The mean plasma glucose concentration increased slightly but not significantly in each group during observation. None of the patients became hypoglycaemic during the treatment. At the end of the first hour of infusion the mean plasma insulin concentration had risen from 7·4 (5·2) to 16·6 (10·9) mU/l in group 1, from 5·0 (3·9) to 14·1 (15·3) mU/l in group 2, and from 8·2 (4·6) to 35·5 (21·1) mU/l in group 3 ($F=3·93$; $df=2,23$; $p<0·05$ by analysis of covariance). At three



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 vasorelaxant 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 cartridges[2] (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.