bicarbonate concentration, which indicated a non-ketoacidotic coma. We believe this to have been due to metolazone.

Controversy over the use of thiazide diuretics in hypertension continues because of their adverse metabolic effects. Consequently, the use of this group of drugs for hypertension may diminish. The use of metolazone, however, may increase in refractory oedema or sodium retention (due to congestive heart failure, hepatic cirrhosis, and renal disease) as a loop diuretic has a synergistic effect when given with a thiazide.

5 Adrenergic blocking drugs have been associated with carbohydrate intolerance—and propranolol particularly with recurrent non-ketotic hyperosmolar diabetic coma—but in our patient metoprolol was continued without ill effect. Fonesca and Phear found that 5 adrenergic blocking drugs are not of great importance in the pathogenesis of the hyperosmolar non-ketotic state.1 Few reports of disturbance of carbohydrate metabolism with metolazone exist, and the Committee on Safety of Medicines (personal communication) has only one report of each of diabetes mellitus, abnormality of electrolyte concentrations, and glycosuria. Metolazone has, however, been shown to influence diabetic control adversely.4 The mechanism of this adverse reaction is not known and is common to all diuretic benzothiazidiazines, including some without diuretic activity such as diazoxide. It may entail both a decrease in the secretion of insulin and an extrapranaptic effect on the liver.5

This case emphasises that despite its different chemical structure metolazone, like chlorothalidone, may be associated with the hyperosmolar non-ketotic diabetic syndrome. Clinicians using this drug in renal failure or sodium retention should be alert to this possibility as well as that of massive natriuresis, so early detection may prevent the development of coma with its attendant high mortality.

Results of combined test of pituitary function

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Growth hormone (mU/1)</th>
<th>Cortisol (µg/dl)</th>
<th>Luteinising hormone (U/L)</th>
<th>Thyroid stimulating hormone (mU/L)</th>
<th>Follicle stimulating hormone (mU/L)</th>
<th>Oestradiol (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>250</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>410</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>260</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>350</td>
</tr>
<tr>
<td>45</td>
<td>1</td>
<td>390</td>
<td>7</td>
<td>8</td>
<td>0</td>
<td>420</td>
</tr>
<tr>
<td>60</td>
<td>2</td>
<td>390</td>
<td>7</td>
<td>8</td>
<td>0</td>
<td>420</td>
</tr>
<tr>
<td>90</td>
<td>2</td>
<td>420</td>
<td>7</td>
<td>8</td>
<td>0</td>
<td>420</td>
</tr>
<tr>
<td>120</td>
<td>3</td>
<td>470</td>
<td>7</td>
<td>8</td>
<td>0</td>
<td>420</td>
</tr>
</tbody>
</table>

Basal prolactin concentration 595 mU/l (normal <350 mU/l); thyroxine 88 nmol/l (6-9-12 ng/100 ml); normal (75-160 nmol/l), and free thyroxine 11.5 pmol/l (normal 9-11 ng/100 ml); 0-7-1 ng/100 ml). Concentration: SI to read: prolactin: 1 nmol/l = 13-6 mg/100 ml. Cortisol: 1 nmol/l = 33-6 µg/100 ml. Oestradiol: 1 pmol/l = 0-29 pg/ml.

At 40 minutes she began to complain of frontal headache, which persisted after administration of normoglycaemia at 120 minutes (blood glucose concentration 3-5 mmol/l (63 mg/100 ml)). Her headache worsened. By the third day she had developed blurred vision and a partial left third nerve palsy. Computed tomography showed a low density area within the pituitary tumour indicating infarction. Her visual acuity suddenly deteriorated and bilateral third nerve palsies developed, the left pupil became fixed and dilated. Urgent craniotomy was carried out, and a haemorrhagic and necrotic pituitary tumour was found to be raising and compressing both optic nerves. Decompression was performed. She recovered completely with full restitution of neurological function and was discharged 10 days later. Histological examination of the tumour showed extensive infarction with resulting necrosis and areas of free haemorrhage. Tissue not affected by these vascular changes had the appearance of a chromophobe adenoma.

Comment

The development of pituitary apoplexy during a test of anterior pituitary function raised the possibility that the test was causally related to the illness. Bernstein et al reported a similar case, in which neurological signs developed after a combined test of pituitary function: urgent surgical intervention showed necrosis of a pituitary tumour.

Of the three drugs used in the test, thyrotrophin releasing hormone would seem to be the one most likely to have an aetiological role. Clements et al described a patient with amenorrhea after 200 µg thyrotrophin releasing hormone in a man with a pituitary tumour,4 and Drury et al also reported amenorrhea and headache after injection of thyrotrophin releasing hormone.5 In one of their cases surgical evidence of pituitary apoplexy was found. How thyrotrophin releasing hormone produces this clinical picture is not clear.

The risk of pituitary apoplexy after tests of pituitary function is extremely low, but the condition should be borne in mind because of its potentially fatal outcome.


(Accepted 4 April 1985)

Pituitary apoplexy after combined test of anterior pituitary function

Evidence of infarction or haemorrhage of pituitary adenomas is a common histological finding. Clinically important pituitary apoplexy, a syndrome characterised by headache, vomiting, cranial nerve palsies, decreased consciousness, and occasionally death, is much less common.1 We report the occurrence of pituitary apoplexy after a combined test of anterior pituitary function.

Case report

A 39 year old, previously healthy woman presented to her general practitioner in June 1984 with a history of three months’ galactorrhoea and six months’ secondary amenorrhoea after stopping an oral contraceptive in December 1983. She had no history of menstrual irregularity and had had two normal pregnancies, 10 and 14 years previously. She had been taking an oral contraceptive continuously for four years until December 1983. Serum prolactin concentration was raised at 1959 mU/l (normal range <350 mU/l), and a plain skull x ray film showed ballooning and erosion of the pituitary fossa. Bromocriptine 7-5 mg daily was started in June 1984, and she was referred to our endocrine clinic.

She was seen in August, when her serum prolactin concentration had fallen to 90 mU/l and she had just menstruated for the first time since December 1983. Bromocriptine was stopped, and in view of the enlargement of her pituitary fossa she was admitted for further assessment one month later. Physical examination was unremarkable, blood pressure was 120/80 mm Hg, and the galactorrhoea had resolved. Visual fields were full by perimetry. Computed tomography with enhancement showed an enlarged pituitary fossa with erosion of the floor, dorsum sellae, and anterior clivus, and the left sphenoid sinus was invaded by tumour. There was 9 mm suprasellar extension of a pituitary tumour.

A combined test of anterior pituitary function was carried out after an overnight fast. Insulin 0.15 U/kg, luteinising hormone releasing hormone 100 µg, and thyrotrophin releasing hormone 200 µg were injected intravenously. By 30 minutes she was clinically and biochemically hypoglycaemic (blood glucose concentration 1-3 mmol/l (23 mg/100 ml)) (table).

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