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.²

β Adrenergic blocking drugs have been associated with carbohydrate intolerance—and propranolol particularly with recurrent non-ketotic hyperosmolar diabetic coma³—but in our patient metoprolol was continued without ill effect. Fonesca and Phear found that β adrenergic blockers 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 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 benzothiadiazines, including some without diuretic activity such as diazoxide. It may entail both a decrease in the secretion of insulin and an extrapancreatic effect on the liver.⁵

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

- 1 Fonesca V, Phear DN. Hyperosmolar non-ketotic diabetic syndrome precipitated by treatment with diuretics. *Br Med J* 1982;284:36-7.
- 2 Ostler JR, Epstein M, Smoller S. Combined therapy with thiazide-type and loop diuretic agents for resistant sodium retention. *Ann Intern Med* 1983;99:405-6.
- 3 Podolsky S. A possible role of propranolol in recurrent non-ketotic hyperosmolar diabetic coma. *Diabetes* 1970;19:398.
- 4 Walsh CH, O'Sullivan DJ. A study of the effect of metolazone on carbohydrate metabolism in diabetic subjects. *Journal of the Irish Medical Association* 1974;67:223-6.
- 5 Wales JK, Krees SV, Grant AM, Viktora JK, Wolff FW. Structure activity relationships of benzothiadiazine compounds as hyperglycaemia agents. *J Pharmacol Exp Ther* 1968;164:421-32.

(Accepted 18 March 1985)

Department of Renal Medicine, City Hospital, Nottingham NG5 1PB
PETER A ROWE, MB, MRCP, clinical research fellow

Department of Medicine, Southmead Hospital, Westbury on Trym, Bristol

H G MATHER, MD, FRCP, consultant physician

Correspondence to: Dr Peter A Rowe.

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.^{1,2} 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 clinoids, 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 μ g, and thyrotrophin releasing hormone 200 μ g were injected intravenously. By 30 minutes she was clinically and biochemically hypoglycaemic (blood glucose concentration 1.3 mmol/l (23 mg/100 ml)) (table).

Results of combined test of pituitary function

Time (min)	Glucose (mmol/l)	Growth hormone (mU/l)	Cortisol (nmol/l)	Luteinising hormone (U/l)	Thyroid stimulating hormone (mU/l)	Follicle stimulating hormone (U/l)	Oestradiol E ₂ (pmol/l)
0	4.5	1	250	4	4.2	2	410
30	1.3	1	260	8	7.5		
45	1.3	1					
60	2.4	2	390	7	8.8		
90	2.8	1	420				
120	3.5	< 1	470				

Basal prolactin concentration 595 mU/l (normal < 350 mU/l); thyroxine 88 nmol/l (6.8 μ g/100 ml) (normal 75-160 nmol/l; 5.8-12.4 μ g/100 ml); and free thyroxine 11.6 pmol/l (0.9 ng/100 ml) (normal 9-23 pmol/l; 0.7-1.8 ng/100 ml).

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Cortisol: 1 nmol/l $\approx$ 36.3 ng/100 ml. Oestradiol: 1 pmol/l $\approx$ 0.29 pg/ml.

At 40 minutes she began to complain of frontal headache, which persisted after spontaneous restoration 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 becoming 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.³

Of the three drugs used in the test, thyrotrophin releasing hormone would seem to be the one most likely to have an aetiological role. Cimino *et al* described transient amaurosis after 200 μ g thyrotrophin releasing hormone in a man with a pituitary tumour,⁴ and Drury *et al* also reported amaurosis 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.

- 1 Nakai S, Fukushima T, Feramoto A, Sono K. Pituitary apoplexy: its incidence and clinical significance. *J Neurosurg* 1981;55:187-9.
- 2 Mohr G, Hardy J. Hemorrhage, necrosis and apoplexy in pituitary adenomas. *Surg Neurol* 1982;18:181-9.
- 3 Bernstein M, Hegete RA, Gentili F, *et al*. Pituitary apoplexy associated with a triple bolus test. *J Neurosurg* 1984;61:586-90.
- 4 Cimino A, Corsini R, Radceli E, *et al*. Transient amaurosis in patient with pituitary macro adenoma after intravenous gonadotropin and thyrotrophin releasing hormones. *Lancet* 1981;ii:95.
- 5 Drury PL, Belchetz PE, McDonald WI, *et al*. Transient amaurosis and headache after thyrotrophin releasing hormone. *Lancet* 1982;ii:218-9.

(Accepted 4 April 1985)

Queen Elizabeth Hospital, Birmingham B15 2TH

A J CHAPMAN, MRCP, senior registrar in medicine
G WILLIAMS, MB, BS, preregistration house physician
A D HOCKLEY, FRCS, consultant neurosurgeon
D R LONDON, FRCP, consultant physician

Correspondence to: Dr A J Chapman.