10% of maternal deaths, and the reported mortality is as high as 80% in some series.² Amniotic fluid embolism may occur after diagnostic amniocentesis, but this is uncommon. It is more likely to occur after hypertonic saline or dextrose is injected into the amniotic fluid.¹ In our patient exchange transfusion allowed rapid removal of red cell debris and haemoglobin from the circulation and provided red cells and clotting factors in fresh plasma.

ABO incompatibility between fetal and maternal blood groups appears to have contributed to the severity of our patient's condition; this was similar to the reaction that would be expected after transfusion of ABO incompatible blood. The complete disappearance of a high titre of anti-B immediately after the suspected embolism gives indirect evidence that the rapid deterioration was due to amniotic fluid embolism. Amniotic fluid is known to contain fetal blood group substances,⁴ and the findings above may be relevant to experiments in which amniotic fluid was injected into animals in an attempt to define the pathogenesis.⁵

We believe that exchange transfusion helped to change the course of events and contributed to a successful outcome in this patient.

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1 Morgan M. Amniotic fluid embolism: review. *Anaesthesia* 1979;34:20-32.

2 Killam A. Amniotic fluid embolism. *Clin Obstet Gynaecol* 1985;28:32-6.

3 Courtney LD, Allington M. Effect of amniotic fluid on blood coagulation. *Br J Haematol* 1972;29:353-6.

4 Teichler-Zallen D, Doherty RA. Fetal ABO blood group typing using amniotic fluid. *Clin Genet* 1983;23:120-4.

5 Steiner PE, Lushbaugh CC. Maternal pulmonary embolism by amniotic fluid. *JAMA* 1941;117:1245-50.

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Danazol and benign intracranial hypertension

Danazol is used in the treatment of endometriosis, menorrhagia, benign breast disease, and hereditary angio-oedema.¹ We report three cases of benign intracranial hypertension in patients treated with danazol.

Case reports

Case 1—A healthy 23 year old woman was prescribed danazol 600 mg daily for endometriosis. Twelve weeks later she presented with a month's history of severe frontal headache and diplopia on lateral gaze. She had taken no other medication. She weighed 67 kg, and her blood pressure was 132/72 mm Hg. She had bilateral haemorrhagic papilloedema with constricted visual fields and enlarged blind spots. Visual acuities were 6/9 bilaterally. No other abnormal signs were detected. The results of routine haematological and biochemical investigations, skull radiography, electroencephalography, and computed brain tomography were normal. The lumbar cerebrospinal fluid pressure was 300 mm H₂O, microscopy normal, protein concentration 0.1 g/l, glucose 3 mmol/l.

Danazol was discontinued, but 10 days after admission she developed a left abducens nerve palsy. This resolved within two days, and papilloedema had resolved three weeks later. She remained well three months later.

Case 2—A 36 year old woman received danazol 400 mg daily in May 1984 for irregular periods and menorrhagia. She became amenorrhoeic and gained weight. In January 1985 she presented with a fortnight's history of bifrontal headache. She had stopped taking danazol a few days previously because of the headache. Her blood pressure was 130/70 mm Hg and she weighed 82 kg. The only abnormal physical finding was bilateral papilloedema. The results of baseline investigations, including electroencephalography and computed brain tomography, were normal. The cerebrospinal fluid findings were: pressure >300 mm H₂O, protein 0.38 g/l, glucose 3.5 mmol/l, microscopy normal. Full recovery was attained with weight reduction and diuretic treatment. She remained well two years later.

Case 3—A 24 year old woman was prescribed danazol 400 mg daily for endometriosis. Six months later she was admitted with a two month history of headache and diplopia. She had discontinued danazol five weeks before admission because of the headache. She weighed 62 kg and her blood pressure was 120/80 mm Hg. There was bilateral papilloedema with constricted

visual fields. The results of examination were otherwise normal, as were those of routine investigations including electroencephalography and computed brain tomography. The cerebrospinal fluid was not examined. Benign intracranial hypertension was diagnosed and treatment started with chlorthalidone. Her papilloedema resolved within six weeks. Inadvertent treatment with danazol two years later was associated with headache and diplopia, which cleared when she stopped taking the drug. She remained well eight years later.

Comment

Benign intracranial hypertension is a diagnosis of exclusion, typically occurring in obese young women, often with recent considerable weight gain. Although it is not life threatening, it may result in visual failure. In our patients treatment with danazol was temporally related to the onset and resolution of this syndrome. The patients in cases 1 and 3 were atypical for idiopathic benign intracranial hypertension, being non-obese. In case 3 inadvertent rechallenge resulted in recurrence of symptoms. Danazol suppresses the pituitary-ovarian axis by inhibiting gonadotrophin secretion. It has weak androgenic activity and may cause fluid retention and weight gain.¹ The pathophysiological mechanisms proposed in benign intracranial hypertension include cerebrospinal fluid hypersecretion,² impaired absorption,³ and abnormalities of microvasculature.⁴ Danazol induced fluid retention may aggravate these abnormalities. Raised intracranial pressure may also result from cerebral venous sinus thrombosis. Other associations include pregnancy, menarche, hypervitaminosis A, steroid withdrawal, and tetracycline treatment.⁵

There are no published reports of benign intracranial hypertension associated with danazol. The Committee on Safety of Medicines has no other reports of this condition with danazol, although headaches and visual disturbances are frequently reported (personal communication). The manufacturers are aware of two other cases of raised intracranial pressure in patients treated with danazol (Winthrop, personal communication). Intracranial hypertension should be considered in any woman with headache or visual symptoms during treatment with danazol.

1 Martindale. *The extra pharmacopoeia*. 28th ed. Reynolds JEF, ed. London: Pharmaceutical Press, 1982:1409-10.

2 Donaldson JO. Pathogenesis of pseudotumor cerebri syndromes. *Neurology (NY)* 1981;31:877-80.

3 Johnston I, Paterson A. Benign intracranial hypertension II. CSF pressure and circulation. *Brain* 1974;97:301-12.

4 Raichle ME, Grubb RL, Phelps ME, Gado MH, Caronna JJ. Cerebral hemodynamics and metabolism in pseudotumor cerebri. *Ann Neurol* 1978;4:104-11.

5 Walters BNJ, Gubbay SS. Tetracycline and benign intracranial hypertension: report of five cases. *Br Med J* 1982;282:19-20.

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Clinical evaluation of lysuride in the management of hyperprolactinaemia

Bromocriptine is a semisynthetic ergot alkaloid that acts as a dopamine agonist and is highly effective in achieving normoprolactinaemia in most patients with raised serum prolactin concentrations. Some patients, however, may have unacceptable side effects. Lysuride hydrogen maleate (lisuride; Revanil, Schering UK) is an 8- α -ergolene which has potent dopamine agonist activity both in vitro and in vivo; currently there are few data available about the incidence of side effects with lysuride in relation to its clinical efficacy. We have therefore assessed the efficacy of lysuride in 24 consecutive women presenting with hyperprolactinaemia.

Patients, methods, and results

All 24 patients (age range 19-42) presented with a serum prolactin concentration (mean of three estimations) above 360 mU/l, which is the upper limit of normal in

our laboratory (mean 2060 mU/l; range 450-4050 mU/l). No patient had evidence of a prolactin secreting macroadenoma on computed tomography. No other endocrine abnormality was found after full endocrine assessment, and treatment was initiated with lysuride, the starting dose of 0.1 mg being taken at night in the middle of a snack. The dose of lysuride was then gradually increased by 0.1 mg in the middle of food until normoprolactinaemia was achieved, unacceptable side effects ensued, or a daily dose of 1.2 mg was reached. Patients seeking pregnancy were instructed to stop treatment within 48 hours of missing a period. Lysuride was the first dopamine agonist used in 22 patients, and in two it was introduced because of unacceptable side effects with bromocriptine. Treatment was continued for one to 40 months (mean 5.4 months).

In 23 cases lysuride (mean dose 0.4 mg daily; range 0.1-1.2 mg/day) appreciably reduced the serum prolactin concentration, values becoming normal in eight cases (figure). Symptoms and signs of hyperprolactinaemia improved in

Change in serum prolactin concentrations in 24 women treated with lysuride. ●-----● Patient with rapidly expanding pituitary lesion.

parallel with the fall in prolactin concentrations. In the remaining case failure to suppress was associated with a rapidly expanding pituitary lesion, which necessitated surgical intervention. Of 13 patients presenting with primary or secondary infertility, five became pregnant while receiving treatment. Gestation was uneventful and all babies were normal. In three cases lysuride was successfully reintroduced after delivery in order to suppress lactation. Of the eight patients who failed to conceive while taking lysuride, three had ovulation confirmed by serial progesterone estimations. The two patients intolerant of bromocriptine were successfully transferred to lysuride with return to normal of their serum prolactin values.

Sixteen patients (67%) given lysuride stopped treatment within one to four months before reaching a dose sufficient to lower prolactin concentrations to normal because of unacceptable side effects. In the whole series these included nausea (16 cases), drowsiness (17), dizziness (14), depression (12), lethargy (four), constipation (two), bloating (one), and headache (one).

Comment

These data confirm that lysuride is an effective prolactin lowering agent in hyperprolactinaemia, leading to arrest of galactorrhoea, resumption of ovulatory cycles, and hence fertility. The high incidence of side effects encountered in this study, however, which led to withdrawal of the drug in 16 of the 24 patients before an optimum dose was reached, appears to be a substantial disadvantage. Drowsiness was particularly common and may relate to the antiserotonergic properties of the drug. Other side effects were similar to those associated with bromocriptine. Interestingly, however, the two patients who had been intolerant of bromocriptine subsequently successfully changed to lysuride. Intolerance of one drug may not therefore necessarily lead to intolerance to another dopamine agonist.^{2,3} Structural analogues of lysuride, particularly transdihydrolysuride, may offer advantages over the parent compound, and a recent report suggests that this compound may be comparatively free of side effects.⁴

In conclusion, our findings confirm the efficacy and safety of lysuride as a prolactin lowering agent in hyperprolactinaemic hypogonadism and infertility. In view of the high occurrence of side effects we suggest that it represents a second line treatment in this condition but may be useful in patients intolerant of bromocriptine.

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- 1 Chiodini P, Liuzzi A, Cozzi R, *et al.* Size reduction of macroprolactinomas by bromocriptine or lisuride treatment. *J Clin Endocrinol Metab* 1981;53:737-43.
- 2 Grossman A, Bouloux P, Loneragan R, Rees LH, Wass JAH, Besser GM. A comparison of the endocrine profiles and clinical activity of mesulergine and pergolide in the treatment of hyperprolactinaemia. *Clin Endocrinol* 1985;22:611-6.
- 3 Casson IF, Walker BA, Hipkin LJ, Belchetz PE. Intolerance of bromocriptine: is metergoline a satisfactory alternative? *Br Med J* 1985;290:1783-4.
- 4 Graf KJ, Horowski R, Dorow R. Rapid regression of macroprolactinomas by the new dopamine partial agonist terguride. *Acta Endocrinol* 1986;111:460-6.

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Does atenolol have an effect on calcium metabolism?

Hypercalcaemia is often an incidental finding during biochemical investigation, being found in 1.1% of the general population¹ and 3.6% of patients in hospital.² The most common cause is primary hyperparathyroidism. Ten per cent of patients with sarcoidosis have hypercalcaemia, but hypercalciuria is much more common.³ It is therefore possible that β antagonists may be given to some patients with unsuspected disturbances in their calcium metabolism. I report on the effects of the β_1 antagonist atenolol on the calcium balance of two patients.

Case reports

Case 1—A 61 year old man with angina was treated with atenolol 100 mg/day. He had been under investigation for two years for mild but persistent asymptomatic hypercalcaemia, which was thought to be due to primary hyperparathyroidism. He was not taking any other drugs.

Case 2—A 51 year old woman with diabetes controlled by diet and with a diagnosis of sarcoidosis was prescribed atenolol 100 mg/day for hypertension. She was not taking any other drugs. After three weeks atenolol was stopped because of side effects.

The table shows the results of measurements of plasma concentration and urinary excretion of calcium and phosphate in both cases.

Comment

In both these cases atenolol caused decreases in plasma calcium concentration and urinary calcium excretion and an increase in plasma phosphate concentration. These changes appeared to be reversible in the patient studied after withdrawal of atenolol (case 2) and have not previously been reported.

It is not known how atenolol caused these changes. The non-selective β antagonist propranolol can reduce basal parathyroid hormone concentrations,⁴ and it has been successful in treating a case of hyperparathyroidism.⁵ Different mechanisms are responsible for hypercalcaemia in hyperparathyroidism and in sarcoidosis, which suggests that atenolol may have more than one action.

The recent observation that untreated asymptomatic hypercalcaemia constitutes a risk factor for premature death suggests that further studies on the effects of atenolol on calcium metabolism are indicated.¹

In summary, the results show that atenolol may have an effect on calcium and phosphate metabolism. Although the mechanisms of action remain unknown, in cases where plasma concentration and urinary excretion of calcium and phosphate are measured the effects of any concomitant use of β antagonists must be considered.

I am grateful to Dr W B Thomson for allowing me to report these cases.

- 1 Palmer M, Adam H, Bergstrom R, Jakobson S, Akerstrom G, Ljunghall S. Survival and renal function in untreated hypercalcaemia. *Lancet* 1987;i:59-62.
- 2 Keating FR, Jones JD, Elveback LR. Distribution of serum calcium and phosphorus values in unselected ambulatory patients. *J Lab Clin Med* 1969;74:507-14.