SIDE EFFECTS OF DRUGS

Cirrhosis and haemolysis complicating methyldopa treatment

Haemolysis is a recognised complication of methyldopa treatment.[1] Chronic hepatitis may also be induced by methyldopa and progress to cirrhosis if the drug is continued.[2] We describe here a patient who developed severe haemolytic anaemia after two years on methyldopa and was also found to have active cirrhosis.

Case report

A 68-year-old English woman had suffered from psoriasis for many years. It was usually mild and had needed intermittent treatment with various topical ointments, including betamethasone. A severe exacerbation had occurred four years before admission and had responded to an 11-month course of oral prednisolone. She had never taken methotrexate. Twenty-six months before admission she had presented with symptoms and signs of right and left ventricular failure and had been found to have a blood pressure of 200/120 mm Hg.

Treatment—She had responded rapidly to treatment with methyldopa, 1·5 g/day, frusemide 40 mg/day, and digoxin 0·25 mg/day. Four months later an acute generalised eczematous reaction had occurred. All drugs had been stopped for three weeks but the rash had persisted and her heart failure rapidly become more severe. Treatment had been restarted with the same drugs in the same doses. The rash had responded rapidly to topical fluocinonide, and she had left hospital much improved 11 days later. She had taken the methyldopa, frusemide, and digoxin regularly during the next 21 months, and had remained reasonably well and active until the onset of jaundice. She had never drunk alcohol regularly or heavily. No relevant family history was known.

Adverse effect—The patient was admitted complaining of jaundice, itching, and malaise, which had increased over three weeks. She was short of breath on slight exertion; her ankles and legs had become swollen; and her motions were loose, pale, and offensive. Mental confusion was noticed on admission, and this rapidly became severe. Examination showed moderate jaundice, anaemia, purpura on both arms, and pitting oedema to waist level. Both legs showed psoriatic patches and scratch marks. The pulse rate was 56 beats/min, blood pressure 130/70 mm Hg, and the central venous pressure was 8 cm above the manubriosternal angle. The heart was dilated and abundant moist sounds were heard at both lung bases. The liver was enlarged 12 cm below the rib-margin, tender, hard and irregular. The spleen could not be felt. Ascites was suspected but the signs were obscured.

Investigations showed: haemoglobin 5·6 g/dl; reticulocytes 32%; direct Coombs test positive; antinuclear factor titre 1/100; urea 16·1 mmol/l (97 mg/100 ml), bilirubin 79 μmol/l (4·6 mg/100 ml), aspartate transaminase 24 IU/l, alkaline phosphatase 14 KAU/dl, albumin 33 g/l, total plasma protein 68 g/l, some increase in globulins on electrophoresis; prothrombin time 18 s (control 14 s). Hepatitis B antigen and anti-smooth muscle and anti-mitochondrial antibodies were not detected. Severe erythrocyte autoagglutination prevented blood group determination. A ^{99}Tc-liver scan confirmed liver enlargement with reduced patchy uptake. Liver biopsy showed fibrosis and early nodular regeneration, with destruction of the lobular pattern. The portal areas contained a moderate chronic inflammatory exudate. Limiting plates were eroded, and liver cells adjacent to the inflamed portal areas were hydropic and enlarged, but rosettes were seen only occasionally. Hepatocytes not affected by the portal inflammation were vacuolated, presumably by fat. Iron stains were negative and alcoholic hyaline was not seen. The picture was that of a low grade but aggressive chronic hepatitis at the stage of early cirrhosis.

Treatment included withdrawal of methyldopa, transfusion with group O rhesus-negative blood, and steroids. The haemolysis slowly subsided and the jaundice improved. Unfortunately the mental confusion persisted. Bronchial pneumonia supervened and the patient died 10 weeks after admission.

At necropsy early cirrhosis was confirmed. There was bronchial pneumonia, and an unsuspected perisplenic abscess. The brain was macroscopically normal. Histological examination of liver specimens showed that the biopsy specimen was representative and that the histological picture had changed very little. There was heptic venous congestion but no thrombosis. The vasculature of the right kidney showed prominent hypertensive change. The left kidney showed severe chronic pyelonephritis and mild acute pyelitis.

Comment

Haemolytic anaemia is a rare reaction to methyldopa, although about 20% of patients treated may develop a positive reaction on a Coombs test.[1] In this patient severe haemolysis with multiple autoagglutinins was almost certainly a reaction to methyldopa. The cirrhosis can also be attributed to methyldopa, although the relation is less secure. The histological picture and the positive antinuclear factor titre suggest an autoimmune process. Liver size and function were normal when the drug was started, and cardiac cirrhosis was virtually excluded by the biopsy. Recent reports[2 3] have emphasised the risk of chronic low-grade hepatitis during methyldopa treatment, producing few symptoms, little disturbance of liver function tests, but progressing insidiously to cirrhosis.

The cause of the mental confusion is obscure. Once established it changed little and failed to respond to steroids or a trial of bowel sterilisation. Possibly the cerebral circulation was obstructed by erythrocyte aggregates during the severe haemolysis, but exudates and other retinal changes that would have suggested multiple microinfarction were never seen, and there was no necropsy evidence to support this explanation.

The association of haemolysis, active cirrhosis, and a positive antinuclear factor titre in this patient suggests that methyldopa can disturb the immune systems in much the same way as systemic lupus erythematosus. Methyldopa hypersensitivity may be a multisystem disorder, and the occurrence of one component of the syndrome should stimulate a search for others.

[1] Goodman, L S, and Gilman, A (editors), *The Pharmacological Basis of Therapeutics*. 5th edn, p 709. New York, Macmillan, 1975.
[2] Toghill, P J, *et al*, *British Medical Journal*, 1974, **3**, 545.
[3] *Lancet*, 1976, **2**, 299.

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Warwick Hospital, Warwick
STEPHEN L HYER, MB, BS, house physician
ALAN J KNELL, MRCP, PHD, consultant physician

Gross oedema occurring during treatment for depression

We have recently investigated a patient with gross oedema that appeared to be due to combined treatment with a monoamine oxidase inhibitor and a benzodiazepine.

Case report

A 64-year-old unemployed Englishman had been treated for five years with multiple psychotropic drugs for a recurrent depressive psychosis. These had included imipramine, amitriptyline, clomipramine, iprindole, chlordiazepoxide, diazepam, lorazepam, nitrazepam, and chlormethiazole in varying combinations and doses.

Treatment—Sixteen weeks before he presented at hospital he had been started on phenelzine 15 mg three times a day increasing to 30 mg three times a day, chlordiazepoxide 10 mg three times a day, and chlormethiazole 1500 mg at night. This was the first time he had received a monoamine oxidase inhibitor and he continued on these drugs until he was admitted to hospital with leg oedema.

Adverse effect—When he was admitted the leg swelling had persisted for 10 weeks. He did not admit to any other physical symptoms on questioning. Examination showed only massive bilateral pitting oedema of the legs. In particular, there was no evidence of cardiac, hepatic, or renal disease; deep venous thrombosis; or lymphoedema. Investigations, including full blood count, measurement of sedimentation rate, blood urea, electrolytes, and plasma proteins, and liver function tests, all gave normal results. As no definitive cause for his oedema was found his psychotropic drugs were stopped and frusemide 40 mg/day was started. After six weeks he was free of oedema without further diuretic treatment and his weight had fallen from 114 kg on admission to 101 kg. Subsequently he remained well and chlormethiazole was restarted without recurrence of oedema.

Comment

Mild ankle oedema has been reported in patients taking monoamine oxidase inhibitors,[1] and it has been noted in patients on antidepressive treatment with combinations of tricyclics and monoamine oxidase inhibitors.[2] In our patient the gross oedema might have been due to phenelzine alone but we are unaware of other reports of this complication and our patient was unwilling to test this hypothesis by taking the drug again. Massive oedema with ascites has, however, been described in a woman taking isocarboxazid, diazepam, and amitriptyline over 10 weeks.[3] We wonder, therefore, whether the combination of a monoamine oxidase inhibitor with a benzodiazepine might have been responsible for the fluid retention in our patient.

[1] Griffith, G C, *American Journal of Cardiology*, 1960, **6**, 1103.
[2] Gander, D R, *Lancet*, 1965, **2**, 107.
[3] Child, J A, *Postgraduate Medical Journal*, 1969, **45**, 288.

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General Hospital, Nottingham NG1 6HA
A GOONEWARDENE, MB, BS, senior house officer
P J TOGHILL, MD, FRCP, consultant physician

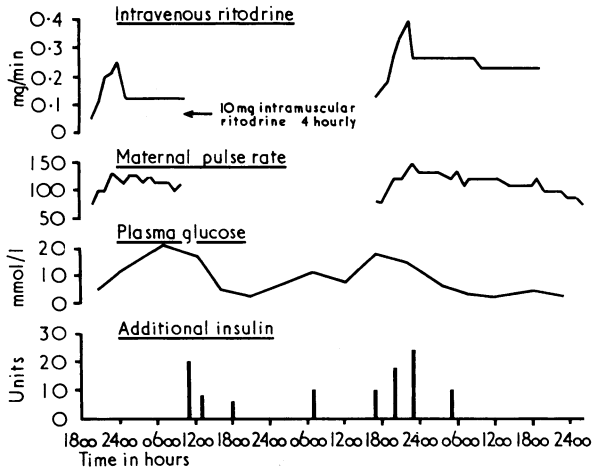
Insulin requirements in pregnant diabetics with premature labour controlled by ritodrine

Ritodrine hydrochloride is a beta-sympathomimetic drug which has been used in the management of premature labour to suppress uterine contractility.[1] We report here its use in suppressing uterine contractility in diabetic women.

Case 1

A 21-year-old primagravid Caucasian housewife had had insulin-dependent diabetes since the age of 10 years. There was no history of other serious illness, allergy, or hypertension and no evidence of cardiovascular disease. Before pregnancy she weighed 67 kg (standard for height 57 kg). Her only medication was insulin 100 units/day (28 units Actrapid and 20 units Semitard in the morning; 20 units Actrapid and 32 units Semitard in the evening). At 31 weeks she went into spontaneous labour.

She was treated initially with intravenous ritodrine as shown in the figure; 120 mg was given over 14 hours. The plasma glucose level rose overnight from 5·7 to 21·3 mmol/l (103-384 mg/100 ml). She had ketonuria, and 20 additional units of insulin were given. When contractions ceased she was given intramuscular ritodrine 10 mg every four hours for the next 28 hours, during which 24 units of insulin were given in addition to her normal requirements. Strong uterine contractions then recurred and ritodrine infusion was resumed. Over the next 24 hours, during which a total of 293 mg of ritodrine was given, her insulin requirements, assessed by frequent plasma glucose estimations, amounted to 60 extra units. Thereafter she received two 10-mg doses of ritodrine intramuscularly followed by oral ritodrine, 10 mg every six hours. There was no apparent increase in her insulin requirements on this dose. Despite continuous oral treatment she went into labour again at 32½ weeks. As before, the pattern of a greatly increased insulin requirement in association with intravenous ritodrine was observed, 56 extra units of insulin being required over a 15-hour infusion of 330 mg of ritodrine. When contractions stopped oral ritodrine 10 mg every six hours was given and her insulin dose could be reduced to the pretreatment level. At 35½ weeks she spontaneously delivered a healthy girl weighing 2800 g, whose subsequent progress was uneventful.



Case 1. Ritodrine and insulin treatment and plasma glucose concentrations during premature labour.
Conversion: SI to traditional units—Glucose: 1 mmol/l 18 mg/100 ml.

Case 2

A 25-year-old para 1+2 Caucasian housewife had had insulin dependent diabetes for one and a half years. She had no relevant medical history. She weighed 64 kg before pregnancy (standard 62 kg). She was receiving insulin as her only treatment, 124 units/day (40 units Actrapid and 38 units Semitard in the morning; 22 units Actrapid and 24 units Semitard in the evening). At 36 weeks she went into spontaneous labour.

It was decided to inhibit uterine contractions until the lecithin: sphingomyelin ratio in the amniotic fluid could be determined. She received intravenous ritodrine. The dose was gradually increased to 0·2 mg/min, a total dose of 130 mg being given over 12 hours. During this time she showed glycosuria and ketonuria and required an extra 32 units of insulin. For a further week she was maintained on oral ritodrine 10 mg every six hours, which had no evident effect on her insulin requirement. At 38 weeks she delivered a healthy girl weighing 3200 g, whose subsequent progress was satisfactory.

Both patients developed agitation and tachycardia during the infusion. Blood pressure was unaffected and there were no other side effects.

Comment

In non-diabetic pregnant women glucose tolerance is evidently little effected by ritodrine given orally,[2] but it is appreciably impaired when the drug is given intravenously.[3] There are no previous reports of its use in pregnant diabetics. The fact that the insulin requirement increased during intravenous infusion but not when the drug was given intramuscularly or orally probably reflects the relative doses given by the different routes. The drug has been shown to increase the cardiac work load[4] and may therefore be inappropriate for the occasional pregnant diabetic in whom there is reason to suspect ischaemic heart disease. Clearly, however, an effective inhibitor of uterine contractility is needed for pregnant diabetics since the condition is associated with a high incidence of spontaneous premature labour, the commonest necropsy finding in infants of diabetic mothers being pulmonary hyaline membrane disease.[5]

In both our patients premature labour was inhibited by intravenous infusion of ritodrine hydrochloride without serious untoward effects on mothers or infants. Provided that the strong hyperglycaemic effect of the drug is anticipated and countered by appropriate monitoring and adjustment of the insulin dose, there seems to be a place for this agent in the management of pregnant diabetics.

[1] Wesselius De Casparis, A, *et al*, *British Medical Journal*, 1971, **3**, 144.
[2] Blouin, D, Murray, M A F, and Beard, R W, *British Journal of Obstetrics and Gynaecology*, 1976, **83**, 711.
[3] Bergstein, N A M, *et al*, in *Proceedings of the International Symposium on the Treatment of Fetal Risks*, ed K Baumgarten and A W Casparis. Vienna, University of Vienna, 1972.
[4] Beiniaz, J, Ivankouich, A, and Scommegna, A, *American Journal of Obstetrics and Gynecology*, 1974, **118**, 910.
[5] Farquhar, J W, *Clinics in Endocrinology and Metabolism*, 1976, **5**, 237.

Diabetic and Dietetic Department, Royal Infirmary, Edinburgh EH3 9YW
JUDITH M STEEL, MRCP, senior registrar
JOHN PARBOOSINGH, BSC, MRCOG, consultant obstetrician