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 she still maintained a normal oedema-free state, but she had been stopped for three weeks. The rash had persisted and her heart failure had resolved. Treatment had been restarted with the same drugs in the same doses. The rash had resolved rapidly to topical fluocinolone, and she had left hospital much improved 11 days later. She had taken the methyldopa, frusenide, 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 piorotic patches and scratch marks. The pulse rate was 56, 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 × 10⁶/mm³; direct Coombs test positive; antinuclear factor titre 1:100; urea 16.1 mmol/l (97 mg/100 ml), bilirubin 79 mmol/l (4.6 mg/100 ml), aspartate transaminase 24 U/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 antinuclear antibodies were not detected. Severe erythrocyte autoagglutination prevented blood group determination. A WBC/liver-scan confirmed liver enlargement with reduced patchy uptake. Liver biopsy showed hyalinosis and mononuclear inflammatory infiltration, 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 psephic 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 hepatic 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.3 In this patient severe haemolysis with multiple auto-

agglutinins 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 reports4 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 micro-infarction 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.


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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, chlorozoxazepax, 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, chlorozaxepoxax 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 frusenide 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.