Alpha Methyldopa and Haemolytic Anaemia


SUMMARY

A patient treated with alpha methyldopa who developed a severe haemolytic anaemia of the gamma type, with a positive direct Coombs test, is presented. The incidence of such an anaemia is 0,1 - 0,3%; it is usually a mild haemolytic anaemia. Severe haemolysis is extremely rare. The mechanism of the haemolytic anaemia is thought to be that alpha methyldopa acts as a heterospecific hapten. The management of patients with a direct positive Coombs test, is discussed. Therapy should be maintained unless haemolysis occurs, in which case alpha methyldopa should be withdrawn. Steroids should only be used if severe haemolysis continues.


A positive direct Coombs test (DCT), with or without haemolysis, in patients on antihypertensive treatment with alpha methyldopa, was first reported by Breckenridge et al. Less than 20 cases of severe haemolytic anaemia (haemoglobin less than 7,0 g/100 ml) have been reported in the medical literature, following the advent of alpha methyldopa therapy. This case report is presented as we believe it to be the first documented report of severe haemolytic anaemia in the South African literature.

CASE REPORT

A 65-year-old White male presented to the outpatient department on 18 April 1971, complaining of severe attacks of chest pain, suggestive of crescendo angina. On examination his blood pressure was 170/110 mmHg and he had a pulse rate of 96 per minute. There were no signs of congestive cardiac failure, but a gallop rhythm was present. The electrocardiogram showed severe left ventricular strain, with ischaemic change and an occasional ventricular premature systole. Chest X-ray showed a moderate left ventricular contour. The full blood count performed on admission was entirely normal, with a haemoglobin of 15.1 g/100 ml (Table I).

Treatment was commenced with digoxin, 0,25 mg twice daily, furosemide 40 mg daily, and potassium supplements daily. In addition, alpha methyldopa 250 mg twice daily, propranolol 20 mg thrice daily and glyceryl trinitrate sublingually, when required, were administered. The patient experienced considerable symptomatic relief on this therapy and remained well until 7 March 1972.

At this stage the patient presented at the outpatient department complaining of increasing angina and dyspnoea over the past month. On examination his blood pressure was 100/70 mmHg with a pulse rate of 80 per minute, and he was very dyspnoeic at rest. He appeared to be in moderate cardiac failure and was clinically pale, with a haemoglobin of 6,3 g/100 ml (Table I).

Investigation of his anaemia showed a haemoglobin concentration of 6,3 g/100 ml, a packed cell volume of 18%, and a mean corpuscular volume of 100 mm³. The presence of marked spherocytosis was noted and the reticulocyte count was 14%. The serum iron was 94 pg/100 ml with a total iron binding capacity of 236 pg. The percentage saturation was 40%. Serum vitamin B₁₂ was 270 pg/ml. A normoblastic hyperplastic bone marrow with abundant free iron was present, this was in keeping with a haemolytic anaemia. Haemolytic studies showed a strongly positive DCT, a positive indirect Coombs test, and auto-agglutinins at 4°C were positive. There was also an increased osmotic fragility and autohaemolysis at 48 hours. These findings confirmed the presence of a haemolytic anaemia, which was of the gamma type.

The patient was mildly jaundiced, with a total bilirubin of 3,7 mg/100 ml and a conjugated bilirubin of 2,0 mg/100 ml. The serum aspartate transferase and alkaline phosphatase were normal. A barium meal was normal, and the augmented histamine test gave a maximal acid output of 3,1 mEq in the first hour, with resting acid.

As soon as a Coombs-positive haemolytic anaemia of the gamma type caused by alpha methyldopa was suspected, the alpha methyldopa therapy was stopped. Because of the patient's severe angina, packed red blood cells were transfused slowly until the haemoglobin was 11,0 g/100 ml. Within three weeks of discontinuing the alpha methyldopa therapy, the reticulocyte count had dropped from 14% to 4%, and the bilirubin returned to

TABLE I. SERIAL BLOOD STUDIES

<table>
<thead>
<tr>
<th>Date</th>
<th>Haemoglobin (g/100 ml)</th>
<th>Coombs test</th>
<th>Reticulocyte count</th>
</tr>
</thead>
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<tr>
<td>22.4.68</td>
<td>15,1</td>
<td>+</td>
<td>14.0%</td>
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</tr>
<tr>
<td>5.6.72</td>
<td>12,9</td>
<td></td>
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</table>

*Date received: 10 August 1972
normal. Following the transfusion the haemoglobin remained constant at 11.0 g/100 ml. Steroid therapy was not given. The patient's cardiac failure and severe angina also settled once the anaemia had been corrected.

DISCUSSION

The incidence of a positive DCT in patients treated with alpha methyldopa, varied from 10% to 36% in various series analysed. In 1966 it was estimated that approximately 20,000 people in Britain had an alpha methyldopa induced positive DCT. In addition, haemolysis to a minor degree insufficient to cause anaemia, was fairly common.

Severe haemolysis, enough to produce a haemolytic anaemia, was, however, rare and the estimated incidence is 0.1 - 0.3% of patients treated with alpha methyldopa. The anaemia in these patients is usually slight, with a haemoglobin of 9.0 g/100 ml or more. A severe haemolytic anaemia with a haemoglobin of less than 7.0 g/100 ml was much rarer, and only 20 documented case reports appear in the literature surveyed. Possibly not all the severe haemolytic anaemias secondary to alpha methyldopa administration have been documented, nevertheless a severe haemolytic anaemia is still a rare phenomenon.

The time of onset of the positive DCT and anaemia has been found to vary from 12 to 52 weeks after commencement of therapy. The positive DCT may take up to two years to disappear after withdrawal of the drug, and if the drug is re-introduced, Breckenridge suggests that it does not always become positive again on rechallenging.

It has been shown that there is a direct relationship between the dosage of alpha methyldopa and the incidence of a positive DCT, the highest incidence being in patients taking more than 2 g of alpha methyldopa a day.

The antibody produced is always of the gamma G type. The mechanism of the haemolysis is at present uncertain, but current work seems to indicate that alpha methyldopa acts as a heterospecific hapteen. A positive antinuclear factor (ANF), is found in about 15% of patients on alpha methyldopa, but not all patients with a positive ANF had a positive DCT, and vice versa. Lupus erythematous cells have been detected in only 4 patients on alpha methyldopa who had positive DCTs, and in only 1 patient who developed a haemolytic anaemia.

The management of patients on alpha methyldopa who exhibit a positive DCT without haemolysis is controversial, but most authorities accept that treatment should be maintained, due to the great efficacy of the drug in treating mild and moderate hypertension. The significance of a positive DCT alone is as yet undetermined, and may possibly be of no pathological significance. It has been recommended that all patients on alpha methyldopa should have a Coombs test performed one year after commencement of therapy so that the physician has a record of whether the DCT is positive or negative.

A patient with a positive DCT is at risk if pregnancy or major surgery is anticipated. In pregnancy it can lead to diagnostic difficulties (if rhesus incompatibility is present), and in patients undergoing emergency surgery, it can seriously hamper blood crossmatching in an emergency situation. Continued administration of alpha methyldopa therefore should be strictly avoided in patients falling into these two categories.

Management of patients with a positive DCT and a haemolytic anaemia, has not been uniform. Some patients have been treated by withdrawal of the drug, others by withdrawal of the drug with additional steroid therapy, and others with steroid therapy, while administration of alpha methyldopa has continued. No adequate series has been documented owing to the small number of cases seen. Guy's Hospital Report suggests that in future a strict regimen of treatment should be instituted, along the following lines: withdrawal of alpha methyldopa as soon as the diagnosis is suspected; and the introduction of steroids only if haemolysis continues and the patient's blood picture shows rapid deterioration.

The prognosis for the patient with a severe haemolytic anaemia is uncertain. In analysing the cases reported, it is notable that all 7 patients treated without steroids survived and fared well. Only 11 out of 17 patients treated with steroids survived. The causes of death were usually reported as unconnected with haemolysis, i.e. congestive cardiac failure, pulmonary embolism and a bleeding duodenal ulcer being among causes listed. The two groups (those treated with steroids and those without), may not be strictly comparable, as the steroid group may have included patients who were more severely ill, due to factors other than the haemolytic anaemia.

With further study of the role played by alpha methyldopa in the aetiology of haemolytic anaemia, it is to be hoped that further knowledge of the pathogenesis of autoimmune warm agglutinin haemolytic anaemia, will be gained.

We should like to thank the Medical Superintendent of Victoria Hospital, Wynberg, for permission to publish; and the laboratory staff of Dr M. C. Botha, for performing the haemolytic studies.

REFERENCES