Intermittent claudication complicating beta-blockade

Intermittent claudication is an occasional side effect of beta-adrenergic blockade but clinical details are lacking. Beta-blocking agents may exacerbate intermittent claudication in patients with severe peripheral arterial insufficiency. The following cases suggest that they may also provoke claudication in patients with previously asymptomatic peripheral arterial disease.

Case 1
A man aged 54 without previous cardiovascular symptoms was found to be hypertensive. He was treated with methyldopa and, because of probable paroxysmal nocturnal dyspnoea, with bendrofluazide. After six months propranolol 120 mg daily was substituted for methyldopa. Three weeks later he developed cold extremities and bilateral calf claudication at 150 yards. After eight weeks’ treatment, during which the blood pressure fell from 220/125 to 200/120 mm Hg, propranolol was withdrawn. Claudication began to improve after three weeks and resolved within five.

Seven weeks after stopping propranolol the patient could play golf. After the dose was both bilateral, all peripheral pulses were palpable. The resting Doppler pressure index was normal, but Doppler sonography indicated generalized atherosclerosis of the lower limbs without pronounced vessel narrowing. The electrocardiogram (ECG) showed left ventricular hypertrophy. There was no radiographic evidence of cardiac decompensation.

Case 2
A woman aged 60 without previous cardiovascular symptoms had a transient hemiplegia. Her blood pressure was 220/120 mm Hg. She was treated with practolol 300 mg daily. Six months later she developed bilateral calf claudication at 100 yards; blood pressure was unchanged and there were no signs of widespread distal arterial disease. ECG and chest x-ray showed no evidence of cardiac decompensation. Methyldopa and bendrofluazide were substituted for practolol. One month later the blood pressure was 180/100 mm Hg and right calf claudication had resolved. Left calf claudication and the peripheral pulses were, however, unchanged. Left phenol sympathectomy was performed. After three months severe left calf claudication persisted, but right-sided symptoms had not recurred.

Case 3
A man aged 59 without previous cardiovascular symptoms sustained an anterior myocardial infarction. Despite digoxin and frusemide, signs of cardiac decompensation persisted for three months. Four months after infarction he developed angina, and propranolol 120 mg daily was added to his treatment. Two months later he had no angina but complained of cold feet. After a further three months he developed bilateral calf claudication; the clinical signs indicated bilateral superficial femoral artery occlusions with poor distal flow. Without a change in his drug therapy, a left phenol sympathectomy was performed. Six months later, on the same drugs, bilateral claudication persisted but was less severe.

Case 4
A woman aged 56 with a history of angina developed atrial fibrillation and acute left heart failure; there was no evidence of myocardial infarction. She reverted to sinus rhythm and cardiac failure resolved. Digoxin and frusemide were continued, and four months later propranolol 160 mg daily was added because of angina. Five months after starting propranolol and one month after the dose was increased to 240 mg daily she developed bilateral calf claudication. The clinical signs indicated widespread distal arterial disease. Practolol 600 mg daily was substituted for propranolol. Symptoms persisted and without a further change of drug treatment bilateral phenol sympathectomies were performed.

Discussion
From these and other similar cases we have concluded that, although not listed by the drug manufacturers, claudication is an important and potentially reversible side effect of cardioselective and non-selective beta-blockade. Presumably the drop in cardiac output causes a critical reduction in peripheral perfusion and hence unmask previously asymptomatic arterial disease.

The incidence of claudication complicating beta-blockade may be higher in patients with myocardial ischaemia, and thus with established atheromatous disease, than has been reported in hypertensive patients; patients with cardiac decompensation may be particularly vulnerable. We recommend that patients, especially those with a history of cardiac decompensation, should not be given beta-blocking agents without careful assessment of their peripheral vascular status.

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Normotensive primary aldosteronism

Primary aldosteronism is an uncommon condition, accounting for less than 1% of unselected hypertensives. The condition classically presents with hypertension of only moderate degree and symptoms related to hypokalaemia. This classic picture, however, is not often seen. Hypokalaemia may be mild and symptomless and patients with malignant hypertension have been described. We report a case of normotensive primary aldosteronism due to adrenal adenoma, a condition that has not been reported before.

Case report
A 40-year-old man was admitted to hospital as an emergency after developing severe generalized weakness associated with acral circumscribed cyanosis. He reported two similar attacks during the previous three years, each resolving without sequelae within three days. There was no family history of periodic paralysis and he denied taking medicines or liquorice. Examination showed generalised muscle weakness with normal tendon jerks. Blood pressure recorded on six occasions over one month before starting treatment and while taking a normal ward diet (sodium content 100-150 mmol/l (Meq)), potassium 2-4 mmol/l (2-4 Meq/l), chloride 100 mmol/l (100 Meq/l), and bicarbonate 30 mmol/l (30 Meq/l). While on a 10-mmol sodium diet plasma renin activity was <3 μmol/min (<3 ng/ml/min) both lying and standing (normal for our laboratory: 25-31 μmol/min (32-40 ng/ml/min) lying, and 31-62 μmol/min (40-80 ng/ml/min) standing). Peripheral venous aldosterone (measured at the MRC Blood Pressure Unit in Glasgow by radioimmunoassay after paper chromatographic separation) was 1180 pmol/l (42.5 ng/100 ml) on a free ward diet at 10 am after two hours of recumbancy (normal <500 pmol/l (<180 ng/100 ml)), and 800 pmol/l (28.8 ng/100 ml) at 12 noon after walking (a normal range was not available but the observed fall in aldosterone on ambulation is characteristic of aldosterone-producing adenoma rather than idiopathic adrenal hyperplasia, in which the level usually rises under these conditions). The left adrenal venous plasma aldosterone was 340 pmol/l (12-3 ng/ml) and that in the inferior vena cava above the adrenal veins was normal (33-5 ng/ml). The left adrenal venogram was normal but the right adrenal vein could not be catheterized. Adrenal scanning after administering 131I-lodochloramide showed dense uptake on the right and minimal uptake on the left. The electrocardiogram showed flattening of T waves and prominent U waves in keeping with hypokalaemia. Chest x-ray films and an intravenous pyelogram were normal. Hypokalaemia was corrected initially with spironolactone 75 mg daily but this caused impotence. The right adrenal, bearing a tumour 2 cm in diameter, was removed. The presence of a benign adenoma was confirmed histologically. After operation serum potassium remained normal and blood pressure was 120/80 mm Hg.
Comment

Normotensive primary aldosteronism has not been described with adrenal adenoma, although normotension in the face of aldosterone overproduction by an adrenal carcinoma has been reported. In our patient the reason for the normotension is not clear. It has been suggested that since it is difficult to reproduce the syndrome of primary aldosteronism by administering aldosterone alone there may be other factors, such as the concomitant production of corticosterone by the tumour. Corticosterone levels were not measured in this patient. Induction of hypertension in man administering large doses of aldosterone alone has been reported, so the explanation of normotension in our patient remains obscure. This case showed the importance of considering the diagnosis of primary aldosteronism in any patient with hyponatraemia whatever the blood pressure. The condition is readily distinguished from Bartter's syndrome by finding a low plasma renin activity.

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Secondary dyserythropoietic activity resembling Di Guglielmo's disease in sickle-cell anaemia

Dyserythropoiesis occurs in many diseases including deficiencies of vitamin B12, or folate, iron deficiency, defects of haemoglobin synthesis and other haemoglobinopathies, and primary sideroblastic anemias. Classic dyserythropoiesis with both morphological and serological characteristics has not been described, so far as we know, in sickle-cell anaemia. We describe three patients with sickle-cell anaemia in which dyserythropoiesis has been seen. In two patients the clinical presentation and haematological appearances, including cytochemical reactions, suggested Di Guglielmo's disease.

Case report

A boy aged 8 years presented with an enlarged spleen, mild jaundice, and extreme conjunctival and buccal pallor. He was undervit for his age and had a fever of about 39 C. Apart from a haemic murmur at the heart there were no other important physical findings. The two other patients had similar histories and physical findings.

Haematological investigations including cold antibody lysis test and the acidified serum lysis test were carried out according to the methods of Dacie and Lewis. Haemoglobin 6·2 g dl−1; packed cell volume 0·19+; mean corpuscular haemoglobin concentration 32·+; total white blood count 32·×10⁹ (32 000 mm³); normal differentials; platelet count 188×10⁹ (188 000 mm³); reticulocytes 12·+. Haemoglobin A2 and F levels were not raised beyond normal in sickle-cell disease. Haemoglobin electrophoresis showed the genotype of patients as SS. The cells were agglutinated and lysed by anti-S serum but there was no agglutination with anti-I serum. The acidified serum test result was negative. Morphology of the cells showed sickle forms of red cells with numerous erythroblasts in the peripheral blood. There was erythroblast multinularity in the bone marrow smear samples. Many of the erythroblasts showed periodic-acid Schiff (PAS) positivity.

Conservative management with folic acid, antimalariais, and anaesthetics was carried out despite the fact that the erythroblast-PAS-positivity with relative leucopenia and clinical presentation suggested that the patients might have erythraemic myelosis of Di Guglielmo's type.

Comment

These three cases of sickle-cell anaemia appear to have been complicated by erythroid dysplasia with morphological and serological characteristics suggesting dyserythropoietic activity. Two patients showed PAS positivity in the erythroblasts, leucopenia, and an unusually large number of erythroblasts in both peripheral and bone marrow smears, with marked heptosplenomegaly. These findings raised the possibility of the rare Di Guglielmo's disease, particularly in view of the intensity of PAS positivity in the erythroblasts. Chemotherapy was contemplated but not carried out, since it had not been shown that PAS positivity does not occur in the erythroblasts of sickle-cell anaemia. PAS positivity has been described in the erythroblasts in several other conditions including thalassaemia, which had been excluded in these patients by the finding of normal haemoglobin A2 levels. A diagnosis of Di Guglielmo's disease could not be sustained, however, since both patients have steadily improved on the usual conservative management.

The secondary nature of the dyserythropoietic activity is suggested because, although erythroblasts still persist in these patients, both morphological and serological results have changed to normal. Our thesis, therefore, is that in individual cases of sickle-cell anaemia, as in other diseases, impaired deoxyribonucleic acid or ribonucleic acid metabolism may occur. This may lead to both morphological (erythroid multinularity, internuclear chromatin bridges) and membrane abnormalities with increased sensitivity to lysis by anti-I serum. As this condition is only secondary to the underlying disease, it will disappear with improved management.

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