Phaeochromocytoma with myocarditis managed with α -methyl-*p*-tyrosine

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Summary

A case of bilateral phaeochromocytoma with catecholamine-induced myocarditis is described. The two operations needed allowed comparison of the use of α -methyl-*p*-tyrosine alone and in conjunction with adrenergic blocks in the management of the patient. The combination of both drugs was particularly successful in the relief of symptoms and reduction of catecholamine metabolism as monitored by 4-hydroxy-3-methoxymandelic acid (HMMA) excretion.

As myocarditis is a potentially fatal complication, further investigation of the combined use of α -methyl-*p*-tyrosine and adrenergic blocking drugs is suggested in the pre-operative management of patients with phaeochromocytoma.

Introduction

The pre-operative management of phaeochromocytoma is concerned primarily with the control of hypertension and the reversal of peripheral vasoconstriction, and the consequent hypovolaemia. It is also important to be aware of the possible development of a potentially fatal, catecholamine-induced myocarditis. During surgery, manipulation of the tumour may cause release of catecholamines which may not only lead to dysrhythmias, but may also have a direct toxic action on the myocardium (Kline, 1961). After removal of the tumour, severe hypotension may occur, in some cases contributed to by haemorrhage, complicated by full adrenergic blockade. Careful pre-operative preparation using adrenergic blocking drugs may lead to good control of blood pressure, enable the plasma volume to be restored and give some protection against dysrhythmias (Ross *et al.*, 1967). Nevertheless, the concentration of catecholamines, both circulating and in the tumour, will still remain elevated and may pose serious problems for anaesthetist and surgeon.

Recently, α -methyl-*p*-tyrosine (α -MPT) an inhibitor of tyrosine hydroxylase, the rate limiting en-

zyme in catecholamine synthesis, has aroused interest. When administered to patients with phaeochromocytoma there is reduced excretion of HMMA which presumably reflects decreased synthesis of catecholamines in the tumour, and this is associated with symptomatic relief (Engelman *et al.*, 1968a). Moreover, this depletion reduces the risks of dysrhythmias and swings of blood pressure during tissue handling. The drug is rapidly excreted and is therefore given in divided doses. It has been suggested that up to 75% inhibition of catecholamine synthesis can be achieved in man with doses of 2-4 g/24 hr (Engelman *et al.*, 1968b). Although the use of α -MPT in the management of phaeochromocytoma has been described by Engelman *et al.* (1968a) and Sjoerdsma *et al.* (1965), the following case of a bilateral phaeochromocytoma provided an unusual opportunity to observe the effects of α -MPT alone and in combination with adrenergic blocking drugs in the preparation for the removal of the two tumours.

Case report

A 31-year-old woman was admitted to hospital on 22 January 1973 with a 3-year history of sweating attacks.

These attacks increased in frequency, and 3 months before admission were occurring daily and were then accompanied by headache, vertigo, palpitations and progressive visual failure. There were no other symptoms, but there was a family history of hypertension and cerebrovascular disease.

Examination revealed an obese (86.5 kg) woman with a cold, moist skin and marked pallor. The supine blood pressure of 200/130 mmHg was accompanied by a sinus tachycardia of 110/min, an apical gallop rhythm and mild ankle oedema. There was bilateral papilloedema with haemorrhages and a right paracentral scotoma. Urine testing revealed proteinuria.

Routine investigations, including haemoglobin, blood count, chest X-ray and electrocardiograph, were normal (Fig. 1a). The urinary catecholamine

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FIG. 1. Electrocardiographs (a) on first admission; (b) before second admission showing extensive T-wave inversion consistent with a catecholamine-induced myocarditis.

FIG. 2. Effect of α -methyl-*p*-tyrosine on HMMA excretion (a) during the course of the first adrenalectomy; (b) during the course of the second adrenalectomy.

excretions were as follows: 4-hydroxy-3-methoxymandelic acid (HMMA); 140–230 $\mu\text{mol}/24\text{ hr}$ (normal < 36.0 $\mu\text{mol}/24\text{ hr}$); methylated catecholamines 9–14 $\mu\text{mol}/24\text{ hr}$ (normal < 6.0 $\mu\text{mol}/24\text{ hr}$); total catecholamines 10–17 $\mu\text{mol}/24\text{ hr}$ (normal < 1.18 $\mu\text{mol}/24\text{ hr}$). Qualitative, phenolic acid, paper chromatography on the urine indicated a predominance of noradrenaline. Arteriography revealed a mass over the left kidney consistent with a left adrenal tumour.

The patient was started on phenoxybenzamine and propranolol which effectively controlled the blood pressure. Urinary excretion of catecholamines remained abnormal and α -MPT was added to the regimen, 1 g/24 hr in divided doses, increasing to 2 g/24 hr over 10 days. Urinary excretion of HMMA fell to within the normal range (Fig. 2a), the attacks of sweating ceased and the doses of α - and β -blocking drugs were reduced without deterioration in the control of the blood pressure. Body-weight increased by 4.8 kg and simultaneously Hb and haematocrit fell owing to expansion of the plasma volume.

The observed side effects of α -MPT appeared to be dose-related and consisted only of drowsiness at 1 g/24 hr. Increasing the dose to 2 g/24 hr produced salivation, emotional lability and Parkinsonism. These effects, presumably due to depletion of CNS dopamine, disappeared within 48 hr when the dose was reduced. α -MPT crystalluria has been described (Engelman *et al.*, 1968a) but was not observed in this patient, and a high fluid intake was maintained during the administration of the drug to keep the urine volume high. The urine from each micturition was measured and divided equally: one portion being stored in acid for catecholamine assays, the other being retained without preservative for crystal investigation.

Left adrenalectomy was performed 14 days after the introduction of α -MPT. Under routine anaesthesia the left adrenal gland was explored through a loin incision. A 35-g cystic adrenal tumour was removed, and on section appeared a benign pheochromocytoma. Pulse and blood pressure were measured throughout the operation by intra-arterial catheter and remained steady. Supportive pressor amines and adrenergic blocking drugs were unnecessary. The post-operative course was uneventful.

Within 1 month of discharge, on no drugs, increased urinary excretion of catecholamines was observed and there was a return of symptoms. Adrenal venography with vena caval sampling for catecholamines suggested a second tumour in the remaining adrenal. On re-admission to hospital the only abnormal findings were of a blood pressure of 170/110 mmHg and marked pallor with sweating.

The electrocardiograph, however, had become grossly abnormal with pronounced T wave inversions

in leads I and AVL and throughout the precordial leads (Fig. 1b). Although HMMA excretion at this time was less than observed pre-operatively, these electrocardiographic changes were consistent with the development of a myocarditis due to chronic catecholamine hypersecretion. Preparation for surgery was by α -MPT alone (2 g/24 hr). The blood pressure and urinary excretion of HMMA fell to normal (Fig. 2b), but the symptoms were not completely relieved and the electrocardiograph remained abnormal. Isotope studies indicated an increase by 15% of plasma volume while on α -MPT therapy. The operative procedure was followed as before, and a 22-g right adrenal pheochromocytoma removed, which appeared histologically benign.

On one occasion during surgery the diastolic blood pressure rose to 120 mmHg but settled spontaneously. Following the operation there was a fall in blood pressure to 100/70 mmHg which was immediately corrected by infusion of 500 ml blood. Post-operative management differed only in the need for steroid replacement (cortisone acetate 37.5 mg/24 hr). The patient was discharged asymptomatic and normotensive. At follow-up 3 months later there was no recurrence of symptoms and urinary excretion of catecholamines remained normal. Repeated electrocardiographs revealed progressive resolution of the abnormalities seen during admission.

Discussion

α -MPT was used in combination with α - and β -blocking drugs before the first operation, but was administered alone before the second adrenalectomy. Because there was incomplete relief of symptoms and some fluctuation in blood pressure when α -MPT was used alone, it was felt that combined therapy gave a smoother pre- and intra-operative course.

The urinary excretion of methylated amines and catecholamines appeared to fluctuate markedly during α -MPT therapy. This was possibly due to analytical interference by the production of α -methyl derivatives of dopa, dopamine and noradrenaline (Engelman *et al.*, 1968b). Measurement of urinary HMMA was the most useful method for monitoring the effects of α -MPT on catecholamine metabolism.

Myocarditis

Myocarditis is an uncommon complication of pheochromocytoma but is well documented as being a cause of sudden death (Kline, 1961; Van Vliet, Burchell and Titus, 1966). It is thought to be due to a direct toxic action of catecholamines on the myocardium producing muscle necrosis and inflammatory cell infiltration. Animal studies support this hypothesis (Van Vliet *et al.*, 1966), and it would, therefore, seem possible for myocardial damage to occur even in the presence of adrenergic blockade.

For this reason the usefulness of α -MPT as a routine addition to the pre-operative regime appears to be further justified.

The widespread T wave abnormalities seen in this patient were in keeping with the changes documented elsewhere (Van Vliet *et al.*, 1966; Pelkonen and Pitkänen, 1963). These changes persisted in the absence of hypertension but gradually resolved following the second adrenalectomy.

The advantage of having reduced concentrations of both circulating and tumour catecholamines at the time of operation, and the possibility of preventing a myocarditis, would seem to warrant further investigation of α -MPT (in conjunction with adrenergic blocking agents) in the routine pre-operative management of pheochromocytoma.

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Caroli's disease with intrahepatic gall-stones and *Salmonella* infection

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Summary

At operation for small bowel intussusception, a 26-year-old man was found to have an enlarged liver and spleen. Subsequent investigations suggested bile passage infection associated with numerous intrahepatic gall-stones but symptomatic cholangitis did not present until 5 months later. Retrograde cholangiography showed cavernous ectasia of the bile ducts which contained gall-stones.

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Bile aspirated from the liver contained *Salmonella agona*. Despite treatment with ampicillin he remains a chronic *Salmonella* carrier. The importance is stressed of searching for enteric organisms in the bile and faeces of patients with chronic biliary disease especially when associated with cholelithiasis.

Introduction

Chronic calculous disease is a well known concomitant of the typhoid carrier state. More rarely these two conditions are associated with the extremely uncommon Caroli's disease (Waldram,