Treatment of a Pheochromocytoma with a β -Adrenergic Blocking Agent*

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Current theory (Alquist, 1948) is that the adrenergic receptors of the sympathetic system are of two kinds. The α -receptors promote vasoconstriction, tachycardia, hypertension, and inhibition of bowel movement. The action of the β -receptors, however, while generally vasodilator, may not only cause hypertension by excitation of the myocardium, but in addition may lead to paroxysmal cardiac arrhythmias. In accordance with this concept, long-term control of hypertension in patients with pheochromocytoma has been repeatedly demonstrated with drugs such as phenoxybenzamine (Dibenzylamine), which are competitive inhibitors of the α -receptors. These drugs have no action on the sympathetic β -receptors and they are consequently unable to avert the complication of paroxysmal cardiac arrhythmias. β -adrenergic blocking agents, however, have been developed (Black, Crowther, Shanks, Smith, and Dornhorst, 1964) and have been used primarily in the treatment of arrhythmias induced by digitalis and anaesthetics and to a very limited extent in pheochromocytoma (Dornhorst and Laurence, 1963).

This note is the first report of the successful removal of a pheochromocytoma in a child, under cover of both phenoxybenzamine and DL-propranolol (Inderal), the most recent and least toxic of the β -receptor blocking agents.

Case Report

M.W., aged 9, presented with a one-year history of severe headaches associated with nervousness, anxiety, and some sweating. Three weeks before admission she had noted a rapid deterioration in vision. Physical examination showed her to be a thin, anxious girl with a moist skin who weighed 30 kg. The blood pressure ranged between 140/90 and 210/170 mm. Hg, and she had a grade IV retinopathy. Laboratory studies showed normal haematology, urinalysis, blood urea nitrogen,

electrolytes. Excretion of 4-hydroxy-3-methoxy mandelic acid (HMMA) was 5 mg./24 hr. (normal < 8 mg./24 hr.). The intravenous pyelogram and chest x-ray were normal. Treatment with reserpine did not affect her hypertension. Shortly thereafter the inulin clearances were found to be 138 and 85 ml./m.² minute, and the PAH clearances 358 and 461 ml./m.² minute. However, the ¹³¹I hippurate renogram showed a marked diminution in renal vascularity. The urinary HMMA was then 26 mg./24 hr. The catecholamines were 1,900 μ g./24 hr. (normal < 100 μ g./24 hr.), and the metanephrines 14.0 and 12.9 mg./24 hr. (normal < 1.2 mg./24 hr.). With biochemical proof of a pheochromocytoma, treatment was started with phenoxybenzamine 10 mg., every 8 hours, which relieved all symptoms and maintained her blood pressure steadily between 120/80 and 130/90 mm. Hg for the ensuing month before operation.

Phenoxybenzamine was discontinued 36 hours before operation, and propranolol was then given, every 8 hours, in a dose of 2.5 mg. which was increased to 5 mg. after the first two doses. She was confined to bed, though her blood pressure remained unchanged. Premedication with meperidine HCl (Demerol) 50 mg. and atropine 0.2 mg. preceded a rise in blood pressure to a steady level around 150/100 mm. Hg.

Anaesthesia was induced with thiopentone and succinylcholine, which provoked an evanescent rise in blood pressure to 270/150 mm. Hg, and was maintained without incident by thiopentone, succinylcholine, fluoroxene, nitrous oxide, and oxygen. Before laparotomy a two-channel superior vena caval infusion was started, and a brachial arterial catheter was inserted to facilitate synchronous pressure and ECG monitoring.

The operation proved to be very difficult technically. The tumour was intimately related to both left renal vessels and, spreading medially, covered the anterior wall of the aorta for a distance of 5-6 cm. The superior mesenteric artery was also enveloped in the mass and the tumour adhered so closely to these vessels that the appearances were those of a malignant growth. Complete removal of the mass proved to be impossible without concomitant left nephrectomy, though every effort was made to avoid this, including consideration of temporary excision and perfusion of that organ.

In spite of considerable manipulation of the abdominal contents and of the tumour, there were no sudden

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changes in blood pressure which fell gradually during dissection of the mass. This was probably due to blood loss, as it was corrected by blood transfusion alone as was the accompanying sinus tachycardia of 180-190 per minute. Following removal of the mass, the expected hypotension developed and this responded well to i.v. noradrenaline which was continued in diminishing quantities for 36 hours after the operation.

At no time during the operation did any cardiac arrhythmia develop, though during the first 24 hours after operation atrial extrasystoles (1-3 per minute) were occasionally noted on the cardiac monitor, and these were suppressed by one dose of propranolol 1 mg. i.v. No further ectopic beats were seen after the noradrenaline was discontinued.

Her post-operative course was satisfactory despite a moderate sinus tachycardia which persisted for about 10 days. Her blood pressure stabilized near 120/75 mm. Hg, and her convalescence has been without incident.

Discussion

The pharmacological control of blood pressure and heart rate in patients with phaeochromocytoma affords some special hazards. Reserpine and guanethidine can bring about the release of peripheral stores of catechols and can precipitate hypertensive crises or arrhythmias. There are objections to using β -blocking drugs without concomitant α -blockade in these cases, because of the theoretical danger of hypertension that could accompany an unbalance of β and α activity. Equally, α -blockade alone may actually increase catechol secretion and will not prevent cardiac arrhythmia. In the immediate pre-operative period, premedication with atropine can provoke hypertension and cardiac arrhythmia (Swan, 1949) and some relaxants have similar actions. Barbiturates do not stimulate catecholamine release but they may cause ventricular arrhythmias in the presence of hypoxia or hypercapnoea (Robertson, 1962). Tranquillizers such as chlorpromazine are α -blocking agents and they may thus potentiate hypotension in these cases.

During anaesthesia (Crandell and Myers, 1964; Robertson, 1962) ether, cyclopropane, and trichloroethylene stimulate the secretion of catecholamines (Wood-Smith and Stewart, 1964). Halothane, an α -blocking agent, while not increasing the secretion of catecholamines itself, is also known to predispose

to cardiac arrhythmia in the presence of increased circulating catecholamines (Wood-Smith and Stewart, 1964).

Following the removal of a phaeochromocytoma, the development of a sinus tachycardia is common and can be attributed to the fact that noradrenaline causes hypertension and bradycardia. The sudden removal of excess catechols stimulating the peripheral vasomotor nerves results in their temporary unresponsiveness to normal catechol levels, with the result that the baroreceptors respond with a compensatory tachycardia. It is unlikely in any event that the tachycardia in this case is attributable to the drug therapy, because all medications would have been eliminated within 48 hours after operation, and β -blocking drugs have been shown usually to cause bradycardia.

The unpredictable response to surgery in these patients warrants careful therapeutic control; experience in this case justifies the continued use of α - and β -blocking agents.

Summary

The use of propranolol, a new sympathetic β -blocking agent, in a case of phaeochromocytoma is described. The drug is advocated in this condition, along with an α -blocking agent, to prevent the occurrence of cardiac arrhythmia, due either to excess catechol production or to drug-induced sensitivity of the β -receptors. The interrelationship of this drug with other drugs used in phaeochromocytoma is discussed briefly.

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