Noradrenaline producing phaeochromocytomas with absent pressor response to beta-blockade

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**SUMMARY** In 2 patients with phaeochromocytoma, effective beta-blockade was obtained with propranolol (40 mg twice a day for 3 days) or acebutolol (400 mg twice a day for 3 days) without any effect on the blood pressure. In both patients the excretion of noradrenaline predominated over that of adrenaline, a picture found in most cases of phaeochromocytoma. A hypertensive response to beta-blockade might be expected in patients with an adrenaline-secreting tumour. It cannot be a regular event or constitute a diagnostic test in patients with suspected phaeochromocytoma.

Beta-adrenergic blockade can unmask the alpha-vasoconstrictor action of adrenaline in man (Vlachakis et al., 1977). A hypertensive effect of propranolol has been described in phaeochromocytoma (Prichard and Ross, 1966). Yet neither acebutolol nor propranolol had any effect on the blood pressure in 2 of our patients with phaeochromocytoma.

Out of 16 consecutive patients with phaeochromocytoma, 9 had been given beta-blockers before phaeochromocytoma was diagnosed (propranolol in 6, acebutolol in 2, and oxprenolol in 1). None of the 9 patients reported an increase in symptoms related to hypertension, and no evidence of increased blood pressure was reported in their records. Accurate data were available in the following 2 cases.

**Case reports**

A 38-year-old woman was referred on account of a blood pressure of 190/124 mmHg. She had had episodic nausea and headache for 13 years. Anti-hypertensive therapy was stopped a month before admission to hospital for complete investigation. This included urinary screening for catecholamines and a therapeutic test with acebutolol in which blood pressure, heart rate, and plasma renin activity were measured after 3 days on placebo and 3 days on acebutolol 400 mg twice a day (Ménard et al., 1976). Beta-blockade by acebutolol decreased the heart rate by 20 per cent and the plasma renin activity by 78 per cent but had no effect on the blood pressure (Fig). Phaeochromocytoma was diagnosed from the 24-hour urinary excretion of vanillylmandelic acid (46 mmol), metanephrine (2395 mg), noradrenaline (6413 nmol), and adrenaline (224 nmol). Angiography showed a mass in the right adrenal. A phaeochromocytoma weighing 25 g was removed and thereafter the patient was normotensive.

A 49-year-old man was referred because of high blood pressure, 210/132 mmHg. His hypertension was asymptomatic and untreated. Investigations included a therapeutic test with propranolol 40 mg twice a day conducted as described above for acebutolol. After 3 days on propranolol, the heart rate decreased by 20 per cent, and plasma renin activity by 90 per cent, but the blood pressure was unchanged (Fig.). The 24-hour urinary excretion of vanillylmandelic acid, metanephrines, nonadrenaline, and adrenaline was 46 mmol, 1190 mg, 728 nmol, and 6 nmol, respectively. A phaeochromocytoma was removed from the left adrenal and the patient became normotensive.

**Discussion**

A potential danger of beta-blockade in patients with phaeochromocytoma is the paradoxical rise in blood pressure linked to 'adrenaline reversal': Dornhorst and Laurence (1963) stated that administration of pronethalol to patients with phaeochromocytoma not already receiving phenoxybenzamine might cause a serious rise in blood pressure by abolishing the dilator (beta) action of adrenaline on peripheral vessels, especially in muscle, while leaving the constrictor (alpha) actions unopposed. In 5 patients with phaeochromocytoma, Prichard and Ross (1966) found a
rise in blood pressure after administration of propranolol. The rise in blood pressure was neither dose-related nor constant. In fact, it occurred in only 12 out of 20 experiments with doses ranging from 10 to 100 mg orally. The authors did not state how variability in blood pressure was taken into account in defining the control levels, but they did suggest that the vasopressor response to propranolol may be of diagnostic value in phaeochromocytoma.

Since the report by Prichard and Ross (1966), there has been little recorded evidence to support the assertion that beta-adrenergic blockade may evoke a hypertensive response in phaeochromocytoma. Thomas et al. (1977) reported an immediate fall of the blood pressure in a patient with phaeochromocytoma after intravenous practolol. Briggs et al. (1978) saw a hypertensive response in a patient with an adrenaline-secreting phaeochromocytoma treated with labetalol. In the 2 cases reported by Wark and Larkins (1978), pulmonary oedema followed several days or weeks after the introduction of propranolol, but in neither patient was the blood pressure raised.

In our patients the effectiveness of beta-blockade was shown by a consistent decrease in heart rate and plasma renin activity. The absence of a fall in blood pressure in response to beta-blockade suggests that the renin-angiotensin system was not contributory in maintaining the hypertension. The absence of a rise in blood pressure is at variance with the suggestion of Prichard and Ross (1966). A possible explanation for this discrepancy in our first patient is her having had a beta-1 receptor antagonist, acebutolol, whereas the patients of Prichard and Ross had propranolol: in normal volunteers, Johnsson (1975) found the mean blood pressure was decreased during adrenaline infusion, unchanged during infusion of adrenaline with metoprolol (another beta-1 receptor antagonist), and increased during infusion of adrenaline with propranolol. A more likely explanation in both our patients is the dominance of noradrenaline over adrenaline production, since it has been shown in hypertensive men that beta-blockade does not modify the pressor response to noradrenaline (Vlachakis et al., 1977).

Beta-blockers are widely used in the treatment of hypertension, and their prescription in patients with unsuspected phaeochromocytoma cannot be a rare event. Their administration to such patients without previous alpha-blockade might be harmful where adrenaline is the predominating catecholamine; where noradrenaline predominates it would merely be useless. Fortunately, noradrenaline is the dominant or the sole catecholamine in the tumour and in the urine of most patients with phaeochromocytoma: this was the case in 30 of the 35 patients of von Euler and Ström (1957), and in all the 24 patients of Crout and Sjoerdmsma (1964).

In patients with suspected phaeochromocytoma, the vasopressor response to propranolol is not an appropriate diagnostic test. Beta-blockers may be useful in prevention and treatment of tachycardia. They should not be used before alpha-adrenergic blockade when the tumour produces a significant amount of adrenaline.

References

Fig. Effects of beta-blockade on diastolic blood pressure, pulse rate, and plasma renin activity in 2 patients with phaeochromocytoma. The first patient (solid line) received acebutolol 400 mg twice a day; the second patient (broken line) received propranolol 40 mg twice a day. Values for supine diastolic blood pressure (diastolic BP) and pulse rate are the means of 5 determinations (±1 SD) at day 3 and day 6, and the means of 2 determinations on the other days. PRA, plasma renin activity after walking for 1 hour.
on hemodynamic effects induced by adrenaline and physical work. *Acta Pharmacologica et Toxicologica*, 36, Suppl. 5, 59-68.


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