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Pharmacological management of pheochromocytoma

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Pheochromocytomas are rare neuroendocrine tumours, arising from the chromaffin cells of the adrenal medulla and due to the hypersecretion of catecholamines are associated with high cardiovascular morbidity and mortality if left untreated. Currently the only definitive therapy is the surgical resection of the tumour. However, surgery in itself carries a very high risk of evoking a massive release of catecholamines into the circulation, resulting in one or more of serious cardiovascular complications including fatal hypertensive crisis and cardiac arrhythmias. Moreover, postoperatively, the sudden drop in catecholamine levels may result in hypotension and hypoglycaemia. To prevent these problems, patients with pheochromocytoma must undergo pharmacologic blockade of catecholamine synthesis and effects before surgery (1). The introduction of pharmacological pretreatment in the 1950s reduced the perioperative mortality rate from as high as 45% to < 2% (2–4).

The main goal of preoperative management of a pheochromocytoma patient is to normalize blood pressure, heart rate and function of other organs; restore volume depletion and prevent a patient from surgery-induced catecholamine storm and its consequences on the cardiovascular system (5). Several drugs have been recommended for this purpose, including selective and non-selective α- and β-adrenoceptor antagonists, calcium channel blockers and drugs that inhibit catecholamine synthesis.

The two most commonly used α-adrenergic antagonists are phenoxybenzamine and doxazosin (6). Phenoxybenzamine is a non-selective, non-competitive α-adrenergic antagonist with a plasma half-life of 24 hours. Starting dosages of 20–40 mg daily are titrated depending on patient response. Non-selective α-adrenergic blockade can result in reflex tachycardia, for which the addition of a β-adrenergic blocker is often required for symptomatic relief from tachycardia or tachyarrhythmias. Selective postsynaptic α1-receptor antagonists, such as prazosin and doxazosin, have been used to escape from some of the side effects of phenoxybenzamine. Since these drugs leave the presynaptic receptors on the neuronal surface open, they do not produce reflex tachycardia. They also have a shorter duration of action, permitting more rapid adjustment of dosage and a reduced duration of postoperative hypotension. The calcium channel blockers are useful in patients who are normotensive but have paroxysmal episodes of hypertension, because they are less likely to cause significant orthostatic hypotension. α-Methyl-para-tyrosine competitively inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis (7). Treatment with metyrosine reduces tumour stores of catecholamines, decreases the need for intraoperative medication to control blood pressure, lowers intraoperative fluid requirements, and attenuates blood loss (8). Based on the fact that pheochromocytoma is accompanied by reduced intravascular volume, it is common to increase sodium intake both orally and intravenously simultaneously with the antihypertensive therapy.

In conclusion, the pharmacological treatment of pheochromocytoma has to meet three basic goals: (1) to oppose any catecholamine associated medical problems; (2) to treat hypertension and tachyarrhythmias and (3) to restore intravascular volume. The introduction into practice of the modern treatment methods has lead to significant increase of cure rates and reduction of complications during the last 50 years.

Once the diagnosis of a pheochromocytoma is made, appropriate preoperative medical management is necessary to reduce the risk for perioperative complications. There are currently no randomized prospective clinical trials to establish the optimal preoperative pharmacological management of pheochromocytoma and it is doubtful whether these will ever be performed in view of the low prevalence of this disorder. Therefore, the best available evidence is derived from retrospective studies, patient series and case reports. As a result, there is no clear consensus regarding the drug of choice. The most commonly used drugs are selective and non-selective α-blockers, β-blockers, calcium channel blockers and inhibitors of catecholamine synthesis (9).

Non-selective α-antagonists Since the early 1950s, phenoxybenzamine has been widely used as the main drug for preoperative management of a pheochromocytoma. It is a non-competitive α1- and α2-

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antagonist, with a maximal effect four to six hours after administration and a pharmacological half-life of 24 hours. A regular starting dose is 10 mg twice daily, which can be increased to a daily dose of 80 to 100 mg/day. As the correct dose is approached, paroxysmal hypertensive episodes are brought under control, and when the right dose is achieved, the patient becomes normotensive or mildly hypotensive. Disadvantages of phenoxybenzamine are the occurrence of reflex tachycardia and excessive orthostatic hypotension. Reflex tachycardia is caused by blockade of α2-receptors localized in the presynaptic membrane. Stimulation of the α2-receptor inhibits norepinephrine release. Therefore, α2-receptor blockade will interrupt this negative feedback mechanism thus resulting in increased occurrence of tachyarrhythmias. Other disadvantages of phenoxybenzamine are central sedation and prolonged duration of action. Continuing α-receptor antagonism in combination with the postoperative decrease in catecholamine levels can result in prolonged hypotension after surgery (10). Furthermore, it should be mentioned that compared with α1-adrenoceptor blockers, phenoxybenzamine is an expensive drug.

Selective α1-antagonists Currently used selective α1-adrenoceptor blocking agents are prazosin and doxazosin (5, 11). They are specific, competitive and short-acting α1-adrenergic antagonists. Doxazosin has a half life of 16 to 30 hours and can be given in a single dose varying between 1 and 8 mg. Prazosin has a much shorter half-life of 2 to 3 hours and needs to be ingested three to four times daily. Prazosin is administered in doses of 2 to 5 mg three times a day and doxazosin is given in doses of 2 to 8 mg per day. However, they have the potential for severe postural hypotension immediately after the first dose, especially prazosin, and therefore should be given just as the patient is ready to go to bed. Because of a short half-life of α1-adrenergic antagonists, these drugs should also be given in the morning before surgery. In some centres, phenoxybenzamine is used first and then replaced by α1-adrenergic antagonists before surgery to reduce postoperative hypotension (12).

β-blockers β-adrenoceptor blockers should never be used alone and should be commenced only after adequate pretreatment with α-adrenergic blockade, because unopposed β-adrenoceptor receptor stimulation can induce a catastrophic hypertensive crisis (4,5,13). The main purpose of their administration is to prevent occurrence of catecholamine- or α-blockers – induced tachyarrhythmias (5,10). Cardioselective β1-blockers are preferred such as atenolol, given in doses of 12.5 to 25 mg two or three times a day, and metoprolol in doses 25–50 mg three to four times a day (5). Caution is warranted when administering β-antagonists to patients with severe left ventricular dysfunction, a condition, which is not uncommon with a pheochromocytoma due to cardiomyopathy induced by chronic exposure to high catecholamine levels (14).

Calcium channel blockers Calcium channel blockers reduce arterial blood pressure by inhibiting the norepinephrine-mediated transmembrane calcium influx in vascular smooth muscle. They are used as an add-on therapy to α-blockers in patients with poor blood pressure control or when there are severe side effects with the α-antagonists (5). These drugs do not produce hypotension and, therefore, may be used safely in patients who are normotensive but have occasional episodes of paroxysmal hypertension (9). Amlodipine is given in a dose from 10–20 mg, and nicardipine in a dose from 60–90 mg per day. Nifedipine is given in a dose from 30–90 mg and verapamil in a dose from 180–480 mg per day.

Inhibitors of catecholamine synthesis α-Methyl-L-tyrosine or metyrosine is an analogue of tyrosine that competitively inhibits tyrosine hydroxylase, which catalyzes the conversion of tyrosine to dihydroxyphenylalanine, the first step of catecholamine synthesis (15). It significantly but not completely depletes catecholamine stores with maximum effect after about 3 d of treatment. Metyrosine facilitates blood pressure control both before and during surgery, especially during the induction of anaesthesia and surgical manipulation of the tumour when extensive sympathetic activation or catecholamine release occurs (16). Treatment is started at a dose of 250 mg orally every 8 to 12 hour and, thereafter, the dose is increased by 250 to 500 mg every 2 to 3 days or as necessary up to a total dose of 1.5 to 2.0 g per day (5). It is centrally acting and therefore can result in sedation, anxiety, psychic disturbance, and extrapyramidal side Patients may also experience severe diarrhea necessitating treatment with anti-diarrhoeal agents (9). Metyrosine and α-adrenoceptor blockers when used together result in less labile blood pressure during anesthesia and reduced intraoperative blood loss, and reduced volume replacement during surgery compared with the use of α-adrenoceptor blockers alone (5,16,17).

Currently, there is no consensus as to when to start adrenergic blockade while preparing a patient for surgery. In most medical centers, adrenergic blockade usually starts 7–14 days preoperatively to have adequate time to normalize blood pressure and heart rate and to expand the contracted blood volume (5,18,19). Volume expansion should be optimized preoperatively by the administration of i.v. saline or

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colloid, because this minimizes the blood pressure fluctuations that can occur intraoperatively with the administration of antihypertensive agents.

In spite the lack of large randomized, prospective, and controlled studies evidence from retrospective studies, suggest that α-adrenoceptor blockade is currently the preferred choice in preoperative management of pheochromocytoma patients (10, 12). Calcium channel blockers and β-adrenoceptor blockers are most often used as co-drugs when blood pressure cannot be well controlled while on α-adrenoceptor blockade or if tachyarrhythmia occurs. At some medical institutions, metyrosine is given to all patients, and at others only to those patients who have highly active tumours associated with difficult-to-treat symptoms and signs of catecholamine excess.

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