

# Preoperative pharmacological management of phaeochromocytoma

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## ABSTRACT

Phaeochromocytoma is a rare catecholamine-secreting neuroendocrine tumour with a high cardiovascular morbidity and mortality if left untreated. Surgical resection is the only curative therapy. During surgery there is a high risk of massive release of catecholamines, which can result in potentially fatal hypertensive crises and cardiac arrhythmias. Administration of vasoactive drugs such as (non)selective  $\alpha$ - and  $\beta$ -antagonists and calcium channel blocking agents have reduced the operation risk. Guidelines for the preoperative medical management of the patient with a phaeochromocytoma are mainly based on retrospective studies and case reports. We reviewed the relevant literature on this subject. In addition, we compared the several preoperative treatment protocols of the eight university medical centres in the Netherlands.

## KEYWORDS

Phaeochromocytoma, preoperative management

## INTRODUCTION

Phaeochromocytoma is a rare catecholamine-secreting neuroendocrine tumour, with an estimated prevalence among hypertensive patients of 0.1 to 0.6%. Approximately 90% of phaeochromocytomas arise in the adrenal gland, and about 10% originate from extra-adrenal chromaffin tissue.<sup>1</sup> In hereditary cancer syndromes such as multiple endocrine neoplasia type 2 and von Hippel-Lindau syndrome, phaeochromocytoma can occur bilaterally in both adrenal glands.<sup>2</sup> Symptoms and signs of a phaeochromocytoma result from an uncontrolled release of catecholamines (norepinephrine, epinephrine, dopamine). Catecholamines are agonists of  $\alpha$ - and  $\beta$ -adrenoceptors

(table 1). Most patients suffer from hypertension, which can be paroxysmal or sustained.<sup>3</sup> The classic triad of complaints consists of headache, perspiration and palpitations. Other clinical findings can be orthostatic hypotension, tremor, pallor, panic attacks, visual disturbances and weight loss.<sup>4</sup> A phaeochromocytoma is a potentially life-threatening disease with a highly increased risk for cardiovascular complications as myocardial infarction, coronary spasms, arrhythmias, cardiomyopathy, stroke and pulmonary oedema.<sup>3,5-8</sup> Surgical resection is the only curative therapy. The first successful operation was performed by Roux in 1926.<sup>9</sup> Initially, surgical resection of a phaeochromocytoma was faced with a high perioperative mortality rate of 20 to 45%.<sup>10</sup> This mortality rate dropped to 0 to 2.9% during the second half of the last century.<sup>11</sup> Important developments which have contributed to this major reduction in perioperative mortality rate are better imaging techniques for accurate preoperative tumour localisation, improvements in surgical and anaesthetic techniques, and better preoperative medical management.

**Table 1.** Catecholamine effects on  $\alpha$ - and  $\beta$ -adrenoceptors

Receptor	Effect	Catecholamine
$\alpha_1$	Vasoconstriction (venous & arterial), intestinal relaxation, stimulation of glycogenolysis, uterus contraction, mydriasis	Norepinephrine
$\alpha_2$	Inhibition norepinephrine release (presynaptic), vasoconstriction, lowering insulin release, sedation	Epinephrine and norepinephrine
$\beta_1$	Positive chronotropy, positive dromotropy & positive inotropy, stimulation renin release, lipolysis	Epinephrine and norepinephrine
$\beta_2$	Vasodilatation (muscle), bronchodilatation	Epinephrine

We reviewed the relevant literature on the preoperative pharmacological management of a pheochromocytoma. Original studies written in English and published between 1960 and 2005 were retrieved by a search in PubMed using the following MESH headings and/or text words: pheochromocytoma, preoperative management or surgery and phenoxybenzamine or doxazosin or prazosin or calcium channel blockers. We also used the references of the articles found. We included only articles with sufficient information on the outcome of one or more preoperative regimens. For this article we identified 26 articles, one prospective study, seven case or patient series and the remaining retrospective studies.

## PHAECHROMOCYTOMA AND PERIOPERATIVE RISKS

Surgery in itself carries a very high risk of evoking a massive release of catecholamines into the circulation, resulting in one or more of the serious cardiovascular complications mentioned previously. Induction of anaesthesia, intubation, first incision, creation of a pneumoperitoneum and tumour manipulation are critical moments for such an uncontrolled catecholamine release.<sup>12-14</sup> Postoperatively, the sudden drop in catecholamine levels may result in hypotension and hypoglycaemia. Catecholamines inhibit insulin secretion and stimulate glycogenolysis and lipolysis. Normalisation of the excessive catecholamine secretion after tumour resection in the presence of empty glycogen storages can lead to a 'rebound' hyperinsulinaemia, thus resulting in hypoglycaemia. There is a positive correlation between the perioperative complication rate and the size of the tumour, length of the operation and the serum levels of catecholamines.<sup>15</sup>

## PREOPERATIVE PHARMACOLOGICAL MANAGEMENT

The goals of preoperative pharmacological treatment are optimal control of hypertension and of the other pheochromocytoma-related symptoms, and prevention of perioperative complications. Several drugs have been recommended for this purpose, including selective and non-selective  $\alpha$ - and  $\beta$ -adrenoceptor antagonists, calcium channel blockers, and drugs that inhibit catecholamine synthesis. However, there are no randomised controlled trials addressing the optimal medical treatment of a 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. According to some studies, preoperative

treatment with adrenoceptor blocking agents is not obligatory.<sup>16,17</sup> No difference in perioperative mortality or morbidity was found in a retrospective study comparing 31 patients receiving adrenoceptor antagonists preoperatively with 29 patients who did not, although intraoperative blood pressure rises were more pronounced in the latter group.<sup>18</sup> It should be noted, however, that  $\alpha$ - and  $\beta$ -antagonists were administered during surgery in both groups if indicated. Besides preoperative pharmacological treatment, preoperative restoration of the circulating volume is also recommended by most authorities. The prevailing hypothesis is that the patient with a pheochromocytoma has a reduced intravascular volume as a result of catecholamine-mediated vasoconstriction.<sup>19,20</sup> Administration of  $\alpha$ -antagonists results in vasodilatation, leading to intravascular volume depletion. This needs to be compensated for by a high sodium diet or a saline infusion.

## NONSELECTIVE $\alpha$ -ANTAGONISTS

Since the early 1950s, phenoxybenzamine has been widely used as the main drug for preoperative management of a pheochromocytoma. It is a noncompetitive  $\alpha_1$ - and  $\alpha_2$ -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 (maximum 1 mg/kg). To ensure adequate blood pressure control, it is recommended that the blood pressure should not be higher than 160/90 mmHg, with orthostatic hypotension not exceeding 80/45 mmHg.<sup>5</sup> Disadvantages of phenoxybenzamine are the occurrence of reflex tachycardia and excessive orthostatic hypotension. Reflex tachycardia is caused by blockade of  $\alpha_2$ -receptors localised in the presynaptic membrane. Stimulation of the  $\alpha_2$ -receptor inhibits norepinephrine release. Therefore,  $\alpha_2$ -receptor blockade will interrupt this negative feedback mechanism, eliciting undesirable chronotropic and inotropic effects (figure 1). Other disadvantages of phenoxybenzamine are central sedation and prolonged duration of action. Continuing  $\alpha$ -receptor antagonism in combination with the postoperative decrease in catecholamine levels can result in prolonged hypotension after surgery. Despite these disadvantages, several retrospective studies suggest that preoperative treatment with phenoxybenzamine has resulted in a significant reduction in operation mortality.<sup>21-27</sup> The need for intraoperative  $\alpha_2$ -receptor blockade (phentolamine) is also reduced in pretreated patients.<sup>25</sup> It is probably sufficient to start phenoxybenzamine four to seven days preoperatively, as no clinically relevant benefit has been demonstrated with a longer preoperative treatment period.<sup>13,21</sup>

## SELECTIVE $\alpha_1$ -ANTAGONISTS

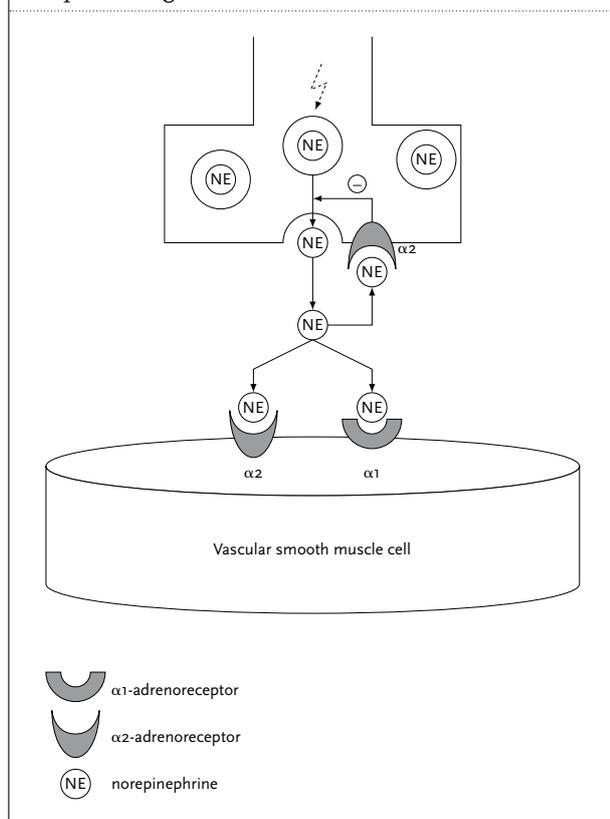
Theoretically, selective  $\alpha_1$ -antagonists offer several advantages when compared with phenoxybenzamine. These drugs do not elicit reflex tachycardia, in the absence of  $\alpha_2$ -receptor affinity (figure 1). In addition, these drugs have a relatively short duration of action as a result of their competitive inhibition. Consequently, adequate dose titration could be achieved more quickly and the risk period for postoperative hypotension could be shortened. The  $\alpha_1$ -antagonists doxazosin and prazosin are registered in the Netherlands. Doxazosin has a half-life of 16 to 30 hours and can be administered in a single dose varying between 1 to 16 mg. Prazosin has a much shorter half-life of two to three hours and needs to be ingested three to four times daily. In a retrospective study including 35 patients with phaeochromocytoma, eight patients were treated with phenoxybenzamine (20-120 mg per day) and 27 patients with doxazosin (2-16 mg per day).<sup>28</sup> All patients in the phenoxybenzamine group received a  $\beta$ -blocker as standard treatment vs only nine patients in the doxazosin group. Administration of doxazosin was accompanied by a lower preoperative diastolic blood pressure (78 vs 92 mmHg) and a lower

intraoperative heart rate (78 vs 94 beats/min) during tumour manipulation. The patients receiving doxazosin required more phentolamine intraoperatively, although this difference (11.1 vs 9.6 mg) was not statistically significant. However, they required less labetalol (15.8 vs 33.1 mg,  $p=0.080$ ). In addition, postoperative recovery seemed to be better with doxazosin, as reflected by a higher blood pressure (116/64 vs 100/55 mmHg) and a lower demand for intravenous fluids with less oedema. Mortality rate, however, was not different between the two groups.<sup>28</sup> Another retrospective study was not able to demonstrate a difference between phenoxybenzamine, doxazosin and prazosin with respect to blood pressure control and amount of postoperative fluid replacement.<sup>29</sup> In yet another report with only four patients, adequate blood pressure control was not achieved with prazosin, which even resulted in postponement of surgery in one patient.<sup>30</sup>

## BETA-ANTAGONISTS

The main goal of preoperative  $\beta$ -receptor blockade is prevention of cardiac arrhythmias.<sup>22,31,32</sup> Propranolol, atenolol and metoprolol are commonly used for this purpose. Administration of a  $\beta$ -antagonist is absolutely contraindicated in the absence of effective  $\alpha$ -receptor blockade, as unopposed stimulation of  $\alpha$ -receptor mediated vasoconstriction and loss of the  $\beta$ -receptor mediated vasodilatation may cause a dangerous rise in blood pressure.<sup>33</sup> This has also been described with the use of the combined  $\alpha$ - and  $\beta$ -antagonist labetalol, which demonstrates a relatively stronger antagonism towards the  $\alpha$ -receptor.<sup>34</sup> Caution is warranted when administering  $\beta$ -antagonists to patients with severe left ventricular dysfunction, a condition which is not uncommon with a phaeochromocytoma due to cardiomyopathy induced by chronic exposure to high catecholamine levels.<sup>3</sup> Preoperative treatment with  $\beta$ -antagonists is likewise predominantly based on pathophysiological considerations and retrospective studies. Beta-antagonist sometimes fail in preventing cardiac arrhythmias, and these drugs are not indicated in every patient.<sup>3</sup> Orchard *et al.* describe 108 patients with a phaeochromocytoma, 95 of whom received an  $\alpha$ - and  $\beta$ -antagonist. Of these, five patients developed a cardiac arrhythmia, despite the fact that they all were on  $\beta$ -antagonists.<sup>21</sup> In another retrospective study, patients were pretreated with phenoxybenzamine alone or with the combination of phenoxybenzamine and propranolol. The frequency of cardiac arrhythmias during surgery was not found to be different between individuals who were treated preoperatively with propranolol and those who were not.<sup>36</sup>

**Figure 1.** Mechanism of action of  $\alpha_1$ - and  $\alpha_2$ -adreno-receptor antagonists



## CALCIUM CHANNEL BLOCKERS

Calcium channel blockers cause smooth muscle relaxation in peripheral and coronary arteries through inhibition of the epinephrine-stimulated calcium influx. Consequently, peripheral vascular resistance is reduced and catecholamine-induced spasms of coronary arteries might be prevented.<sup>37</sup> As with  $\beta$ -antagonists some calcium channel blockers have to be used carefully in patients with left ventricular dysfunction. Although it has been found that calcium channel blockers influence the release of catecholamines *in vitro*, this has not been demonstrated *in vivo*.<sup>38-40</sup> Calcium channel blockers can also be given intravenously during surgery. There are a few studies describing the effect of calcium channel blockers administered before or during surgery. Proye *et al.* reported good results with intraoperative use of nicardipine. They measured a 42% reduction of systemic vascular resistance and achieved an effective blood pressure control, despite a significant rise in catecholamine levels during tumour manipulation.<sup>37</sup> In another study, 29 out of 113 phaeochromocytoma patients undergoing surgery were successfully treated with a calcium channel blocker.<sup>17</sup> Lebuffe *et al.* recently described a group of 105 patients who had been treated preoperatively with a calcium channel blocker. Blood pressure was well controlled intraoperatively, and the perioperative mortality rate in this retrospective series was relatively low at 2.8%.<sup>41</sup>

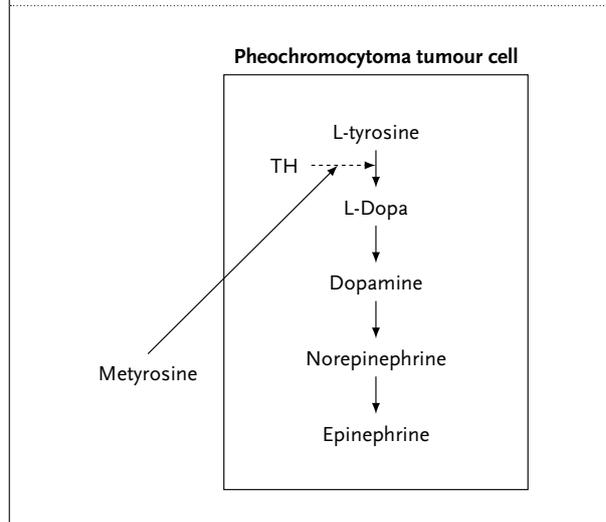
## METYROSINE

Metyrosine ( $\alpha$ -methylparatyrosine) is a competitive inhibitor of tyrosine hydroxylase, the key enzyme in catecholamine synthesis, catalysing the conversion of l-tyrosine into L-Dopa (figure 2).<sup>42</sup> It is usually chosen as a second-line drug, if blood pressure cannot be adequately controlled with  $\alpha$ - and  $\beta$ -antagonists. The regular dose is 0.5 to 4 g per day. Side effects of metyrosine are fatigue, diarrhoea, anxiety, depressive mood and crystalluria. Two retrospective studies suggested that addition of metyrosine to phenoxybenzamine results in a better intraoperative blood pressure control, less need for intraoperative phentolamine and a decreased postoperative demand of vasopressors.<sup>23,43</sup>

## PREOPERATIVE VOLUME THERAPY

Based on the concept that phaeochromocytoma is accompanied with a reduced intravascular volume, it has been common practice to increase sodium intake (orally or intravenously) simultaneously with antihypertensive

**Figure 2.** Metyrosine inhibits the synthesis of norepinephrine and epinephrine by inhibiting the enzyme tyrosine hydroxylase (TH) which catalyses the conversion of L-tyrosine into L-Dopa



therapy. However, study data supporting this clinical approach are limited. Retrospective studies demonstrated fewer complications and less use of vasopressor agents during the postoperative period in patients who received preoperative volume therapy compared with those who did not.<sup>44,45</sup> It should be noted that these studies included historic controls and, therefore, observed benefits could also be the result of other factors, such as improvements in surgical and anaesthetic techniques during the study period.

## PREOPERATIVE MANAGEMENT OF PHAEOCHROMOCYTOMA IN THE NETHERLANDS

The different preoperative treatment protocols for patients with a phaeochromocytoma which are currently applied by the eight Dutch university medical centres are described in table 2. It is shown that the choice between phenoxybenzamine and doxazosin is equally distributed, whereas calcium channel blockers are not prescribed. Intravenous volume therapy to prevent postoperative hypotension is part of most protocols. Preoperative preparation takes at least seven days in the majority of university medical centres, which also depends on the waiting time before surgery. Patients were routinely admitted to hospital in some centres, but most often preoperative treatment was started in the outpatient clinic.

**Table 2.** Preoperative management of phaeochromocytoma in the university medical centres in the Netherlands

Centre	$\alpha$ -antagonist	$\beta$ -antagonist	OpC/HS	IV volume
Rotterdam, Erasmus MC	Doxazosin	Always	OpC/HS	On indication
Nijmegen, UMCN St Radboud	Phenoxybenzamine	Always	HS	Always
Maastricht, UM	Phenoxybenzamine	Tachycardia	HS	On indication
Amsterdam, AMC	Phenoxybenzamine	Always	OpC	Always
Utrecht, UMCU	Doxazosin	Always	OpC	Always
Leiden, LUMC	Doxazosin	Tachycardia	OpC/HS	Always
Amsterdam, VUMC	Doxazosin	Tachycardia	OpC	Always
Groningen, UMCG	Doxazosin	Tachycardia	OpC/HS	Always

OpC = outpatient clinic, HS = hospital stay, IV = intravenous.

## CONCLUSION

During the past decades resection of a phaeochromocytoma has been accompanied with a major decrease in the perioperative morbidity and mortality. Although randomised, prospective, controlled trials are lacking, data from most retrospective studies demonstrate that preoperative administration of effective antihypertensive agents has contributed to this improvement in surgical outcome. In the absence of solid study data, the choice for a particular blood pressure lowering regimen is also based on pathophysiological considerations and personal experience. Both the nonselective  $\alpha$ -antagonist phenoxybenzamine and the selective  $\alpha_1$ -antagonist doxazosin are very effective agents for preoperative blood pressure regulation in patients with phaeochromocytoma. If tachycardia occurs, addition of a  $\beta$ -antagonist is often indicated.

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