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Approach to the Patient: Perioperative Management of the Patient with Pheochromocytoma or Sympathetic Paraganglioma

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Pheochromocytomas and sympathetic paraganglioma (PPGL) are rare chromaffin cell tumors originating in the adrenal medulla and sympathetic paraganglia, respectively, which share the capacity to synthesize and release catecholamines. The incidence of PPGL has increased in recent years. Surgical resection is the only curative treatment for PPGL. Management of patients with PPGL is complex and should be done by a specialized multidisciplinary team in centers with broad expertise. Surgical resection of a PPGL is a high-risk procedure for which optimal pretreatment with antihypertensive drugs is required in combination with state-of-the-art surgical procedures and anesthesiological techniques. In this article we discuss the underlying evidence and the pros and cons of presurgical medical preparation. Finally, the areas of uncertainty and controversies in this field are addressed.

Key Words: perioperative management, pheochromocytoma, sympathetic paraganglioma, alpha-receptor blockade

Case Presentation

A 20-year-old otherwise healthy male was referred to the department of internal medicine of his local hospital for the evaluation of possible pheochromocytoma following a 1-year history of paroxysmal headaches accompanied by a pounding heartbeat, diaphoresis, and nausea. Eight months prior, he had undergone neurological and cardiological evaluation for these symptoms, with unremarkable findings on brain computed tomography (CT) scan, cerebrospinal fluid examination, electrocardiogram (EKG), ergometry and echocardiography. The biochemical diagnosis of pheochromocytoma/

paraganglioma was now confirmed by a >10-fold elevation of urinary excretion of both metanephrine and normetanephrine. Abdominal CT revealed a 7.8-cm mass in the right adrenal gland (Fig. 1). While waiting for a ¹²³I-metaiodobenzylguanide (MIBG) scintigraphy, he developed transient confusion and paralysis of his right forearm, which spontaneously recovered within 3 hours. A cerebral hemorrhage was ruled out by CT. The next day he collapsed, following complaints of chest pain and nausea. His systolic blood pressure measurement was up to 212 mmHg. EKG showed ST-elevations with elevated cardiac-specific troponins, after which he was admitted to the cardiac care unit. On physical

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Abbreviations: CT, computed tomography; EKG, electrocardiogram; FDG, fluorodeoxyglucose; MIBG, ¹²³I-metaiodobenzylguanide; PET, positron emission tomography; PPGL, pheochromocytomas and sympathetic paraganglioma.

Figure 1. Abdominal computed tomography (CT) scan revealing a large mass with eccentric necrosis in the right adrenal (left). ^{18}F -fluorodeoxyglucose (^{18}F FDG) positron emission tomography–CT scan showing a ^{18}F FDG-avid heterogeneous mass of the right adrenal gland with no evidence for metastatic spread (right).

examination he was pale, with a blood pressure of 124/80 mmHg and a regular pulse rate of 104 beats per minute. A transthoracic echocardiogram showed a diffusely dyskinetic left ventricle with a reduced ejection fraction of 20%. The patient was then transferred to our tertiary medical center for emergency treatment of suspected myocardial infarction. Coronary angiography, however, demonstrated normal coronary arteries and the cardiac ischemia was attributed to coronary spasms. Aortic dissection was ruled out by CT angiography. Measurement of plasma metanephrines (LC/MS) revealed very high concentrations of normetanephrine (58.966 pmol/L; reference: $n < 495$), metanephrine (9.750 pmol/L; $n < 295$) and methoxytyramine (166 pmol/L; $n < 00$). Intravenous administration of phentolamine and esmolol was initiated and the patient was admitted to the intensive care unit. After hemodynamic stabilization he was transferred to the endocrinology ward. His left ventricular ejection fraction had improved to 60%. Supine systolic blood pressure varied between 104 and 134 mmHg and his pulse rate was around 80 bpm while on oral treatment with phenoxybenzamine 30mg 3 times daily, metoprolol tartrate 75mg 2 times daily as well as a high-sodium diet. To rule out metastases, a ^{18}F -fluorodeoxyglucose (^{18}F FDG) positron emission tomography (PET)-CT scan was performed, showing a ^{18}F FDG-avid heterogeneous mass of the right adrenal gland with no further abnormalities (Fig. 1). He was then planned for laparoscopic surgery.

Background

Pheochromocytomas and sympathetic paragangliomas (PPGL) are rare neuroendocrine tumors derived from

chromaffin tissue of the adrenal medulla and the extra-adrenal sympathetic paraganglia in the thorax and abdomen, respectively (1). PPGL have the capacity to produce and release excessive amounts of catecholamines into the circulation. In contrast, paragangliomas in the head and neck area (HNPPGL) have a parasympathetic origin and usually do not produce catecholamines (2).

PPGL can occur at almost any age, with a mean age at diagnosis of 51 ± 16 years and an age-standardized incidence rate of 0.46 and 0.11 per 100 000 person years for pheochromocytoma and sympathetic paraganglioma, respectively (3). Genetic predisposition plays an important role, as shown by the finding that approximately 40% of all PPGL patients harbor a germline mutation and another 30% have a somatic mutation in one of the more than 20 susceptibility genes identified thus far (4–9).

The clinical presentation of PPGL has changed profoundly over the years. Nowadays, the majority of new cases with PPGL are detected in the presymptomatic stage as a result of DNA mutation screening programs and the widespread use of imaging techniques revealing PPGL as an incidental finding (10–13). Conversely, approximately 7% of all adrenal incidentalomas are unmasked as PPGL (14).

The clinical picture of PPGL is highly heterogeneous. Hypertension may be sustained or paroxysmal, whereas 17% to 32% of patients remain normotensive (13, 15). Headache, sweating, and palpitations are among the most common complaints, but only a minority of PPGL patients present with this classical triad (13). PPGL are most feared for the development of life-threatening cardiovascular events,

which may lead to significant morbidity and mortality (16-20). The pathophysiology of these so-called pheochromocytoma crises is largely explained by the exposure to paroxysmal high surges of catecholamine levels in response to various stimuli, resulting in acute blood pressure elevations, vasoconstriction, cardiomyocyte dysfunction, and promotion of atherothrombosis (15, 21-25).

PPGL are diagnosed biochemically by the demonstration of elevated plasma or urinary levels of the O-methylated free metabolites of epinephrine, nor-epinephrine or dopamine, specifically, metanephrine, normetanephrine and 3-methoxytyramine, respectively. In general, elevations of plasma metanephrines larger than twice the upper reference level or elevations of 2 or more metabolites is highly suggestive of a PPGL (26).

After biochemical confirmation of the diagnosis, anatomical imaging (i.e., CT, magnetic resonance imaging) is used to localize the PPGL and functional imaging studies (e.g., ^{123}I -MIBG, ^{18}F -FDOPA, ^{68}Ga -DOTA-SSA) serve to search for metastatic disease in patients who are at high risk, including those with *SDHB* mutations, large tumors (>5 cm), extra-adrenal location, or a noradrenergic biochemical phenotype (27). The majority of PPGL are benign, in which case curative treatment by surgical resection can be offered. Resection of a PPGL, however, is a high-risk procedure requiring perioperative management by a specialized multidisciplinary team in centers with broad expertise.

Surgical Approach

Minimally invasive adrenalectomy is the preferred surgical approach for most pheochromocytomas (28, 29). Different techniques exist, including the laparoscopic transperitoneal, posterior retroperitoneal, and lateral retroperitoneal approaches (29). In a recent meta-analysis based on predominantly retrospective studies, it was concluded that these endoscopic techniques provide superior perioperative and recovery outcomes without an increased complication rate compared with open adrenalectomy (30). Lateral transperitoneal adrenalectomy and posterior retroperitoneoscopic adrenalectomy have been evaluated in 2 relatively small randomized controlled trials, demonstrating either no difference or superiority of the posterior approach with respect to duration of surgery, hospital stay, and complication rate (31, 32). In a large multicenter study of patients with a pheochromocytoma, conversion from laparoscopic to open adrenalectomy was reported with a frequency of 7.7% (33). Open adrenalectomy

as the primary surgical approach is recommended for large (e.g., >6 cm) or invasive pheochromocytomas and paragangliomas (28). In experienced hands, laparoscopic resection of a paraganglioma might be performed for relatively easy accessible, small, and noninvasive tumors (28, 34, 35). Adrenal cortex-sparing surgery should be considered in patients with hereditary PPGL, because of a high risk for bilateral pheochromocytomas. In a large series of patients with either synchronous or metachronous bilateral pheochromocytomas, adrenal insufficiency developed in all patients after total bilateral adrenalectomy, but in only 23.5% after cortical-sparing surgery (36). Although the pheochromocytoma recurrence rate was higher in the cortical-sparing group (13% vs 0.7%), this was not associated with decreased survival. It is of paramount importance to provide perioperative glucocorticoid stress coverage in case of bilateral adrenal surgery or unilateral adrenalectomy in a patient who has previously undergone adrenal surgery on the contralateral side.

Approach to Perioperative Management

The only curative treatment of a PPGL is surgical resection. In the early days, it soon became evident that surgery was a hazardous procedure, with a high mortality rate of approximately 40% (37, 38). In particular, there was a high occurrence of life-threatening cardiovascular complications. These are explained by the uncontrolled and massive release of catecholamines into the circulation in response to various mechanical (e.g., endotracheal intubation, incision, peritoneal insufflation, tumor manipulation) and pharmacological stimuli (e.g., metoclopramide, some neuromuscular-blocking agents). Over the years, the perioperative mortality rate has dropped significantly, to about 0% to 3%, when performed in a center with extensive expertise (39-41). Major developments in PPGL management that most likely have contributed to this strong improvement of surgical outcome are optimization of presurgical treatment with antihypertensive drugs, advances in medical imaging allowing precise localization of the tumor, introduction of minimally invasive surgery, and refinement of anesthesiological techniques.

In view of the potential deteriorating effects of PPGL on the cardiovascular system, each patient should have a thorough preoperative examination of cardiac function and blood pressure (39, 42). In addition to history taking and physical examination, this should include an EKG, echocardiography, and 24-hour ambulatory blood pressure monitoring.

α -Adrenergic receptor blockers

Administration of antihypertensive agents has been the mainstay of optimal presurgical treatment of patients with PPGL. Primary goals of the antihypertensive treatment are relief of symptoms, control of blood pressure, and prevention of cardiovascular complications, both before and during surgery. For this purpose, α -adrenergic receptor blockers are recommended as the treatment of first choice (28). This class of antihypertensive drugs was first introduced in 1949 and has become part of routine clinical care since (43, 44). Thus, there is a longstanding experience with the use of these agents in this clinical setting. In addition, administration of α -adrenergic receptor blockers is a good example of targeted pharmacological therapy, as these drugs block specifically the overstimulation of α -adrenergic receptors by the high levels of circulating catecholamines. Either selective or nonselective α -adrenergic receptor blockers may be given (41, 45) (Table 1). These drugs are started at least 7 to 14 days before surgery in gradually increasing dosages until blood pressure targets are achieved. Most experience has been gathered with phenoxybenzamine, a nonselective and noncompetitive α_1 - and α_2 -adrenergic receptor blocker. The initial oral dose is usually 10 mg twice a day, which

might be increased to a maximum dose of 1 mg/kg body weight. Sometimes, even higher doses are needed (41, 46). Blockade of the presynaptic α_2 -adrenergic receptor interrupts the negative feedback of (nor)epinephrine on the neuronal catecholamine secretion, which explains the relative frequent occurrence of reflex tachycardia with the use of phenoxybenzamine. A practical disadvantage is that, due to its limited indication area, phenoxybenzamine is expensive and also difficult to obtain in several countries. Alternatively, a selective and competitive α_1 -adrenergic receptor blocker such as doxazosin, prazosin, or terazosin might be given (47–49). Relative to phenoxybenzamine, these drugs have a shorter duration of action and cause less reflex tachycardia. Doxazosin has been studied most extensively and is often started in a dose of 4 mg once or twice a day, with dose escalation up to 48 or 56 mg per day if needed (41, 46, 50–52) (Table 1). Retrospective studies comparing the efficacy of phenoxybenzamine and doxazosin have yielded conflicting results (46, 49–51). The efficacy of phenoxybenzamine and doxazosin has recently been investigated in PRESCRIPT, the first randomized controlled trial on presurgical treatment in patients with a PPGL (41). The primary endpoint, defined as the total duration of blood pressure during surgery

Table 1. Suggested Presurgical Oral Treatment of Patients With PPGL

Drug	Starting dose	Incremental dose steps ^a	Dose range	Comments
phenoxybenzamine or doxazosin ER	10mg q.d. 4mg q.d.	20mg 4mg	10-140mg 4-56mg	Preferably started at least 7-14 days prior to surgery, also in case of normotension. Doses higher than starting dose are administered b.i.d.
nifedipine ER or amlodipine or metoprolol ER	30mg q.d. 5mg q.d. 250mg t.i.d. 50mg q.d.	30mg 5mg 250-500mg 50mg	30-90mg 5-10mg 750-2000mg 50-200mg	Add-on to α -adrenergic receptor blockade in case of persistent hypertension (BP supine >130/80 mmHg, SBP upright >110 mmHg)
propranolol or atenolol	20mg t.i.d. 25mg q.d.	20mg 25mg	20-240mg 25-100mg	Add-on in case of tachycardia (HR supine >80bpm, HR upright >100bpm). Preferably be started after sufficient preparation with α -adrenergic receptor blockade (≥ 3 -4 days)
high sodium chloride diet	≥ 15 grams	-	-	Restoration of intravascular volume depletion; prevention of preoperative orthostatic hypotension and postoperative hypotension
and				Diet should be started >7-14 days before surgery
saline 0.9% i.v.	2L /24h	-	-	Intravenous saline should be started 24h before surgery

Supine BP >160/100 mmHg 24h before planned surgery; consider postponement of surgery. Surgery is usually performed in the morning, and the last dosage of each oral drug should preferably be administered on the evening before surgery. In case surgery begins after 12.00 AM, the last dosage of each oral drug should be administered at 07.00 AM on the day of surgery. Only the administration of 0.9% saline should be continued during surgery. Abbreviations: ER, extended-release; q.d., one a day; b.i.d., twice daily; t.i.d., 3 times daily; i.v., intravenous; BP, blood pressure; SBP, systolic blood pressure; HR, heart rate.

^aDose adjustments preferably every 2–4 days at the discretion of the clinician and guided by the response on blood pressure and/or heart rate.

outside a predefined target range, was found not to be different between these 2 drugs. It was shown, however, that phenoxybenzamine resulted in less hemodynamic instability during surgery.

Alternatives to α -adrenergic receptor blockers

There are a few alternative drugs for α -adrenergic receptor blockers (Table 1). Metyrosine inhibits the enzymatic activity of tyrosine hydroxylase, which catalyzes the rate limiting step in catecholamine biosynthesis. This results in a reduction of circulating catecholamine levels by 50% to 80% (53). The initial oral dose is usually 250 mg 3 times a day, which may gradually be increased to a maximum daily dose of 4 g. In general, metyrosine is prescribed in combination with an α -adrenergic receptor blocker, in particular phenoxybenzamine (54–56). A few case reports suggested that monotherapy with metyrosine is less effective (57, 58). Similar to phenoxybenzamine, metyrosine is expensive and has a limited availability in several countries. In addition, metyrosine is accompanied by several side effects, in particular somnolence, which has been reported in up to 96% of patients (53). Other side effects are related to decrease of circulating dopamine levels such as depression, anxiety, galactorrhea, and sometimes extrapyramidal symptoms (45, 59). Crystalluria may also develop, especially at higher doses, necessitating prophylaxis with a high fluid intake.

Calcium channel blockers represent another class of drugs that are the most often used add-on drug to α -adrenergic receptor blockers in case adequate blood pressure control is not achieved sufficiently (41, 45, 49) (Table 1). Presurgical monotherapy with calcium channel blockers has been described in patients with PPGL (60–62), but the Endocrine Society guideline recommends to consider this option only in case of normal or mildly elevated preoperative blood pressure levels or severe orthostatic hypotension with an α -adrenergic receptor blocker (28).

Treatment of tachycardia

Tachycardia frequently occurs in patients with PPGL, either as a direct result of excessive release of catecholamines by the chromaffin tumor or as a side effect of α -adrenergic receptor blockers with development of reflex tachycardia. Tachycardia is treated with β -adrenergic receptor blockers, but it is imperative that these drugs should only be initiated in a patient who is already receiving an α -adrenergic receptor blocker for several days. Neglect of this basic treatment principle may result in a pheochromocytoma crisis with serious cardiovascular complications due to unopposed stimulation

of α -adrenergic receptors with ensuing strong peripheral vasoconstriction (63). Both nonselective and β 1-selective adrenergic receptor blockers might be used, as there is no evidence of superiority of one over the other (28) (Table 1). Labetalol is a combined selective α 1- and nonselective β -adrenergic receptor blocker and is not recommended for presurgical treatment as it may provoke additional blood pressure elevation or even a hypertensive crisis (64–66). This is explained by a more effective antagonism of the β - than α 1-adrenergic receptor in a ratio of 3:1 and 7:1 after oral and intravenous administration, respectively (67).

Preoperative goals

It is common practice to use a high-sodium diet during treatment with α -adrenergic receptor blockers and to administer 1 to 2 liters of saline during the last 24 hours prior to surgery (28, 45, 68). The rationale is to reduce the risks of preoperative orthostatic hypotension and postoperative hypotension. There is, however, limited evidence supporting this approach (69–71). Recently, the concept of volume deficiency has been challenged in a small study using esophageal Doppler monitoring during adrenal surgery in patients with either a pheochromocytoma or a nonfunctioning adrenal tumor (72).

There is no consensus with respect to the optimal presurgical blood pressure and heart rate targets, as randomized comparative studies are lacking. A seated blood pressure target <130/80 mmHg and an upright systolic blood pressure >90 mmHg have been proposed previously (28). The last recommendation has been corroborated by the demonstration of more intraoperative hemodynamic instability in patients with a presurgical systolic blood pressure <90 mmHg on standing (41, 46). Suggested heart rate targets in seated and upright position are 60 to 70 bpm and 70 to 80 bpm, respectively (28).

Drugs to be avoided

Several medications have been implicated in precipitating a pheochromocytoma crisis (28, 73). Such observations are largely based on case reports, which often hampers to establish a direct causal relationship between use of a specific drug and the suspected adverse event. It is good practice, though, to avoid the use of these drugs in patients with PPGL. In cases when there is no alternative treatment, these drugs should only be given after adequate α -adrenergic receptor blockade has been achieved. The mechanism by which certain drugs cause a pheochromocytoma crisis vary from direct or indirect (i.e., through histamine) stimulation of

catecholamine release, direct stimulation of α -adrenergic receptors or blockade of β -adrenergic receptors, inhibition of norepinephrine re-uptake, or interference with catecholamine metabolism. Drug classes that should be avoided are dopamine D2 receptor antagonists (e.g., metoclopramide, droperidol), sympathomimetics (e.g., ephedrine, dexamphetamine), some β -adrenergic receptor blockers (e.g., labetalol), opioid analgesics (e.g., morphine, tramadol), norepinephrine reuptake inhibitors, including tricyclic antidepressants (e.g., amitriptyline, imipramine), serotonin reuptake inhibitors (e.g., paroxetine, fluoxetine), monoamine oxidase inhibitors (e.g., tranylcypromine, moclobemide), and corticosteroids (e.g., dexamethasone, prednisone) (28, 74). An overview of the drugs to be avoided in anesthetic management will be discussed in more detail below.

Management of the pheochromocytoma crisis

A patient who develops a pheochromocytoma crisis, i.e., severe hemodynamic instability accompanied with organ failure, should first undergo intensive medical stabilization before surgical resection of the PPGL (17). Emergency resection of a PPGL is associated with a high perioperative morbidity and mortality and should therefore be avoided as much as possible (75). In case of a cardiogenic shock, medical stabilization may sometimes require non-pharmacological measures such as the use of an intra-aortic balloon pump or extracorporeal membrane oxygenation (75, 76). Pharmacotherapy is the mainstay of medical stabilization in a patient with a pheochromocytoma crisis. The initial goal of treatment is to control hypertension through intravenous administration of antihypertensive drugs with a rapid onset of action and a relatively short duration, thus enabling effective dose titration (77, 78). There are no evidence-based guidelines with respect to the medical treatment of a pheochromocytoma crisis. Several drugs have been described in the literature, and some of the more frequently recommended agents are mentioned in Table 2. Phentolamine is a competitive α_1 - and α_2 -adrenergic receptor antagonist and is only indicated for treatment of pheochromocytoma-induced hypertension and prevention or treatment of dermal necrosis following intravenous administration or extravasation of norepinephrine. It is contraindicated in patients with coronary artery disease. Urapidil is a competitive α_1 -adrenergic receptor antagonist with central agonistic action at serotonin 5-HT_{1a} receptors (87). In contrast to phentolamine, it does not cause reflex tachycardia and may therefore also be administered to patients with coronary artery disease. Among the class of calcium channel antagonists, nicardipine has been used

most extensively to control hypertension in patients with pheochromocytoma. Alternatively, clevidipine butyrate could be administered, an ultra-short-acting third-generation dihydropyridine (79). Clevidipine is formulated as a lipid emulsion made with soybean oil and egg yolk phospholipids. It should therefore not be given to patients with soybean, soy product, egg, or egg product allergies and in patients with significant deficiencies in lipid metabolism. Sodium nitroprusside is a nitric oxide donor and a potent arterial and venous vasodilator (88). Except when used for short periods of time or at low infusion rates [e.g., <2 μ g/kg per minute] it can result in cyanide accumulation and severe toxicity. The administration should immediately be discontinued if the blood pressure is not adequately controlled after 10 minutes at the maximum recommended rate of 10 μ g/kg per minute. Nitroglycerine (glyceryl trinitrate), also a nitric oxide donor, is predominant a venous vasodilator and compared to sodium nitroprusside has a slightly slower onset of action in decreasing the arterial pressure. However, nitroglycerine may have a greater role when there is concomitant ischemic heart disease, since it increases coronary blood flow by dilating collateral vessels and suppressing coronary vasospasm. Conversely, sodium nitroprusside may reduce coronary perfusion through its greater effect on diastolic arterial pressure, which potentially can induce intracoronary steal (80). Magnesium sulfate is a vasodilating agent that acts through several mechanisms. It inhibits catecholamine release from the adrenal medulla and blocks the α -adrenergic as well as the L-type calcium channel receptor (81, 89, 90). Intravenous administration of magnesium sulfate can be effectively combined with other rapid-acting antihypertensive drugs. In addition, magnesium sulfate reduces the risk of perioperative atrial fibrillation and can be used for treatment of “torsade de pointes” in patients with a long QT-syndrome (91, 92). The antiarrhythmic mechanism of magnesium sulfate is not exactly known, but prevention or correction of hypomagnesemia and antagonism of the L-type calcium channel receptor are likely to contribute. Tachyarrhythmias are best treated with a short-acting drug such as esmolol, a β_1 selective adrenergic receptor blocker (82, 83) (Table 2).

Anesthetic management

The anesthetic management is aimed at providing optimal hemodynamic stability during the surgical procedure and postoperative stage. Some general aspects will be discussed here. More detailed information is described by others (39, 42). Premedication with an anxiolytic drug is recommended. General anesthesia is used

Table 2. Suggested Intravenous Treatment of Hypertension and Tachyarrhythmia in Case of PPGL Crisis or During Surgery

Indication	Drug	Dose	Onset of action	Duration of action (after discontinuation)
Hypertension	magnesium sulfate ^b	loading dose: 40-60 mg/kg followed by infusion of 1-4 g/h	immediate	30 min
Step 1 ^a	phentolamine ^c	bolus: 2.5-5 mg at 1 mg/min, repeated every 3-5 min continuous: 100 mg in 500 mL of 5% dextrose 20-100 mg/h	1-2 min	10-30 min
Step 2	or urapidil	bolus: initial dose: 25-50 mg or continuous: 10-15 mg/h	1-5 min	5-11 h
Step 3	nicardipine	starting dose: 5 mg/h, increased by 2.5 mg/h every 5 min (if needed), maximum dose 15 mg/h	1-5 min	15-30 min, may exceed 12h after prolonged infusion
	or clevidipine	starting dose: 1-2 mg/h, increase by doubling the dose every 90 seconds (if needed), maximum dose 32 mg/h	2-4 min	5-15 min
Step 4	sodium nitroprusside	start: 0.5-1.5 µg/kg/min, doses range: 0.5-4 µg/kg/min, stop administration if no results are achieved after 10 min of infusion, maximal dose for 10 min only	immediate	2-3 min
	or nitroglycerine	infusion adjusted according to response within the range of 10-200 µg/min ^d	2-5 min	5-10 min
Tachyarrhythmias	esmolol ^e	bolus: 500 µg/kg in 1 min, repeat bolus after 5 min (if needed) continuous: 25-100 µg/kg/min, increase infusion rate to 300 µg/kg/min (if needed)	1-5 min	15-30 min
Step 1	amiodarone	loading dose: 5mg/kg followed by infusion of 15 µg/kg/min	1-30 min	1-3 h
Step 2	or lidocaine	loading dose (bolus) 1mg/kg, repeat after 5-10 min (if needed). continuous: 2-4 mg/min (1-2 mg/ml), maximum 300 mg/h	< 2 min	15-20 min

Suggested steps need to be individualized based on e.g., comorbidity, see also text (16, 28, 39, 41, 42, 45, 73, 76, 78-86).

^a Check for adequate pain treatment and depth of anesthesia

^b Also prevention of and treatment for tachyarrhythmias

^c In case of norepinephrine-producing tumor 2 mg before tumor manipulation

^d Tachyphylaxis can occur after a continuous infusion >24h

^e In case of epinephrine- or dopamine-producing tumor 20 mg before tumor manipulation

with or without epidural anesthesia for postoperative pain control. In addition to the standard monitoring systems as defined by the American Association of Anesthesiologists, intra-arterial blood pressure measurement should be performed. A central venous catheter is recommended, pulmonary artery monitoring and transesophageal echocardiography might be considered in patients with cardiac dysfunction. Propofol is commonly used for induction, and may also be applied for total intravenous anesthesia. Alternatively, sevoflurane can be used for maintenance of anesthesia. Other inhalation agents like isoflurane, enflurane, and nitrous oxide have also been administered and shown to be safe. In contrast, desflurane should not be used as it may cause activation of the sympathetic nervous system with hypertension and tachycardia (93). Analgesia is

achieved by using opioids such as fentanyl, remifentanyl, or sufentanil. Neuromuscular blocking agents that can be safely used are vecuronium and rocuronium. Several anesthetic agents are contraindicated because of their potency to stimulate mast cell release of histamine, which may provoke the release of catecholamines from the PPGL (73) (Table 3). Vasoactive agents, antiarrhythmics, and volume therapy are used to correct hemodynamic fluctuations. Ensuring an adequate depth of anesthesia is also important to attenuate hemodynamic instability. Anticipation of impending hemodynamic instability requires optimal communication between the surgeon and the anesthesiologist, in particular at moments with a high risk of large fluctuations in catecholamine levels, e.g., incision, tumor manipulation, or ligation of the major vein draining the

Table 3. Overview of the Medication That Can Be Safely Used and the Potential Precipitants of Adverse Outcomes During Perioperative Anesthesia in PPGL Patients**Sedative-hypnotic agents used for anesthetic induction/maintenance***Inhalation agents*

Safe	Comments
Sevoflurane (42, 73, 94)	
Isoflurane (73, 93, 95-97)	
Enflurane (95, 97, 98)	
Nitrous oxide (94, 97)	
Not safe	
Halothane	Arrhythmogenic, sensitizing the myocardium to circulating catecholamines (94, 95, 99, 100)
Desflurane	Used without incident in some cases, however not recommended, can induce sympathomimetic effects (93, 94, 101-103)

Intravenous agents

Safe	Comments
Propofol (42, 94, 104)	
Etomidate (42, 94, 95)	
Dexmedetomidine (42, 105)	
Not safe	
Ketamine	Sympathomimetic effects (42, 94)
Thiopental (thiopentone)	Used without incident in some cases, however, not recommended, can precipitate hypertensive crises, linked to histamine releasing properties (73, 106-109)

Neuromuscular blocking agents

Safe	Comments
Rocuronium (42, 110)	
Vecuronium (42, 94, 95, 97, 110, 111)	
Not safe	
Succinylcholine (suxamethonium)	Can precipitate a hypertensive crisis and severe cardiac arrhythmias (94, 95, 112, 113)
Pancuronium	Histamine release, thereby causing severe pressor response (94, 95, 114, 115)
Atracurium	
Tobucurarine	
Mivacurium	Causes histamine release, thereby provoking catecholamine release. associated with severe arterial hypertension and ventricular arrhythmias (94, 95, 110, 116, 117)
Cisatracurium	Adverse reactions linked to histamine releasing properties, thereby provoking catecholamine release (73)

Anxiolytic agents

Safe	Comments
Midazolam (41, 73)	
Lorazepam (41, 73)	
Diazepam (41, 73)	No anxiolytic agent is superior

Analgesic agents

Safe	Comments
Fentanyl (42, 73, 94, 104, 118, 119)	
Sufentanil (42, 73, 95, 96, 118)	
Alfentanil (73, 95)	
Remifentanyl (42, 120, 121)	
Not safe	
Morphine	
Hydromorphone	
Pethidine*	These opioids causes histamine release, thereby provoking catecholamine release (73, 95, 122)

Antiemetic agents

Safe	Comments
Ondansetron (123)	
Not safe	
Metoclopramide	
Chlorpromazine	
Prochlorperazine	D2 receptor antagonists: causes indirect, but potent release of catecholamines by stimulation of presynaptic D2 receptors (45)
Domperidone	Can induce hypertensive crisis (123)
Droperidol	
Haloperidol	Severe hypertension due to increased catecholamine efflux
(95, 124-126)	
Cisapride	Can stimulate catecholamine release from PPGL cells through activation of serotonin type 4 receptors (127)
<i>Miscellaneous</i>	
Not safe	
Ephedrine	Sympathomimetic effects, stimulates catecholamine release from PPGL (42, 73, 94, 128, 129)
Atropine	Inhibits cardiac vagus and potentiates chronotropic effects of catecholamines (95, 113)

*Pethidine is also known as meperidine, isonipecaine, lidol, operidine, pethanol, and piridosal.

Table 4. Suggested Management of Hypotension During or After PPGL Surgery

Step	MAP <60 mmHg
1	Fluid therapy *in case of bilateral adrenalectomy also start steroid supplementation: hydrocortisone 200mg/24h
2	Phenylephrine Bolus dose: 100 µg
3	Norepinephrine 0.05-0.1 µg/kg/min
4	Terlipressin Bolus dose: 1-3 mg Ephedrine Bolus dose: 5 mg

References (39, 41, 42, 80)

tumor. Hypertension during surgery may be corrected by intravenous administration of rapid-acting blood pressure lowering agents as described in Table 2. Often a combination of 2 or more vasodilating agents is administered in a stepwise manner in order to maintain the blood pressure within the target range.

The blood pressure may suddenly drop after clamping the main draining vein or removal of the tumor. Potential contributing factors are the abrupt decrease in circulating endogenous catecholamine levels resulting in acute peripheral arterial vasodilation and increase in venous capacitance, chronic down-regulation of α -adrenergic receptors, residual effects of presurgical administered α -adrenergic receptor blockers, and hemorrhage. Treatment consists of volume therapy, discontinuation of vasodilating agents, and administration of vasopressors like norepinephrine, phenylephrine, or terlipressin (Table 4).

Post-operative monitoring and complications

Main complications of the immediate postoperative period typically related to PPGL surgery are hypotension, hypoglycemia, and the unanticipated development of adrenal insufficiency. Development of hypotension usually begins in the operating room after removal of the tumor and may last for 24 to 48 hours postoperatively. Treatment consists of administration of intravenous fluids and vasoactive agents (Table 4). It has been suggested that presurgical use of phenoxybenzamine is accompanied by a higher risk of postoperative hypotension compared to doxazosin (50, 130). In the PRESCRIPT study, however, the risk of postoperative hypotension was not different between these 2 drugs (41). Hypoglycemia is another typical postoperative complication, with a reported frequency that varies widely from 4.2% to 43% (131, 132). Catecholamines

have multiple effects on glucose metabolism, including inhibition of insulin secretion and stimulation of glucagon secretion by activating the α_2 - and α_1 -adrenergic receptor, respectively, and stimulation of glycogenolysis, gluconeogenesis, and aerobic glycolysis through activation of the β_2 -adrenergic receptor (133, 134). The sudden drop in catecholamine levels after PPGL resection may thus result in rebound hyperinsulinemia in the presence of depleted glycogen storages. Blood glucose concentrations need to be measured frequently during the first 24 hours after surgery and hypoglycemia should be restored by intravenous administration of dextrose. Acute adrenal insufficiency will develop after bilateral adrenalectomy or after unilateral adrenalectomy in case of contralateral adrenal gland surgery in the past, unless cortex-sparing surgery has been successful. If the clear indication for perioperative glucocorticoid coverage under these circumstances has not been acknowledged by the medical team, the patient is at high risk to develop an Addisonian crisis. Treatment-resistant hypotension combined with hypoglycemia should raise the possibility of postoperative acute adrenal insufficiency and requires immediate treatment with glucocorticoids, after taking a blood sample for urgent measurement of plasma cortisol.

Controversies and Areas of Uncertainty

The level of evidence supporting the presurgical use of antihypertensive agents including α -adrenergic receptor blockers in patients with PPGL is relatively low and mainly based on observational studies and expert opinion. In fact, there are no randomized placebo-controlled trials on this subject. This lack of robust evidence has led several investigators to question the recommended practice of presurgical treatment with α -adrenergic receptor blockers. Several comparative studies describing patients with PPGL who received pre-treatment with α -adrenergic receptor blockers compared with those who did not, suggested that these drugs are not beneficial and might even be harmful by increasing the risk of orthostatic hypotension and postoperative hypotension (130, 135-138). Without exception, however, these studies were retrospective in design and demonstrated several methodological shortcomings. Inevitably, allocation bias plays an important role in each of these studies, as the decision whether or not to initiate α -adrenergic receptor blockade is likely to be affected by the severity of the disease, age of the patient, or the general health status. Confounding might also have resulted from the lack of stratification for various

characteristics such as genotype, secretory profile, and tumor size and location, which are important factors to consider in view of the large heterogeneity among patients with a PPGL. None of these studies defined a presurgical blood pressure target or provided details on the dose titration regimen of the α -adrenergic receptor blocker. In addition, dosages of the α -adrenergic receptor blocker were either not described (135, 137) or probably too low to achieve optimal efficacy. For instance, in the study by Groeben et al, the average daily dosage of doxazosin was 11 mg (136), much lower than the average dosage of 40 mg per day administered in the PRESCRIPT study (41). Furthermore, nearly 40% of subjects who did not receive α -adrenergic receptor blockers in that study were actually treated with one or more antihypertensive drugs (136).

By the nature of their mode of action, presurgical treatment with α -adrenergic receptor blockers provides symptomatic relief and supposedly also reduces the risk of cardiovascular complications during the waiting period until surgery. Although such beneficial cardiovascular effects seem plausible, there are no clear literature data available to support this notion.

Another point of discussion is which clinical variable best reflects the efficacy of presurgical treatment with antihypertensive agents. Preferably, this should be a clinically relevant outcome like cardiovascular morbidity or mortality. In case of PPGL, with the current low risk of perioperative complications, an unrealistic high number of participants would need to be studied in order to demonstrate a significant difference in the occurrence of a hard clinical endpoint between 2 drug regimens. Therefore, the blood pressure pattern during surgery and in the first 24 to 48 hours postoperatively is often chosen as a surrogate endpoint. The intraoperative blood pressure level alone, however, does not adequately represent the degree of hemodynamic instability. It should be realized that anesthesiologists are specifically trained to maintain blood pressure and heart rate within a certain target range and to administer intravenous fluids, vasoactive agents, or antiarrhythmics as soon as the hemodynamics deviate from the target range. Thus, not only blood pressure and heart rate but also the volume of intravenous fluids and the amount of vasoactive agents administered during surgery is a reflection of the degree of hemodynamic instability. Several studies have demonstrated that hemodynamic instability is associated with a higher risk of adverse perioperative events (40, 139, 140). Unfortunately, there is no agreement on the definition of hemodynamic instability, which impairs comparison of studies on this subject. A recently developed score system might be helpful to quantify

the degree of hemodynamic instability (141). It is important to note that none of the studies questioning the value of presurgical treatment with α -adrenergic receptor blockers used a predefined anesthesia management protocol or provided detailed information on the need for intravenous fluids and vasoactive agents (130, 135–137).

Treatment with α -adrenergic receptor blockers has also some disadvantages. Patients may experience side effects such as nasal congestion or orthostatic hypotension. Use of these drugs is probably associated with a higher risk of intraoperative hypotension. For example, a mean arterial pressure <60 mmHg occurred in 73% to 82% of patients in the PRESCRIPT study (41). In the study by Groeben et al, 38% of patients without α -adrenergic receptor blockade developed hypotension (136). Caution is warranted, however, in comparing the results of these studies, due to the aforementioned major differences in study design. If anything, it demonstrates that hypotension also occurs without the use of α -adrenergic receptor blockers.

It is worth mentioning that the studies suggesting that presurgical treatment with α -adrenergic receptor blockers could be omitted in patients with PPGL were performed in specialized centers with dedicated and experienced medical teams. Whether those excellent results will also be achieved in centers with less experience in the management of PPGL remains to be seen. The controversy with respect to the clinical value of presurgical α -adrenergic receptor blockade in modern day medicine can only be resolved by a well-designed placebo-controlled trial. Until then, we recommend to follow the Endocrine Society's guideline that all patients with a hormonally functional PPGL should undergo preoperative blockade, preferably with an α -adrenergic receptor blocker (28). This recommendation is still appropriate today, in view of the long-standing clinical experience with these drugs, their targeted mode of action and the several methodological shortcomings of the studies suggesting these drugs could be safely omitted.

An area of uncertainty is the goal of presurgical treatment, as there are no studies comparing different target levels for blood pressure and heart rate. The PRESCRIPT study demonstrated an association between tumor size, plasma concentration of catecholamines, and use of doxazosin with an increased risk of hemodynamic instability during surgery, but the factors determining the individual risk are largely unknown.

Literature data are limited on the clinical value of presurgical treatment in PPGL patients with a normal blood pressure. It has been shown that hemodynamic

instability might also occur in normotensive patients with PPGL (142, 143). In a retrospective study of normotensive patients with PPGL it was found that subjects pretreated with either doxazosin or phenoxybenzamine demonstrated less hemodynamic instability compared with those who did not receive presurgical α -adrenergic receptor blockade (144). Based on these observations and in agreement with the Endocrine Society's guideline, presurgical antihypertensive treatment is also advised for patients with PPGL and a normal blood pressure.

Back to the Case

In preparation for surgery, α - and β -adrenergic receptor antagonists were continued at the same dose and 2 liters of normal saline was administered during the 24 hours prior to the operation. A minimally invasive lateral transperitoneal adrenalectomy was performed. Intraoperative tumor manipulation triggered elevation of blood pressure up to a maximum systolic value of 180 mmHg, which was easily controlled by a 5 mg intravenous bolus injection of phentolamine. Directly after the tumor removal there was a 5-minute period of hypotension, which was quickly corrected with volume treatment and 30 minutes of norepinephrine infusion. Intraoperative hemodynamics were uneventful otherwise. Postoperatively, the patient developed 2 episodes of hypoglycemia, for which intravenous glucose 5% was administered. He developed no other complications and left the hospital 6 days after surgery. Histopathological examination confirmed the diagnosis of a large pheochromocytoma, with a tumor diameter of 10 cm and a weight of 100 grams. Plasma metanephrines normalized and he remained normotensive, with an average blood pressure of 124/62 mmHg. Germline mutation testing of pheochromocytoma susceptibility genes *VHL*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHAF2*, *TMEM127* and *MAX* was negative, with an otherwise uneventful family history for endocrine tumors. There has been no PPGL recurrence after almost 9 years of annual follow-up. Only an asymptomatic slightly lowered left ventricular ejection fraction (53%) persisted, as a consequence of the prior catecholamine-induced cardiomyopathy.

Additional Information

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