

## An Overview of Anaesthetic Issues in Pheochromocytoma

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### Abstract

*Recent developments in the anaesthetic management of pheochromocytoma are reviewed. A brief summary of its pathophysiology and clinical features is also considered. The main anaesthetic issues involved in the assessment and preparation of these patients in light of the current information are then discussed.*

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### Introduction

New developments in technology, monitoring and pharmacology over the last decade have improved our understanding of pheochromocytoma and its management. This review summarises the pathophysiology and clinical features of pheochromocytoma. It also highlights the recent advances and rationalises these developments to obtain potential benefit during anaesthesia.

### Clinical Aspects

The incidence of pheochromocytoma is reported to be 1.55 to 2.1 per million populations per year.<sup>1</sup> Therefore only one case may be seen in the lifetime of one's clinical practice. The perioperative mortality rate for elective resection of pheochromocytoma is 0% to 3%<sup>2</sup> and in an undiagnosed or ill-prepared patient this can be as high as 50%.<sup>3</sup> In the hypertensive population about 0.1% have pheochromocytoma. Approximately 10% of the tumours are bilateral, 10% are extra-adrenal and 10% are malignant. In children 70% are bilateral, majority being benign and extra-adrenal.<sup>4</sup> The greatest frequency occurs in the fourth and fifth decade of life, with slightly higher female preponderance (60%).<sup>5</sup>

Pheochromocytoma arises in chromaffin cells of neuroectodermal origin, found anywhere in the sympathoadrenal system. It is associated commonly with multiple endocrine adenoma type IIa and b, neurofibromatosis and Von Hippel-Lindau syndrome. It has also been associated with hypercalcaemia and

thyroid C-cell hyperplasia,<sup>6</sup> and pancreatic islet cell tumour.<sup>7</sup>

Pheochromocytoma release large amounts of catecholamines (CCA); adrenaline, noradrenaline and dopamine, and various peptides and ectopic hormones; enkephalins, somatostatin, calcitonin, oxytocin, vasopressin, insulin and adrenocorticotrophic hormones.<sup>8</sup> There is no direct correlation between the concentration of free circulating CCA and the associated haemodynamic effects, due to the down regulation of the adrenergic receptors.<sup>9</sup> Adrenal pheochromocytoma secretes adrenaline and noradrenaline, while extra-adrenal tumours secrete only noradrenaline. Generally the secretion of noradrenaline is greater than adrenaline.

The classical symptoms of pheochromocytoma are headaches, hypertension, palpitations and episodic sweating. Central nervous system manifestations are anxiety, nervousness, psychosis, visual disturbance and tremors. Cardiovascular symptoms include ventricular arrhythmias, cardiac failure with cardiomyopathy, peripheral vasoconstriction with pallor, mottled or gangrenous digits and haemoconcentration. Patient may be thin and anorexic with increased metabolic rate, and have increased blood glucose levels. The tumour size affects symptomatology; patients with tumours less than 30 g usually present with more symptoms and are diagnosed early as more CCA is released into circulation because of decreased storage and metabolising capacity. Tumours greater than 250 g have increased storage and metabolising capacity, and therefore release less CCA

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but more metabolites. Eating, smoking, exercise, changes in body or environmental temperature, postural changes, valsalva manoeuvre, abdominal palpation, carotid sinus massage and pain can precipitate paroxysms. Recently some cases have been reported with haemodynamic instability and hypermetabolic state which were thought to be a malignant hyperthermic condition but were later found to have unsuspected pheochromocytoma.<sup>10,11</sup>

Biochemical diagnosis involves screening urine collections for CCA and metanephrine metabolites. This has a diagnostic specificity of 98% and sensitivity of 100%.<sup>12</sup> The total plasma CCA (adrenaline and noradrenaline) levels usually exceed 10 nmol/L. Pentolinium or clonidine suppression tests are used to differentiate essential hypertension from hypertension due to pheochromocytoma.

After initial diagnosis and having excluded other causes of hypertension, the tumour and its metastases are localised with CT or MRI scan using meta iodobenzyl guanidine (MIBG). This is a procedure of choice, as it is non-invasive, safe and very accurate.<sup>13</sup> It can also be localised by positron emission tomography after administration of hydroxyephedrine or 18F fluorodeoxyglucose.<sup>12</sup>

#### Preanaesthetic Assessment

There should be close cooperation between physician, cardiologist, surgeon and the anaesthetist for an uneventful outcome. The anaesthetist should verify the history, assess severity of hypertension and look for end-organ effects, especially CCA-induced cardiomyopathy with failure, which is associated with high mortality.<sup>14</sup>

Presence of arrhythmias, hypertrophy, cardiomyopathy, ischaemia and infarction can be detected by electrocardiograph. Radiological examination may reveal the presence of cardiomegaly and pulmonary oedema. Left ventricular function can be assessed by M-mode echocardiography.<sup>15</sup>

Biochemical investigations such as urea, creatinine and electrolytes provide an assessment of the renal function. Scintigraphic renal scans have been advocated to assess bilateral renal function in a rare event that nephrectomy may be necessary to completely remove a pheochromocytoma.<sup>16</sup> A base-line full blood count and haematocrit followed by serial monitoring provide an evaluation of the adequacy of volume expansion with  $\alpha$ -adrenergic blockade. Hyperglycaemia if present may require insulin therapy. If hypercalcaemia is present, the presence of type II multiple endocrine adenomatosis should be suspected.

#### Preanaesthetic Preparation

An uncontrolled situation leading to adrenergic crisis may occur at induction of anaesthesia, intubation, and

intraoperatively during tumour handling.

The patient is prepared for surgery by appropriate  $\alpha$  blockade over a period of 10 to 14 days. Any associated complication such as tachyarrhythmias is treated with  $\alpha$  blockade. Roizen et al<sup>17</sup> have suggested simple guidelines for preoperative preparation of these patients. A number of other regimes have been described but the experience and preference of the attending physician influence the choice.

There are differing views about the initial pharmacological control of pheochromocytoma with  $\alpha$  blockade. Oral phenoxybenzamine 20 mg tds is commonly used for preparation of patients for surgery and those with malignant or metastatic pheochromocytoma not amenable to surgery. Phentolamine and prazosin can also be used. The non-competitive blockade with phenoxybenzamine prevents breakthrough hypertension during CCA surges. Competitive agents such as prazosin lack this safety. With phenoxybenzamine as the initial drug, prazosin is then added if  $\alpha$  blockade is inadequate followed by  $\alpha$ -methyl p tyrosine (AMPT) if necessary. Whichever drug is used, it must be introduced cautiously starting with small dosages and increasing it gradually until orthostatic hypotension occurs indicating adequate  $\alpha$  blockade. The drugs commonly used in the acute and chronic management of pheochromocytoma are described briefly in Table I. During  $\alpha$  blockade the resultant  $\beta$  receptor stimulation produces tachycardia and hypoglycaemia (through increase insulin release).

Tachycardia and arrhythmias are controlled by carefully introducing  $\beta$  adrenergic blockers, such as propranolol 40 mg tds orally. Predominant  $\beta$  antagonism may cause increase blood pressure, heart failure and worsen asthma, but this is less problematic than pure  $\beta$  blockade.  $\beta$  blockade should never be instituted until  $\alpha$  blockade is fully established as unopposed  $\alpha$  stimulation may lead to severe hypertension. Caution is also warranted in patients with cardiomyopathy who may develop pulmonary oedema due to withdrawal of  $\beta$  stimulation.

As vasodilatation proceeds with  $\alpha$  blockade, intravenous volume expansion is required. Spontaneous restoration of plasma volume usually occurs with gradual re-expansion of vascular volume with oral administration of phenoxybenzamine. The initial haemodilution usually resolves over two weeks.<sup>18</sup> Ideally volume expansion is carried out with the guidance of central venous pressure monitoring. If bilateral adrenalectomy is anticipated then steroid cover, as for Addison's Disease, is needed.

Since voltage dependent calcium channels are involved in both secretion and action of CCA, calcium channel antagonism is an attractive therapeutic option. But this does not control cardiac adrenergic stimulation and

TABLE I COMMON DRUGS USED IN MANAGEMENT OF PHAECHROMOCYTOMA

	Dose	T <sub>1/2</sub>	Side effects	Comments
<b>A. Alpha Adrenergic Blocker</b>				
1. Phenoxybenzamine Non-competitive Non-selective (Both $\alpha_1$ & $\alpha_2$ )	Initial (O) 10 to 30 mg/d Max. 80 to 300 mg/d	24 h	Main—postural hypotension Others—sedation, nasal congestion, dry mouth	Preferred drug for preoperative preparation
2. Phentolamine Competitive Non-selective	Bolus (IV) 1 mg Infusion 20 mg in 500 ml 5% dextrose (Titrate to blood pressure)	10 to 15 min	Main—hypotension, tachycardia, arrhythmia, myocardial ischaemia/infarction	For acute control in hypertensive crisis
<b>B. Beta Adrenergic Blocker</b> (After adequate $\alpha$ blockade)				
1. Propranolol Non-selective ( $\beta_1$ & $\beta_2$ )	Initial (O) 80 to 120 mg/d Max. 480 mg/d IV 1 to 10 mg	3 to 5 h	May induce cardiac failure, bronchospasm, fatigue	Oral bioavailability—25% (Extensive 1st pass hepatic metabolism)
2. Atenolol Selective $\beta_1$	Initial (O) 50 to 100 mg/d Max. 300 mg/d IV 2.5 to 10 mg/d	5 to 8 h	Severe bradycardia between CCA surges	No 1st pass hepatic metabolism Oral bioav.—50 %
3. Esmolol Selective $\beta_1$	Bolus (IV) 500 ug/kg/min Infusion 50 to 200 ug/kg/min	8 min		For rapid intraoperative control of heart rate
4. Labetolol Mixed $\alpha$ and $\beta$ blocker $\beta > \alpha$ (5 to 10x) Selective $\alpha$ ( $\alpha_1$ ) Non-selective $\beta$ ( $\beta_1$ & $\beta_2$ )	Initial (O) 50 to 100 mg/d Max. 1200 mg/d IV 0.25 mg/kg slowly upto 20 mg	4 to 6 h	May cause hypertension (weak $\alpha$ blockade)	Not to be used as sole drug due to poor and unpredictable control of hypertension
<b>C. Arterio-Veno Dilator</b>				
Sodium nitroprusside	Initial infusion 0.5 to 1.5 ug/kg/min Mean 3 to 5 ug/kg/min Titrate to blood pressure	2 to 3 min	Main—hypotension Others—cyanide toxicity, methaemoglobinemia	Abrupt cessation may cause rebound hypertension
<b>D. Calcium Channel Blocker</b> (Voltage dependent calcium channels are involved in secretion and action of CCA)				
1. Diltiazem	Initial (O) 60 to 120 mg/d Max. 360 mg/d	3 to 5 h	Bradycardia and exacerbate cardiac failure	Does not control cardiac adrenergic stimulation and CCA synthesis <sup>19</sup>
2. Nifedipine	Initial (O) 30 mg/d Max. 180 mg/d	1 to 2 h	Hypotension, Peripheral oedema	
<b>E. False Transmitter to Block CCA Synthesis</b>				
Alpha methyl p tyrosine (AMPT) <sup>20</sup> Reduces CCA synthesis by 40% to 80% May require adrenergic blockade if incomplete control	Initial (O) 1 g/d Max. 4 g/d	-	Crystaluria, Extra pyramidal and psychic disturbances	Useful if inoperable and malignant tumour, resistant to $\alpha$ blockade

catechol synthesis is not decreased.<sup>19</sup>  $\alpha$ -methyl p tyrosine<sup>20</sup> inhibits tyrosine hydroxylase and by forming a false transmitter, reduces CCA synthesis by 40% to 80%. This is useful in patients who have an inoperable or a malignant tumour or are resistant to  $\alpha$  blockade. However, the control of hypertension may be incomplete and may still require additional adrenergic blockade.

### Premedication

It is most appropriate to administer an anxiolytic sedative preferably a benzodiazepine to decrease CCA release. Opioids such as morphine, which theoretically cause histamine release and hence can induce CCA release, are undesirable. Buprenorphine as a premedicant, is claimed to be cardiovascularly more stable with no histamine release. It is also a potent

analgesic with anxiolytic and sedative properties.<sup>21</sup> Atropine is best omitted as it causes tachycardia and even severe hypertension.

Droperidol, an anti-emetic, can block  $\alpha_2$  receptors and inhibit CCA re-uptake.<sup>22</sup> It also disinhibits the presynaptic dopaminergic receptors, which are responsible for inhibiting CCA release by chromaffin cells, thus promoting CCA release.<sup>23</sup> This produces an increase in circulating CCA levels, which manifest as paradoxical pressor effect.

Some advocate subtotal adrenergic blockade on the day of operation with the assumption that any hypertensive spikes associated with surgical manipulation will help localise the tumour and any secondaries. However this is potentially dangerous and unnecessary in the present era of advanced imaging and localising techniques. Patients often develop hypertensive swings during tumour handling despite complete and aggressive pharmacological blockade. Therefore it is best to continue medication until the day of the operation.

### Anaesthetic Techniques

The fundamental principle is the provision of a standard stable general anaesthesia by preventing CCA surges due to anaesthetic drugs or manoeuvres, surgical stimulation, tumour handling and clamping with ligation of venous drainage of tumour.

Various anaesthetic techniques have been employed successfully in perioperative management of phaeochromocytoma patient. There are proponents of regional anaesthesia alone or in combination,<sup>24</sup> with general anaesthesia and neurolept techniques.<sup>25</sup> However the choice of technique does not influence the outcome of the operation. Although regional anaesthesia protects against adrenergic responses to surgery, it cannot inhibit CCA surges provoked by tumour handling. Furthermore extensive extradural blockade may complicate the already difficult haemodynamic situation.<sup>17</sup>

The patient is transferred very cautiously onto the operating table to avoid any straining which may cause CCA release. Before induction, baseline monitoring is established. A large bore intravenous line and an arterial line are placed after local anaesthesia. The latter allows for direct continuous pressure measurement, crucial during those critical moments and for blood sampling. A central venous catheter is usually already *in situ* if it is used preoperatively in preparing the patient for surgery. If not, it can be placed under local anaesthetic infiltration, preferably prior to induction or following induction. The question of hypotension occurring after induction due to contracted intravenous volume should not arise in an adequately prepared patient. Monitoring by pulmonary artery catheter is indicated if there is any

doubt about the left ventricular function. Transoesophageal echocardiography has also been used perioperatively, to assess left ventricular function.<sup>26</sup> Routine monitoring in the form of electrocardiography, capnography, inspired oxygen concentration, pulse oximetry, neuromuscular blockade, temperature and urine output is also established.

Amongst the induction agents, thiopentone has been most frequently used but there is some reservation about its histamine releasing property. Etomidate provides cardiovascular stability but causes pain on injection and involuntary movements, which can trigger CCA release. Propofol seems a logical choice as it produces vasodilatation and to a certain extent counteracts the hypertensive response to tracheal intubation. Midazolam is very useful in facilitating coinduction.

Suxamethonium, a depolarising muscle relaxant is undesirable because of its sympathetic stimulation and associated muscular fasciculation, which may mechanically squeeze the tumour. Tubocurarine, atracurium and mivacurium are best avoided as they have been shown to release histamine. Pancuronium cause tachycardia and hypertension due to its indirect sympathomimetic action. Vecuronium clearly is the non-depolarising muscle relaxant of choice. Of the most recent agents, rocuronium and cisatracurium may have a place as they release the least histamine and afford cardiovascular stability.

Nitrous oxide is not contraindicated. Out of the three common inhalation agents, isoflurane is preferred because it does not sensitise the myocardium to CCA. Halothane and enflurane have arrhythmogenic potential especially in presence of CCA, the former more than the later. Recently sevoflurane has been used successfully in patients with phaeochromocytoma, tricuspid atresia and pulmonary artery stenosis.<sup>27</sup> Its rapid uptake and elimination allows easier control of depth of anaesthesia and haemodynamics of patient.

Opioids such as fentanyl and alfentanil do not release histamine and can be administered either as boluses or as infusions. In cultured neuronal cells, fentanyl at much higher than usual clinical doses inhibited noradrenaline uptake, with a maximum concentration of 100  $\mu\text{mol/L}$  producing 95% inhibition. Morphine, in contrast, had no such effect.<sup>28</sup> Both morphine and pethidine do release variable amounts of histamine. Sufentanil has been used as a general anaesthetic supplement and in the epidural space. It being 5 to 10 times more potent than fentanyl is more effective in blocking stress response to surgical stimulation.<sup>29,30</sup>

The decision to reverse neuromuscular blockade at the end of surgery or electively ventilating and monitoring the patient in the intensive care unit until stability is

achieved, depends on the intraoperative course and preoperative state of the patient. The drugs used for neuromuscular blockade reversal should be a combination of neostigmine and glycopyrrolate. Anti-muscarinic effects of glycopyrrolate coincide with the cholinergic effects of neostigmine and hence produce less tachycardia. Although the tumour is removed by now and CCA have a short half life, there may be residual CCA in circulation and the tachycardia associated with atropine can lead to a hypertensive spike.

### Perioperative CCA Release

Sodium nitroprusside, phentolamine, prazosin, nitroglycerin and various other agents such as magnesium sulphate,<sup>31</sup> nicardipine<sup>32</sup> and diltiazem<sup>33</sup> have been used to control intraoperative rises in blood pressure. Prostaglandin E-1, a vasodilator has been tried as an infusion to control blood pressure during pheochromocytoma surgery but without much success.<sup>34</sup> Sodium nitroprusside, a potent arterio-venodilator, is commonly used as a titratable intravenous infusion because it has a rapid and brief action. It produces minimal reflex tachycardia and tachyphylaxis. With the small quantity used cyanide toxicity is not a problem. Phentolamine may be used to control acute hypertensive crisis because it acts fast and has a short half-life. But the  $\alpha_1$  adrenergic receptor blockade is incomplete and interaction with  $\alpha_2$  adrenergic receptor may displace it from  $\alpha_1$  receptor, which may result in hypertension. It is also associated with tachycardia and tachyphylaxis. Therefore it is used commonly in boluses rather than as an infusion. Nitroglycerin does not offer smoothness of control and large dosages may be required because it is mostly a venodilator. Magnesium inhibits CCA release from chromaffin cells and alters the adrenergic receptors response.<sup>33,34</sup> However its use is associated with increased sedation, muscular weakness and occasionally respiratory paralysis requiring prolonged postoperative ventilation.

$\beta$  blockers such as propranolol, atenolol and labetalol (Table I) have been used to control tachycardia and blood pressure. Currently esmolol<sup>32</sup> is the best choice because of its rapid and short duration of action, making it easily titratable, both to control the heart rate and blood pressure. Ventricular arrhythmias are more easily controlled by lignocaine. Amiodarone can be used to control supraventricular arrhythmias.<sup>35</sup>

After the adrenal veins are ligated and the tumour removed, hypotension may occur. This is frequently amenable to modest fluid load and discontinuation of vasodilators and  $\beta$ -blockers. Blood is transfused appropriately according to the losses. A properly prepared patient will be unable to mount a sympathetic response to volume loss therefore any blood loss must be replaced immediately. If blood pressure does not respond to volume replacement then an infusion of a vasopressor

such as noradrenaline or phenylephrine is required as a temporary measure. Recently an angiotensin II analog has been used to manage post excision hypotension.<sup>36</sup> Autotransfusion can be used to control hypotension following removal of pheochromocytoma. This avoids the side effects of blood transfusion and minimises the change in intravascular volume after removal of the tumour as most of the blood, which is lost, is reinfused. Furthermore the circulating CCA present in this blood will help maintain the blood pressure.<sup>37</sup> But it may also lead to a significant elevation of the blood pressure because the CCA levels present may still be 3 to 20 times that of the normal range. Platelets are known to actively concentrate CCA during their life span and their destruction by suction or centrifugation may probably be responsible for the elevated levels of CCA in the collected blood.<sup>38</sup>

If the tumour is inoperable then an attempt is made to remove as much as possible of the active tissue. Subsequently adrenergic blockade is required for life. Suppression of CCA synthesis with AMPT can be tried. Radio-necrosis with high dose I<sup>31</sup> MIBG<sup>39</sup> and tumour embolisation with gelfoam<sup>40</sup> has also been suggested.

### Postoperative Care

Immediate postoperative care of the patient takes place in an intensive care unit, where the patient can be closely monitored. The three most important complications in the immediate postoperative period are hypertension, hypotension and hypoglycaemia.

Hypertension may be due to the patient recovering from anaesthesia or pain. It could also be due to some residual tumour or persistence of high plasma CCA levels, which may take a few days to return to normal values. Therefore appropriate measures are taken such as, alleviation of pain with parenteral opioids, epidural analgesia or clonidine and continuation or re-institution of anti-hypertensive medication.

Hypotension is uncommon if the patient is adequately prepared preoperatively with good pharmacological control and volume expansion. However, more volume replacement may be required. Also there should be a high index of suspicion for intra-abdominal bleeding.

After removal of the tumour the pancreatic beta cell suppression disappears and insulin levels increase. The previous lipolysis and glycogenolysis is no longer present both due to removal of tumour and  $\alpha$  blockade.<sup>18</sup> Hypoglycaemia with associated encephalopathy may occur and the residual adrenergic blockade may mask valuable symptoms and signs.<sup>41</sup> Therefore the blood glucose level is monitored closely in the early postoperative period and intraoperatively glucose containing intravenous replacement fluids are started at the time of tumour removal.

## Conclusion

Despite recent anaesthetic advances, the basic anaesthetic management of pheochromocytoma has not changed considerably. Due to its rarity, anaesthetic experience is usually limited. It is best that such cases are referred to a tertiary hospital, where the anaesthetists are more familiar with the management. With the backup of extra resources they are capable of handling the magnitude of potential problems and complications for an uneventful outcome.

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