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Adverse Drug Reactions in Patients with Phaeochromocytoma

Incidence, Prevention and Management

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Abstract

The dangers of phaeochromocytomas are mainly due to the capability of these neuroendocrine tumours to secrete large quantities of vasoactive catecholamines, thereby increasing blood pressure and causing other related adverse events or complications. Phaeochromocytomas are often missed, sometimes only becoming apparent during therapeutic interventions that provoke release or interfere with the disposition of catecholamines produced by the tumours. Because phaeochromo-

cytomas are rare, evidence contraindicating use of specific drugs is largely anecdotal or based on case reports. The heterogeneous nature of the tumours also makes adverse reactions highly variable among patients. Some drugs, such as dopamine D_2 receptor antagonists (e.g. metoclopramide, veralipride) and β-adrenergic receptor antagonists (β-blockers) clearly carry high potential for adverse reactions, while others such as tricyclic antidepressants seem more inconsistent in producing complications. Other drugs capable of causing adverse reactions include monoamine oxidase inhibitors, sympathomimetics (e.g. ephedrine) and certain peptide and corticosteroid hormones (e.g. corticotropin, glucagon and glucocorticoids). Risks associated with contraindicated medications are easily minimised by adoption of appropriate safeguards (e.g. adrenoceptor blockade). Without such precautions, the state of cardiovascular vulnerability makes some drugs and manipulations employed during surgical anaesthesia particularly dangerous. Problems arise most often when drugs or therapeutic procedures are employed in patients in whom the tumour is not suspected. In such cases, it is extremely important for the clinician to recognise the possibility of an underlying catecholamine-producing tumour and to take the most appropriate steps to manage and treat adverse events and clinical complications.

Phaeochromocytomas are rare catecholamine-producing neuroendocrine tumours, usually arising from the adrenal medulla and less frequently from sympathetic paraganglia (extra-adrenal paragangliomas). The sudden outpouring of catecholamines from these tumours can result in an 'explosive' appearance of clinical manifestations and disastrous or lethal complications. For this reason, phaeochromocytomas have been likened to 'pharmacological time bombs' that, if not recognised, are almost invariably fatal.

Unsuspected phaeochromocytomas can become apparent during the course of therapies or administration of drugs that provoke release or interfere with the disposition of catecholamines produced by the tumour, sometimes with devastating consequences or death. Other adverse reactions to therapies may occur independently of any direct influences of drugs on the release or disposition of catecholamines, occurring instead to secondary changes in physiological status associated with the presence of a phaeochromocytoma.

This article reviews the state of knowledge regarding adverse drug reactions and contraindicated medications in patients with phaeochromocytoma and outlines strategies to avoid and manage such events. Because of the numerous drugs that target central and peripheral neuronal catecholamine systems, this article initially discusses the pharmacology of catecholamine systems, the signs and symptoms of catecholamine excess and how various agents can act on catecholamine systems to produce adverse reactions. Because such reactions are most troublesome in patients in whom the tumour is unsuspected, this article also reviews current knowledge concerning the prevalence of detected and undetected tumours and how recognition of phaeochromocytoma is often made difficult by the constellation of associated obscuring clinical conditions and presentations.

1. Pharmacology of Catecholamine Systems

Phaeochromocytomas are dangerous, mainly because of the pathophysiological effects of the catecholamines produced and released by these tumours. Thus, understanding the mechanisms of how catecholamines are stored, released, cleared and metabolised, and how they act on end-organs is essential for appreciation of what drugs may cause adverse reactions in a patient with phaeochromo-

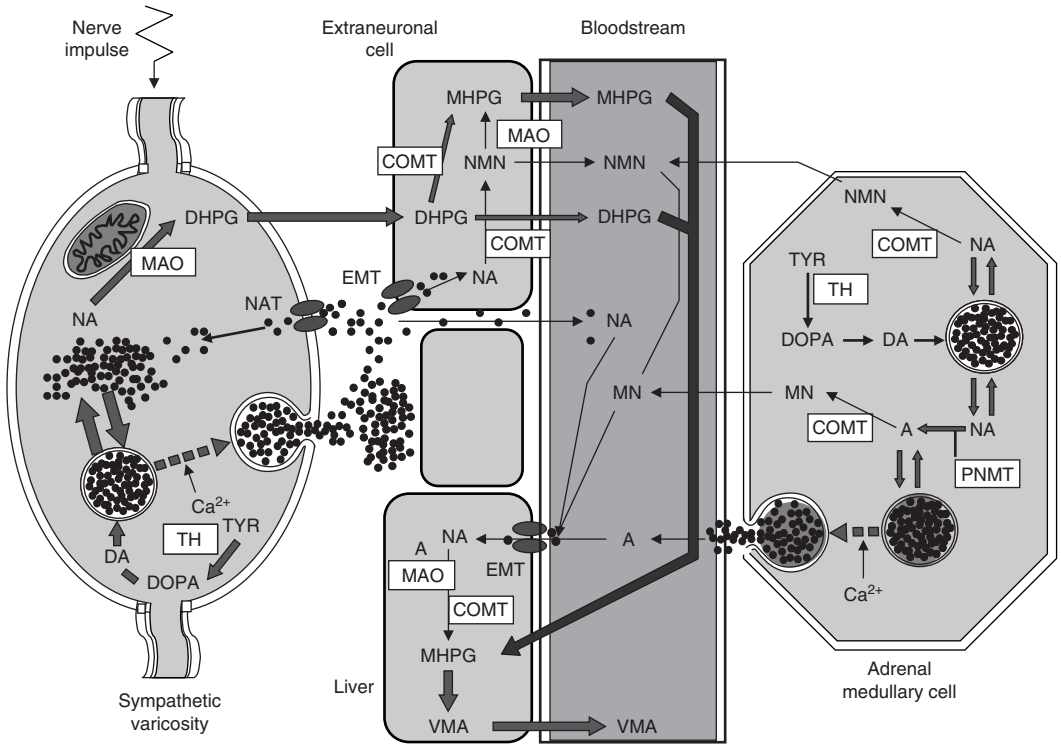

Fig. 1. Diagram illustrating the pathways of catecholamine synthesis, release and metabolism for noradrenaline and adrenaline produced and stored in sympathetic nerves and in the adrenal medulla. Differences in arrow thickness reflect different relative fluxes through pathways. Pathways for sulphate conjugation are not shown. **A** = adrenaline (epinephrine); **COMT** = catechol-*O*-methyltransferase; **DA** = dopamine; **DHPG** = dihydroxyphenylglycol; **DOPA** = dihydroxyphenylalanine; **EMT** = extraneuronal monoamine transporter; **MAO** = monoamine oxidase; **MHPG** = methoxyhydroxyphenylglycol; **MN** = metanephrine; **NA** = noradrenaline (norepinephrine); **NAT** = noradrenaline transporter; **NMN** = normetanephrine; **PNMT** = phenylethanolamine-N-methyltransferase; **TH** = tyrosine hydroxylase; **TYR** = tyrosine; **VMA** = vanillylmandelic acid.

cytoma and how such adverse reactions may be produced and treated.

Catecholamines stored in secretory granules exist in a highly dynamic equilibrium with the surrounding cytoplasm, with passive outward leakage of the amines into the cytoplasm, counterbalanced by inward active transport under the control of vesicular monoamine transporters (figure 1).[1] The driving force for vesicular monoamine transport is provided by an adenosine triphosphate-dependent vesicular membrane proton pump that maintains an H^+ electrochemical gradient between cytoplasm and the acidic granule matrix.[2] Disruption of this gradient in situations of energy depletion or lowered intracellular pH, such as occurs with ischaemia, anoxia or cyanide poisoning, can result in a rapid and massive loss of monoamines from storage vesicles into the neuronal cytoplasm.

Regulated secretion of catecholamines from neuronal synaptic vesicles or adrenal chromaffin granules occurs by calcium-dependent exocytosis.[3,4] Release of vesicular contents can also occur by calcium-independent constitutive secretion, a ubiquitous cellular pathway responsible for transport of proteins to the plasma membrane and extracellular environment, but which, in chromaffin cells, also contributes to basal catecholamine release.[5,6] Additionally, catecholamine secretion may occur by calcium-independent non-exocytotic processes involving increased loss of catecholamines from storage vesicles into the cytoplasm and reversal of the normal inward carrier-mediated transport to outward

transport of catecholamines into the extracellular environment.[7]

The various pathways of catecholamine secretion provide numerous points of action for drugs to provoke catecholamine release from phaeochromocytomas. However, in contrast to the highly regulated secretion of catecholamines from normal sympathoadrenal sources, release of catecholamines from phaeochromocytomas occurs autonomously without regulatory control from the CNS. Studies in primary cultures of human phaeochromocytoma cells indicate alterations in modulatory components of the exocytotic machinery that may contribute to indiscriminate calcium-dependent exocytosis.[8,9] Actions of secretogogues on cell surface receptors linked to calcium-dependent exocytotic pathways may also provoke catecholamine release from a phaeochromocytoma. Examples include receptors for histamine,[10,11] glucagon,[12,13] angiotensin II[14] and vasopressin,[15] which when stimulated can lead to catecholamine release by tumours. Displacement of catecholamines from storage vesicles by sympathomimetic amines followed by non-exocytotic release into the extracellular compartment provides another example of how phaeochromocytomas may be pharmacologically provoked to release catecholamines.

Drugs that influence the processes of catecholamine removal and metabolism may also affect levels of catecholamines in extracellular fluids and at effector sites. However, since the enzymes responsible for metabolism of catecholamines have intracellular locations, the primary mechanism limiting the lifespan of catecholamines in the extracellular space is by uptake into cells by active transport mechanisms (figure 1). Uptake is facilitated by transporters that belong to two families of proteins in mainly neuronal or extraneuronal locations.[16] Neuronal catecholamine transporters provide the principal mechanism for rapid termination of the signal in neuronal transmission, whereas the transporters at extraneuronal locations are more important for limiting the spread of the signal and for clearance of catecholamines from the bloodstream. For the noradrenaline (norepinephrine) released by sympathetic nerves, about 90% is removed back into nerves by neuronal uptake, 5% is removed by extraneuronal uptake and 5% escapes these processes to enter the bloodstream.[16,17] In contrast, for catecholamines released directly into the bloodstream from the adrenals (and presumably also from phaeochromocytomas) about 90% are removed by extraneuronal monoamine uptake.[16] Because of the importance of active uptake mechanisms for the rapid clearance of circulating catecholamines, any drug that inhibits these mechanisms could theoretically produce adverse reactions in a patient with phaeochromocytoma.

Neuronal uptake of catecholamines is followed by sequestration of the amines into storage vesicles or metabolism by monoamine oxidase (MAO). Extraneuronal uptake is followed by metabolism by MAO and catechol-*O*-methyltransferase (COMT). Due to the redundancy of intracellular pathways for metabolism or storage, and because of the importance of neuronal and extraneuronal uptake for clearance of catecholamines, blockade of MAO or COMT alone has little effect on catecholamine clearance.[18] Therefore, inhibition of catecholamine deamination or *O*-methylation might not be expected to be a problem in patients with phaeochromocytoma. However, adverse effects of MAO inhibitors are well known to be mediated via the 'cheese effect', where dietary tyramine escapes metabolism and enters the systemic circulation, causing sympathoneural release of noradrenaline and dangerous increases in blood pressure.[19] Similar effects on catecholamine release from phaeochromocytomas can be troublesome after consumption of certain foods or beverages with high tyramine contents (e.g. aged cheeses, cured meat products, sauerkraut, red wine).

2. Signs and Symptoms of Catecholamine Excess

The clinical manifestations of phaeochromocytoma are diverse and highly variable (table I), largely resulting from the haemodynamic and metabolic actions of circulating catecholamines or, less commonly, due to effects of other amine hormones

Table I. Signs and symptoms of phaeochromocytoma

Sign/symptoms	Frequency[a]
Signs	
Hypertension	++++
sustained hypertension	++
paroxysmal hypertension	++
Postural hypotension	++
Tachycardia or reflex bradycardia	+++
Pallor	++
Flushing (rare)	+
Weight loss	+
Fasting hyperglycaemia	++
Decreased gastrointestinal motility	+
Increased respiratory rate	+
Psychosis	+
Symptoms	
Headaches	++++
Palpitations	++++
Excessive sweating	++++
Anxiety/nervousness	+++
Tremulousness	++
Pain in chest/abdomen	++
Weakness, fatigue	++
Nausea/vomiting	++
Dizziness or faintness	+
Paraesthesias	+
Constipation (rarely diarrhoea)	+
Visual disturbances	+

a Highest (++++) to lowest (+) frequency.

or co-secreted neuropeptides.[20] Differences in the secretion of noradrenaline and adrenaline (epinephrine) by tumours and differing potencies of the two catecholamines on α- and β-adrenoceptors are thought to contribute to the highly variable clinical manifestations of phaeochromocytoma.[21,22]

Hypertension due to α-adrenergic-mediated vasoconstriction may be sustained or paroxysmal, presumably reflecting continuous versus periodic secretion of catecholamines. Some patients also present with periods of hypertension alternating with hypotension, including a significant proportion with orthostatic hypotension.[23] Decreased intravascular volume, preferential activation of β_2-adrenoceptors by adrenaline and desensitisation of α-adrenoceptors due to sustained increases in circulating catecholamines may predispose to periods of hypotension.

The most frequent symptoms of phaeochromocytoma (severe headaches, generalised inappropriate often drenching sweating and palpitations) are almost invariably paroxysmal in nature; these symptoms may also occur, but are less pronounced, when hypertension is sustained. Other signs or symptoms include anxiety, some tremulousness, occasionally pain in the chest or abdomen, nausea, vomiting, weakness, fatigue, prostration, dizziness or faintness, blurry vision, hypertensive retinopathy when hypertension is severe and sustained, constipation, occasionally diarrhoea, paraesthesias and facial pallor.[20] Paroxysmal attacks usually occur weekly, but may occur several times daily or once every few months; 80% last less than an hour but rarely they last for several days.

Certain signs and symptoms such as palpitations, anxiety, tremor, dyspnoea, hyperglycaemia and paroxysmal hypertension are more common in patients with phaeochromocytomas producing substantial amounts of adrenaline.[21,22,24] Paroxysmal hypertension occurs more frequently in patients with adrenaline-producing tumours and sustained hypertension in patients with high circulating levels of noradrenaline. Accordingly, relative to tumour size, noradrenaline-producing tumours show larger and more consistent increases in plasma and urinary catecholamine levels than adrenaline-producing tumours.[25,26] Consistently elevated catecholamine levels have been proposed to lead to downregulation of adrenoceptors, and consequently a lesser occurrence of hypertension and other symptoms of catecholamine excess. Such influences, combined with adaptive changes in vascular volume, may contribute to lack of concordance between elevations in blood pressure and plasma catecholamines in many patients with phaeochromocytoma.[27]

Phaeochromocytomas that produce predominantly dopamine are rare, occurring mainly as paragangliomas.[28,29] Patients with predominantly dopamine-producing tumours are usually normotensive and do not present with the classic symptoms of phaeochromocytoma. Nausea has been reported in several patients with dopamine-producing tumours,[29,30] presumably related to the emetic effects

of dopamine. Presence of orthostatic hypotension has also been reported, which might reflect the vasodilatory actions of dopamine and reduced blood volume secondary to dopamine-induced natriuresis.

3. Prevalence of Detected and Undetected Phaeochromocytomas

The inherent danger of an undiagnosed phaeochromocytoma is reinforced by the findings of several autopsy studies indicating that these tumours are more common than usually considered, often remaining undetected throughout life and frequently contributing to premature death. Two large autopsy series from before 1982 indicated surprisingly high prevalences of phaeochromocytoma of between 0.09% and 0.12%.[31,32] More recent autopsy series have indicated a lower prevalence of 0.05%,[33,34] presumably reflecting improved disease detection during life. Nevertheless, at reported annual detection rates of 2–5 cases per million,[35-37] corresponding to prevalences of 0.015–0.04% for tumours diagnosed during life, the 0.05% prevalence in recent autopsy series indicates that between 56% and 77% of all phaeochromocytomas remain overlooked. As suggested by the various autopsy studies,[31-34] most of these undiagnosed tumours presumably contribute to premature death.

Patients with high blood pressure and symptoms of catecholamine excess are those in whom the tumour is most frequently suspected. At reported prevalences of 0.2–0.6% for phaeochromocytomas in unselected hypertensive patients,[37-39] there does appear to be a 5- to 40-fold higher prevalence of the tumour detected among patients with hypertension than among members of the general population (0.015–0.04% prevalence). Nevertheless, current imprecision in biochemical testing means that it is neither cost effective nor appropriate to test for the tumour in every patient with hypertension.[40]

Adding to the problem of poor rates of tumour detection, it is now increasingly clear that patients with phaeochromocytoma do not always present with hypertension, and therefore selecting only those patients with sustained or paroxysmal high blood pressure would not guarantee greatly improved rates of tumour detection. In particular, normal blood pressure and lack of symptoms of catecholamine excess characterise many phaeochromocytomas detected during screening performed as part of a surveillance plan in patients with an identified hereditary condition predisposing to the tumour.[41,42] Normotension and lack of symptoms are also common in patients in whom phaeochromocytomas are found as incidentalomas during imaging studies for unrelated conditions.[43,44]

4. Associated Clinical Conditions and Differential Diagnosis

The crucial initial step for the detection of a phaeochromocytoma is to first think of the tumour. However, due to highly diverse manifestations, the clinical presentation of a phaeochromocytoma is not always clear, and manifestations may suggest a variety of other diseases. Thus, phaeochromocytoma has been justly designated ‘the great mimic’.

Signs and symptoms of catecholamine excess from a phaeochromocytoma in some patients may be veiled behind or suggest another clinical condition (e.g. shock, cardiomyopathic heart failure, stroke, pulmonary oedema, pre-eclampsia, severe migraine). Such conditions usually result from the pathological effects of high circulating levels of catecholamines, but are frequently misdiagnosed for a more usual underlying cause.[45] For this reason, phaeochromocytomas can challenge the clinical acumen of even the best clinicians. The tumours may remain unrecognised for many years after the first clinical or laboratory manifestations appear.

Because phaeochromocytomas may masquerade as many different clinical conditions requiring therapeutic intervention (table II), adverse reactions can occur when a drug used to treat or evaluate the condition is contraindicated in a patient with phaeochromocytoma. Awareness of such conditions and drug complications is important for avoidance of contraindicated medications and for prompt recognition of an underlying phaeochromocytoma unmasked by drug therapy. Such awareness can also be helpful for appreciation of how these drugs may confound interpretation of biochemical test results

Table II. Associated clinical conditions and differential diagnosis of phaeochromocytoma

Conditions	Manifestations, relevant cues and considerations
Hypertensive crisis	Unexplained severe hypertension – suspect phaeochromocytoma when history indicates signs and symptoms of catecholamine excess, or crisis is provoked by recognised factors (e.g. surgical anaesthesia, pregnancy and labour, medications)
Shock, cardiovascular collapse[a]	Unexplained shock may be accompanied by abdominal pain, signs consistent with pulmonary oedema, intense mydriasis unresponsive to light stimulation, profound weakness, diaphoresis, cyanosis, hyperglycaemia and leukocytosis – ensure blood pressure recordings are not confounded by severe peripheral vasoconstriction
Phaeochromocytoma multisystem crisis	Multiple organ failure, lactic acidosis, hyperthermia, encephalopathy, accompanied by hypertension or hypotension. In phaeochromocytoma often associated with pulmonary oedema, renal failure and myocarditis/cardiomyopathy due to toxic levels of catecholamines
Dilated or hypertrophic cardiomyopathy and heart failure[a]	Rarely thickening of left ventricular wall and interventricular septum due to hypertrophic and toxic effects of catecholamines; invariably associated with hypertension
Myocardial infarction, anginal pectoris	Infarction may be apparent with normal coronary arteries; often associated with arrhythmias and angina
Stroke, cerebrovascular accidents[a]	In phaeochromocytoma invariably secondary to severe hypertension
Acute pulmonary oedema; adult respiratory distress syndrome	Dyspnoea; often associated with hypertensive crisis and cardiomyopathy; usually cardiogenic; less commonly non-cardiogenic
Acute intestinal pseudo-obstruction, paralytic ileus, bowel ischaemia, megacolon	Decreased gastrointestinal motility secondary to adrenergic activation; often unresponsive to laxatives and enemas; α-adrenergic receptor antagonists (α-blockers) [e.g. phentolamine] can be useful
Acute renal failure or renal artery stenosis (very rare)[a]	May occur secondary to phaeochromocytoma for numerous reasons; biochemical diagnosis may be confounded by anuria, invalidating urinary tests, and uraemia, which can interfere with plasma tests. Renal artery stenosis is very rarely caused by compression of the artery by an adjacent pheochromocytoma; renal failure is very rare in phaeochromocytoma
Baroreflex failure[a]	Acute hypertension and tachycardia followed by labile hypertension and hypotension; usually due to denervation of baroreceptors following carotid body tumour resection, neck irradiation or trauma
Migraine and cluster headaches	In phaeochromocytoma attributable mainly to hypertension; headache is rarely the sole presenting symptom of phaeochromocytoma
Panic attacks, anxiety disorder[a]	Consider phaeochromocytoma when accompanied by hypertension and other symptoms of catecholamine excess
Pre-eclampsia	Hypertension in pregnancy due to phaeochromocytoma is often misdiagnosed as pre-eclampsia; paroxysmal or labile hypertension and presence of spells should immediately arouse suspicion of phaeochromocytoma; may have elevated catecholamine or metabolite levels if it converts to eclampsia with convulsions
Diabetes mellitus	Catecholamine-induced hyperglycaemia; consider phaeochromocytoma particularly in young diabetic patients with hypertension and normal bodyweight
Sleep apnoea[a]	Hypertension and sympathetic nerve hyperactivity with increases in plasma and urinary catecholamine levels
Carcinoid syndrome,[a] systemic mastocytosis	Flushing is a more usual presentation than in phaeochromocytoma; hypertension is rare but can occur; wheezing, diarrhoea and heart valve lesions

a May be associated with elevated catecholamine and catecholamine metabolite levels even in the absence of phaeochromocytoma.

in the differential diagnosis of the presenting condition and a possible underlying phaeochromocytoma.

One of the most dangerous situations for a patient with an unsuspected phaeochromocytoma is presentation in the emergency room as unexplained shock.[46-49] In the differential diagnosis of shock, phaeochromocytoma should be suspected when circulatory collapse is accompanied by significant abdominal pain, signs consistent with pulmonary oedema, intense mydriasis unresponsive to light stimulation, profound weakness, diaphoresis, cyanosis, hyperglycaemia and leukocytosis. It is also important to recognise that shock in a patient with phaeochromocytoma may be precipitated by contra-

indicated drugs (e.g. dopamine receptor antagonists, tricyclic antidepressants, corticosteroids, corticotropin).[50-57] Abrupt cessation of catecholamine secretion by the tumour in a patient with a constricted circulatory volume and desensitised adrenoceptors, following a prolonged period of catecholamine-induced hypertension, is thought to represent the main mechanism responsible for shock in patients with phaeochromocytoma. Decreased cardiac output caused by catecholamine-induced cardiomyopathy or myocardial infarction may also contribute to shock.

Shock may also be accompanied or followed by multisystem organ failure, an even more rare and very serious presentation of phaeochromocytoma, where early detection of the tumour can be crucial to improve a patient's chances of survival and to avoid administration of contraindicated drugs.[58-63] Phaeochromocytoma multisystem crisis is defined as multiple organ failure, lactic acidosis, temperature often >40°C, encephalopathy and hypertension and/or hypotension.[58] As in hypertensive crises or shock due to phaeochromocytoma, a multisystem crisis may be provoked in a patient with unsuspected and untreated tumour by surgical anaesthesia or by contraindicated drugs. Patients often have pulmonary oedema, sometimes necessitating ventilation,[60-63] and occasionally acute anuric renal failure requiring haemodialysis.[60,61] The presentation can easily be mistaken for septicaemia, delaying appropriate treatment. Fever and acute inflammatory symptoms may be caused by interleukin-6 production by the tumour.[64] Therefore, phaeochromocytoma should be included in the differential diagnosis in a patient with unexplained shock.

The pregnant patient with a phaeochromocytoma masquerading as pre-eclampsia represents another highly dangerous situation.[51,65-67] If such tumours remain undiagnosed during pregnancy, they carry a high risk of mortality for mother and fetus. Use of certain medications, such as antiemetics,[51,68] can carry a high risk for provoking a hypertensive crisis in the pregnant patient with phaeochromocytoma.

A wide variety of other less severe, but still dangerous clinical conditions, can also occur secondary to phaeochromocytoma.[69] Such conditions include dilated or, rarely, hypertrophic cardiomyopathy and heart failure;[70-73] myocardial ischaemia or infarction;[74-76] varying arrhythmic conditions;[77-79] strokes and other cerebrovascular accidents;[80-82] aortic aneurysms;[83,84] intestinal pseudo-obstruction, intestinal obstruction with ischaemic necrosis, megacolon and other gastrointestinal emergencies;[85-88] renal artery stenosis and renal failure;[89-92] cardiac and non-cardiac pulmonary oedema;[93,94] and even gangrene and tissue necrosis resulting from peripheral ischaemia.[95-98] Many of these conditions result from the pathophysiological effects of the large amounts of catecholamines produced by the tumour. Excessive levels of catecholamines can directly affect the myocardium, causing myocardial necrosis, probably due to vasoconstriction. Pulmonary oedema can result from cardiomyopathy or may be due to pulmonary venoconstriction and increased pulmonary capillary permeability.

Less acutely dangerous clinical conditions that may be confused with an underlying phaeochromocytoma include baroreflex failure, postural tachycardia syndrome, migraine and cluster headaches, diencephalic (autonomic) epilepsy, anxiety disorders and panic attacks, diabetes mellitus, carcinoid syndrome, systemic mastocytosis and sleep apnoea.[20,99] Medications used to treat any of these conditions may include some drugs contraindicated in patients with phaeochromocytoma, thereby contributing to associated morbidity and mortality. The use of β-adrenergic blockers to treat hypertension, arrhythmias or other cardiac conditions provides a classic example of the use of a drug that may unmask phaeochromocytoma as the true cause of the presenting condition.[100,101]

5. Medications and Procedures Associated with Adverse Reactions

Medications with potential to cause adverse reactions in patients with phaeochromocytoma cover numerous classes of drugs and many individual agents used in the management or treatment of a wide variety of medical conditions (table III). Be-

Table III. Main classes of drugs with contraindications in phaeochromocytoma

Drug class	Relevant clinical uses
β-Adrenergic receptor antagonists (β-blockers)[a]	To treat conditions that result from phaeochromocytoma (e.g. hypertension, cardiomyopathy, heart failure, panic attacks, migraine, tachycardia and cardiac dysrhythmias)
Dopamine D_2 receptor antagonists	Control of nausea, vomiting, psychosis, hot flashes and for tranquillising actions
Tricyclic antidepressants	Treatment of insomnia, neuropathic pain, nocturnal enuresis in children, headaches, depression (rarely)
Monoamine oxidase inhibitors	Non-selective agents rarely used as antidepressants (due to 'cheese effect')
Sympathomimetics[a]	Control of low blood pressure during surgical anaesthesia; decongestants; antiobesity agents
Chemotherapeutic agents[a]	Antineoplastic actions; treatment of malignant phaeochromocytoma
Opioid analgesics[a]	Surgical anaesthesia
Neuromuscular blocking agents[a]	Surgical anaesthesia
Peptide and corticosteroid hormones[a]	Diagnostic testing

a Some drugs may have therapeutic or diagnostic use in phaeochromocytoma, but usually only after pretreatment with appropriate antihypertensives (e.g. phenoxybenzamine).

cause phaeochromocytomas are rare, available evidence contraindicating use of specific drugs in patients with these tumours is based mainly on case reports and anecdotal evidence. Moreover, because of the highly heterogeneous nature of these tumours, some patients may show entirely different responses to a drug than others. Findings of lack of adverse reactions to a given drug in one patient with the tumour does not guarantee that the same drug will be safe to use in another patient.

While some classes of drugs, such as dopamine D_2 receptor antagonists (e.g. metoclopramide), appear more dangerous in consistently producing adverse reactions, others, such as tricyclic antidepressants (e.g. amitriptyline), seem more inconsistent in producing complications. Use of such drugs nevertheless clearly carries some risk, which should be carefully considered and evaluated whenever a phaeochromocytoma is present or suspected. Risks associated with contraindicated medications or procedures can be easily avoided or minimised by appropriate safeguards (e.g. blockade of α-adrenoceptors). Problems more often arise when certain drugs are used or medical procedures are carried out in patients in whom the tumour is not suspected. In such cases, it is extremely important for the clinician to recognise the possibility of an underlying catecholamine-producing tumour and to take the most appropriate steps to manage and treat any adverse events and clinical complications.

5.1 Surgical Anaesthesia

The presence of an undiagnosed phaeochromocytoma during surgical anaesthesia has been termed 'the anaesthesiologist's nightmare'.[102] As indicated by numerous case reports, such a situation has a high risk of significant morbidity and mortality and is a nightmare not just for members of the surgical team but also for the patient and the patient's family.[103-117] Provided the tumour is diagnosed and there is appropriate preoperative preparation of the patient, most phaeochromocytomas can, however, be resected safely by an experienced surgical team.[118] The frequency of significant adverse intraoperative events and postoperative complications under these conditions is low.

Most volatile anaesthetics used today are potent vasodilators that tend to decrease blood pressure. Therefore, any hypertensive crisis associated with surgical anaesthesia is unlikely to result from a direct effect of such agents on the vasculature. Hypertensive crises and other adverse events during general anaesthesia in patients with phaeochromocytoma occur mainly during administration of inducing agents or as a result of other drugs and manipulations employed during surgical procedures (table IV). Responses to anaesthetics, muscle relax-

Table IV. Potential precipitants of adverse outcomes during surgical anaesthesia

Drug/procedure	Details
Procedures and mechanical manipulations	Intubation; insufflation of peritoneum; diathermy; direct palpation of mass
Opioid analgesics	Thiopental sodium, nalbuphine, pethidine (meperidine), morphine, diamorphine; used as inducing agents; adverse reactions linked to histamine-releasing properties
Neuromuscular-blocking agents	Tubocurarine, suxemethonium chloride (succinylcholine), mivacurium chloride, atracurium besilate, cisatracurium besilate; adverse reactions linked to histamine-releasing properties
Tranquilisers and antiemetics	Droperidol, metoclopramide; used as inducing agents; adverse reactions due to dopamine receptor antagonism
Sympathomimetics	Ephedrine; stimulates catecholamine release from phaeochromocytomas
Vagolytic agents	Atropine; raises heart rate and may further impair reflex control of circulatory reflexes

ants, opioids and benzodiazepines (involving release of histamine and other vasoactive mediators from basophils and mast cells) may predispose some patients with phaeochromocytoma to adverse reactions during general anaesthesia.[119]

Some of the earlier volatile anaesthetics, such as halothane and cyclopropane (no longer used clinically), have been reported to sensitise the myocardium to the arrhythmogenic effects of catecholamines; arrhythmogenic effects do not seem to be a significant problem with newer anaesthetics such as isoflurane, sevoflurane and desflurane.[120-122] Nevertheless, myocardial depression, blunted vasopressor responses and decreased baroreflex sensitivity after volatile anaesthetics may aggravate haemodynamic instability in a patient with phaeochromocytoma.[123,124] Such effects may be particularly troublesome in a patient with an unrecognised tumour who has not been appropriately prepared for surgery. Lack of preoperative correction of a contracted intravascular volume may then lead to a significant hypotensive response to the vasodilator effects of inhaled anaesthetics; this is usually treated with sympathomimetics such as ephedrine, which in a patient with phaeochromocytoma are likely to provoke release of catecholamines from the tumour and lead to a hypertensive crisis.[125] As discussed in section 1, sympathomimetics stimulate release of catecholamines via a non-exocytotic, carrier-mediated mechanism.

Intraoperative hypertensive crises in patients with phaeochromocytoma have been reported during operative manipulations, such as insufflation of the peritoneum,[126] diathermy,[127] intubation[128,129] and most frequently after direct palpation of a mass.[107,112,130] During endotracheal intubation, there are two significant stimuli that frequently increase heart rate and blood pressure, even in patients without phaeochromocytoma: the laryngoscopy itself and insertion of the endotracheal tube. Both of these very potent stimuli could conceivably contribute to hypertensive crises observed during intubation in patients with undiagnosed phaeochromocytomas.

Other commonly reported problems occur with the use of anaesthetic-inducing agents.[102,104,108-110,131,132] Among these, the antipsychotic tranquilliser, droperidol used alone or as a formulation with fentanyl, has been a relatively common reported cause of hypertensive crises in patients with phaeochromocytoma.[104,109,131,132] Today, however, this drug is seldom used in anaesthesia.

An effect of droperidol to block uptake of catecholamines into vesicles, thereby stimulating non-exocytotic secretion, has been suggested by one group as the mechanism for the pressor effect of the drug in patients with phaeochromocytoma.[131] The antagonist action of the drug at D_2 receptors, with subsequent inactivation of a chromaffin cell dopaminergic-inhibitory system for modulating catecholamine release, has also been proposed as a mechanism for the hypertensive response in patients with phaeochromocytoma.[133] A mechanism in-

volving dopamine receptors seems likely, considering that other dopamine receptor antagonists, such as metoclopramide, can also provoke catecholamine release from phaeochromocytomas.[134] Because of its antiemetic properties, metoclopramide is occasionally used during induction of anaesthesia when there is concern about aspiration of vomitus. The drug should not be used in the preparation for surgical anaesthesia of any patient with a possible phaeochromocytoma.

Other drugs used during induction of anaesthesia may stimulate mast cell release of histamine, a secretogogue that provokes catecholamine release from phaeochromocytomas.[11,20,135] Agents with histamine-releasing properties include the opioid analgesics, thiopental sodium, nalbuphine, pethidine (meperidine), diamorphine and morphine,[136,137] and the neuromuscular-blocking agents tubocurarine, suxemethonium chloride (succinylcholine) mivacurium chloride, atracurium besilate and cisatracurium besilate.[138-140] Suxemethonium chloride also causes muscle fasciculation, thereby potentially increasing intra-abdominal pressure, which may additionally provoke catecholamine release by a phaeochromocytoma.[141,142]

Individual differences in response to the histamine-releasing properties of the various drugs and differences in responsiveness of phaeochromocytomas to histamine may lead to unpredictable hypertensive effects in patients not appropriately prepared for surgery. Even when patients with diagnosed phaeochromocytoma have received appropriate preoperative preparation for surgical anaesthesia, inducing agents with known histamine-releasing properties are best avoided, and alternatives considered.[143] Other narcotics, such as fentanyl, alfentanil and sufentanil, or muscle relaxants, such as alcuronium chloride, gallamine triethiodide, rocuronium bromide and vecuronium bromide, appear to have minimal effects on histamine release.[136,138-140] Atropine and other vagolytics are also best avoided, since parasympathetic blockade raises the heart rate and may further impair reflex circulatory control mechanisms.

5.2 β-Adrenergic Receptor Antagonists

Use of β-adrenergic receptor blocking drugs to treat persistent tachycardia or arrhythmias is often indicated for patients with phaeochromocytoma, particularly before and during surgical anaesthesia, but only after adequate blockade of α-adrenoceptor-mediated vasoconstriction. The danger of using β-blockers without first blocking catecholamine-mediated vasoconstriction is illustrated by numerous reports of severe hypertension, adverse reactions and even death after β-blockade in some patients with phaeochromocytoma.[52,53,100,101,129,144-152]

Numerous different β-adrenergic blockers have been implicated in precipitating adverse reactions in patients with phaeochromocytoma, with most problems reported with non-selective blockers (table V). The mechanism for β-blocker-associated adverse events is generally ascribed to inhibition of β_2-adrenoceptor-mediated vasodilation, leaving α-adrenoceptor-mediated vasoconstrictor responses to catecholamines unopposed. As discussed in section 4, because patients with undiagnosed phaeochromocytoma often present with conditions commonly treated using β-blockers (e.g. hypertension, cardiomyopathy and heart failure, panic attacks, migraine headache, tachycardia and cardiac dysrhythmias), there is significant danger that such patients so treated will experience an adverse reaction, including hypertensive crises, pulmonary oedema and shock.[52,53,144,145] When such adverse reactions occur in a patient on β-blockers, the presence of a phaeochromocytoma should be immediately suspected.

Table V. β-Adrenergic receptor antagonists (β-blockers) implicated in adverse reactions in patients with phaeochromocytoma

Antagonist	Selectivity
Propranolol	Non-selective
Penbutolol	Non-selective
Timolol	Non-selective
Nadolol	Non-selective
Sotalol	Non-selective
Labetalol	Non-selective, also blocks α-adrenergic receptors
Metoprolol[a]	Cardioselective

a Based on a single case of an unusual arrhythmic reaction.

Sibal and colleagues[101] reported five patients presenting to intensive care units because of unexplained acute severe cardiopulmonary dysfunction, all of whom were prescribed β-blockers for conditions that likely resulted from an unsuspected phaeochromocytoma. All but one patient were normotensive at initial presentation; four had sinus tachycardia and three presented with features of cardiomyopathy or heart failure, for which they were prescribed β-blockers; the two other patients were prescribed propranolol for panic attacks or for migraine prophylaxis. Following β-blockade, patients either presented with severe hypertensive crises and symptoms of catecholamine excess (n = 3) or showed further severe deterioration in cardiopulmonary function (n = 2). Two of the five patients developed pulmonary oedema, including one who also developed acute renal failure; haemodynamic collapse occurred in the other after induction of surgical anaesthesia for a presumed ruptured gall bladder.

Pulmonary oedema presenting as the main adverse reaction after administration of propranolol to patients with an undiagnosed phaeochromocytoma has been reported elsewhere.[52,144-146,150] Penbutolol, another non-selective β-blocker, has also been reported to cause pulmonary oedema in a patient with phaeochromocytoma.[53] In another case, a severe hypertensive crisis accompanied by pulmonary oedema and followed by shock, atrial-ventricular block and cardiac arrest occurred after administration of the non-selective β-blocker, timolol.[147] In this particular case, the β-blocker was administered as eye drops as part of a routine postoperative procedure after cataract extraction. It was surmised that, in contrast to oral administration where much of the drug undergoes first pass hepatic removal and metabolism, administration by the ocular route might have led to more direct entry of the drug into the systemic circulation. Other adverse reactions ascribed to non-selective β-adrenergic blockade in patients with undiagnosed phaeochromocytoma include severe hyperkalaemia after nadolol[148] and a dramatic increase of syncope episodes accompanied by severe supine hypertension after sotalol.[152]

Labetalol, because of its dual blocking actions on α- and β-adrenergic receptors, was proposed in early reports to be useful in managing patients with phaeochromocytoma.[153,154] However, the non-selective β-adrenoceptor blocking actions of labetalol predominate over the α-adrenoceptor blocking actions (in a ratio of 7 : 1); subsequent reports clearly indicate that the drug has similar properties to other non-selective β-adrenergic blockers in predisposing patients with phaeochromocytoma to hypertensive crises.[129,149,155-157] Labetalol used alone as the only agent to block α-adrenoceptor-mediated vasoconstriction is therefore contraindicated in patients with established or suspected phaeochromocytoma.

Because β-blocker associated predisposition to hypertensive crises in patients with phaeochromocytoma is believed to result from inhibition of β_2-adrenoceptor-mediated vasodilation (with unopposed α-adrenergic vasoconstriction), it might be presumed that cardioselective β_1-adrenoceptor blocking drugs may be administered without adverse effect. Indeed, with few exceptions, such as a report of an unusual arrhythmic reaction to metoprolol,[151] almost all adverse reactions to β-blockade in phaeochromocytoma patients have involved non-selective β-blockers. In one report of a normotensive patient with an undiagnosed phaeochromocytoma, adverse effects only became apparent when the patient was switched from a cardioselective to a non-selective β-blocker.[148] Therefore, cardioselective β-blockers (such as atenolol, esmolol and metoprolol) are favoured over non-selective blockers for the management of patients with phaeochromocytoma. Nevertheless, because of incomplete specificity and likelihood of some actions on β_2-adrenoceptors, even those β-blockers deemed cardioselective should only be administered to patients with phaeochromocytoma once there is adequate control of blood pressure by α-adrenoceptor blockade or other means.[158]

Since the actions of adrenaline on skeletal muscle β_2-adrenoceptor-mediated vasodilator responses far predominate over those of noradrenaline, a hypertensive response to β-blockade might be expected to be more likely in patients with phaeochromo-

cytomas that secrete mainly adrenaline compared with those secreting mainly noradrenaline. This suggestion is supported by a report showing lack of pressor responses to β-adrenoceptor blockade in two patients with phaeochromocytomas that produced predominantly noradrenaline.[159] Unfortunately, however, almost all published reports on adverse reactions to β-adrenoceptor blockade do not specify the types of catecholamines produced by the tumours. It therefore remains best to err on the side of caution and never administer a β-blocker to any patient with phaeochromocytoma without first blocking α-adrenoceptor mediated vasoconstriction.

5.3 Dopamine Receptor Antagonists

Nausea with or without vomiting is a relatively frequent symptom occurring in about 25–40% of patients with symptomatic phaeochromocytoma.[20] Drugs with antagonist actions on D_2 receptors can be effective antiemetic agents, but in patients with phaeochromocytoma, they may also dramatically increase release of catecholamines from the tumour, with profound pressor effects (table VI).[134,160] Metoclopramide is without doubt the D_2 receptor antagonist antiemetic drug with the most notorious record for provoking hypertensive crises in patients with undiagnosed phaeochromocytoma, in some cases, with disastrous sequelae including shock, multiple organ failure and death.[56,57,68,90,161-167]

The action of metoclopramide to provoke catecholamine release from phaeochromocytomas is so well established that the drug has been used under controlled conditions as a provocative agent to diagnose the tumours.[160,168,169] Although significant increases in blood pressure and plasma catecholamine levels after drug administration may suggest phaeochromocytoma, the test can return false-negative results and is not without risk to patients with the tumour.[170] The drug can also lead to mild increases in catecholamine levels and blood pressure in patients with hypertension but no phaeochromocytoma.[171] Given the significant advances in other biochemical tests used for diagnosis of phaeochromocytoma (in particular, measurements of plasma or urinary fractionated metanephrines), use of provocative tests is now rarely warranted.

Table VI. Dopamine D_2 receptor antagonists implicated in adverse reactions in patients with phaeochromocytoma

Antagonist	Principal therapeutic use
Metoclopramide	Antiemetic
Sulpiride	Antipsychotic
Amisulpride	Antipsychotic
Tiapride	Antipsychotic
Chlorpromazine	Antipsychotic, antiemetic
Prochlorperazine	Antipsychotic, antiemetic
Droperidol	Antipsychotic, antiemetic
Veralipride	Menopausal symptoms

Adverse reactions to other D_2 receptor antagonists include sudden death in two patients with undiagnosed phaeochromocytoma who were treated with the antipsychotic drug sulpiride.[172,173] A severe hypertensive crisis with headaches, nausea and vomiting occurred in another patient with undiagnosed phaeochromocytoma that was unmasked after the patient received benzamide antipsychotics, amisulpride and tiapride, for treatment of agitation and aggressiveness.[174] Other antipsychotics with dopamine receptor antagonist activity reported to cause adverse reactions in patients with undiagnosed phaeochromocytoma include the phenothiazine antipsychotic and antiemetic drugs, such as chlorpromazine and prochlorperazine.[50,51,175] As discussed in section 5.1, the antipsychotic tranquilliser droperidol (formerly used for induction of anaesthesia) represents another D_2 receptor antagonist known to provoke hypertensive crises in patients with phaeochromocytoma.[104,109,131,132]

In another report, administration of the centrally acting D_2 receptor antagonist veralipride was followed by clinical presentation of an acute coronary syndrome (ST-segment depression in inferior and lateral leads, elevated troponin 1 levels), which was subsequently determined to reflect an undiagnosed phaeochromocytoma.[176] In this particular case, the drug was prescribed for treatment of hot flashes. The use of centrally acting antidopamineric drugs, such as veralipride, in the treatment of postmenopausal symptoms,[177] therefore makes it particularly important not to miss phaeochromocytoma in the dif-

ferential diagnosis of hot flashes before such drugs are prescribed.

A direct action of dopamine receptor antagonists on phaeochromocytoma tumour cells is supported by consistent findings from several groups of expression of D_2 receptors in the adrenal medulla and in tumour tissue.[178-180] Further support is provided by findings that nicotine-induced secretion of catecholamines from the isolated cat adrenal gland is markedly increased by the dopamine receptor antagonist droperidol and inhibited by the dopamine receptor agonist apomorphine.[133] The presence of D_2 autoreceptor mechanisms that modulate catecholamine release has been further extensively characterised in rat phaeochromocytoma PC12 cell lines.[181,182] Other mechanisms have also been proposed to contribute to the effects of dopamine receptor antagonist drugs on catecholamine secretion from phaeochromocytomas.[183] However, available evidence indicates that the main mechanism probably involves blockade of D_2 autoreceptor-mediated secretion.

The numerous accounts of adverse reactions to D_2 receptor antagonists in patients with phaeochromocytoma serve to emphasise the need for immediate suspicion of the tumour in any patient where such drugs evoke a hypertensive crisis, apparent myocardial infarction, shock or multisystem crisis. Suspicion of a tumour can be particularly important in previously hypertensive patients where there may be other characteristic symptoms of catecholamine excess, but the tumour should also be suspected even where the presentation is subtler and the patient has been normotensive. It should be additionally recognised that some antipsychotic drugs, such as clozapine, can produce a state that mimics phaeochromocytoma with increases in urinary output of noradrenaline and blood pressure and accompanying symptoms of catecholamine excess.[184,185]

5.4 Antidepressants

Tricyclics represent the antidepressant drugs most recognised for producing adverse reactions in patients with phaeochromocytoma (table VII). Apart from use in the treatment of depression, tricyclics also have clinical utility for treatment of insomnia, neuropathic pain, migraine and other conditions.

Table VII. Antidepressants implicated in adverse reactions in patients with phaeochromocytoma

Class	Specific agents
Noradrenaline (norepinephrine) reuptake inhibitors (tricyclic antidepressants)[a]	Imipramine, desipramine, amitriptyline, clomipramine
Selective serotonin reuptake inhibitors[b]	Paroxetine, fluoxetine
Monoamine oxidase inhibitors	Tranylcypromine, phenelzine, moclobemide

a Other inhibitors of noradrenaline reuptake also have potential for adverse reactions in patients with phaeochromocytoma.

b Adverse reactions to serotonin reuptake inhibitors were at high doses likely involving cross-reactive effects on noradrenaline reuptake.

Adverse reactions in patients with undiagnosed phaeochromocytoma have been described after use of imipramine in six reports,[54,186-190] and in one report after desipramine.[191] Interestingly, three of the six reports of phaeochromocytomas unmasked in patients receiving imipramine involved children, aged 8–14 years, who were administered the drug to treat nocturnal enuresis.[187,189,190] In all cases, hypertension or symptoms of catecholamine excess became apparent soon after the children took the first dose of the drug. In two of the three reports,[187,190] it was noted that nocturnal enuresis resolved following removal of the tumour, suggesting a causal relationship of enuresis to the presence of phaeochromocytoma. Polyuria was reported in 25% of children with phaeochromocytoma,[192] and may contribute to enuresis.

The other three reports of adverse reactions in patients with phaeochromocytoma after imipramine involved adults who were given the drug for treatment of depression or headache.[54,186,188] Two patients presented with hypertension and the other presented with left ventricular failure and cardiogenic shock within 2 days after starting imipramine.

One report of an adverse response to desipramine involved a middle-aged woman with a history of severe headaches.[191] The patient reported nausea with vomiting, which began shortly after administration of the tricyclic for depression. On presenta-

tion in the emergency room she was hypotensive, had a marked tachycardia and brief episodes of profuse sweating. Severe supine hypertension developed, accompanied by marked orthostatic hypotension. The patient made a full recovery after diagnosis and resection of a large left adrenal phaeochromocytoma.[191]

Other reports of adverse reactions involving severe hypertensive responses to tricyclic antidepressants in patients with undiagnosed phaeochromocytoma have been described after use of the noradrenaline reuptake inhibitor amitriptyline[193] and the mixed noradrenaline and serotonin reuptake inhibitor clomipramine.[194] Reports of adverse reactions to other selective serotonin reuptake inhibitors are by comparison relatively rare, but have been published for paroxetine and fluoxetine.[195,196] In both cases, a previously unsuspected phaeochromocytoma was unmasked by development of severe paroxysmal hypertension, interspersed with intervals of hypotension, and occurring after administration of escalating doses of the serotonin reuptake inhibitors. In both cases, the effects of the drugs to unmask phaeochromocytoma were thought to result from incomplete selectivity of the drugs to inhibit serotonin reuptake and additional effects at high doses in impairing noradrenaline reuptake.

The mechanism responsible for hypertensive responses to tricyclic antidepressants in patients with phaeochromocytoma is generally ascribed to inhibition of the neuronal uptake process that normally removes noradrenaline from neuroeffector junctions and terminates the signal in sympathoneural transmission. However, while this mechanism is extremely important for removal of noradrenaline released at neuroeffector junctions, it makes a relatively minor contribution to removal of noradrenaline that escapes from these junctions into the circulation or the catecholamines released directly into the bloodstream from the adrenals.[16] Removal of circulating catecholamines is facilitated predominantly by extraneuronal monoamine transporters that are insensitive to the effects of tricyclic antidepressants. Since phaeochromocytomas express the same cell membrane noradrenaline transporters present on sympathetic nerves,[197] it seems possible that inhibition of those transporters might facilitate greater escape into the circulation of the catecholamines released locally within tumours.

Production of hypertensive crises accompanied by symptoms of catecholamine excess, a presentation similar to that in patients with phaeochromocytoma, is a well known hallmark of the 'cheese effect' in patients taking MAO inhibitors.[198,199] These often severe reactions, resulting from inhibition of MAO type A catalysed inactivation of dietary tyramine, have discouraged the therapeutic use of MAO inhibitors. Presumably as a consequence of the highly restricted use of non-selective MAO inhibitors, reports of adverse reactions to these drugs in patients with unsuspected phaeochromocytoma are rare.

One case has been reported of a hospitalised patient with intractable depression who was treated with tranylcypromine 10mg and who developed discrete episodes of acute anxiety, flushing, headache and severe hypertension, even under conditions of a controlled diet free of tyramine.[200] Phaeochromocytoma was diagnosed and the tumour removed, but without normalisation of the patient's mental state. Because inhibition of MAO has minimal effect on the circulatory clearance of catecholamines,[18] it seems that the adverse reaction in this patient might have reflected inhibition of deamination processes within the tumour. Due to the ability of tyramine to provoke catecholamine release from phaeochromocytomas, a considerably more severe adverse reaction would have been expected without a controlled diet to lessen any adverse effects of dietary tyramine.

With these considerations in mind, all MAO inhibitors with actions on the type-A form of the enzyme are contraindicated in patients with, or who are suspected to have, a phaeochromocytoma. Other drugs with a propensity for inhibition of MAO type A may also present problems. Linezolid, a novel oxazolidinone antibacterial, is one such drug with MAO-inhibitory properties where some degree of caution may be warranted in the patient with established or suspected phaeochromocytoma.[201]

5.5 Sympathomimetics

Sympathomimetics include a diverse array of drugs that mimic stimulation of the sympathetic nervous system, either through direct actions on adrenergic receptors or indirect actions of the drugs to stimulate release of catecholamines (table VIII). Because of these actions, such drugs have significant potential to produce adverse reactions in patients with phaeochromocytoma.[202] Effects of sympathomimetics include nervousness, insomnia, loss of appetite, nausea, vomiting, dizziness, palpitations and headaches. Changes in heart rate and blood pressure, skin rashes, itching, abdominal pain, weight loss, digestive problems, toxic psychosis and psychotic episodes are also possible.

Over-the-counter use of nasal decongestants such as formulations containing ephedrine, pseudoephedrine or phenylpropanolamine provide the most common use of sympathomimetics. Due to their anorexic actions, some sympathomimetics such as amfepramone (diethylpropion), fenfluramine and phentermine have been used as antiobesity agents. As previously reviewed elsewhere,[203] some of the medications used to assist weight loss carry a high risk of adverse reactions in certain patient populations. Patients with phaeochromocytoma are likely to have a higher risk of adverse effects from such weight-loss medications. Other sympathomimetics, such as dexamfetamine, are used for treatment of narcolepsy, while others, such as methylphenidate, are increasingly prescribed for treatment of attention deficit hyperactivity disorder. Sympathomimetics, such as salbutamol (albuterol), terbutaline and isoprenaline, with primary effects on peripheral β-adrenoceptors are used in the treatment of asthma. Those with actions on peripheral α-adrenoceptors, such as ephedrine and catecholamines, are used in conditions where it is appropriate to raise blood pressure by inducing vasoconstriction (e.g. surgical anaesthesia as discussed in section 5.1). Some of these drugs, and others that are illegal (e.g. amfetamine, cocaine), may also be abused for recreational purposes.

Table VIII. Sympathomimetics implicated in adverse reactions in patients with phaeochromocytoma

Drug	Relevant use
Ephedrine	IV circulatory support
Noradrenaline (norepinephrine)	IV circulatory support
Adrenaline (epinephrine)	IV circulatory support
Dopamine	IV circulatory support
Dobutamine	IV circulatory support
Dopexamine	IV circulatory support
Pseudoephedrine	Nasal decongestant
Phenylpropanolamine	Nasal decongestant
Amfepramone	Antiobesity agent
Fenfluramine	Antiobesity agent
Phentermine	Antiobesity agent
Dexamfetamine	Narcolepsy
Methylphenidate	ADHD
Salbutamol (albuterol)	Bronchodilator
Terbutaline	Bronchodilator
Isoprenaline	Bronchodilator
Amfetamine	Illicit recreational
Cocaine	Illicit recreational

ADHD = attention deficit hyperactivity disorder; **IV =** intravenous.

Among the various sympathomimetics, perhaps those with the propensity to cause the most problems in patients with phaeochromocytoma are the indirectly acting sympathomimetics (e.g. ephedrine or pseudoephedrine) that may induce catecholamine release from tumours.[202] However, reported cases are rare, but do include one patient with phaeochromocytoma who developed severe hypertension, cardiomegaly and congestive heart failure after overuse of nasal decongestants.[204] Cases involving the unmasking of phaeochromocytoma by other sympathomimetics include a patient who had two perioperative hypertensive crises, apparently related to use of phentermine for treatment of obesity.[205] Although published cases of adverse reactions to sympathomimetics in patients with phaeochromocytoma are rare, it seems prudent to carefully consider administration of such drugs to any patient suspected of harbouring these tumours.

More commonly reported problems with sympathomimetics have been associated with cases of pseudophaeochromocytoma, where the tumour was suspected because of clinical complications of the sympathomimetic agents, often further complicated by false-positive biochemical test results due to interference with analytical measurements of catecho-

lamines and catecholamine metabolites.[206-210] Some of these cases include patients with Munchausen syndrome, who have deliberately self-administered sympathomimetic amines or catecholamines.[207,209,210]

5.6 Peptide and Corticosteroid Hormones

Possibly because of aberrant expression of receptors, phaeochromocytomas can secrete catecholamines in response to peptide hormones, such as corticotropin and glucagon (table IX). Among the hormones established to cause complications in patients with phaeochromocytoma, corticotropin stands out as particularly problematic. In 1962, Ramsay and Langlands[211] reported a patient with phaeochromocytoma in whom corticotropin administration precipitated a fatal hypertensive crisis with an elevation of blood pressure to 300/190mm Hg. In another report, in 1966, injection of corticotropin for diagnostic purposes caused hypertensive crises in three patients with phaeochromocytoma, leading to pulmonary oedema and death in two.[212] The danger of using the corticotropin stimulation test in any patient who might have a phaeochromocytoma was stressed in 1968 by Steiner et al.[213] Those conclusions were further supported in 1974 by Critchley et al.,[214] who presented findings highlighting the danger of administering corticotropin and metyrapone in patients with phaeochromocytoma. A hypertensive crisis after injection of corticotropin in a patient with an adrenaline-producing phaeochromocytoma was subsequently reported in 1990 by Jan et al.,[215] further documenting the dangers of the corticotropin stimulation test in patients with undiagnosed phaeochromocytoma.

Glucagon represents another peptide hormone with well established effects in evoking catecholamine release and causing hypertensive crises in patients with phaeochromocytoma. Similar to the use of metoclopramide as a provocative agent to diagnose the phaeochromocytoma,[160,168,169] the effects of glucagon on catecholamine release from phaeochromocytomas have also led to use of this peptide hormone as a provocative diagnostic agent.[11,216-218] Since the therapeutic use of glucagon is limited, its reported adverse effects outside of its use for diagnosis of phaeochromocytoma are rare. Problems, including life-threatening hypertensive crises, have been reported with use of intravenous glucagon as a test in patients with diabetes,[219] and when the peptide has been employed during endoscopic radiological examinations.[220,221] Responses to glucagon in phaeochromocytoma appear to reflect aberrant expression of receptors on tumour cells,[12] with differences in responses among patients reflecting variable expression of the receptor in tumours (G. Eisenhofer, unpublished observations).

Table IX. Peptide hormones and corticosteroids implicated in adverse reactions in patients with phaeochromocytoma

Class	Specific agents
Peptide hormones and analogues	Corticotropin, glucagon, saralasin
Corticosteroids	Dexamethasone, betamethasone, prednisone, methylprednisolone, hydrocortisone

Angiotensin II is another vasoactive peptide proposed to contribute to catecholamine release and hypertension in patients with phaeochromocytoma.[14] Although there is one report of a hypertensive crisis after administration of saralasin,[222] most reported experience with this angiotensin II analogue has indicated vasodepressor responses in patients with phaeochromocytoma.[223-225]

In addition to the potential of peptide hormones for increasing catecholamine release by phaeochromocytomas, there are also several anecdotal reports that exogenous corticosteroids may precipitate hypertensive crises in patients with these tumours. Manger and Gifford[20] report in their book (p 144) a case of a 46-year-old male who was in otherwise good health until he received an injection of corticosteroid for dermatitis; he then developed chest pain, hypertension, pyrexia, tachycardia with premature ventricular contractions and atrial fibrillation, culminating in death. A phaeochromocytoma was revealed at autopsy. In another case, reported by Page and associates,[226] a patient with a predominantly adrenaline-secreting phaeochromocytoma developed severe paroxysmal hypertension several hours

after receiving hydrocortisone, prednisone and corticotropin.

Prednisone administered to another patient to treat vasculitis led to attacks of palpitations and tremor with blood pressure reaching 240/140mm Hg.[227] Stopping the prednisone ameliorated the attacks. A phaeochromocytoma was diagnosed and resected. Maintenance of corticosteroid treatment thereafter was uncomplicated, indicating that the catecholamine crises in this patient were related to acute administration of prednisone. Other cases have been reported of hypertensive crises in patients with phaeochromocytoma, where prednisone was administered as part of the chemotherapeutic regimen for treatment of lymphoma.[228,229] In these two cases, however, it was unclear whether other components of the chemotherapeutic cocktail may have also contributed to the crises.

More recently, Brown et al.[76] reported a case of haemorrhagic phaeochromocytoma unmasked by systemic administration of dexamethasone and presenting as myocardial infarction with severe labile hypertension. In this particular case, the temporal nature of the occurrence of signs and symptoms indicated a strong causal relationship with corticosteroid therapy. It was also suggested that the corticosteroid may have contributed to tumour haemorrhage.

During the writing of this article, the authors became aware of four other cases of phaeochromocytoma where the occurrence of catecholamine crises appeared related to administration of corticosteroids. Three of these cases involved the unmasking of phaeochromocytomas after administration of dexamethasone or betamethasone, which in one patient was administered during the course of anti-inflammatory therapy (A.L. Rosas, unpublished observations) and in the other two as part of dexamethasone-suppression tests to evaluate adrenal incidentalomas (A. Kasperlik-Zaluska, personal communication). Two patients experienced severe complications of haemorrhagic phaeochromocytomas, including shock and mutisystem crises, culminating in death in one patient and a difficult recovery in the other. The third patient had a hypertensive crisis, but recovered after emergency room treatment with antihypertensives. The fourth patient, with established malignant phaeochromocytoma, had a severe hypertensive crisis within hours after intravenous hydrocortisone, administered as part of an experimental protocol for treatment of the patient's malignancy (K. Pacak, unpublished observations). Imaging studies performed before and after the event indicated that a large bone metastasis had become necrotic in the intervening period, suggesting that the necrotic process might have contributed to the crisis in this patient.

5.7 Radiocontrast Agents

Use of radiocontrast during computed tomography (CT) and magnetic resonance imaging is frequently cited as a potential trigger for catecholamine release and hypertensive crises in patients with phaeochromocytoma. This contention is based on early reports of hypertensive responses and adverse reactions to injection of contrast media during angiography or venography.[230-232] Findings that intravenous injections of contrast medium caused large and unpredictable increases in plasma catecholamine levels in some patients with phaeochromocytoma further suggested increased likelihood of dangerous reactions to radiocontrast in patients without adequate α-adrenergic blockade.[233] CT without contrast was subsequently recommended for initial tumour localisation in patients with phaeochromocytoma.[234]

Adverse reactions to radiocontrast media may be related to direct chemotoxic effects, the physicochemical properties of the contrast media and anaphylactic reactions.[235] Histamine release from mast cells during anaphylactic reactions may be particularly troublesome in patients with phaeochromocytoma.[119]

When considering the safety of radiocontrast agents, it is important to appreciate that early reports of hypertensive crises in patients with phaeochromocytoma invariably involved administration of high-osmolality ionic contrast agents; such agents have higher potential for adverse reactions than low- or iso-osmolality non-ionic radiographic contrast

agents available today.[236] Several large population-based studies have indicated that use of newer radiocontrast agents carry a low risk of adverse reactions in all but the highest risk groups of patient (i.e. those with renal impairment, severe cardiac disease, multiple myeloma, polycythaemia, severe allergies or history of reactions to contrast).[237-240]

Intravenous injections of the non-ionic contrast medium iohexol have been shown to be without effect on plasma concentrations of catecholamines in patients with phaeochromocytoma.[241] Thus, while some clinicians may still consider it prudent, most experts in the field believe it is no longer absolutely necessary to administer adrenergic blockers before imaging studies involving non-ionic contrast agents.

The improved imaging characteristics of contrast-enhanced or delayed-contrast enhanced CT clearly provide important benefits for interpretation of results that can easily outweigh any risk associated with use of radiocontrast agents. However, decisions about whether to delay imaging studies until adequate adrenergic blockade has been achieved or even to avoid use of radiocontrast agents should take into account the presence of other factors that may increase the risk of adverse reactions in the patient with phaeochromocytoma (e.g. previous history of allergy to contrast or renal impairment).

5.8 Miscellaneous

Other therapeutic agents that may cause hypertensive crises or other adverse events in patients with phaeochromocytoma include cytotoxic chemotherapeutic agents,[242] betahistine,[243] opioid narcotics,[244] naloxone,[245] and a combination of caffeine and ergotamine used in the treatment of migraine headaches.[246]

Combination chemotherapy with cyclophosphamide, vincristine and dacarbazine, although not usually curative, can be useful for treatment of some patients with malignant phaeochromocytoma.[247] These and other antineoplastic agents have been reported to cause hypertensive crises in occasional patients with phaeochromocytoma.[228,229,242] It is therefore important that there is good control of blood pressure with adrenergic receptor blockers or other drugs before chemotherapy is initiated. Similarly, reports of transient increases in blood pressure after 131I-metaiodobenzylguanidine at high doses used for treatment of malignant phaeochromocytoma indicate a need to consider precautionary antihypertensive therapy prior to this form of targeted radiopharmaceutical therapy.[248,249]

Betahistine is a structural analogue of histamine used in the symptomatic treatment of vertigo, including vestibular disorders such as Meniere's disease.[243] The drug presumably may provoke hypertensive crises in patients with phaeochromocytoma through a similar mechanism to that of histamine; activation of histamine H_1 receptors, followed by G-protein-coupled mobilisation of calcium stores to trigger exocytotic secretion of catecholamines.[10]

Reports of hypertensive crises in patients with phaeochromocytoma after administration of heroin (diamorphine)[244] presumably reflect the effects of opioid narcotics to stimulate histamine release from mast cells. From examination of the effects of the opioid antagonist naloxone, there are also suggestions that endogenous opioids may modulate catecholamine release from phaeochromocytomas, particularly those tumours that produce adrenaline.[250] Based on isolated reports that tramadol may produce hypertensive crises, this novel analgesic with opioid and non-opioid modes of action is also contraindicated in patients with phaeochromocytoma.[251]

Hypoglycaemia in susceptible patients, or which may be induced by insulin, has been suggested as a possible trigger for provoking catecholamine release and leading to hypertensive crises in some patients with phaeochromocytoma.[166,252] Such an effect could be hypothesised to occur secondary to increased secretion of glucagon and the well known effects of that peptide hormone to provoke catecholamine release from tumours. However, in one report on the subject, there was no association between the hypoglycaemic trigger for attacks and increases in circulating glucagon levels.[252]

Production of paroxysmal hypertension in a patient with a previously undiagnosed phaeochromo-

cytoma has been reported in association with use of dipping tobacco (snuff).[253] Apart from this single case, reports establishing an association between the use of tobacco products and acute adverse reactions in patients with phaeochromocytoma are scarce. Nicotine is nevertheless well established to stimulate calcium-dependent exocytotic release of catecholamines from chromaffin cells and to increase plasma levels of catecholamines.[254,255] Therefore, it is possible that high doses of nicotine might provoke catecholamine release from a phaeochromocytoma.

Dietary supplements or herbal remedies with sympathomimetic effects or actions on adrenergic systems may represent other potential hazards for patients with diagnosed or undiagnosed phaeochromocytomas. Examples include dietary supplements that contain ephedrine alkaloids (e.g. ephedra, ma huang, 'Metabolife') and which have been identified to cause hypertension, palpitations, stroke, seizures and even death. These particular supplements are now banned in the US, but may pose threats elsewhere.[256] Herbal remedies containing yohimbine (e.g. yohimbe bark extract) and sold as virilising agents may also present problems in patients with phaeochromocytoma, since yohimbine can stimulate sympathoneural noradrenaline release and elevate blood pressure.[257,258] Due to a paucity of information on active ingredients and the limited reporting of adverse reactions, the risks associated with specific dietary supplements or herbal remedies in patients with phaeochromocytoma are largely unknown.

6. Prevention and Management of Adverse Reactions

The prevention or successful management of hypertensive crises and other adverse reactions in patients with phaeochromocytoma depends substantially on whether the tumour has already been recognised. In patients in whom the tumour has been diagnosed, most adverse reactions can be avoided by prompt attention to recommended practices for patient management; under these circumstances, when severe hypertension or other problems arise, medical staff can at least be prepared with an appropriate course of action.

The scenario for successful management of adverse reactions when phaeochromocytoma has not been recognised can be much more problematic. In this situation, the outcome is less favourable for the patient, and often grim. Successful management here depends largely on how quickly the underlying tumour is recognised; even then, progression to circulatory collapse and multisystem organ failure can render recovery unlikely.[46,47,49,58,61,62] Reports with a favourable outcome are relatively rare.[48,59,63] The patient who survives such serious adverse reactions is lucky.

6.1 Preoperative Management

Cure for phaeochromocytoma and prevention of related adverse events requires skilful management and total surgical removal of the tumour. Once phaeochromocytoma is diagnosed, it is imperative that patients are appropriately prepared for surgery. The goal for preoperative management of patients with phaeochromocytoma is to decrease the incidence of end-organ damage and perioperative morbidity and mortality.

The First International Conference on Phaeochromocytoma held in 2005 featured a special moderated session to discuss and reach agreement about appropriate management and therapeutic options for patients with phaeochromocytoma. Ensuing recommendations were published in the proceedings of the symposium,[158] in a subsequent review article[259] and at the website of the Pheochromocytoma RESearch Support ORganization (PRESSOR).[260]

It was recommended that all patients with biochemically established phaeochromocytomas or paragangliomas, including those who are normotensive, should receive appropriate preoperative medical management to block the effects of released catecholamines. Due to wide-ranging practices and international differences in available or approved therapies, and without evidence-based studies comparing different therapies, there was no specific recommendation about preferred drugs for preoper-

ative blockade. α-Adrenergic receptor antagonists and calcium channel antagonists are generally recommended for blood pressure control. For tachyarrhythmias, β-blockers or calcium channel antagonists are recommended. It was emphasised that if β-blockers are used, they should be used only after adequate pretreatment with α-blockers. Volume expansion was also recommended before, during and after surgery.

A detailed history, physical examination and complete laboratory and cardiac evaluation are essential in preparation of the patient with phaeochromocytoma for surgery. In some cases, echocardiography can be helpful to delineate the degree of cardiac compromise, especially in patients with longstanding hypertension. However, the value of preoperative echocardiography in patients without cardiac symptoms or clinical evidence of cardiac involvement has been questioned.[261] Assessment of reduced myocardial contractility using Doppler echocardiography appears to better predict risk of perioperative collapse than conventional echocardiography.[262] Cardiovascular function is optimised by relaxation of the constricted vasculature, expansion of the reduced plasma volume, and normalisation of blood pressure for 1–2 weeks before operation. Normalisation of blood volume minimises the possibility of protracted hypotension or shock resulting from sudden diffuse vasodilation at the time of tumour removal.

Phenoxybenzamine, a long acting, noncompetitive α-blocker, has been recommended since the mid-1950s and remains the drug most often used for preoperative control of blood pressure. The drug is administered orally, beginning with a dose of 10–20mg twice daily. The dose is gradually increased until blood pressure control is achieved, up to 100mg twice daily (1 mg/kg) for 1–2 weeks before surgery. Daily doses of 20–40mg are usually adequate. Institutional protocols vary considerably. For example, at some centres, a supplemental dose (0.5–1.0 mg/kg) is administered at midnight before surgery, while at others it is withheld 1–2 days before surgery. The time-honoured therapeutic goal is to maintain blood pressure no higher than 160/90mm Hg and for orthostatic changes not to exceed 80/45mm Hg. The main adverse effects of phenoxybenzamine are orthostatic hypotension (which may persist into the postoperative period), reflex tachycardia, fatigue and central somnolence. Although the elimination half-life of phenoxybenzamine is 24 hours, clinical effects may last up to 7 days after discontinuation of therapy.

Alternatives to phenoxybenzamine include selective α_1-blockers, such as doxazosin, prazosin and urapidil. Since these drugs do not block presynaptic α_2-adrenergic receptors, they have less propensity to produce tachycardia. Thus, β-blockers are seldom required. Doxazosin is an orally administered, selective, competitive, α_1-antagonist with a plasma half-life of 20 hours.[263] It can be administered by mouth at a dose of 1–16 mg/day. The shorter duration and different mechanism of action (competitive inhibition) of doxazosin compared with phenoxybenzamine, allow for rapid dose adjustments and more precise titration before surgery, thereby decreasing the extent of postoperative hypotension.[263] Prazosin is a competitive, selective α_1-blocker with a half-life of 2−3 hours, requiring administration two to three times daily.[264,265] For this reason, the drug is seldom used for preoperative preparation of the patient with phaeochromocytoma. Urapidil, which is available in oral and intravenous preparations, has a similarly short half-life of 2.7 hours.[266,267] When used in patients with phaeochromocytoma, it is usually administered by a continuous infusion.[266]

Calcium channel antagonists inhibit catecholamine-induced intracellular calcium flux, relaxing coronary and peripheral arteries.[268] These agents may also prevent catecholamine-associated coronary spasm, and are therefore useful in phaeochromocytoma associated with myocarditis and/or coronary vasospasm. They do not cause orthostatic or postoperative hypotension, and may be the drug of choice in the preparation for surgery of normotensive patients with phaeochromocytoma. They are also useful when combined with α-blockers in cases of resistant hypertension. Nifedipine, a dihydropyridine calcium channel antagonist, has been used with

good results to control blood pressure in preparation for surgery. The dose of nifedipine is from 30 to 90 mg/day.

α-Methyl-para-tyrosine (methyltyrosine) inhibits tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, and reduces tumour catecholamine stores. It is usually chosen as a second-line drug, at a dose of 250mg three to four times daily and can provide a useful adjunct for preoperative management in patients with highly active tumours where blood pressure remains poorly controlled despite optimum therapy with α-blockers or calcium channel antagonists alone or in combination.[269]

Since a reduced intravascular volume often accompanies a phaeochromocytoma, most clinicians increase sodium intake after the initiation of antihypertensive therapy, and often use preoperative fluid loading before surgery.[270] Although controlled clinical studies are lacking, a few retrospective studies[270-272] have shown fewer complications related to hypotension and less use of vasopressors in patients who received preoperative hydration compared with historical controls who did not. However, even when seemingly adequate α- and β-blockade were instituted preoperatively, haemodynamic instability can still occur during surgery.

6.2 Intraoperative Management

Given the likelihood of intraoperative haemodynamic lability, continuous monitoring of arterial and central venous pressures is important. Maintenance of cardiovascular stability in the perioperative period is a challenge for the anaesthesiologist. There can be profound changes in heart rate and arterial blood pressure at various steps during surgical procedures. Such changes can be extreme, rapid and unexpected, with hypertension alternating with hypotension. Pharmacological management requires immediate availability of specific drugs, which should be titratable and have a rapid onset and short duration of action.

Intravenous phentolamine has been traditionally used to treat hypertensive crises in patients with phaeochromocytoma. Due to availability of other drugs with better pharmacokinetic profiles and fewer adverse effects, phentolamine is now seldom used for such purposes. Intravenous vasodilators such as sodium nitroprusside, nicardipine, fenoldopam and nitroglycerin provide more effective short-term control of intraoperative hypertension (table X). These agents are easily titratable minute to minute, have a short duration of action and can be used alone or in combination with other vasodilators.

Sodium nitroprusside is a non-selective arterial and venous vasodilator. The drug must be given by intravenous infusion and should be protected from light (because of rapid degradation when exposed to light or alkaline conditions). Onset of action is within 30 seconds, peak effect within 2 minutes and termination of effect 3 minutes after termination of infusion.[273] The drug causes a moderate reflex tachycardia. Cyanide toxicity with resulting lactic acidosis can occur when doses >5 μg/kg/min are administered over long periods of time.[274,275] Hypertension can be controlled in most patients by doses between 0.5 and 5 μg/kg/min.[273,276] If doses >10 μg/kg/min are required for >10 minutes, the dose must be reduced and/or another vasodilator introduced. Toxicity can occur at lower rates of administration when used for >24 hours, or in patients with renal insufficiency.[277-279]

Nicardipine, a dihydropyridine calcium channel antagonist for intravenous use has been successfully used during surgery with good results in a few studies.[280-282] Because the drug can prevent catecholamine-induced coronary vasospasm, nicardipine is especially useful in those cases of phaeochromocytoma presenting with catecholamine-induced myocarditis.

Intravenous infusions of magnesium sulfate have been described in several reports as effective as the sole agent or in combination with other vasodilators for intraoperative haemodynamic control and treatment of perioperative hypertensive crises.[281,283] Magnesium sulfate not only decreases catecholamine release, but is also an α-antagonist, antiarrhythmic and vasodilator even in the presence of elevated catecholamine levels.

Table X. Treatment of hypertensive crisis: intravenous (IV) drugs[a]

Drug	Preparation	Dose	Details
Sodium nitroprusside: nitrodilator, direct arterial > venous vasodilator; onset 30s, peak effect 2 min	50mg in 250mL D5%W	0.5–5.0 μg/kg/min via infusion, central line preferred	Cyanide toxicity/lactic acidosis; do not use for >24h at high doses (>5 μg/kg/min); maximum dose: 10 μg/kg/min for no more than 10 min; tachycardia, protect from light
Nicardipine: dihydropyridine calcium-channel antagonist, arterial vasodilator	25mg in 250mL D5%W	Loading: 1–2.5mg over 1–2 min, then 5–15 mg/h via infusion	Moderate reflex tachycardia; minimum effect on cardiac contractility; prevents catecholamine-induced coronary spasm
Magnesium sulfate: vasodilator, antiarrhythmic; decreases catecholamine secretion	40g in 500mL Ringer's solution	Loading: 1–2g IV, then 1–3 g/h via infusion	Adverse effect: muscular weakness; monitor serum magnesium level
Fenoldopam: arterial vasodilator; dopamine DA_1 receptor agonist; no effect on DA_2 receptors	10mg in 250mL NS	0.1 μg/kg/min up to 1.6 μg/kg/min	No bolus dose recommended; reno-protective; tachycardia
Phentolamine: competitive, non-selective α-adregenergic receptor antagonist (α-blocker); 19 min half-life	100mg in 500mL D5%W	IV bolus: 5–15mg; IV infusion rate: 0.2–2 mg/min	No longer primary agent; may use as initial therapy (IM or IV) until other vasodilators available
Urapidil: peripheral selective α_1-adrenergic receptor antagonist; 2.7h half-life	12.5g in 250mL NS	IV bolus: 10–50mg; IV infusion: initial rate 2 mg/min, maintenance 9 mg/h	Additional CNS actions. Not available in the US for clinical use. Doses of 150–200 mg/h may be required in phaeochromocytoma
Esmolol: selective β_1-adrenergic receptor antagonist; short acting: 9 min half-life	2.5g in 250mL NS	Loading: 500 μg/kg over 1 min then 50–300 μg/kg/min via infusion	Mostly used as adjuvant and to control tachycardia; use only after α-blockade or vasodilator therapy

a These are general guidelines and each drug should be titrated to blood pressure. Continuous monitoring of blood pressure with an arterial line is recommended.

D5%W = 5% dextrose in water; **IM** = intramuscular; **NS** = 0.9% sodium chloride (normal saline).

Supraventricular and ventricular arrhythmias during surgical anaesthesia can be common, either because of high levels of circulating catecholamines or as an adverse effect of non-selective α-blockers. Supraventricular arrhythmias such as sinus tachycardia can usually be controlled with the short-acting β-blocker, esmolol. Other β-blockers such as propranolol and metoprolol can also be used, but have longer durations of action and cannot be titrated as effectively. Ventricular arrhythmias may be treated with lidocaine, and other agents, depending on the arrhythmia.

Profound hypotension can occur anytime during surgery, but is a particularly common occurrence after venous clamping and tumour isolation.[284] Hypotension before tumour venous clamping is usually secondary to overzealous vasodilator use, anaesthetic agents, hypovolaemia secondary to blood loss, mechanical obstruction of venous return or insufficient preoperative fluid loading. Hypotension is most appropriately managed by judicious administration of intravenous fluids, and by correcting the primary cause. Vasopressors are rarely needed in this situation, but choice of the appropriate drug is important. As discussed in section 5.5, ephedrine is contraindicated up until complete resection of the tumour. Other sympathomimetics that act directly to cause α-adrenergic-mediated vasoconstriction without provoking catecholamine release (e.g. phenylephrine) provide alternative agents. Hypotension following venous clamping and isolation of the tumour is likely due to several factors, including acutely decreased circulating catecholamines in the face of downregulated adrenergic receptors. Effects of non-competitive long-acting α-blockers, such as phenoxybenzamine, used in the preparation of patients for surgery may also be a factor.

Appropriate preoperative hydration, intraoperative fluid and blood replacement, timely discontinuation of vasodilators, position changes (head down-Trendelenburg position) and the use of vasopressors can all be used to minimise the duration and extent

of hypotension after tumour isolation. Infusions of sympathomimetics such as norepinephrine or phenylephrine are usually effective in low doses, and are often necessary only for a short time. When hypotension following tumour isolation is refractory to such agents, alternatives such as vasopressin can be useful.[285-287] Vasopressin can be used in small bolus doses and maintained as a continuous infusion.

Attention to metabolic status is of utmost importance both intra- and postoperatively. Haemodynamic lability can lead to acid-base derangements. Profound hypoglycaemia following resection of phaeochromocytoma has been reported.[288] Although mostly transient and easily treated with intravenous infusions of glucose, occasional cases have been reported of prolonged hypoglycaemia lasting for up to 6 days postoperatively.[289] The mechanism appears to involve an acute reversal of catecholamine-induced inhibition of insulin secretion with resultant rebound excessive secretion.[290]

6.3 Emergency Management of the Undiagnosed Phaeochromocytoma

Treatment of a hypertensive crisis due to phaeochromocytoma outside of the operating room follows some of the same guidelines as during surgery, and should be carried out in an intensive care unit. Intravenous infusions of vasodilators (such as sodium nitroprusside, nicardipine and fenoldopam) provide the most effective agents for the treatment of the crises (table X). If these vasodilators are unavailable, or in emergency situations outside of an intensive care setting, phentolamine may be considered for initial treatment. Administration of phentolamine may be given as an intravenous bolus of 2.5–5mg at 1 mg/min. If necessary, this dose can be repeated every 5 minutes until hypertension is adequately controlled. Phentolamine can also be given as a continuous infusion (100mg of phentolamine in 500mL of 5% dextrose in water) with an infusion rate adjusted to the patient's blood pressure during continuous blood pressure monitoring. Urapidil, a selective α_1-blocker, can be administered to treat a hypertensive crisis in intravenous bolus doses of 10–50mg.[291] A second 50mg dose can be administered if no effect is observed within 5 minutes. Alternatively, the drug can be administered by continuous infusion at an initial rate of 2 mg/min and a maintenance infusion of 9 mg/h. Dosages of 150–200 mg/h are often needed to treat hypertension during surgery for phaeochromocytoma. Although unavailable in the US, urapidil has been advocated elsewhere for the management of hypertensive emergencies outside of the intensive care setting.[292]

Therapeutic options are limited for patients presenting with shock and multiorgan failure, especially in circumstances where an underlying phaeochromocytoma is actually suspected. As discussed by Bergland,[46] not only is diagnosis enigmatic, but appropriate treatment can also present a paradox. In some patients with catecholamine-induced shock, vasoconstriction may be so severe peripherally that reliable blood pressure measurements are compromised, obscuring severe central hypertension. In this particular situation, administration of vasopressors would be inappropriate, whereas counter-intuitive therapy aimed at a vasodilatory response seems warranted. Assessment of volume status and cardiac function is critical in this situation. Measurements of pulmonary arterial, wedge and central venous pressures and/or echocardiography are essential to determine volume status, myocardial and pulmonary function. When hypovolaemic shock is clearly present, then volume expansion is of utmost importance.

Correcting metabolic acidosis and improvement of peripheral perfusion with judicious use of colloids and crystalloids is imperative. Similarly renal function should be assessed and protected as necessary. As reported by Olson et al.,[293] identification and correction of hypocalcaemia may also be particularly important in patients with phaeochromocytoma-associated cardiogenic shock. These authors proposed that the adverse effects of hypocalcaemia on cardiac contractility might represent an important mechanism contributing to heart failure and shock in patients with phaeochromocytoma. In such situations, replacement of ionised calcium could preserve cardiac function and reduce mortality.

Pulmonary oedema is common in cases of phaeochromocytoma-associated shock and may require intubation and lung-protective ventilatory strategies to maintain oxygenation. Hypertensive encephalopathy, hyperthermia, hyperglycaemia and hepatic failure may further complicate prognosis and therapeutic options and add to the high mortality of this condition. If phaeochromocytoma is suspected, then immediate attempts should be made to localise the lesion. Any recommendation to await biochemical confirmation of catecholamine excess is made impractical by the seriousness of the patient's condition and likely delay in obtaining laboratory results. An abdominal CT scan may be the most practical imaging option in a patient with multiple lines on cardiac and ventilatory support. Urgent but carefully considered and planned surgery may present the only chance for a successful outcome, even when the haemodynamic situation is unfavourable.[48,58,59,63]

7. Conclusions

There are numerous drugs and diagnostic or therapeutic manipulations and procedures that can cause serious adverse events or even fatal complications in patients with phaeochromocytoma. However, when these tumours have been diagnosed and appropriate precautions are instituted, the risks of adverse events are minimal. The dangers of adverse events are most troublesome in those patients in whom the tumour remains unsuspected. In such situations, the only truly effective means to avoid potentially catastrophic sequelae is for clinicians to quickly recognise the possibility of an underlying tumour and promptly employ the appropriate therapeutic counter measures. Recognition is the key, but this can be significantly hampered by the highly variable presentation of the tumour and its mimicry of many other much more common clinical conditions. Reliance on mainly anecdotal evidence for adverse drug reactions and unpredictable responses of phaeochromocytomas to the various drugs and procedures capable of causing adverse events represent other factors that can make recognition of an underlying tumour extremely difficult. The clinician capable of recognising an adverse reaction to an undiagnosed phaeochromocytoma must be highly observant and skilled; the patient who escapes unscathed from such a reaction is lucky.

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