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Pheochromocytoma Anesthetic Management

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ABSTRACT

Pheochromocytomas are catecholamine producing tumors and although uncommon present a great challenge to the anesthesiologist since it has nonspecific clinical symptoms and risk of critical events, including death when not previously diagnosed. Clinical manifestation is variable, unspecific and depends on the catecholamine production profile. The classic triad of headache, palpitation and diaphoresis is present in up to 70% of the cases and only 50% have sustained hypertension. The best approach for pheochromocytoma treatment is surgical excision of the affected adrenal gland. The introduction of alpha adrenergic blockade medication, such as phentolamine and phenoxybenzamine had the highest impact in perioperative mortality reduction due to inhibition of the deleterious effect of vasoconstriction. The majority of anesthetic techniques and drugs are considered safe. Post-operative care in intensive care unit is advisable since patients may present instability of blood pressure and hypoglycemia. Genetic testing should be done in first-degree relatives of confirmed cases or when a genetic syndrome is suspected.

Keywords: Pheochromocytoma; Anesthesia Management

1. Introduction

Pheochromocytomas are catecholamine producing tumor originated from chromaffin cells and up to 80% are located in the adrenal gland. Although uncommon they present a great challenge to the anesthesiologist since it has unspecific clinical symptoms, complex and not widely available diagnosis testing and risk of critical events, including death when not diagnosed. New research has found that up to 30% of pheochromocytoma cases are associated with autosomal genetic mutation [1,2].

2. Objectives

The proposal of this article is review the recent literature about clinical manifestation, diagnosis criteria, treatment options and anesthetic management of pheochromocytoma.

3. Method

For the review, scientific articles published between 2000 and 2012 in the PubMed Central (PMC-NCBI) databank where selected, preferably review and meta-analysis written in English containing the MeSH terms pheochromocytoma, phaechromocytoma, anesthesia and anaesthesia. Case report, experimental studies and uncommon presentations were excluded.

4. Results

The search retrieved 124 original articles respecting the inclusion and exclusion criteria described. From the original research 18 articles where selected for this review.

4.1. Clinical Manifestation and Diagnosis

The clinical manifestation is variable, unspecific and depends on the catecholamine production profile. The classic triad of headache, palpitation and diaphoresis is present in up to 70% of the cases and only 50% have sustained hypertension. The annual incidence is estimated in 2 to 8 cases per million in general population and prevalence of 0.1% to 0.6% in hypertensive population [3,4].

The best exam for diagnosis is the measurement of plasmatic metanephrines (Sensitivity of 99% and specificity of 89%) and since many medications can influence this test (**Table 1**) proper patient preparation is of upmost importance. The best option for topographic location is

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the use of catecholamine synthesis metabolic marker such as scintigraphy with ^{123}I-MIBG and PET scan with ^{18}F-fluorodopamine [3,4].

4.2. Treatment Options

The best approach for pheochromocytoma treatment is the surgical excision of the affected adrenal gland. Due to retroperitoneal anatomic positioning the preferably technique is laparoscopy [4].

For metastatic disease, there are other options like symptomatic treatment with adrenergic blockers, radiotherapy with ^{133}I-MIBG, chemotherapy and conventional radiotherapy. The prognosis of this presentation is poor with less than 50% survival in 5 years [1,4].

4.3. Anesthetic Management

An optimal pre-anesthetic management is vital for pheochromocytoma treatment and the goal is clinical control of the disease with reduction of plasmatic catecholamine levels. The introduction of alpha adrenergic blockade medication (**Table 2**), such as phentolamine and phenoxybenzamine had the highest impact in perioperative mortality reduction because it inhibits the deleterious effect of vasoconstriction [5-7].

Table 1. Medications that influence laboratory testing or treatment of pheochromocytoma.

Class	Mechanism of action	Medication	Clinical use
Antagonism of D2 dopaminergic receptors	Inhibition of catecholamine release antagonism in sympathetic ganglia	Metoclopramide	Antiemetic and prokinetic
		Droperidol, chlorpromazine	Antiemetic and antipsychotic
Inhibition of noradrenaline reuptake	Increase noradrenaline concentration	Imipramine, amitriptyline	Neuropathic pain, migraine, depression and insomnia
Inhibition of monoamine oxidase	Inhibition of catecholamine degradation pathway	Seleginine	Parkinson disease
β adrenergic antagonist	Increase of α adrenergic effects	Propranolol, metoprolol	Cardiac arrhythmia, hypertension, cardiomyopathies
		Timolol	Glaucoma
Sympathomimetic	Stimulate the catecholaminergic release from pheochromocytoma	Ephedrine, pseudoephedrine, phenylephrine	Decongestant
		Amfepramone, fenfluramine	Anorectics
		Methylphenidate	Attention-deficit hyperactivity disorder
		Albuterol, terbutaline	Bronchodilator
		Cocaine, amphetamine and derivatives	Local anesthetic, psych stimulant
		Vasoactive drugs	Hemodynamic support

Table 2. Mechanism of action and pharmacokinetics of medications used for pheochromocytoma control.

Medication	Mechanism of action	Duration	Metabolization	Excretion	Elimination t½	Proteic binding	Distribution volume
Phentolamine	Competitive inhibition of α adrenergic receptors	15 to 30 minutes	Hepatic	Urinary	19 minutes	50%	Unknown
Phenoxybenzamine	Noncompetitive blockade of α adrenergic receptors	Greater than 72 hours	Unknown	Urinary and fecal	24 hours	Unknown	Unknown
Doxazosin	Competitive inhibition of α_1 adrenergic receptors	Greater than 24 hours	Hepatic	Urinary and fecal	22 hours	98%	2 l/Kg
Prazosin	Competitive inhibition of α_1 adrenergic receptors	10 to 24 hours	Hepatic	Urinary and fecal	2 to 3 hours	92% to 97%	0.5 l/Kg
Metoprolol	Competitive inhibition of β_1 adrenergic receptors	5 to 8 hours	Hepatic	Urinary	3 to 8 hours	12%	5.5 l/Kg
Labetalol	Competitive inhibition of α_1 and β adrenergic receptors	2 to 18 hours	Hepatic	Urinary	5 hours	50%	9.4 l/Kg
Nicardipine	Dihydropyridine calcium channel blockers	8 hours	Hepatic	Urinary and fecal	2 to 4 hours	Greater than 95%	8.3 l/Kg
Nifedipine	Dihydropyridine calcium channel blockers	Unknown	Hepatic	Urinary	2 to 5 hours	92% to 98%	0.7 l/Kg
Clevidipine	Dihydropyridine calcium channel blockers	5 to 15 minutes	Plasma esterases	Urinary and fecal	15 minutes	99%	0.17 l/Kg
Metyrosine	Inhibition of tyrosine hydroxylase	Unknown	Unknown	Urinary	3 to 4 hours	Unknown	Unknown

During surgery the objective is maintenance of hemodynamic stability, since normal surgical stimuli (patient positioning, anesthesia induction, intubation, and tumor manipulation) may cause severe hypertension. The majority of anesthetic techniques and drugs are considered safe. Along with regular surgical monitoring, invasive blood pressure measurement is highly recommended [7-13].

After tumor excision hypotension may begin due to residual effect of alpha adrenergic antagonists, increase in venous capacitance and intraoperative bleeding, but is usually manageable leading to a near zero perioperative mortality in recent studies [14-17].

4.4. Post-Operative Management

Is advisable the post-operative care in intensive care unit since many patients may present blood pressure instability (up to 50% may have hypertension and increase of plasmatic levels of catecholamine) and hypoglycemia (patients may have a decreased glycogen level due to the increase in glycogenolysis and lipolysis caused by adrenergic stimulus) [18-21].

Lifelong follow up with plasmatic dosage of catecholamine and metanephrine is recommended since there are cases of late tumoral relapse in literature. Genetic testing should be done in first-degree relatives of confirmed cases or when genetic syndrome is suspected (café au lait spots, cerebellar tumor, thyroid medullar carcinoma, hyperparathyroidism) [8,9].

5. Discussion

Although uncommon type of tumor, pheochromocytomas present a great challenge to the anesthesiologist, since it has unspecific clinical symptoms, complex detection tests and possibility of unfavorable results, including death when not previously diagnosed.

Familiar or personal history of critical perioperative events associated with a detailed physical examination during pre-anesthetic evaluation are the main tools for the suspicion of these tumors.Clinical control with alpha adrenergic antagonistmedication had the highest impact in reduction of perioperative mortality and the majority of the experts consider adequate 14 to 21 days of treatment before surgery.

During surgery hemodynamic instability may arise due to nociceptive stimulus or tumoral manipulation, therefore hypotensive medications should be ready before anesthetic induction (**Table 3**). Commonly symptomatic adjuvant medication used in anesthesia (metoclopramide, droperidol) should be judiciously selected since it may trigger adrenergic crisis (**Table 1**). Postoperative care in an intensive care unit is recommended.

Table 3. Mechanism of action and pharmacokinetics of medications used for acute blood pressure control in pheochromocytoma.

Medication	Mechanism of action	Duration	Metabolization	Excretion	Elimination t½	Proteic binding	Volume of distribution
Nitroglycerin	Venous vasodilatation mediated by nitric oxide	3 to 5 minutes	Hepatic	Urinary	1 to 4 minutes	60%	3 l/Kg
Nitroprussiate	Vasodilatation mediated by nitric oxide	1 a 10 minutes	Hepatic	Urinary	2 minutes	Unknown	0.3 l/Kg
Phentolamine	Noncompetitive inhibition of α adrenergic receptors	15 a 30 minutes	Hepatic	Urinary	19 minutes	50%	Unknown
Urapidil	Antagonism of α_1 adrenergic receptors	3 hours	Hepatic	Urinary	3 to 5 hours	75% to 80%	0.5 l/Kg
Nicardipine	Inhibition of slow calcium channels	8 hours	Hepatic	Urinary and fecal	2 to 4 hours	Greater than 95%	8.3 l/Kg
Fenoldopam	Agonist of dopaminergic D1 and α_2 adrenergic receptors	15 minutes	Hepatic	Urinary	5 minutes	85% to 90%	0.6 l/Kg
Magnesium sulfate	Noncompetitive antagonism of endogenous calcium receptor	30 minutes	Unknown	Urinary	Unknown	40%	0.4 l/Kg
Esmolol	Competitive blockade of β_1 adrenergic receptors	10 to 30 minutes	Plasma esterases	Urinary	10 minutes	55%	3.2 l/Kg
Lidocaine	Reduce permeability of biological membranes to sodium	10 to 20 minutes	Hepatic	Urinary	2 hours	60% to 80%	2 l/Kg

All patients with pheochromocytoma should have lifelong follow up since late relapse have been reported. Relatives of confirmed pheochrmocytomas cases should receive information about the increased risk of catecholaminergic crisis.

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