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## Pheochromocytoma

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**Synonyms and related keywords:** catecholamine-secreting tumor, extra-adrenal pheochromocytomas, paragangliomas, life-threatening hypertension, cardiac arrhythmias, familial pheochromocytoma, sporadic pheochromocytoma, multiple endocrine neoplasia 2A, multiple endocrine neoplasia 2B, MEN 2A, MEN 2B, neurofibromatosis, von Hippel-Lindau disease, VHL disease, atrial fibrillation, ventricular fibrillation, myocarditis, myocardial infarction, MI, dilated cardiomyopathy, pulmonary edema, pheochromocytoma-induced hypertensive crises, hypertensive encephalopathy, stroke, cerebral infarction, mural thrombus, intracerebral hemorrhage, Von Recklinghausen disease, Sipple syndrome, tuberous sclerosis, Bourneville disease, Epiloia, Sturge-Weber syndrome, Cushing syndrome, postural hypotension, hypertensive retinopathy, cafe au lait spots, neurofibromas, tachyarrhythmias, hyperglycemia, hypercalcemia

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### INTRODUCTION

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**Background:** Pheochromocytoma is a rare catecholamine-secreting tumor derived from chromaffin cells. Tumors that arise outside the adrenal gland are termed extra-adrenal pheochromocytomas or paragangliomas. Because of excessive catecholamine secretion, pheochromocytomas may precipitate life-threatening hypertension or cardiac arrhythmias. If the diagnosis of a pheochromocytoma is overlooked, the consequences could be disastrous, even fatal; however, if a pheochromocytoma is found, it is potentially curable.

The term pheochromocytoma (*phios* means dusky, *chroma* means color, and *cytoma* means tumor) refers to the color the tumor cells acquire when stained with chromium salts. Roux performed the first surgical resection of a pheochromocytoma in Lausanne, Switzerland in 1926. Later the same year, Charles Mayo performed the first surgical resection in the United States.

**Pathophysiology:** The clinical manifestations of a pheochromocytoma result from excessive catecholamine secretion by the tumor. Catecholamines typically secreted, either intermittently or continuously, include norepinephrine and epinephrine and rarely dopamine. The biological effects of catecholamines are well known. Stimulation of alpha-adrenergic receptors results in elevated blood pressure, increased cardiac contractility, glycogenolysis, gluconeogenesis, and intestinal relaxation. Stimulation of beta-adrenergic receptors results in an increase in heart rate and contractility.

Catecholamine secretion in pheochromocytomas is not regulated in the same manner as in healthy adrenal tissue. Unlike the healthy adrenal medulla, pheochromocytomas are not innervated, and catecholamine release is not precipitated by neural stimulation. The trigger for catecholamine release is unclear, but multiple mechanisms have been postulated, including direct pressure, medications, and changes in tumor blood flow.

Relative catecholamine levels also differ in pheochromocytomas. Most pheochromocytomas contain norepinephrine predominantly, in comparison with the normal adrenal medulla, which is composed of roughly 85% epinephrine. Familial pheochromocytomas are an exception because they secrete large amounts of epinephrine. Thus, the clinical manifestations of a familial pheochromocytoma differ from those of a sporadic pheochromocytoma.

#### Frequency:

- **In the US:** Pheochromocytomas are rare, reportedly occurring in 0.05-0.2% of hypertensive individuals. Patients may be completely asymptomatic. A retrospective study from the Mayo Clinic revealed that in 50% of cases, the diagnosis was made at autopsy (Beard, 1983). Approximately 10% of pheochromocytomas are discovered incidentally. Pheochromocytomas may occur in certain familial syndromes, including multiple endocrine neoplasia (MEN) 2A and 2B, neurofibromatosis, and von Hippel-Lindau (VHL) disease.

**Mortality/Morbidity:** Although pheochromocytomas are rare, making the diagnosis is critical because the malignancy rate is 10%, they may be associated with a familial syndrome, they may precipitate life-threatening hypertension, and the patient may be cured completely with their removal.

- **Cardiovascular morbidity:** Many cardiac manifestations are associated with pheochromocytomas. Hypertension is the most common complication. Cardiac arrhythmias, such as atrial and ventricular fibrillation, may occur because of excessive plasma catecholamine levels. Other complications include myocarditis, signs and symptoms of myocardial infarction, dilated cardiomyopathy, and pulmonary edema, either of cardiac or noncardiac origin.
- **Neurologic complications:** A pheochromocytoma-induced hypertensive crisis may precipitate hypertensive encephalopathy, which is characterized by altered mental status, focal neurologic signs and symptoms, or seizures. Other neurologic complications include stroke due to cerebral infarction or an embolic event secondary to a mural thrombus from a dilated cardiomyopathy. Intracerebral hemorrhage also may occur because of uncontrolled hypertension.

**Race:** Pheochromocytomas occur in people of all races, although they are diagnosed less frequently in blacks.

**Sex:** Pheochromocytomas occur with equal frequency in males and females.

**Age:** Pheochromocytomas may occur in persons of any age. The peak incidence, however, is between the third and the fifth decades of life. Approximately 10% occur in children. In children, 50% of pheochromocytomas are solitary intra-adrenal, 25% are present bilaterally, and 25% are extra-adrenal.

## CLINICAL

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**History:** The classic history of a patient with a pheochromocytoma includes spells characterized by headaches, palpitations, and diaphoresis in association with severe hypertension. These 4 characteristics together are strongly suggestive of a pheochromocytoma. In the absence of these 3 symptoms and hypertension, the diagnosis may be excluded. The spells may vary in occurrence from monthly to several times per day, and the duration may vary

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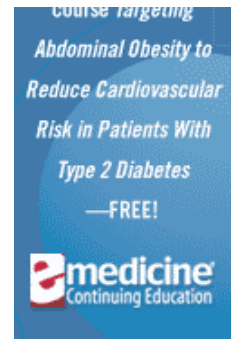
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from seconds to hours. Typically, they worsen with time, occurring more frequently and becoming more severe as the tumor grows.

- Symptoms include the following:
  - Headache
  - Diaphoresis
  - Palpitations
  - Tremor
  - Nausea
  - Weakness
  - Anxiety, sense of doom
  - Epigastric pain
  - Flank pain
  - Constipation
  - Weight loss
- Pheochromocytomas are known to occur in certain familial syndromes. These include MEN 2A and 2B, neurofibromatosis (von Recklinghausen disease), and VHL disease. The MEN 2A and 2B syndromes, which are autosomally inherited, have been found to have germline mutations in the *ret* proto-oncogene. The *ret* proto-oncogene, located on chromosome 10, encodes a tyrosine kinase receptor involved in the regulation of cell growth and differentiation. Pheochromocytomas occur bilaterally in the MEN syndromes in as many as 70% of cases. Pheochromocytomas occur in 1% of neurofibromatosis cases. VHL syndrome is associated with pheochromocytomas, cerebellar hemangioblastomas, and renal cell carcinoma.
  - MEN 2A (Sipple syndrome) is characterized by medullary thyroid carcinoma, hyperparathyroidism, pheochromocytomas, and Hirschsprung disease. Over 95% of cases of MEN 2A are associated with mutations in the *ret* proto-oncogene affecting 1 of 5 codons in exon 10 (codons 609, 611, 618, 620) or exon 11 (codon 634).
  - Medullary thyroid carcinoma, pheochromocytoma, mucosal neurofibromatosis, intestinal ganglioneuromatosis, Hirschsprung disease, and a marfanoid body habitus characterize MEN 2B. A germline missense mutation in the tyrosine kinase domain of the *ret* proto-oncogene (exon 16, codon 918) has been reported to be present in 95% of patients with MEN 2B.
  - Pheochromocytoma, cerebellar hemangioblastoma, renal cell carcinoma, renal and pancreatic cysts, and epididymal cystadenomas are associated with VHL disease. One study found that this syndrome was present in nearly 19% of patients with pheochromocytomas (Neumann, 1993). More than 75 germline mutations have been identified in a VHL suppressor gene located on chromosome 3.
  - Congenital anomalies (often benign tumors) of the skin, nervous system, bones, and endocrine glands characterize neurofibromatosis, or von Recklinghausen disease. Only 1% of patients with neurofibromatosis have been found to have pheochromocytomas, but as many as 5% of patients with pheochromocytomas have been found to have neurofibromatosis.
  - Other neuroectodermal disorders associated with pheochromocytomas include tuberous sclerosis (Bourneville disease, epiloia) and Sturge-Weber syndrome.
  - Pheochromocytomas may produce calcitonin, opioid peptides, somatostatin, corticotropin, and vasoactive intestinal peptide. Corticotropin hypersecretion has caused Cushing syndrome, and vasoactive intestinal peptide overproduction causes watery diarrhea.

**Physical:** The clinical signs associated with pheochromocytomas include hypertension (which may be paroxysmal in 50% of cases), postural hypotension, retinopathy, fever, pallor, tremor, café au lait spots, or neurofibromas.

- Clinical signs
  - Hypertension (paroxysmal in 50% of cases)
  - Postural hypotension: This results from volume contraction.



- Hypertensive retinopathy
- Weight loss
- Pallor
- Fever
- Tremor
- Neurofibromas
- Café au lait spots: These are patches of cutaneous pigmentation, which vary from 1-10 mm and occur any place on the body. Characteristic locations include the axillae and intertriginous areas (groin). They vary from light to dark brown, hence the name café au lait.
- Tachyarrhythmias
- Pulmonary edema
- Cardiomyopathy
- Ileus
- Laboratory features
  - Hyperglycemia
  - Hypercalcemia
  - Erythrocytosis

**Causes:**

- Precipitants of a hypertensive crisis
  - Anesthesia induction
  - Opiates
  - Dopamine antagonists
  - Cold medications
  - Radiographic contrast media
  - Drugs that inhibit catecholamine reuptake, such as tricyclic antidepressants and cocaine
  - Childbirth

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**Other Problems to be Considered:**

Alcohol withdrawal  
 Labile essential hypertension  
 Hyperventilation  
 Orthostatic hypotension  
 Multiple pharmacologic agents (monoamine oxidase inhibitors [MAOIs], decongestants, sympathomimetics)  
 Illegal drug use (phencyclidine [PCP], lysergic acid diethylamide [LSD], cocaine)  
 Migraine headache  
 Autonomic neuropathy  
 Stroke  
 Toxemia of pregnancy  
 Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome

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**Lab Studies:**

- The choice of diagnostic test should be based on the clinical suspicion of a pheochromocytoma. Plasma metanephrine testing has the highest sensitivity (96%) for detecting a pheochromocytoma, but it has a lower specificity (85%) (Kudva, 2003). In comparison, a 24-hour urinary collection for catecholamines and metanephrines has a sensitivity of 87.5% and a specificity of 99.7%.
  - High-risk patients, including those who have a genetic syndrome that predisposes them to pheochromocytoma (eg, MEN 2A or 2B, VHL disease or neurofibromatosis, a prior history of a pheochromocytoma, a family history of a pheochromocytoma), should be screened with plasma metanephrine testing. In these scenarios, a higher-sensitivity test that lacks specificity is justified.
  - A fractionated plasma free metanephrine level may be measured in a seated, ambulatory patient with a standard venipuncture.
  - Patients at lower risk for a pheochromocytoma, including those with flushing spells, poorly controlled hypertension, or adrenal incidentalomas with an adrenocortical appearance, should be screened with a 24-hour urine collection for catecholamines and metanephrines. This test has a high specificity and acceptable sensitivity.
- Perform a 24-hour urine collection for creatinine, total catecholamines, vanillylmandelic acid, and metanephrines.
  - Measure creatinine in all collections of urine to ensure adequacy of the collection.
  - The collection container should be dark and acidified and should be kept cold to avoid degradation of the catecholamines.
  - Metanephrine levels are considered the most sensitive and specific test for a pheochromocytoma, while vanillylmandelic acid is the least specific test and has a false-positive rate greater than 15%.
  - Some authors have good experience with evaluating epinephrine and norepinephrine separately (in part to confirm the total catecholamine level and in part to determine if levels reflect the high norepinephrine-to-epinephrine ratio expected) and, for the same reason, normetanephrines.
  - Dopamine levels are not useful in this test because most of the dopamine is of renal origin.
  - Optimally, collect urine during or immediately after a crisis.
  - Major physical stress and multiple drugs may interfere with the assay and cause false elevations of the metanephrines. These drugs include tricyclic antidepressants, levodopa, labetalol, ethanol, sotalol, amphetamines, buspirone, benzodiazepines, methylodopa, and chlorpromazine.
  - Compounds that decrease 24-hour urine levels of metanephrines are methyltyrosine, which inhibits tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis; methylglucamine, which is present in radiocontrast media; and reserpine.
- Provocative testing, although used in the past, rarely is needed. Agents used in the past to provoke a catecholamine surge include histamine, tyramine, glucagon, and metoclopramide. Suppression tests using phentolamine and clonidine can also be used for diagnostic purposes.
- Chromogranin A is an acidic monomeric protein that is stored with and secreted with catecholamines. Plasma levels of chromogranin A reportedly are 83% sensitive and 96% specific for identifying a pheochromocytoma. Chromogranin A levels are sometimes used to detect recurrent pheochromocytomas.

**Imaging Studies:**

- Over 90% of pheochromocytomas are located within the adrenal glands, and 98% are within the abdomen. Extra-adrenal pheochromocytomas develop in the paraganglion chromaffin tissue of the sympathetic nervous system. They may occur anywhere from the base of the brain to the urinary bladder. Common locations for extra-adrenal pheochromocytomas include the organ of Zuckerkandl (close to origin of the inferior mesenteric artery), bladder wall, heart, mediastinum, and carotid and glomus jugulare bodies.
- Only perform imaging studies after biochemical studies have confirmed the diagnosis of a pheochromocytoma. MRI is preferred over CT scanning. MRI has a reported sensitivity of up to 100% in detecting adrenal pheochromocytomas, does not require contrast, and does not expose the patient to ionizing radiation. MRI is also superior to CT scanning for detecting extra-adrenal pheochromocytomas. Typically, (approximately 70% of cases), pheochromocytomas appear hyperintense on T2-weighted images because of their high water content.
- CT scanning of the abdomen has an accuracy of 85-95% for detecting adrenal masses with a spatial resolution of 1 cm or greater. CT scanning is less accurate for lesions smaller than 1 cm. Differentiating an adenoma from a pheochromocytoma is more difficult using CT scanning. While most pheochromocytomas have CT attenuation greater than 10 Hounsfield units (HU), they rarely contain sufficient intracellular fat to have an attenuation of less than 10 HU. In addition, most pheochromocytomas have enhancement loss that is similar to that of adrenal metastases and significantly less than that of adrenal adenomas. However, in patients in whom pheochromocytomas are strongly suspected, adrenal pheochromocytomas cannot be entirely excluded from the list of differential diagnoses of adrenal neoplasms with less than 10-HU attenuation value and greater than 60% washout on delayed scanning.
- A scan with iodine I 131–labeled metaiodobenzylguanidine (MIBG) is reserved for cases in which a pheochromocytoma is confirmed biochemically but CT scanning or MRI do not show a tumor. The molecular structure of iodine I 123 MIBG resembles norepinephrine and concentrates within adrenal or extra-adrenal pheochromocytomas. This isotope has a short half-life and is expensive. It frequently is used in cases of familial pheochromocytoma syndromes, recurrent pheochromocytoma, or malignant pheochromocytoma. In the United States, only <sup>131</sup>I-labeled MIBG is available, whereas <sup>123</sup>I MIBG is used in Europe and Japan.
- A somatostatin receptor analog indium In 111 pentetreotide is less sensitive than MIBG and may be used to visualize pheochromocytomas that do not concentrate MIBG.
- Positron emission tomography (PET) scanning has been used as an imaging modality and has shown promising results. PET of 18F-fluorodeoxyglucose, which is selectively concentrated as part of the abnormal metabolism of many neoplasms, has been demonstrated to detect occult pheochromocytomas. Pheochromocytomas usually show increased uptake on PET scanning, as do adrenal metastases. The most impressive results to date have been with 6-[18F] fluorodopamine PET scanning and carbon 11 hydroxyephedrine PET scanning. Results of these studies suggest that PET scanning performed with both of these radioisotopes is extremely useful in the detection and localization of pheochromocytomas. Further study results with these agents are eagerly awaited.

#### Other Tests:

- Once the diagnosis of pheochromocytoma is made, perform additional studies to rule out a familial syndrome, such as MEN 2A or 2B.
  - Obtain a serum intact parathyroid hormone level and a simultaneous serum calcium level to rule out primary hyperparathyroidism (part of MEN 2A).
  - Obtain a serum calcitonin level. Some investigators advocate a pentagastrin infusion test; however, genetic screening tests for the *ret* proto-oncogene may obviate the need for this provocative test.
  - Perform screening for mutations in the *ret* proto-oncogene in any patient with a familial syndrome or to distinguish a sporadic pheochromocytoma from a familial pheochromocytoma. Mutation analysis involves amplification of sequences, including exons 10, 11, 13, 14, and 16 of the *ret* proto-oncogene from the patient's genomic DNA, followed by sequence analysis. Particular attention is given to specific sequences for the codons known to be hot spots for mutations causing the MEN 2A and 2B syndromes. Over 95% of cases of MEN 2A and 85% of cases of familial medullary thyroid cancer are associated with mutations affecting 1 of 5 codons in exon 10 (codon 609, 611, 618, and 620) or exon 11 (codon 634). Over 95% of individuals with MEN 2B have a germline mutation in codon 918 of exon 16.
  - Obtain a consultation with an ophthalmologist to rule out retinal angiomas, and consider brain MRI to exclude cerebellar hemangioblastomas (VHL disease).
  - Obtain a CT scan of the kidneys and pancreas to rule out cysts.
- Patients with seizures, unexplained shock, weight loss, cardiomyopathy, neurofibromatosis, and/or orthostatic hypotension should be screened for pheochromocytomas.

#### Procedures:

- Because of the high sensitivity of MRI and CT scanning, procedures are rarely indicated for localization of pheochromocytomas.
  - Selective venous sampling is seldom performed to localize pheochromocytomas but has occasionally been used to detect extra-adrenal pheochromocytomas that were not detected at surgery. This procedure generally is not helpful in detecting extra-adrenal tumors because catecholamine levels have marked variability. An exception to this rule, however, occurs if the

norepinephrine concentration is greater than the epinephrine concentration in the venous effluent. Because the primary catecholamine produced and stored in the adrenal gland is epinephrine, a ratio of norepinephrine to epinephrine that is greater than 1 suggests a pheochromocytoma.

- Arteriography is rarely indicated and provides little additional information compared with MRI or CT scanning. More importantly, use of radiocontrast dye imposes a serious risk of inducing a hypertensive crisis.

**Histologic Findings:** Pheochromocytomas vary from 2 g to 3 kg but, on average, weigh 100 g (healthy adrenal gland weighs 4-6 g). These tumors are well encapsulated, highly vascular, and appear reddish brown on cut section.

Histologically, the tumor cells are arranged in balls and clusters separated by endothelial-lined spaces; this classic pattern characteristic of pheochromocytoma is termed *zellballen*. The cells vary in size and shape and have finely granular basophilic or eosinophilic cytoplasm. The nuclei are round or oval with prominent nucleoli. Nuclear giantism and hyperchromasia are common.

**Staging:** Approximately 10% of pheochromocytomas are malignant. Direct invasion of surrounding tissue or the presence of metastases determines malignancy. Unfortunately, no reliable clinical, biochemical, or histological features distinguish a malignant from a benign pheochromocytoma. Factors that suggest a malignant course include large tumor size and DNA ploidy pattern (aneuploidy, tetraploidy). Common metastatic sites include bone, liver, and lymph nodes.

## TREATMENT

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**Medical Care:** Surgical resection of the tumor is the treatment of choice and usually results in cure of the hypertension. Careful treatment with alpha- and beta-blockers is required preoperatively to control blood pressure and prevent intraoperative hypertensive crises.

- Start alpha blockade with phenoxybenzamine 7-10 days preoperatively to allow for expansion of blood volume.
- The patient should undergo volume expansion with isotonic sodium chloride solution. Encourage liberal salt intake.
- Initiate a beta-blocker only after adequate alpha blockade. If beta blockade is started prematurely, unopposed alpha stimulation could precipitate a hypertensive crisis.
- Administer the last doses of oral alpha- and beta-blockers on the morning of surgery.

**Surgical Care:** Both an experienced anesthesiologist and an experienced surgeon are crucial to the success of the operation. Surgical mortality rates are less than 2-3% with an experienced anesthesiologist and surgeon.

- Use an arterial line, cardiac monitor, and Swan-Ganz catheter. Administer stress-dose steroids if bilateral resection is planned.
- An anterior midline abdominal approach was used in the past; however, in current practice, laparoscopic adrenalectomy is the preferred procedure for lesions smaller than 8 cm. If the pheochromocytoma is intra-adrenal, remove the entire adrenal gland. In the case of a malignant pheochromocytoma, resect as much of the tumor as possible.



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Medical therapy is used for preoperative preparation prior to surgical resection, acute hypertensive crises, and primary therapy for patients with metastatic pheochromocytomas. Preoperative preparation requires combined alpha and beta blockade to control blood pressure and to prevent an intraoperative hypertensive crisis. Alpha-adrenergic blockade, in particular, is required to control blood pressure and prevent a hypertensive crisis. High circulating catecholamine levels stimulate alpha-receptors on blood vessels and cause vasoconstriction.

Phenoxybenzamine (Dibenzyline) is the preferred alpha-blocker in preparation for surgery. After effective alpha blockade, administer a beta-blocker. Beta-blockers are needed to control the tachycardia associated with high circulating catecholamine levels and alpha blockade. Beta-adrenergic blockers are used if significant tachycardia occurs after alpha blockade. Only administer beta-adrenergic blockers after adequate alpha blockade because unopposed alpha-adrenergic receptor stimulation can precipitate a hypertensive crisis. Noncardioselective beta-blockers, such as propranolol (Inderal) or nadolol (Corgard), are often used; however, cardioselective agents, such as atenolol (Tenormin) and metoprolol (Lopressor), also may be used.

Labetalol (Trandate, Normodyne) is a noncardioselective beta-adrenergic blocker and selective alpha-adrenergic blocker that has been shown to be effective in controlling hypertension associated with pheochromocytoma. It has also been associated with paradoxical episodes of hypertension thought to be secondary to incomplete alpha blockade. Thus, its use in the preoperative treatment of patients with pheochromocytoma is controversial.

During surgery, intravenous phentolamine, a rapid-acting alpha-adrenergic antagonist, is used to control blood pressure. Rapid-acting intravenous beta-blockers, such as esmolol, are also used to normalize blood pressure. Selective alpha<sub>1</sub>-blocking agents, such as prazosin (Minipress), terazosin (Hytrin), and doxazosin (Cardura), have more favorable adverse effect profiles and are used when long-term therapy is required (metastatic pheochromocytoma). These medications are not used to prepare patients for surgery because of their incomplete alpha blockade.

**Drug Category: Alpha-adrenergic receptor blockers** -- At low doses, alpha-adrenergic receptor blockers may be used as monotherapy in the treatment of hypertension. At higher doses, they may cause sodium and fluid to accumulate. As a result, concurrent diuretic therapy may be required to maintain the hypotensive effects of alpha-receptor blockers.

<b>Drug Name</b>	Phenoxybenzamine hydrochloride (Dibenzyline) -- Long-acting adrenergic alpha-receptor blocker that can produce and maintain a chemical sympathectomy. Lowers supine and upright BPs. Does not affect parasympathetic nervous system.
<b>Adult Dose</b>	10 mg PO bid, increase by 10 mg qod until optimum dose achieved Dose range: 20-40 mg PO bid/tid

<b>Pediatric Dose</b>	Not established
<b>Contraindications</b>	Documented hypersensitivity; patients in whom a fall in BP is undesirable
<b>Interactions</b>	When used concurrently, alpha-adrenergic agonists decrease effects of medication; beta-blockers increase toxicity
<b>Pregnancy</b>	C - Safety for use during pregnancy has not been established.
<b>Precautions</b>	Caution in cerebral or coronary arteriosclerosis and renal impairment; can worsen symptoms of respiratory tract infections
<b>Drug Name</b>	Doxazosin mesylate (Cardura) -- Quinazoline compound that is a selective alpha1-adrenergic antagonist. Inhibits postsynaptic alpha-adrenergic receptors, resulting in vasodilation of veins and arterioles and decrease in total peripheral resistance and BP.
<b>Adult Dose</b>	1 mg PO qd; may increase to 2 mg qd thereafter and titrate to higher doses; not to exceed 8 mg qd
<b>Pediatric Dose</b>	Not established
<b>Contraindications</b>	Documented hypersensitivity
<b>Interactions</b>	Effects decrease with coadministration of NSAIDs; effects increase with coadministration of diuretics and antihypertensive medications
<b>Pregnancy</b>	B - Usually safe but benefits must outweigh the risks.
<b>Precautions</b>	Caution in renal impairment; may cause marked hypotension following first dose; rarely (<1 in 1000 patients), priapism may occur
<b>Drug Name</b>	Phentolamine mesylate (Regitine) -- Nonselective alpha-adrenergic blocking agent. Drug action is transient and alpha-adrenergic blockade incomplete. Often used immediately prior to or during adrenalectomy to prevent or control paroxysmal hypertension resulting from anesthesia, stress, or operative manipulation of the tumor. Alpha1- and alpha2-adrenergic blocking agent that blocks circulating epinephrine and norepinephrine action, reducing hypertension that results from catecholamine effects on alpha-receptors.
<b>Adult Dose</b>	5-15 mg IV; used to control intraoperative hypertensive crises
<b>Pediatric Dose</b>	0.05-1 mg/kg per dose IV/IM, repeat q2-4h prn until hypertension is controlled; used prior to surgical removal of a tumor or to treat acute paroxysmal hypertensive crisis
<b>Contraindications</b>	Documented hypersensitivity; coronary or cerebral arteriosclerosis; renal impairment; myocardial infarction or a history of a myocardial infarction
<b>Interactions</b>	Concurrent administration of epinephrine or ephedrine may decrease phentolamine effects; ethanol increases phentolamine toxicity
<b>Pregnancy</b>	C - Safety for use during pregnancy has not been established.

<b>Precautions</b>	Caution in tachycardia, peptic ulcer, and gastritis; cerebrovascular occlusions and myocardial infarctions can occur following administration
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**Drug Category: Vasodilators** -- Reduce systemic vascular resistance, allowing more forward flow and improving cardiac output.

<b>Drug Name</b>	Nitroprusside (Nipride) -- Direct vasodilator that relaxes arterial vessels and venous smooth muscle. Has short half-life and effect disappears within 5 min of stopping infusion. May use to control paroxysmal hypertension intraoperatively. Produces vasodilation and increases inotropic activity of heart. At higher dosages may exacerbate myocardial ischemia by increasing heart rate.
<b>Adult Dose</b>	Begin infusion: 0.3-0.5 mcg/kg/min IV; use increments of 0.5 mcg/kg/min, titrate to desired effect Average dose: 1-6 mcg/kg/min IV; infusion rates >10 mcg/kg/min may lead to cyanide toxicity
<b>Pediatric Dose</b>	Administer as in adults
<b>Contraindications</b>	Documented hypersensitivity; idiopathic hypertrophic subaortic stenosis; atrial fibrillation or flutter
<b>Interactions</b>	None reported
<b>Pregnancy</b>	C - Safety for use during pregnancy has not been established.
<b>Precautions</b>	Caution in increased intracranial pressure, hepatic failure, severe renal impairment, and hypothyroidism; in renal or hepatic insufficiency, levels may increase and can cause cyanide toxicity; sodium nitroprusside can lower BP (only use in patients with mean arterial pressures >70 mm Hg)

**Drug Category: Beta-adrenergic receptor blocking agents** -- These agents compete with beta-adrenergic agonists for available beta-receptor sites.

<b>Drug Name</b>	Propranolol hydrochloride (Inderal) -- Nonselective beta-adrenergic receptor blocker. After primary treatment with an alpha-receptor blocker, may be used as adjunctive therapy if control of tachycardia becomes necessary before or during surgery. May be used to treat excessive beta-receptor stimulation in patients with inoperable metastatic pheochromocytoma. Has membrane-stabilizing activity and decreases automaticity of contractions. Not suitable for emergency treatment of hypertension. Do not administer IV in hypertensive emergencies.
<b>Adult Dose</b>	Preoperative preparation: 10 mg PO tid/qid, titrate up prn; 60 mg/d in divided doses is usual dose required During surgery: 1-3 mg IV to control tachycardia (careful monitoring) Metastatic pheochromocytoma: 30 mg PO in divided doses
<b>Pediatric Dose</b>	1 mg/kg PO qd, titrate prn; IV not recommended
<b>Contraindications</b>	Documented hypersensitivity; uncompensated congestive heart failure; bradycardia; cardiogenic shock; AV conduction abnormalities
<b>Interactions</b>	Coadministration with aluminum salts, barbiturates, NSAIDs, penicillins, calcium salts, cholestyramine, and rifampin may decrease effects; calcium channel blockers, cimetidine, loop diuretics, and MAOIs may increase toxicity;

	toxicity of hydralazine, haloperidol, benzodiazepines, and phenothiazines may increase
<b>Pregnancy</b>	B - Usually safe but benefits must outweigh the risks.
<b>Precautions</b>	Beta-adrenergic blockade may decrease signs of acute hypoglycemia and hyperthyroidism; abrupt withdrawal may exacerbate symptoms of hyperthyroidism, inducing thyroid storm; withdraw drug slowly and monitor closely
<b>Drug Name</b>	Atenolol (Tenormin) -- Selectively blocks beta1-receptors with little or no affect on beta2 types.
<b>Adult Dose</b>	50 mg PO qd; increase to 100 mg/d if necessary
<b>Pediatric Dose</b>	1-2 mg/kg PO qd
<b>Contraindications</b>	Documented hypersensitivity; congestive heart failure; pulmonary edema; cardiogenic shock; AV conduction abnormalities; heart block (without a pacemaker)
<b>Interactions</b>	Coadministration with aluminum salts, barbiturates, calcium salts, cholestyramine, NSAIDs, penicillins, and rifampin may decrease effects; haloperidol, hydralazine, loop diuretics, and MAOIs may increase toxicity
<b>Pregnancy</b>	C - Safety for use during pregnancy has not been established.
<b>Precautions</b>	Beta-adrenergic blockade may reduce symptoms of acute hypoglycemia and mask signs of hyperthyroidism; abrupt withdrawal may exacerbate symptoms of hyperthyroidism and cause thyroid storm; monitor patients closely and withdraw drug slowly; during an IV, carefully monitor BP, heart rate, and ECG

**Drug Category:** *Tyrosine kinase inhibitors* -- Used to inhibit catecholamine synthesis in pheochromocytoma.

<b>Drug Name</b>	Metyrosine (Demser) -- Inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis. In patients with pheochromocytoma, administration of metyrosine reduces catecholamine biosynthesis by 35-80% as measured by urinary catecholamine levels. Indicated in malignant pheochromocytoma or pheochromocytoma when surgery is contraindicated. Inhibits catecholamine synthesis in pheochromocytoma. Can be useful in patients who are refractory to phenoxybenzamine therapy, or can be administered as adjunct to phenoxybenzamine therapy.
<b>Adult Dose</b>	250 mg PO qid initially, titrated up by 250-500 qd prn; not to exceed 4 g qd in divided doses; monitor clinical symptoms and catecholamine excretion Optimal benefits: 2-3 g PO divided qid (typically) Preoperatively: Administer for at least 5-7 d
<b>Pediatric Dose</b>	<12 years: Not established >12 years: Administer as in adults
<b>Contraindications</b>	Documented hypersensitivity
<b>Interactions</b>	Ethanol, TCAs, opiate agonists, barbiturates, benzodiazepines, H1-blockers, or other CNS agents can result in additive sedative effects; extrapyramidal effects of haloperidol, metoclopramide, molindone, or phenothiazines can be increased

<b>Pregnancy</b>	C - Safety for use during pregnancy has not been established.
<b>Precautions</b>	Instruct patients to maintain adequate fluid balance (daily urinary volume of $\geq 2$ L) to minimize risk of metyrosine-induced crystalluria; increase fluid intake if crystalluria occurs; if crystalluria persists, dosage reduction or discontinuation may be necessary; precipitates extrapyramidal symptoms, including increased salivation, tremor, and speech difficulty; other more infrequent effects include trismus and pseudoparkinsonism; can precipitate or worsen mental depression, resulting in effects such as anxiety, tremulousness, confusion, and psychic disturbances; other adverse effects may include dry mouth, impotence or ejaculation dysfunction (failure to ejaculate), hematologic toxicity, galactorrhea, swelling of the breasts, peripheral edema, and urticaria

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**Further Inpatient Care:**

- Test plasma free metanephrines 2 weeks postoperatively. If results are within the reference range, patient survival approaches age-matched controls.
- Assure resolution of the hypertension and any associated complications.

**Further Outpatient Care:**

- Obtain plasma metanephrine levels yearly for 5 years. Assure that blood pressure is under control.
- The 5-year survival rate for people with nonmalignant pheochromocytomas is greater than 95%. In those with malignant pheochromocytomas, the 5-year survival rate is less than 50%.

**Patient Education:**

- For excellent patient education materials, see [eMedicinehealth.com](http://www.emedicinehealth.com) and see the patient education article [High Blood Pressure](#).

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**Medical/Legal Pitfalls:**

- The major pitfalls are in not considering the diagnosis in a timely manner or in ordering a test that provokes a hypertensive crisis with complications. The symptoms of pheochromocytoma may be quite vague and misrepresented by the patient. Most difficult are the true episodic secreting pheochromocytomas wherein the blood pressure may appear normal between paroxysms. Because this constitutes failure to diagnose a potentially curable problem with otherwise life-threatening consequences, pheochromocytomas have attracted litigation.

**Special Concerns:**

- Pregnancy
  - Pheochromocytoma occurring during pregnancy carries a grave prognosis, with maternal and fetal mortality rates of 48% and 55%, respectively.
  - Maternal mortality is virtually eliminated and the fetal mortality rate is reduced to 15% if the diagnosis is made antenatally.
  - Administer alpha-adrenergic blockade (phenoxybenzamine) as soon as the diagnosis is confirmed.
  - Surgically remove the tumor as soon as possible during the first 2 trimesters after proper preparation. Pregnancy need not be terminated.
  - Spontaneous abortion is very likely.

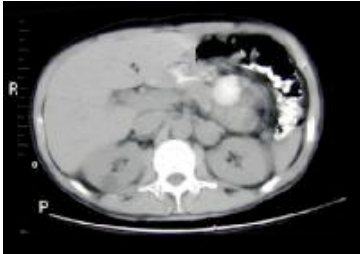
- During the third trimester, as soon as fetal lung maturity is confirmed, perform surgical removal of the tumor and follow with cesarean delivery.

## PICTURES

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**Caption:** Picture 1. Pheochromocytoma. Abdominal CT scan demonstrating left suprarenal mass of soft tissue attenuation representing a paraganglioma.

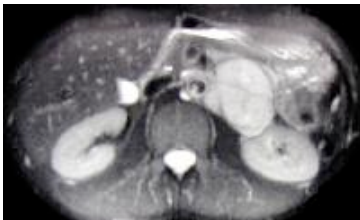


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**Picture Type:** CT

**Caption:** Picture 2. Pheochromocytoma. Axial T2-weighted MRI showing large left suprarenal mass of high signal intensity on a T2-weighted image representing a pheochromocytoma.



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**Picture Type:** MRI

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**NOTE:**

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