

Phenylephrine (Neo-Synephrine)

Uses

- Prescribed mainly as nasal decongestant or ophthalmically for treatment of mydriasis, capillary decongestion.
- Reliable vasopressor in treatment of hypotension.
- Used in obstetric anesthesia for hypotension after spinal. More effective as a prophylactic infusion than bolus doses.
- Prolongs local anesthetic duration in regional anesthesia.
- Available as parenteral IM/IV and various ophthalmic and/or nasal preparations.

Perioperative Risks

- Risk of Htn increases left heart work; may precipitate myocardial ischemia, MI.
- Infusions to augment systolic BP incidence of myocardial ischemia in pts undergoing carotid endarterectomy.
- Increased pulm vascular resistance, right heart work.
- Bradycardia may occur (usually not severe) related to baroreceptor reflex.
- Decreased renal, splanchnic blood flow.
- Systemic absorption of topical preparations may cause Htn, headache, tremulousness, myocardial ischemia.

Worry About

- Increase preload, afterload may worsen LV failure in pts with LV dysfunction.
- Raised PA pressures may worsen RV dysfunction.
- May decrease renal blood flow.

Overview/Pharmacology

- Direct α_1 -agonist activity causes systemic and PA vasoconstriction, resulting in increased impedance to forward flow, reduced BP.
- Rapidly metabolized by MAO.
- IV duration less than 5 min.
- May terminate supraventricular tachycardia by vagal reflex from baroreceptor stimulation.
- Increased SVR during CPB.
- Increased perfusion pressure to vital organs in hypovolemic pts until volume is restored, CPR.
- May be used in conjunction with nitroglycerin to elevate coronary perfusion pressure in hypotensive pts with myocardial ischemia.
- Decreasing R-to-L shunts in pts with cyanotic spells (TOF)
- Vasopressor of choice in hypertrophic cardiomyopathy, systolic anterior motion of mitral valve and

aortic stenosis, when increased inotropy or tachycardia undesirable.

- Advantageous in catecholamine-depleted pts (chronic cocaine or amphetamine abuse), or in those on tricyclic antidepressants or MAO inhibitors, when indirect vasopressors are unpredictable.

Drug Class/Mechanism of Action/Usual Dose

- Synthetic noncatecholamine activates predominantly α -adrenergic receptors (postsynaptic, heart, iris), triggers release of intracellular calcium, resulting in smooth muscle contraction.
- Differs structurally from epinephrine only in lacking 4-hydroxyl group on benzene ring.
- Usual adult dosage
 - IV bolus: 50–100 μ g
 - IV infusion: 20–200 μ g/min
 - Ophthalmic solutions: 2.5–10%
 - Supraventricular tachycardia dose: 150–800 μ g titrated to raise BP

Assessment Points

System	Effect	PE	Test
HEENT	Mydriasis without cycloplegia Increased production of aqueous humor		
CV	Vasoconstriction of veins and arteries Increased systolic and diastolic BP Decreased HR	BP HR	PCWP ECG
RESP	Increased PVR		PCWP, PAP
RENAL	Increased renal blood flow	UO	BUN, Cr

Key References: Dellinger RP, Levy MM, Carlet JM, et al.: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 34(1):17–60, 2008; Habib AS: A review of the impact of phenylephrine administration on maternal hemodynamics and maternal and neonatal outcomes in women undergoing cesarean delivery under spinal anesthesia. *Anesth Anal* 114(2):377–390, 2012.

Perioperative Implications

Preoperative Concerns

- Assess LV function and Hx of CAD.
- Consider arterial catheter if phenylephrine infusion anticipated (carotid endarterectomy, relative hypovolemia).
- Assess renal function (Cr).
- For nasal intubations, phenylephrine can be used as a nasal vasoconstrictor in a mixture with 3–4% lidocaine.

Induction/Maintenance

- Monitor ECG for signs of ischemia due to increased ventricular work or coronary artery spasm.

- May decrease hepatic blood flow due to α -adrenergic-mediated vasoconstriction of portal venous vasculature.

Adjuvants/Regional Anesthesia/Reversal

- Duration may be prolonged in pts on MAO inhibitors.
- Side effects with ophthalmic use occur within 20 min; usually self-limited.
- 2.5% nasal, ophthalmic solutions recommended in infant and elderly populations or in pts with CAD.

Anticipated Problems/Concerns

- Can be titrated slowly to avoid overshoot (with resultant Htn).
- Can be used when severe hypotension presents immediate danger to compromised myocardium or other end organ (e.g., brain).
- With a failing heart, increasing afterload and preload may increase left-sided filling pressures enough to precipitate pulm edema.

Phenytoin

Bozenna R. Jachna | Lee A. Fleisher

Uses

- Management of generalized tonic-clonic (grand mal) and complex partial seizures
- Prophylaxis against seizures after trauma or surgical intervention
- Treatment of ventricular arrhythmias, especially those associated with digitalis or tricyclic antidepressant toxicity
- Treatment of prolonged QT interval
- Treatment of epidermolysis bullosa and chronic pain syndromes

Overview/Pharmacology

- Drug of choice for status epilepticus
- Treatment for acute and chronic seizures
- Onset of action: 30–60 min

- Protein binding >90% in adults
- Elimination half-life: 22 h
- 95% hydroxylated and conjugated in liver with glucuronic acid for renal excretion
- Therapeutic range: 10–20 μ g/mL

Drug Class/Mechanism of Action/Usual Dose

- Hydantoin derivative
- In the CNS, helps to limit nerve impulse generation, thereby limiting spread of seizure focus by:
 - Decreasing influx of Na^+ ions across cell membranes in the motor cortex
 - Decreasing presynaptic Ca^{2+} release
 - Decreasing extracellular K^+ concentration

- In the heart, works to limit reentrant arrhythmias by:
 - Prolonging the effective refractory period and suppressing ventricular pacemaker automaticity
 - Shortening the action potential for status epilepticus (IV and PO dosages are the same)
- Pediatric: Loading dose, 15–20 mg/kg in single or divided doses, then 5 mg/kg per d in divided doses
- Adult: Loading dose, 10–15 mg/kg, then 5–6 mg/kg per d in 3 divided doses
- For treatment of cardiac arrhythmias: 1.5 mg/kg IV every 5 min for maximum dose of 15 mg/kg or 1.5 g

Perioperative Risks

- Hypotension, bradycardia, cardiac arrhythmias and/or collapse with rapid IV administration (likely due to propylene glycol vehicle)
- Venous irritation and/or pain
- Decreased efficacy of muscle relaxants

Concerns

- Pts with renal failure, jaundice, or other causes of hypoalbuminemia may exhibit phenytoin toxicity.
- Acute administration may lead to delayed emergence.

- Increased P450 clearance may cause decreased effectiveness of certain drugs: Antibiotics, oral contraceptives, procainamide, midazolam, and oral anticoagulants.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEENT	Nystagmus at toxic levels >20 mg/mL	Gingival hyperplasia with chronic use		
CV	Hypotension, bradycardia, cardiac arrhythmias with rapid administration		Vital signs, monitoring	
RESP	Respiratory depression		Saturation, respiratory rate monitoring	
DERM	Rash; Stevens-Johnson syndrome (rare)			
GI/HEPAT	Constipation, vomiting, nausea, hepatitis; increased hepatic drug metabolism; toxicity in low-albumin states; avoid or limit ethyl alcohol use	GI irritation if not taken with food		Albumin
HEME	Folic acid depletion, hyperglycemia, leukopenia, thrombocytopenia, agranulocytosis			CBC with differential
RENAL	Toxicity in uremic pts			BUN/Cr
CNS	Ataxia, diplopia, drowsiness, lethargy, coma, nystagmus, mood changes		CNS exam	

Key References: University of Maryland Medical Center: Dilantin overdose. <<http://umm.edu/health/medical/ency/articles/dilantin-overdose>>, 2016 (Accessed 11.07.16); Hayashi T, Higuchi H, Tomoyasu Y, et al.: Effect of carbamazepine or phenytoin therapy on blood level of intravenously administered midazolam: a prospective cohort study, *J Anesth* 30(1):166–169, 2016.

Perioperative Implications

Preoperative Concerns

- Pts with renal or liver disease or decreased nutritional states can have increased levels of free phenytoin.

Induction/Maintenance

- Rapid administration of phenytoin may cause hypotension, bradycardia, and arrhythmias. Administer at rate of less than 50 mg/kg per min.
- Larger doses of nondepolarizing muscle relaxants may be required.
- Shorter duration of nondepolarizing muscle relaxants.

- IV-administered midazolam may have a weaker effect in pts medicated with phenytoin.
- Concern with too rapid administration of vehicle (depending on vehicle).

Contraindications

- Hypersensitivity to phenytoin, other hydantoin.
- Pregnancy: Phenytoin crosses the placenta, resulting in congenital malformations (the “fetal hydantoin syndrome”), which results in wide-set eyes, broad mandible, and finger deformities.
- Lactating states, enters breast milk.

- Isolated cases of malignancies: Neuroblastomas have been reported.

Phenytoin Syndrome

- Fever
- Rash
- Psychiatric changes, slurred speech, dizziness, insomnia
- Tremor
- Constipation
- Hepatitis
- Rarely seen: SLE-like syndrome, lymphadenopathy, Stevens-Johnson syndrome, blood dyscrasias, lymphoma, coarsening of facial features, hypertrichosis.

Physostigmine, Eserine

Jeffrey S. Shiffrin

Uses

- Central anticholinergia; used for diagnosis and treatment in patients with a Hx of anticholinergic ingestion and/or exposure: Atropine, scopolamine, belladonna, jimson weed, toxic mushrooms, tricyclics, phenothiazines, antihistamines, benzodiazepines, opiates, inhalation anesthetics, propofol, GHB.
 - “Blind as a bat”: Mydriasis and loss of accommodation
 - “Dry as a bone”: Urinary retention and dry mucous membranes
 - “Hot as a hare”: Hyperthermia from loss due to sweating
 - “Red as a beet”: Cutaneous vasodilation; counteracts hyperthermia
 - “Mad as a hatter”: Fluctuating consciousness, delirium, disorientation, decreased social restraint, slurred speech, incoordination, hallucinations, phantom behaviors, coma, paranoia during recovery
- Postop delirium from agitation to excessive somnolence. Best indication for treatment of combined central and peripheral anticholinergia.

- Glaucoma, ciliary muscle contraction = miosis = facilitates outflow of aqueous humor.
- Treatment for antimuscarinic xenobiotic toxicity (a chemical compound that is foreign to a living organism; e.g., benzodiazepines, tricyclics, antihistamines, jimson weed).
- Reversal of NMB (neostigmine a better choice as it avoids CNS effects).
- Hereditary ataxias.
- Alzheimer disease (may improve short-term memory but not used clinically).
- Analgesia (decreases morphine consumption postop).

Perioperative Risk

- Cholinesterase inhibition = excess acetylcholine. Can lead to three sets of problems: Analogous to organophosphorus compound poisoning, a cholinergic crisis (basically the opposite of anticholinergia syndrome above)
 - Muscarinic cholinergic (parasympathetic) over-stimulation (DUMBELS): D = Defecation, diarrhea, diaphoresis, GI distress; U = urination; M = miosis; B = bronchorrhea, bronchospasm, bradycardia; E = emesis (nausea); L = lacrimation; S = salivation

- Nicotinic cholinergic excess (continuing depolarization of motor endplate, leading to fasciculations at low doses and progressive weakness at high doses)
- CNS (anxiety, confusion, tremors, seizures, respiratory depression, coma)

Worry About

- Reactive airway disease
- Peripheral vascular disease
- Diabetes
- Bowel or bladder obstruction
- Preexisting intraventricular conduction delay, long-QT syndrome
- Preexisting AV block
- Pregnancy (class C)
- Sulfite allergy (contains sodium bisulfite preservative)

Overview/Pharmacology

- Physostigmine is a parasympathomimetic carbamate derived from the beans and/or seeds of an aquatic leguminous plant (calabar or ordeal bean). Used in the Old Calabar region of Nigeria as part of the Eseré witchcraft ritual (believed to test the guilt or innocence of a person accused of a crime).