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 hydantoins.
- 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 Esere witchcraft ritual (believed to test the guilt or innocence of a person accused of a crime).

- Characterized and named *Physostigma venenosum balfour* in 1857 by John Balfour.
- Active alkaloid isolated and called physostigmine by Jobst and Hesse 1864 and independently by Vee and Leven who named it serine in 1865.
- Reversibly binds acetylcholinesterase (AchE), thus inhibiting acetylcholine degradation and increasing synaptic acetylcholine.
- Tertiary amine structure allows penetration of blood brain barrier.
- Prototypical carbamate insecticide.
- Early medical use by 1935 as miotic agent for glaucoma pts, myasthenia gravis treatment, atropine antidote, and reversal agent for curare-induced paralysis.

Drug Class/Mechanism of Action/ Usual Dose

- Physostigmine is a tertiary amine and a competing substrate for cholinesterase enzymes, thus decreasing the breakdown of acetylcholine.
- 1.5 mg given over 60 min = Vd 2.4 ± L/kg; half-life is 16.4 ± 3.2 min; peak plasma concentration 3 ± 0.5 ng/mL; clearance 0.1 L/min per kg.
- Inhibition of plasma cholinesterase within 2 min of infusion start. Half-life of plasma cholinesterase inhibition = 83.7 ± 5.2 min.
- For glaucoma: Not commonly used owing to systemic absorption and side effects. Replaced by other agents. Physostigmine ointment placed 1–3 times daily. Physostigmine solution 0.25%, 0.5% used 1–4 times daily while holding pressure over medial canthus/tear duct to minimize absorption.
- For reversal of central anticholinergia: Physostigmine salicylate (antilirium) 1 mg/mL; dose = 0.04 mg/kg or 1–2 mg IV/IM. IV given slowly, no more that 1 mg/min every 20–60 min as effective and necessary or until side effects develop.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
OPHTH	Constriction of pupils	Glaucoma topical application	Miosis, conjunctival hyperemia	Decreased IOP, red eye
CV	Bradycardia/tachycardia Vasoconstriction/vasodilation, decreased cardiac contractility	Variable depending on CNS vs. peripheral effects and use of other meds (ganglionic blockers, alpha- and beta-blockers)	Slow or irregular HR, asystole, or tachycardia, Htn, or hypotension	ECG, BP
RESP	Bronchoconstriction Bronchorrhea		Wheezing Secretions, "frothing at the mouth"	Auscultation
GI	Parasympathetic stimulation, abdominal cramps		Diarrhea, defecation	
GU	Bladder stimulation		Urination	
CNS	Excess acetylcholine	Somnolence, delirium, coma		

Key References: Taylor P: Anticholinesterase agents. In Brunton L, Chabner B, Knollman B, editors: *Goodman & Gilman's the pharmacological basis of therapeutics*, ed 12, New York, 2011, McGraw Hill, 2011, pp 239–254; Lepousé C, Lautner CA, Liu L, et al.: Emergence delirium in adults in the post-anaesthesia care unit, *Br J Anaesth* 96(6):747–753, 2006.

Perioperative Implications

Preoperative Concerns

- Scopolamine, antihistamines, benzodiazepines (especially in the elderly) can contribute to central anticholinergia.
- Use of jimson weed (belladonna) or hallucinogenic mushrooms.
- Interaction with vasopressors (possible Htn, tachycardia).
- Long-QT syndrome or AVB (increases chance for asystole).
- Tricyclic antidepressant use (asystole has occurred in the treatment of tricyclic overdose).

Induction/Maintenance

- Not used

Postoperative Period

- Many if not all anesthetics can cause anticholinergic signs and symptoms.
- Differential diagnosis: Metabolic (hyper/hypoglycemia, electrolyte imbalance, sepsis, MH, NMS; respiratory (hypoxia, hypercarbia); neurologic (CVA, seizures); psychiatric (narcolepsy, psychosis); iatrogenic (residual NMB, bladder distention, prolonged anesthetic effects/sensitivity).

Anticipated Problems/Concerns

- Physostigmine can be very effective in reversing excessive sedation or agitation associated with anticholinergia. However, anticholinergia is usually self-limited and is a diagnosis of exclusion (although it is confirmed by a positive response to physostigmine). Physostigmine is possibly a better treatment than benzodiazepine for combined central and peripheral anticholinergia. Also, physostigmine side effects are unpredictable and can be severe (asystole, seizures). In general, they are limited to exaggerated parasympathetic effects: N/V, stomach pain, salivation, urination, defecation, miosis, inability to focus, lacrimation, sweating, bronchospasm, bronchorrhea, dyspnea, bradycardia or tachycardia, hypotension or Htn, irregular pulse, and muscular twitching; but weakness, seizures, collapse, coma, pulm edema, and death (i.e., cholinergic crisis) can occur.
- Avoid in pts receiving other cholinergic agents (methacholine, bethanechol).
- Avoid in pts receiving depolarizing NMBs (succinylcholine).
- Atropine is the antidote for physostigmine overdose and central cholinergic symptoms.
- Avoid if long-QT syndrome on ECG.
- Glycopyrrolate is the antidote for peripheral cholinergic excess.

Procainamide (Procan, Procanbid, Pronestyl)

Henry Liu | Rayhan A. Tariq

Uses

- Treats recurrent or sustained hemodynamically stable monomorphic VT (IIa/C)/(IIa/C).* Not indicated for asymptomatic PVCs.
- Treats focal atrial tachycardia in hemodynamically stable pts (IIa/C).
- Treats recurrent atrial flutter (only in combination with AV-nodal-blocking agent) (IIb/A).
- Treats SVT during pregnancy.
- As a backup drug in hemodynamically stable pt with SVT (if adenosine is not successful).

*The first number and lowercase letter refer to the ACC/AHA system of classifying guidelines while the uppercase letter refers to the level of evidence.

Perioperative Risks

- Potential for hypotension secondary to ganglionic blockade more likely than myocardial depression.
- Nausea in pts on oral procainamide (related to levels of N-acetyl procainamide?).
- Chronic use can cause lupus-like syndrome; 25–50% of pts develop rash, small-joint arthralgias positive ANA. Resolves with cessation or administration of N-acetyl procainamide.

Worry About

- Ventricular dysrhythmias if plasma concentration of N-acetyl procainamide (NAPA) >30 μg/mL.
- QT_c prolongation.
- CNS toxicity.
- Hypotension.
- Procainamide-induced lupus syndrome.
- Bone marrow aplasia in 0.5% of pts; may be fatal, mechanism unknown.
- Hypokalemia may exacerbate toxicity.
- Avoid use in pts with myasthenia gravis; it can exacerbate symptoms.

Overview/Pharmacology

- Analog of procaine.
- Na^+ channel blocker (intermediate recovery).
- Decreases automaticity, slows phase 4 depolarization, prolongs refractory periods, thus reducing repolarization abnormalities.
- Highly lipophilic, but no relationship between drug properties and volume of distribution.