- 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.

- Major metabolite NAPA does not block Na^+ channels but equipotent in prolonging action potentials.
- Rapid hepatic conjugation by N-acetyl transferase (half-life 3–4 h) to active metabolite NAPA.
- Renal excretion of unchanged drug as well as NAPA (half-life 6–8 h)
- Procainamide and NAPA have different pharmacologic effects, so sum of concentrations should not be used to guide therapy.
- Slow acetylators more likely to develop lupus-like symptoms; often resolve with administration of NAPA.
- Can cause serious drug interactions with drugs such as ondansetron (QT_c prolongation), flecainide, amiodarone, and others.

Drug Class/Mechanism of Action/Usual Dose

- Class IA antiarrhythmic; Na^+-channel blocker.
- Marked slowing of conduction by blocking sodium channels (SA node and intraventricular conduction).
- IV loading dose (adult): 15–18 mg/kg (if renal impairment, reduce to 12 mg/kg); infuse slowly over 25–30 min; may repeat q5min as needed, not to exceed 1 g.
- IV maintenance dose: 1–4 mg/min IV (reduce infusion by 1/3 in moderate renal and 2/3 in severe renal impairment).
  - Narrow therapeutic window: therapeutic plasma levels are procainamide 4–10 μg/mL, NAPA 15–25 μg/mL
  - Toxic level: Procainamide >10 μg/mL.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Slowing of conduction	Assess for clinically symptomatic bradycardia, heart block, CHF	Auscultation of heart sounds, ECG	Continuous ECG monitoring
RESP	Lupus-related pleuritis or pneumonia	Assess for dyspnea	Auscultation of lung fields	O_2 saturation monitoring
CNS	High plasma concentrations may cause confusion/disorientation and/or seizures; rarely muscle weakness	Evaluate regimen, pt compliance	Monitor blood levels of procainamide and NAPA	Neurologic assessment

Key References: deSouza IS, Martindale JL, Sinert R: Antidysrhythmic drug therapy for the termination of stable, monomorphic ventricular tachycardia: a systematic review, *Emerg Med J* 32(2):161–167, 2015; Pedersen CT, Kay GN, Kalman J, et al.: EHRA/HRS/APHRS expert consensus on ventricular arrhythmias, *Europace* 16(9):1257–1283, 2014.

Perioperative Implications

Preoperative Concerns
- Hx of arrhythmia, ischemic or structural heart disease.
- Ventricular dysfunction.
- Plasma concentration of procainamide.
- May be used to treat contractions in pts with myotonic dystrophies; should be continued periop.

Induction/Maintenance
- Caution with drugs that slow cardiac conduction (e.g., other Na^+ channel blockers, betablockers) and drugs that prolong QT interval
- Use of other Na^+ channel blockers
- Local anesthetic toxicity with major conduction blocks
- Arrhythmias with high plasma concentration of procainamide
- Myocardial depressive effect worsened by hyperkalemia
- Potentiates activity of neuromuscular blockade

Postoperative Period
- Toxicity
- Arrhythmias caused by slowed conduction

Anticipated Problems/Concerns

- Monitor for clinical signs of toxicity: Torsades, heart block, arrhythmias, confusion, lupus syndrome.
- Not well tolerated for long-term control of atrial tachycardias because of dosing regimen, complications.
- In renal pts: Concentrations of procainamide and NAPA may rise to toxic levels; therefore reduce dose, monitor levels of both.

Propylthiouracil—Antithyroid Drugs

Michael F. Roizen

Uses

- RX for hypothyroidism. In USA, 7.5% of pregnant women plus an additional 500,000 people per y develop hyperthyroidism.
- Rx for goiter associated with hyperthyroidism; second drug to methimazole due to greater side effects with PTU except in pregnancy (methimazole has greater side effects on fetus during pregnancy).
- Definitive Rx for control of hyperthyroidism in anticipation of spontaneous remission.
- Rx for hyperthyroidism in conjunction with ^{131}I or ^{125}I to hasten recovery while awaiting effects of radiation therapy.
- Secondary Rx for hyperthyroidism to control disorder in preparation for surgery.

Perioperative Risks

- Side effects of drug: Hypothyroidism; liver failure, especially in pts with liver transplants; be careful in pregnancy.

Worry About

- Agranulocytosis (less than 0.5% of treated pts develop this side effect) and liver problems

Overview/Pharmacology

- Antithyroid drug: Absorbed within 20–30 min; effect begins to decrease in 2–3 h (half-life of methimazole estimated to be 6–13 h).
- Drug and metabolites cleared by renal excretion.
- Antithyroid drugs cross placenta, can be found in breast milk.

Drug Class/Usual Dose

- Antithyroid drug (thioureylene): Interferes directly with synthesis of thyroid hormones by preventing incorporation of iodine into tyrosyl residual thyroglobulin; inhibits coupling of iodotyrosyl residues to form iodothyronines by inhibiting peroxidase enzyme.
- Depletes preformed hormone over time; only then do clinical effects become noticeable (half-life of thyroid hormones is >3 d in circulation).
- Other useful antithyroid drugs include those inhibiting conversion of less active T_4 into more active T_3, such as propranolol; methimazole and carbimazole do not appear to do so with anti–β-blocker effect (e.g., propranolol and others); those that inhibit release of preformed thyroid hormone (e.g., iodine). Also temporarily inhibits synthesis and decreases vascularity of thyroid glands.

Chronic Rx Uses

- Decreased hyperthyroidism and thyrotoxicosis
- Decreased goiter size in hyperthyroidism

Acute Rx Uses
- Relieves symptoms of hyperthyroidism while waiting for ^{131}I or ^{125}I to take effect.