- 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.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEENT	Goiter shrinkage; occasionally goiter develops if hypothyroidism occurs	Snoring, hoarseness, neck pain	Ask pt to vocalize "e"; examine airway, neck	Check CXR (PA, lateral), lateral neck films; if needed, CT scan of neck
CV		Assess CV response to Rx		Rhythm strip or full ECG if CV system is involved by either Hx or PE
GI	Rare hepatotoxicity			SGPT, SGOT
HEME	Mild anemia, thrombocytopenia; agranulocytosis as toxic reaction to propylthiouracil or methimazole (0.05–0.12% of pts)	Hx of sore throat or fever often heralds agranulocytosis	Skin/mucous membranes for infection/petechiae; purpura if at risk	CBC with plt count; differential leukocyte count
DERM		Rare depigmentation of hair		
MS		Pain/stiffness in joints (rare side effect)		
GU	Placenta: Crosses placental barrier and is excreted in breast milk			
CNS		Headache, paresthesia are rare side effects. Shaking, anxiety, emotional instability are signs that hyperthyroidism not yet controlled.	Reflex speed, tremor, nervousness, mental status	
ENDO	Need to assess if euthyroid	Refer to all other systems, especially reflex speed, tremor, heat intolerance, weight loss, fatigue, weakness, anorexia, increased appetite	Reflex speed; HR	Free T_4 level if unable to assess if euthyroid by Hx, PE

Key References: Farling PA: Thyroid disease, *Br J Anaesth* 85(1):15–28, 2000; Nayak B, Burman K: Thyrotoxicosis and thyroid storm, *Endocrinol Metab Clin North Am* 35(4):663–686, 2006; Ross DS: Antithyroid drugs. In Cooper DS, Mulder JE, editors: Waltham, MA, 2015, UpToDate. www.uptodate.com/contents/antithyroid-drugs-beyond-the-basics (Accessed 07.07.2016).

Perioperative Implications/Possible Drug Interactions

Preoperative Concerns
- Assess euthyroid state (see Assessment Points table).
- Fairly certain sign that remission may have occurred is decrease in size of goiter.

Induction/Maintenance
- No interactions known

Adjuvants/Regional Anesthesia/Reversal
- No interactions known

Postoperative Concerns
- Resumption not necessary if surgery to correct hyperthyroidism was successful.
- Be careful with pts who have Hx of liver disease and who are pregnant or breastfeeding.
- Short half-life makes resumption in nonthyroid surgery necessary ASAP, or give medication IV.

Anticipated Problems/Concerns
- Assess for hyperthyroidism, agranulocytosis, and liver dysfunction.

Proton Pump Inhibitors

Benjamin T. Cobb | Norman Randolph | Mark S. Weiss

Uses
- PPIs are used for the prevention and treatment of ulcers in the stomach, esophagus, or duodenum that are caused or exacerbated by stomach acids.
- People in USA receive approximately 21 million prescriptions annually.
- Worldwide, $13.6 billion worth of PPIs are consumed annually.
- PPIs are administered for the treatment of dysphagia, peptic and duodenal ulcer disease, gastroesophageal reflux, Barrett esophagus, Zollinger-Ellison syndrome, ulcers caused by NSAIDs, and eosinophilic esophagitis. PPIs are also used in the treatment of ulcers caused by *Helicobacter pylori*.

Perioperative Risks
- N/V, diarrhea, flatulence, abdominal pain.
- Interstitial nephritis and rhabdomyolysis.
- Possible mildly exaggerated effects of thiopental and/or other potent vasodilators.
- Inhibit CYP450 liver enzymes: (1) Drugs such as clopidogrel (Plavix) cannot be metabolized to active form and (2) PPIs increase free carvedilol levels.
- Displace protein-bound drugs (e.g., warfarin, sulfonylureas, thiopental, methotrexate).

Overview/Pharmacology
- Administered in an inactive (lipophilic) form in which they can enter the target cell. The acid environment in the cell protonates the drug and converts it into the activated form that binds to the proton pump.
- Metabolized by the liver, excreted by kidney and colon.
- Inhibit the cytochrome P450 system, causing variation in other medication effects.
- Displace protein-bound drugs, thus increasing their effects.

Drug Class/Mechanism of Action/Usual Dose
- PPIs suppress gastric acid production by binding to H+/K+ ATPase (i.e., the proton pump) in gastric parietal cells, causing long lasting suppression of acid secretion. The proton pump is at the terminal stage of acid production, and PPIs are up to 99% effective in decreasing gastric acid content as well as increasing the gastric pH.
- Omeprazole 20–40 mg PO for chronic GI symptoms
- Pantoprazole 40–80 mg IV q12–24h for acute GERD and GI bleeding
- Alternatives: antacids, sucralfate, tricyclic antidepressants, H_2-receptor antagonists, other PPIs (esomeprazole, lansoprazole), endoscopic interventions, and surgical interventions