Perioperative Implications

Preoperative Concerns
- Oral administration of usual doses to normotensive pts usually produces minimal effects.
- Possible Htn, tachycardia in sensitive pts.
- Those with concomitant hyperthyroidism, ischemic heart disease, or prostatic hypertrophy may be more at risk.
- May increase irritability of the heart muscle and result in multifocal PVCs.
- May be teratogenic; avoid use in pregnant pts if possible; avoid use in breastfeeding women.
- Geriatric pts may be especially sensitive.
- Overdose may cause hallucinations, CNS depression, seizures, and death.

Monitoring
- Routine

Induction
- Increased absorption of pseudoephedrine with antacid administration

Airway
- Improvement of airway edema and congestion related to mucosal hyperemia is often seen.

Maintenance
- Careful administration/titration of other sympathomimetic drugs

Regional Anesthesia
- Pts may be more prone to urinary retention with regional techniques that block sacral roots.

Postoperative Concerns
- Resumption of drug should not pose particular problems once vital signs are stable.

Anticipated Problems/Concerns
- Caution in administering other sympathomimetic agents.
- β-adrenergic blocking drugs may increase pressor effect.
- Antihypertensive effects of reserpine; methyldopa may be diminished.

Pyridostigmine Bromide

J. Lance LaFleur | Krishna Boddu | Lee A. Fleisher

Uses
- Therapy for MG, which is caused by decreased postsynaptic ACh receptors.
- Antagonism of nondepolarizing NMBDs.
- Therapy for glaucoma.
- Therapy for atony of GI and urinary tracts.

Perioperative Risks
- Muscarinic effects on GI, respiratory, and CV systems.
- Prolonged response to succinylcholine if administered shortly afterward by inhibition of pseudocholinesterase and increased postsynaptic depolarization.
- Paralysis may be prolonged by excessive doses, which can produce a depolarizing NMB

Pharmacology
- Oxydiaphoretic (acid-transferring) inhibitor of AChE.
- Transfers a carbamate group to AChE and forms a covalent bond at the esteratic site.
- Quaternary ammonium ion, which is poorly lipid soluble; does not effectively penetrate GI tract or blood-brain barrier (no CNS side effects).
- Onset is within 10–15 min (vs. 5–10 min for neostigmine); duration is 4 h (similar to neostigmine).
- 20% as potent as neostigmine.
- Renal excretion accounts for approximately 75% of elimination.
- Very large volume of distribution with extensive tissue storage.
- Oral bioavailability is 7.6 ± 2.4%.

Drug Class/Mechanism of Action/Usual Dose
- Reversibly inhibits AChE, which increases the concentration of ACh at the motor endplate.
- May be administered PO, IV, or IM
- Dose is 0.1–0.4 mg/kg IV.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Bradyarrhythmias, hypotension	Presyncope, angina, confusion	HR, BP, orthostasis	ECG
RESP	Increased secretions, bronchospasm	Dyspnea, wheezing	Auscultation	PFTs
GI	Increased secretions, increased motility, spasms	Diarrhea, abdominal pain	Palpation	Lytes

Key References: Barash PG, Cullen BF, Stoelting RK: *Clinical anesthesia*, ed 5, Philadelphia, 2006, Lippincott Williams and Wilkins, pp 297–300, 848; Blichfeldt-Lauridsen L, Hansen BD: Anesthesia and myasthenia gravis, *Acta Anaesthesiol Scand* 56(1):17–22, 2012.

Perioperative Implications

Preoperative Concerns
- In MG pts, skeletal muscle response to repetitive impulses is augmented by increased availability of Ach.
- Chronic administration in MG pts may alter effects of NMBDs, and some may consider omission or reduction of morning dose on the day of surgery.

Induction/Maintenance
- Although nicotinic effects are desirable, muscarinic effects should be attenuated by an anticholinergic (typically glycopyrrolate 0.05 mg per 1 mg of pyridostigmine).

Postoperative Period
- Incidence of recurarization in renal pts is not increased as clearance of both AChE inhibitors and NMBDs is similarly affected.
- MG pts taking >750 mg/d have greater potential for respiratory insufficiency.
- Myasthenic and cholinergic crises may occur after periop alterations in AChE inhibitor therapy.

Anticipated Problems/Concerns
- If maximal dose of pyridostigmine (0.4 mg/kg, or 20 mg in adults) fails to antagonize the residual blockade, it is not advisable to redose the AChE inhibitor, as this may lead to further motor weakness.
- Causes of inadequate antagonism include profound blockade, respiratory acidosis, hypokalemia, hypermagnesemia, hypothermia, verapamil, and antibiotics such as aminoglycosides and polypeptides.

Rifampin

Matthew B. Ellison | Matthew P. Jordan | Manuel C. Vallejo

Uses
- Antibiotic therapy for TB (yearly incidence 2.96:100,000 in USA) and *Neisseria meningitidis* infection (yearly incidence 0.3:100,000 in USA).
- Also used to treat Hansen disease (leprosy) and Legionnaires disease and as prophylaxis against *Haemophilus influenzae* type B.
- Treatment of opioid-induced pruritus associated with the cholestatic jaundice of malignancy
- Administered PO or IV
- 10% of pts receiving rifampin develop chemical hepatitis; 16 deaths per 500,000 receiving drug.

Perioperative Risks
- Hepatic dysfunction, most likely in presence of preexisting liver disease and when used in combination with other hepatotoxic agents like isoniazid.
- Decreased duration of action of narcotics and barbiturates due to P450 (CYP2D6) enzyme induction.
- Pts receiving antiarrhythmic therapy, digoxin, theophylline, phenytoin, or glucocorticoid therapy may need increased doses of these drugs due to enzyme induction.

Overview/Pharmacology
- Complex macrocytic antibiotic approved by FDA in 1971.
- Water-soluble at acidic pH; inhibits gram-positive and many gram-negative organisms, incl *Escherichia coli*, *Pseudomonas*, *Proteus*, *Klebsiella*, *Neisseria meningitidis*, *H. influenzae*, *Mycobacterium tuberculosis*.
- Increases in vitro activity of streptomycin and isoniazid.

- Primarily eliminated by biliary clearance (30–40%) with up to 30% of the dose excreted in urine.
- Half-life 3–5 h; increased with hepatic dysfunction.

Worry About

- Induces hepatic microsomal (P450, CYP2D6) activity and decreases half-life of hepatically metabolized drugs; this effect may last for several weeks after the drug is discontinued.
- Theoretically increases risk of halothane hepatitis.
- Hemolytic anemia, thrombocytopenia (rare).

Drug Class/Mechanism of Action/Dose

- Semisynthetic derivative of rifamycin B, produced by *Streptomyces mediterranei*.
- Inhibits DNA-dependent RNA polymerase in bacteria and mycobacteria; nuclear eukaryotic RNA polymerase not affected.
- Administered for chemoprophylaxis of meningococcal infections, with beta lactams for staphylococcal endocarditis, osteomyelitis, and methicillin-resistant *Staphylococcus aureus* infections; also used in conjunction with isoniazid and streptomycin for active TB.
- Typical adult and pediatric dose: Tuberculosis—10 mg/kg/d or 10 mg/kg PO twice weekly (max 600 mg); *Neisseria meningiditis*—600 mg q12h for 2 d; *Haemophilus influenzae* Type B prophylaxis—600 mg/d PO/IV for 4 d.
- Possible interaction of rifampin with 5HT3 and opioid system as well as mediators of itching proposed. Dose: 300 mg IV 3 times daily.
- Should be administered PO 1 h before or 2 h after meals.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
GENERAL		Fatigue, drowsiness, dizziness, ataxia, confusion, weakness		
HEENT	Secreted in saliva, tears		Orange sputum, tears, conjunctiva, sweat	
GI	Hepatic dysfunction (rare with normal pre-Rx hepatic function)	N/V	Jaundice	Elevated transaminases
HEME	Thrombocytopenia, hemolytic anemia	Bruising/ bleeding		Plt count, Hgb/Hct, microscopic exam
RENAL	Interstitial nephritis, ATN, renal failure (with high doses)		Orange urine	Cr clearance, light-chain proteinuria

Key References: Wallace R, Philley J, Griffith D: Antimycobacterial agents. In Bennett J, Dolin R, Blaser M, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, PA, 2015, Elsevier, pp 463–478; Stoelting R, Hillier S: Antimicrobials. In Stoelting R, Hillier S, editors: *Pharmacology & physiology in anesthetic practice*, ed 4, Philadelphia, PA, 2006, Lippincott Williams & Wilkins, pp 542–543.

Perioperative Implications/Possible Drug Interactions

Preoperative Concerns

- Decreased duration of action of benzodiazepines, narcotics, barbiturates due to hepatic (P450, CYP2D6) enzyme induction.
- Adequacy of preexisting drug regimens should be verified (see Special Considerations).

Induction/Maintenance

- Decreased narcotic and analgesic efficacy: barbiturates, methadone, diazepam, midazolam; beta-blockers have increased clearance, decreased duration of action.
- Halothane metabolism increases, with increased risk of hepatotoxicity.

Adjuvants/Reversal

- Mycobacteria quickly develop resistance when rifampin is used alone (within 40 h); administer with isoniazid and/or streptomycin.

Special Considerations

- Risk of hepatic dysfunction increased periop due to preexisting hepatic disease and alcohol use.
- Delays oral absorption of ASA.
- Decreases in half-life requiring larger doses to maintain adequate therapeutic levels: Digoxin, digitoxin, quinidine, propranolol, metoprolol, verapamil, coumadin, theophylline, phenytoin, prednisone, cortisol, cyclosporine, oral hypoglycemic agents, ketoconazole, fluconazole
- Can precipitate opioid withdrawal symptoms in an opioid-dependent pt by enhancing the hepatic enzymatic metabolism of opioids.
- May increase metabolism of oral contraceptives and anticoagulants, thus decreasing the effectiveness of these medications.

Anticipated Problems/Concerns

- 10% of pts may develop hepatitis; pts with preexisting liver disease are at higher risk.
- Rifampin induces microsomal enzyme activity in the liver, resulting in decreased efficacy and duration of action of hepatically metabolized drugs; this may last for weeks after the drug is discontinued.

Selective Estrogen Receptor Modulators

Lyndsay M. Hoy | Lee A. Fleisher

Uses

- Critical components in treatment algorithm for invasive and/or in situ breast cancer, breast cancer chemoprevention in high-risk pts, and postmenopausal osteoporosis (raloxifene only)

Perioperative Risks

- VTE, particularly if the pt has a history of recent chemotherapy, prior irradiation, or long-term SERM use
- Microvascular complications following free-flap breast reconstruction surgery

Worry About

- Periop SERM management
- Endometrial cancer (tamoxifen only)
- Unpleasant side effect profile affecting pt quality of life and medication adherence

Overview/Pharmacology

- SERMs inhibit breast tumor growth via competitive antagonism of estrogen; also decrease bone demineralization and improve lipid profile via estrogen agonist properties.
- Shape of ligand binding to ERs is highly influential in determining spectrum of estrogen agonist/antagonist expression in target tissues.
  - SERMs competitively bind to shape-sensitive ligand binding domain on ERs, triggering a complex cascade of molecular networks.
  - SERM-ER complex undergoes conformational dynamic changes to become estrogenic or antiestrogenic, thereby recruiting subsequent cofactors and promoting or degrading specific gene transcription via posttranslational modification of multiple kinase pathways.
  - Differential expression of two ER isoforms (alpha, beta) at target sites with varying levels of ligand affinity, cofactor binding, and estrogen activity may contribute to intrinsic SERM success vs. resistance.

Mechanism of Action/Usual Dose

- Tamoxifen
  - Routinely used for prevention of breast cancer in women at high risk and also as adjuvant endocrine therapy in pts who are ER-positive.
  - Metabolically activated to hydroxylated metabolites with high ER affinity.
  - Long half-life (2 wk).
  - Blocks effects of endogenous estrogen in normal and neoplastic breast tissue; conversely produces estrogen-like effects in uterus, bone, liver, and coagulation system.
  - Adjuvant tamoxifen therapy for 5–10 y may reduce 15-y risk of mortality and local breast cancer recurrence.
  - Administered as a 20-mg pill taken daily.
- Raloxifene
  - Alternative to tamoxifen for women at increased risk of uterine cancer; unlike tamoxifen, lacks estrogen activity in uterus.
  - Estrogen effects on bone/lipids; estrogen antagonist effects on breast/uterus.
  - Only agent currently approved for prevention and treatment of postmenopausal osteoporosis.
  - Short-acting.
  - Administered as 60-mg pill taken daily.