Drug Effects

System	Effect	Assessment by Hx	PE	Test
CV	Raynaud phenomenon (rare)	Color changes in fingers	Observation	
RESP	Interstitial pneumonitis (10%) Pulm fibrosis (1%)	Dose (>250 U), age (>65 y) Previous lung disease	Dyspnea, fine rales and cough, fever	PFTs (decreased TLC, decreased VC)
GI	N/V			
HEME	Not associated with pancytopenia			
DERM	Mucocutaneous toxicity (50%)	1–3 wk after start of medication (dose 150–200 U)	Urticaria, hyperpigmentation, hyperkeratosis, alopecia	

Key References: Aakre BM, Efem RI, Wilson GA, et al.: Postoperative acute respiratory distress syndrome in patients with previous exposure to bleomycin, *Mayo Clin Proc* 89(2):181–189, 2014; Donat SM, Levy DA: Bleomycin associated pulmonary toxicity: is perioperative oxygen restriction necessary? *J Urol* 160(4):1347–1352, 1998.

Perioperative Implications

Preoperative Preparation/Concerns

- Assess bleomycin cumulative dose; there is a dose–toxicity relationship; toxicity increases dramatically with a cumulative dose>450 U.
- Assess age (>65 y).
- Assess previous Hx of lung disease and smoking.
- Ask about previous radiation to thorax.
- Consider PFTs, CXR, and ABG.

Perioperative Period

- Limit delivered O_2 to <30% if adequate for O_2 sat >89%. (Controversial: Conflicting evidence/case reports regarding association of higher FiO_2 with pulm morbidity.)
- Limit fluids and avoid fluid overload. Minimize blood transfusion.
- Consider monitoring of CVP.
- Consider arterial monitoring and sampling.
- Use upper limit alarm for percentage of O_2 delivery.

Postoperative Period

- Keep delivered O_2 to <30% if adequate for O_2 sat >89%.
- Limit fluids.
- Corticosteroid use for pulm toxicity is controversial.

Anticipated Problems/Concerns

- Cyclophosphamide and radiation Rx (thorax) potentiate pulm toxicity.
- Cisplatin potentiates renal insufficiency.
- Vinca alkaloids (vincristine, vinblastine, VP-16) potentiate Raynaud phenomenon.
- Mitomycin C exhibits similar properties to those of bleomycin but with milder effects.

Buprenorphine

Veena Graff

Uses

- Management of opioid addiction
- Management of chronic pain ("off-label" use for SL buprenorphine and buprenorphine TD patch)

Perioperative Risks

- Challenges in pain management throughout periop period
- Respiratory depression
- Can cause neonatal abstinence syndrome

Overview/Pharmacology

- High affinity on mu opioid receptors; slowly binds to and slowly dissociates from receptors; therefore buprenorphine has a long duration of action.
- Agonist effects increase in linear fashion with increasing dose, but a ceiling effect exists; therefore there is no further analgesic benefit beyond certain doses.
- 95% bound to plasma proteins.
- Poor oral bioavailability due to extensive first-pass metabolism; therefore most commonly used routes of administration are SL by TD, IV, and IM.
- Half-life: SL ~37 h, TD ~26 h, IV ~3 h
- Time to peak plasma concentrations: SL ~1–3 h, IM ~1 h, TD ~steady state achieved by 72 h.
- Buprenorphine concentration in CSF is approximately 15–25% of the plasma concentration.
- Metabolism: N-dealkylation via CYP3A4 to active metabolite, norbuprenorphine. Also by glucuronidation by uridine diphosphate glucuronosyltransferase isoenzymes to buprenorphine 3-beta-O-glucuronide.
- Clearance: Dependent on hepatic blood flow.
- Excretion: Mostly in feces; 10–30% eliminated in urine.

Drug Class/Mechanism of Action/Usual Dose

- An opioid with mixed agonist-antagonist activity
- Classified as a Schedule III controlled substance under the Controlled Substances Act.
- Partial agonist at Mu-opioid receptors, delta-opioid receptors, and opioid receptor–like receptors (ORL-1).
- Antagonist at kappa-opioid receptors.
- Can precipitate opioid withdrawal if pt has full agonists in bloodstream.
- Best time to start and how to start: When pt is having clear and objective withdrawal symptoms. Titrate dosage quickly in 2–4-mg increments with the goal of reaching an appropriate dose within 1–2 wk.
- SL: Maintenance dose between 4–24 mg daily; adjustments made in 2- to 4-mg increments. Combination of buprenorphine/naloxone maintenance dose between 4 mg/1 mg and 24 mg/6 mg daily.
- TD delivery system (patch): Buprenorphine patch dosages are available in 5, 7.5, 10, 15, and 20 µg/h every wk.

Drug Effects

System	Effect	Assessment by Hx	PE	Test
CV	Hypotension; also possible tachycardia and Htn if opioid withdrawal is precipitated	Low BP: Light-headedness, dizziness. High BP: anxiety, jitteriness	VS, CV exam	ECG to rule out any other arrhythmias
RESP	Respiratory depression, apnea, hypercarbia, hypoventilation	Lethargy, slow, deep breaths	Lung exam	ABG to assess pH and $PaCO_2$
HEPAT	Hepatitis induced with preexisting liver disease	RUQ pain	Abdominal exam	ALT, AST, alk phos, total bilirubin
GI	N/V	N/V	Abdominal exam	
CNS	Mental status changes, dizziness, headache	Mini-mental status exam	Neuro, HEENT exam	
PSYCH	Abuse, diversion, addiction	Inappropriately using, selling	Psychological exam	Urine drug screen, pill counts

Key References: Lutfy K, Cowan A: Buprenorphine: a unique drug with complex pharmacology, *Curr Neuropharmacol* 2(4):395–402, 2004; Sen S, Arulkumar S, Cornett E, et al.: New pain management options for the surgical patient on methadone and buprenorphine. *Curr Pain Headache Rep* 20(3):16, 2016.

Perioperative Implications

Preoperative Concerns
- Periop pain management
- If pt is taking buprenorphine prior to surgery, higher doses of opioids required to manage pain.
- If pt stopped buprenorphine 72 h prior to surgery, opioid dosing may be more manageable.
- Can cause neonatal abstinence syndrome, so watch for acute opioid withdrawal.

Adjuvants/Regional Anesthesia/Reversal
- Utilize nonopioid adjuvants periop, such as neuropathic agents, anti inflammatories, IV acetaminophen, ketamine, and regional anesthetic options.
- Naloxone can be used to reverse buprenorphine, but because buprenorphine has a long duration of action, naloxone infusion is recommended.

Drug Interactions
- CYP3A4 inhibitors can increase concentration of buprenorphine.
- CYP3A4 inducers can decrease concentration of buprenorphine.
- Administering pure agonist opioids while pt is on buprenorphine may not provide effective analgesia.
- Avoid alcohol.

Calcium-Channel Blockers

W. Scott Beattie | Duminda N. Wijeysundera

Uses
- Prescribed to treat Htn, angina, supraventricular arrhythmias, cerebral vasospasm, and HCM.

Perioperative Risks
- CCBs are used chronically in a significant proportion of the surgical population. CCBs are utilized in the treatment of Htn, CAD, or supraventricular arrhythmias and syndromes associated with vascular spasm. CCBs are recommended in combination with ACE inhibitors for diabetic pts with Htn. This class of drug effectively decreases myocardial O_2 demand through its effects on AV conduction, inotropy, and vasodilatation of systemic and coronary vasculature. The dihydropyridine class of CCB given as a single agent has been associated with tachycardia.

Worry About
- Hypotension: A meta-analysis of both cardiac and noncardiac RCTs shows a 50% increase in the incidence of unplanned periop hypotension.
- Neither RCTs nor nonrandomized trials have demonstrated an increased incidence of CHF or the need for inotropic support.
- AV nodal block or asystole has not been demonstrated; however, there is increased utilization of temporary cardiac pacing after cardiac surgery. Bradycardia requiring treatment has been demonstrated in a frequency similar to beta blockers.
- In both cardiac and noncardiac surgery, beneficial effects have been demonstrated; acute withdrawal can precipitate acute coronary ischemia.
- One large nonrandomized study has associated dihydropyridines with increased mortality.
- Neither meta-analyses nor nonrandomized trials have demonstrated any hematologic effects.

Overview/Pharmacology
- Ca^{2+} channels: Functional pores in cardiac and smooth muscle cell membranes allow calcium to flow down an electrochemical gradient. Channels are also present in sarcoplasmic reticulum and mitochondria. Calcium is a primary generator of the cardiac action potential and intracellular events regulating muscular contraction.
- Calcium enters through voltage-dependent or receptor-operated channels. Most of the effects of calcium channel blockers are regulated by components of the L (long-lasting) type receptor.
- Amlodipine is the most widely prescribed calcium channel blocker; has a half-life of 30–50 hr and bioavailability of 60–90%; it is predominately metabolized to inactive metabolites and excreted in urine.
- Verapamil: 90% absorbed PO, 20-35% bioavailability, onset of action 2 h, peak effect of IV/PO 3-4 h, 85% eliminated by first-pass hepatic metabolism with elimination T½ 3-7 h; IV effects almost immediate.
- Diltiazem: 89–90% PO absorption,40–70% bioavailability, PO onset of action <15 min, peak effect 30 min, 60% metabolized by liver, remainder excreted by kidneys, $T_{½}$ 3.5–6.0 h.
- Bepridil: >90% absorption, >80% bioavailability, PO onset of action 2–3 h, peak effect within 8 h, hepatic elimination with $T_{½}$ 26–64 h.
- Hepatic disease may necessitate decreased dosing of verapamil and other CCBs.

Drug Class/Mechanism of Action
- Four classes of CCBs:
  - 1,4 dihydropyridine (e.g., amlodipine, nifedipine, nicardipine).
  - Phenylalkylamines (e.g., verapamil).
  - Benzothiazepines (e.g., diltiazem).
  - Diethylaminopropylamine ether (e.g., bepridil).
- Mechanisms of action: Amlodipine—blockade of a voltage-dependent L-type inactive Ca^{2+}-channel receptor that has recently undergone activation and cannot open; the other three classes bind to specific receptors within the L-type channels.
- The dose of a CCB (e.g., nicardipine, diltazem, verapamil) used periop should be titrated to effect.

Drug Effects

System	Effect	Assessment by Hx	PE	Test
CV	Ischemic protection, myocardial depression, vasodilation, AV conduction slowing	Short-acting nifedipine should be avoided due to risk of reflex tachycardia	Hypotension, bradycardia	BP measurement, ECG, ECHO for ventricular contractility
CNS	Cerebral vasodilation and decreased vasospasm; there is no indication of increased stroke in clinical studies	Ongoing assessment of neurologic status in pts at risk for vasospasm	Changes in neurologic assessment	Cranial Doppler or angiogram
NEURO	Potentiation of NMB	Increased risk of aspiration if extubated with residual block	Prolonged block	Use of NMB monitor
ENDO	Nifedipine delays insulin release and decreases serum glucose in DM; diltiazem has no effect on insulin, glucagon, growth hormone, or cortisol levels	Better glucose control in DM pts on nifedipine	Blood glucose	

Key References: Wijeysundera DN, Beattie WS, Rao V, et al.: Calcium antagonists reduce cardiovascular complication after cardiac surgery: a meta analysis, *J Am Coll Cardiol* 41(9):1496–1505, 2003; Wijeysundera DN, Beattie WS: Calcium channel blockers for reducing cardiac morbidity after noncardiac surgery: a meta-analysis, *Anesth Analg* 97(3):634–641, 2003; Kertai MD, Westerhout CM, Varga KS, et al: Dihydropiridine calcium-channel blockers and perioperative mortality in aortic aneurysm surgery, *Br J Anaesth* 101(4):458–465, 2008.

Perioperative Implications

Preoperative Concerns
- There is little evidence to advocate for continuation or withdrawal of chronic CCBs periop.
- Careful assessment of baseline hemodynamic variables
- Drug interactions: Verapamil increases digoxin levels
- Drug interactions: Inhibition of CYP3A4 markedly increases bioavailability of some CCBs and increases the risk of an adverse drug reaction.

Monitoring
- Routine.
- Pacing capability if associated AV block or CHF.
- Arterial line if BP instability likely.

Airway
- No special concerns

Preinduction/Induction
- Assess hemodynamics and ECG before induction.

Maintenance
- Volatile anesthetics may potentiate vasoactive effects.
- Effects of CCBs can be antagonized by administration of calcium or other pressor agents.

Extubation
- There is a potential for incomplete reversal of NMBs owing to interaction with CCBs on the postsynaptic membrane and blockade of Ca^{2+} channels in skeletal muscle. Check TOF if using NMBs.

Anticipated Problems/Concerns
- Hypotension
- Bradycardia
- AV nodal block and the increased use of temporary pacemakers
- Potential for paradoxical aggravation of myocardial ischemia due reflex sympathetic stimulation and tachycardia