Drug Effects

System	Effect	Assessment by Hx	PE	Test
ENDO	Hypocalcemia	Indication of bisphosphonate Calcium level should be normal before IV administration of bisphosphonate	Chvostek sign Trousseau sign	Serum calcium levels
GI	Heartburn Esophageal irritation Esophagitis Abdominal pain Diarrhea	For safe administration of oral bisphosphonates, pt must be able to remain upright for ≥30 min after administration		
RENAL	Renal clearance	Monitoring of renal function to ensure safe administration of bisphosphonate. The use of bisphosphonate is not recommended in pts with CrCl <30 mL/min		Serum Cr
MS	Osteonecrosis of jaw Atypical femur fractures			Radiography
OTHER	Flu-like symptoms with IV bisphosphonate (low-grade fever, myalgia, arthralgia)	Acute-phase reaction within 24–72 h of infusion		

Key References: Friedman PA: Agents affecting mineral ion homeostasis and bone turnover. In: Brunton LL, Chabner CA, Knollmann BC, editors: *Goodman & Gillman's the pharmacological basis of therapeutics*, ed 12, New York, 2011, McGraw-Hill, pp 1275–1306; Ruggiero SL, Dodson TB, Assael LA, et al.: American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of jaws—2009 update, *J Oral Maxillofac Surg* 67(5 Suppl):2–12, 2009.

Perioperative Implications

Preoperative Concerns

- Guidelines of the American Association of Oral and Maxillofacial Surgeons recommend holding oral bisphosphonates for 3 mo prior to elective dental surgery in pts who have been receiving them for ≥3 y or who are treated with corticosteroids. However, urgent surgery should not be delayed. The oral bisphosphonate should be restarted only when the bone has healed.

Induction/Maintenance

- No known drug interactions

Adjuvants/Regional Anesthesia/Reversal

- No known contraindications

Postoperative Concerns

- Bisphosphonates should be held in pts with postop renal complications.
- In the presence of bisphosphonate-related ONJ, risks and benefits of continuing IV bisphosphonate therapy in oncology pts should be determined in consultation with the treating oncologist, oral/maxillofacial surgeon, and pt.

Drug Interactions

- The absorption of oral bisphosphonates can be greatly decreased in the presence of food, beverages (other than plain water), calcium supplementation, and other drugs. Therefore oral bisphosphonates should be administered on an empty stomach at least 30 min–2 h prior to the ingestion of food, beverages, and other drugs.

Bleomycin

Carin Tauriello | Mark J. Lema

Uses

- Treatment of squamous cell carcinoma
- Treatment of melanomas and sarcomas
- Treatment of testicular carcinoma
- Treatment of Hodgkin and non-Hodgkin lymphoma
- Sclerosing agent for malignant pleural effusion

Perioperative Risks

- Adverse effects >10%.
- Acute febrile reactions (25 -50%).
- Dermatologic:
  - Skin thickening, diffuse scleroderma, onycholysis, pruritus.
  - 50% of pts develop erythema, rash, striae, indu hyperkeratosis, vesiculation, and peeling of the skin; predominantly seen on the palmar and plantar surfaces of the hands and feet.
  - Hyperpigmentation (50%), alopecia, nail bed changes.
  - Effects are usually dose-related and reversible with discontinuation.
- Gastrointestinal: Stomatitis and mucositis (30%), anorexia, weight loss.
- Adverse effects (1 -10%)
  - Miscellaneous: Anaphylactoid-like reactions and idiosyncratic reactions (1% in lymphoma pts).
- Adverse effects <1%
  - Angioedema, cerebrovascular accident, cerebral arteritis, hepatotoxicity, hypoxia, MI, Raynaud's phenomenon, renal toxicity, scleroderma-like skin changes, thrombotic microangiopathy, vomiting.
- Respiratory: Tachypnea, rales, acute or chronic interstitial pneumonitis, and pulm fibrosis (5 -10%).
  - Rapidly progressive interstitial pneumonitis known to occur after general anesthesia using O2 conc >30%, overhydrating pt; postop ARDS.
- FDA Black Box Warning:
  - Idiosyncratic reaction: A severe reaction similar to anaphylaxis has been reported in 1% of lymphoma pts treated with bleomycin. These reactions typically occur after the first or second dose.
  - Pulmonary fibrosis: Most severe toxicity of bleomycin, with risk increasing in elderly pts, those receiving >400 U total lifetime dose, and possibly smokers and pts receiving concurrent O_2 therapy.
  - Experienced physician: Should be administered under the supervision of a physician experienced in delivering chemotherapy.
- Contraindications: Hypersensitivity to bleomycin or any component of the formulation, severe pulm disease, pregnancy.

Worry About

- Sustained O_2 concentration >30%
- Liberal use of maintenance fluids/blood products
- Interstitial pneumonitis
- Postop acute respiratory distress syndrome

Overview/Pharmacology

- 1 U bleomycin = 1 mg activity of bleomycin.
- $T_{½}$ approximately 2 h, but Cr <35 mL/min raises $T_{½}$ exponentially.
- 70% is recovered in urine as active bleomycin.

Drug Class/Mechanism of Action

- Mixture of cytotoxic antibiotics isolated from *Streptomyces verticillus*.
- Cytotoxic action caused by inhibition of DNA synthesis.
- Usual dose: 0.25–0.5 U/kg weekly or twice weekly (10–20 U/m^2) to 400 U (total dose).
- Cause of pulm toxicity is unclear; thought possibly to be related to production of free radicals.

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.