Overview/Pharmacology

- Competitive selective antagonists of beta adrenoreceptors. Binding to receptors is reversible.
- Beta-blockers with intrinsic sympathomimetic activity (e.g., acebutolol) are partial agonists of beta adrenoreceptors that activate the receptors to some extent.
- Partial antagonists cause smaller reductions in HR and CO than beta-blockers without intrinsic sympathomimetic activity.
- Some beta-blockers are also antagonists of alpha$_1$-adrenoreceptors (labetalol, carvedilol) or partial agonists of beta$_2$-adrenoreceptors (nebivolol).
- Selectivity for beta$_1$ adrenoreceptors varies among beta-blockers, with the most selective drugs being nebivolol, followed by bisoprolol, atenolol, and metoprolol.

Drug Class/Mechanism of Action/Usual Dose

- Beta-blockers block interfere with ability of catecholamines and other sympathomimetics to activate beta adrenoreceptors on heart and smooth muscle of airways or blood vessels.
- Chronic administration leads to upregulation of beta adrenoreceptors.
- Routes of clearance include hepatic (metoprolol, carvedilol, propranolol), renal (atenolol, acebutolol), mixed renal and hepatic (bisoprolol, nebivolol), or plasma hydrolysis (esmolol).
- Elimination half-life is specific to individual agents and depends on dose, protein binding, and route of administration (oral vs. IV).

Drug Effects

System	Effect	Assessment by Hx	PE	Test
CV	Decreased HR Decreased CO Decreased contractility Increased CVR Decreased myocardial O_2 consumption	Relief of angina Decreased BP Decreased HR	HR BP	ECG; cardiac stress test
RESP	Increased airway resistance (especially nonselective agents)	Increased wheezing Increased bronchospasm		FEV_1; FEV_1/FVC ratio Increased peak airway pressure
ENDO	Hyperglycemia Hypokalemia			Lab measurements of K^+ and glucose
CNS	Fatigue, lethargy, sleep disturbance, peripheral paresthesia			
OB	Beta-blockers cross placenta and can cause fetal bradycardia, hypotension, or hypoglycemia			

Key References: Frishman WH: β-Adrenergic blockade in cardiovascular disease, *J Cardiovasc Pharmacol Ther* 18(4):310–319, 2013; Wijeysundera DN, Duncan D, Nkonde-Price C, et al.: Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, *Circulation* 130(24):2246–2264, 2014.

Perioperative Implications

Preoperative Concerns

- Long-term beta-blocker Rx must be continued periop (Class I ACC/AHA recommendation).
- May be reasonable for selected pts with ischemia on cardiac stress testing or three or more risk factors on the Revised Cardiac Risk Index (Class IIb ACC/AHA recommendation).
- Abrupt withdrawal results in excess SNS activity within 24–48 h and can lead to unstable coronary syndromes.

Induction/Maintenance

- Beta-blockers may potentiate myocardial depression associated with inhaled or IV anesthetics.

Adjuvants/Regional Anesthesia/Reversal

- Bradycardia can often be reversed with atropine, but life-threatening bradycardia may require a temporary pacemaker.
- Catecholamines (e.g., isoproterenol, dobutamine, epinephrine) can help reverse negative cardiac effects, but very high doses are typically needed. $CaCl_2$ (250–1000 mg in adults) or glucagon (1–5 mg in adults) administered IV can also help reverse myocardial depression.
- In severe overdoses where usual Rx has failed, hyperinsulinemic euglycemia (high-dose insulin with concurrent glucose infusion to maintain euglycemia) may help.

Anticipated Problems/Concerns

- Beta-blocker dose may require temporary adjustment after surgery to account for hemodynamic effects of fluid shifts, epidural analgesia, and other medications. Goal is to avoid hypotension.

Bisphosphonates

Silvia Duong | De Q.H. Tran

Uses

- Oral bisphosphonates:
  - Alendronate (Fosamax), risedronate (Actonel): Prevention and treatment of postmenopausal osteoporosis, prevention and treatment of glucocorticoid-induced osteoporosis, treatment of osteoporosis in men, and Paget disease of bone
  - Etidronate (Didronel): Prevention and treatment of postmenopausal osteoporosis and Paget disease of bone
  - Ibandronate (Boniva) administered PO and IV: Prevention and treatment of postmenopausal osteoporosis
- IV bisphosphonates:
  - Pamidronate (Aredia): Treatment of hypercalcemia of malignancy, osteolysis secondary to bone metastases in breast cancer, osteolytic lesions of multiple myeloma, and Paget disease of bone
  - Zoledronic acid (Zometa): Treatment of hypercalcemia of malignancy, osteolysis secondary to bone metastases in breast cancer, and osteolytic lesions of multiple myeloma
  - Zoledronic acid (Reclast): Prevention and treatment of postmenopausal osteoporosis, prevention and treatment of glucocorticoid-induced osteoporosis, treatment of osteoporosis in men, and Paget disease of bone

Perioperative Risks

- Use of bisphosphonates has been associated with osteonecrosis of the jaw (ONJ) in those undergoing dental surgery. The risk of ONJ is higher (1–12%) among cancer pts receiving higher doses of bisphosphonates. The risk is much lower (1:10,000-100,000) among those who are treated with oral bisphosphonate for osteoporosis.

Overview/Pharmacology

- Oral bisphosphonates are poorly absorbed; bioavailability is only 1–5%.
- After binding to bone surfaces and exerting their effects on osteoclasts, bisphosphonates are retained in the bone for months to years (biologic half-life up to 10 y). Bisphosphonates are gradually and slowly released with the process of bone turnover.
- Bisphosphonates are not metabolized.
- Bisphosphonates are excreted primarily by the kidneys; their elimination decreases linearly with decreased renal function. The use of bisphosphonate is not recommended in individuals with CrCl <30 mL/min.

Mechanism of Action

- Bisphosphonates are analogs of pyrophosphate that adsorb to the surface of bone hydroxyapatite. Bisphosphonates reduce the risk of bone fracture by suppressing osteoclastic bone resorption.
- By interfering with osteoclast-mediated bone resorption, bisphosphonates inhibit calcium release and are used in the management of hypercalcemia.

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.