Drug Class/Mechanism of Action

- Cromolyn sodium (disodium cromoglycate) is a derivative of 2-chromone–carboxylic acid.
- Direct mechanism of action in asthma is poorly defined.
  - One proposed explanation is decrease in accumulation of intracellular Ca^{2+} in sensitized mast cells.
  - Another possible mechanism is Cl^- channel blockade in antigen-sensitized pulm C-fibers.
- Effective in preventing degranulation of mast cells only if given prior to antigenic challenge.

Usual Dose

- Cromolyn sodium inhalation (Intal) via a special nebulizer (20 mg/2 mL) or metered spray (2 puffs [1 mg/puff] 3–4 times daily for asthma).
- 4% liquid nasal spray (Nasalcrom) given as 1 spray to each nostril 3–6 times daily for allergic rhinitis.
- 4% ophthalmic solution (Opticrom) given as 1–2 drops to each eye 4–6 times daily for atopic eye conditions.

Assessment Points

System	Effect	Assessment by Hx	Test
RESP	Inhibition of pulm mast cell degranulation; decreased release of histamine and leukotrienes; reverse or suppress leukocyte activation	Decreased episodes of exercise- or antigen-induced bronchospasm after chronic use	Decreased bronchial hyperactivity as measured by histamine or methacholine challenge

Key References: Undem BJ: Pharmacotherapy of asthma. In Brunton LL, Lazo JS, Parker KL, editors: *Goodman & Gilman's the pharmacological basis of therapeutics*, ed 11, New York, 2006, McGraw-Hill Medical, pp 717–736; Netzer NC, Küpper T, Voss HW, et al.: The actual role of sodium cromoglycate in the treatment of asthma—a critical review, *Sleep Breath* 16(4):1027–1023, 2012.

Perioperative Implications/Possible Drug Interactions

- Continue administration periop. Do not discontinue abruptly.
- Cromolyn sodium is of no benefit in treating an acute exacerbation of asthma.
- Adverse effects are infrequent:
  - Unpleasant taste (most common)
  - Direct irritation (e.g., wheezing, coughing)
  - Dizziness, nausea, rash
  - Urticaria, anaphylaxis (extremely rare)
- No significant drug-drug interactions with cromolyn sodium are known.
- Compatible in a nebulized solution with albuterol, levalbuterol, ipratropium, and budesonide.
- Pregnancy category B, with no known evidence of teratogenicity.

Dabigatran

Kelly Byrne | Antony Aho

Uses

- Stroke prevention in nonvalvular AFIB
- Thromboembolism prophylaxis after total hip and knee replacement
- Treatment and prevention of DVT and PE not related to surgery

Worry About

- Contraindicated in pts with creatinine clearance less than 30 mL/min.
- Use with other anticoagulants will increase the risk of bleeding and is not recommended.
- Use with strong inhibitors of p-glycoprotein (e.g., ketoconazole, itraconazole, cyclosporine) is contraindicated as they increase plasma concentrations of dabigatran.
- Use with mild inhibitors of p-glycoprotein (e.g., amiodarone, quinidine, verapamil) should proceed with caution.
- P-glycoprotein inducers (e.g., rifampicin) will reduce dabigatran plasma concentrations.
- Major hemorrhage occurs in roughly 3.5% and fatal hemorrhage in 0.07% of pts.
- Gastrointestinal upset has been reported in postmarketing surveillance.

Overview/Pharmacology

- Competitive direct thrombin inhibitor that is active after a single dose.
- Inhibits both free and clot-bound thrombin and thrombin-induced platelet aggregation.
- For oral administration, available in 75-, 110-, and 150-mg capsules.
- Doses vary by country, but an indicative dose regime would be as follows: Dosing for prevention of stroke is usually 150 mg 2 times daily; this may be reduced to 110 mg 2 times daily in pts with renal impairment. Dosing for DVT treatment is usually also 150 mg 2 times daily. For prophylaxis following hip or knee joint replacement the usual dose is 110 mg on day 1 followed by 220 mg once daily.
- Oral bioavailability is 3–7%. Not much altered when administered with food but will increase significantly if capsule is broken before oral administration.
- Peak plasma concentration is reached within 2 h
- Approximately 35% plasma protein binding with volume of distribution 50–70 L.
- 80% of dabigatran is renally excreted.
- Half-life is 12–17 h, which is prolonged by renal impairment.
- Not metabolized by and does not induce cytochrome P450.

Test	Effect of Dabigatran	Clinical Usefulness
INR	May be normal or elevated in the presence of therapeutic levels of dabigatran	Not useful
APTT	Usually elevated in presence of therapeutic levels of dabigatran (around 1.3 times normal at steady state)	High APTT in a pt on dabigatran indicates therapeutic levels of dabigatran. However, this lacks sensitivity and a normal result does not exclude therapeutic levels of dabigatran.
TCT	Elevated in presence of even small amounts of dabigatran	Very sensitive predictor of the presence of dabigatran. Can also be elevated by other drugs that effect thrombin (e.g., heparin).
TEG	Unpredictable effect of dabigatran	Not currently useful, but may improve with the use of novel activating agents (e.g., ecarin)
Ecarin clotting time	Sensitive to the presence of small amounts of dabigatran Plasma is diluted in a standard fashion and thrombin time is carried out to estimate dabigatran levels when calibrated against known levels of dabigatran	Not widely available; tends to be used mainly as research tool Shown to be accurate in measuring dabigatran levels but unclear as to how the level correlates with degree of anticoagulation (i.e., at what dabigatran level it is safe to proceed to surgery).

Key References: van RJ, Stangier J, Haertter S, et al.: Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity, *Thromb Haemost* 103(6):1116–1127, 2010; von Heymann C, Rosenthal C, Kaufner L, et al.: Management of direct oral anticoagulants-associated bleeding in the trauma patient, *Curr Opin Anaesthesiol* 29(2):220–228, 2016.

Perioperative Implications

Preoperative Concerns

- Guidelines for stopping dabigatran vary between organizations and depend on pt's bleeding risk and renal function.
- In low-risk pts with normal renal function, stopping dabigatran 2 d prior to surgery should be adequate to allow clearance of most of the drug from the plasma.
- Where there is a high risk of bleeding or with renal impairment or where neuraxial anesthesia is being considered, dabigatran should be stopped at least 4 d prior to surgery.
- Clearance in pts with renal impairment or failure can be highly unpredictable and certain scenarios (e.g., cardiopulmonary bypass) can result in increased levels of dabigatran.
- A normal TCT indicates a return to pt's normal coagulation status.

Regional Anesthesia

- Neuraxial anesthesia is contraindicated in the presence of therapeutic levels of dabigatran. Any elevation of TCT during neuraxial anesthesia may indicate an increased risk of epidural hematoma. Current guidelines suggest stopping dabigatran 5–7 d prior to undertaking neuraxial block.
- Dabigatran can be instituted or restarted 6 h after removal of epidural cath or after a single-shot spinal anesthetic. Dabigatran should not be administered while an epidural cath is in place.
- Dabigatran will increase the risk of bleeding from all types of regional anesthesia. Peripheral nerve blockade is not absolutely contraindicated in the presence of therapeutic levels of dabigatran. The risk/benefit will depend on individual cases. Broadly speaking, however, shallower blocks that allow for compression of the block site if bleeding occurs will be safest.
- There is currently no evidence to support the safety or otherwise of continuing dabigatran during an eye block. Current manufacturers' guidelines are to cease therapy 2–5 d preop.

Reversal/Special Considerations

- Idarucizumab is a specific monoclonal antibody for reversal of dabigatran. It was approved by the FDA in October 2015. Phase 3 trials of its efficacy and safety are continuing.
- Some expert guidelines recommend use of either activated factor VIIIa (FEIBA) or activated factor VIIa to overcome the effect of dabigatran on the coagulation system. Neither of these treatments has been proven to work, although there is some theoretical benefit to their use. There are some supportive data from animal studies.
- Elective or semiacute surgery should be delayed by the time periods indicated by local guidelines, ensuring that the TCT has normalized prior to surgery.
- For acute surgery, idarucizumab, if available, should be administered. If not available, activated charcoal may help reduce absorption of a recently administered dose of dabigatran; otherwise hemodialysis can be useful in reducing plasma levels. Dabigatran plasma levels usually rebound 4–6 h after cessation of dialysis.
- Massive transfusion, dialysis to remove dabigatran, and use of activated clotting factors and prothrombin complex concentrates have been described in case reports, but with mixed success in achieving hemostasis.

Digitalis (Digoxin)

Abhijit S. Nair

Uses

- Treatment of CHF, atrial fibrillation, and flutter.
- Prevention of supraventricular arrhythmias following thoracotomy (controversial).
- Cardiac side effects: Arrhythmias and conduction disturbances.
- Noncardiac side effects: GI—anorexia, N/V, and abdominal pain; CNS—visual disturbances, headache, drowsiness, and confusion.

Perioperative Risks

- Recent systematic review and meta-analysis suggest that use of digoxin is associated with increased mortality risk, especially in pts with atrial fibrillation.
- Cardiac arrhythmia (toxicity) can be precipitated by hypokalemia, hypomagnesemia, hypoxia, hypercalcemia, hypernatremia, and renal failure.
- DC cardioversion can cause severe ventricular arrhythmias in pts with toxic levels.
- AV block (with co-administration of β-adrenergic, Ca^{2+}-channel blocking drugs).

Worry About

- Dosing has a narrow therapeutic index (0.8–2 ng/mL or 1.2–2 nmol/L).
- Avoid in pts with ventricular extrasystole or VT, as it may precipitate VF due to increased cardiac excitability.
- Hyperventilation can cause alkalosis leading to relative hypokalemia toxicity.
- Renal insufficiency (decreased digoxin clearance and need for dose alteration, not appreciably removed by dialysis).

Overview/Pharmacology

- A glycoside extracted from leaves of the foxglove (digitalis lanata), available in oral and IV preparations.
- Has positive inotropic effects, along with negative chronotropic and dromotropic properties.
- Acts by raising intracellular sodium and calcium concentration, along with lowering of potassium concentration due to sarcolemmal Na^+K^+ ATPase inhibition.
- Indirect effect enhances release of acetylcholine at the cardiac muscarinic receptors. This slows conduction and prolongs the refractory period in AV node and bundle of His.

Dosing/Pharmacokinetics

Drug	Onset	Initial Dose (mg)	Maintenance Dose (mg/d)
Digoxin: IV	5–30 min	0.5–1.0	0.25
PO	1–3 h	0.75–1.2	0.125–0.5
Digitoxin: PO	3–6 h	0.8–1.2	0.05–0.3

Excretion

- Digoxin: Renal, mostly unchanged; decreased dose for increased Cr, monitor renal functions (creatinine, potassium)
- Digitoxin: Hepatic degradation

Drug Interactions

- Diuretics: Decreased serum K^+, increased toxicity
- Plasma levels increased by quinidine, amiodarone, verapamil, captopril, erythromycin.
- Plasma levels decreased by antacids, phenytoin, metoclopramide, and cholestyramine.

Treatment for Toxicity

- Due to Na^+/K^+ ATPase inhibition, hyperkalemia may be a feature and should be corrected.
- Hypokalemia exacerbates toxicity and should be corrected.
- Severe bradycardia: Atropine or pacing preferred over catecholamines.
- Ventricular arrhythmias:,Treat with lidocaine or phenytoin.
- Digoxin specific Fab: Indicated for digoxin levels >10 mcg/L, life-threatening arrhythmias, or uncontrolled hyperkalemia, with hemodialysis required in refractory acidosis and hyperkalemia.