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.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEENT			Decreased JVD	
CV	Decreased HR, Increased CO Arrhythmia from toxicity	Decreased SOB, orthopnea Palpitations	Decreased HR rate, size Irregular pulse	CXR: Decreased heart size ECG: Any arrhythmia except AFIB
RESP	Decreased congestion	Decreased SOB, orthopnea	Decreased rales	CXR: Decreased pulm edema
GI	Anorexia from toxicity			Serum digoxin >2 ng/mL
CNS	Headache, confusion from toxicity			Serum digoxin >2 ng/mL
MS	Fatigue from toxicity -and confusion (brain often more affected than heart) can be cause of reversible cognitive dysfunction			Serum digoxin >2 ng/mL

Key References: Ouyang AJ, Lv YN, Zhong HL, et al.: Meta-analysis of digoxin use and risk of mortality in patients with atrial fibrillation, *Am J Cardiol* 115(7):901–906, 2015; Mittal MK, Chockalingam P, Chockalingam A: Contemporary indications and therapeutic implications for digoxin use, *Am J Ther* 18(4):280–287, 2011.

Perioperative Implications

Preoperative Concerns

- Do not discontinue digitalis preop. Withdrawal in heart failure pts may lead to recurrence of failure symptoms.
- When changing from oral to IV therapy, dosage should be reduced by 20–25%.
- Correct and maintain serum K^+, magnesium.
- Decreasing dose with increasing serum creatinine.
- Maintain a high index of suspicion for digoxin toxicity.

Dipyridamole

Sushila Murthy

Uses

- Rx as adjunctive therapy for prophylaxis of thromboembolism with cardiac valve replacement.
- Used for secondary stroke prevention (often combined with aspirin).
- Used in stress tests to evaluate for presence of coronary artery disease.

Perioperative Risks

- Headache
- Plt dysfunction
- Hemorrhage
- Exacerbation of angina pectoris

Worry About

- Potentiation of anticoagulants
- Thrombosis secondary to dipyridamole discontinuation

Overview/Pharmacology

- Reversibly impairs plt function by inhibiting the activity of adenosine deaminase and phosphodiesterase, which causes an accumulation of adenosine, adenine nucleotides, and cyclic AMP.
- May also cause vasodilation.
- Affects hepatic metabolism and fecal elimination.
- Elimination half-life is 10 h.

Drug Class/Mechanism of Action/Usual Dose

- Antiplatelet agent.
- Chronically taken for secondary stroke prevention or prophylaxis of thromboembolism with cardiac valve replacement.
- Used acutely in IV formulation for diagnosis of CAD.
- Usual doses:
  - Dipyridamole 75–100 mg PO q6h
  - Dipyridamole extended release 200 mg/aspirin 25 mg: 1 capsule q12h
  - Evaluation of coronary artery disease: 0.14 mg/kg/min IV for 4 min; max dose: 60 mg; aminophylline should be available for urgent/emergent reversal; dosing of 50–100 mg (range: 50–250 mg) IV push over 30–60 sec
- Alternatives: Aspirin, NSAIDs, thienopyridines (clopidogrel, prasugrel), and GPIIb/IIIa receptor antagonists.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
NEURO	Vasodilation of cerebral vessels	Headache		
CV	Vasodilation of coronary arteries (theoretical increased risk of ischemia)	Chest pain	Hypotension	ECG, stress test, or cath to assess for myocardial ischemia/infarction
HEME	Plt dysfunction	Bleeding, bruising	Hematoma, petechiae	Bleeding time
HEPAT	Serum enzyme elevations and possible hepatic dysfunction		Jaundice	AST, ALT, alk phos
GI	Gastritis, exacerbation of PUD	Abdominal pain, nausea, hematemesis, melena, diarrhea		

Key References: Diener HC, Darius H, Bertrand-Hardy JM, et al.: Cardiac safety in the European Stroke Prevention Study 2 (ESPS2), *Int J Clin Pract* 55(3):162–163, 2001; Breivik H, Bang U, Jalonen J, et al.: Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine, *Acta Anaesthesiol Scand* 54(1):16–41, 2010.

Perioperative Implications/Possible Drug Interactions

Perioperative Concerns

- Lack of data on the safety of dipyridamole if continued in the periop period. Must balance the risk of bleeding and risk of ischemic events. If discontinued, dipyridamole should be stopped at least 2 d before surgery. Combination aspirin and dipyridamole should be discontinued 7–10 d before surgery.

Adjuvants/Regional Anesthesia/Reversal

- Lack of data regarding regional anesthesia and dipyridamole. Current guidelines suggest that when used alone, there is no need to discontinue before neuraxial blockade.

Anticipated Problems/Concerns

- May diminish the therapeutic effect of acetylcholinesterase inhibitors.
- May enhance the effect of adenosine.
- Extended-release dipyridamole use for stroke prevention is not empirically associated with an increased risk of myocardial ischemia or infarction.