CHAPTER 4
Cardiac Surgical Pharmacology

ANTIARRHYTHMICS
- Vaughan Williams classification
- not all drugs can be incorporated into this scheme
- Other Drugs: digoxin, adenosine, and magnesium

Digoxin
- increased slope of phase 4 depolarization
- decreased conduction velocity
- net effect is greatest at the AV node
- conduction is slowed
- refractory period is increased
- effectiveness of digoxin in slowing the ventricular response to atrial fibrillation

Digoxin
- disadvantages of digoxin
  - slow onset of action and many side effects
  - proarrhythmia effects
  - rarely for rate control in acute atrial fibrillation because of the advent of IV amiodarone and diltiazem

Adenosine
- endogenous nucleoside
- electrophysiologic effect similar to that of acetylcholine
- decreases AV node conductivity
- primary antiarrhythmic effect is to break AV nodal reentrant tachycardia
- IV dose of 100 to 200 µg/kg: for paroxysmal supraventricular tachycardia
**Adenosine**
- Adverse effects: Bronchospasm
- Short-lived
- Plasma half-life is so short (1 to 2 seconds)
- Ideal for treating reentry dysrhythmia, in which transient interruption can fully suppress the dysrhythmia

**Magnesium**
- Appropriate acid-base status and electrolyte balance
- Magnesium deficiency is common in the perioperative period
- Magnesium administration has been shown to decrease the incidence of postoperative dysrhythmia

**Amiodarone**
- One of the most administered intravenous antiarrhythmics
- Broad spectrum of efficacy
- Developed originally as an antianginal agent because of its vasodilating effects, including coronary vasodilation

**Pharmacokinetics**
- Complex drug
- Lipophilic
- Variable absorption (35 to 65%) after oral administration and is taken up extensively by multiple tissues with interindividual variation and complex pharmacokinetics
- True elimination half-life: extremely long, up to 40 to 60 days
- huge volume of distribution (~60 L/kg)
- a long duration of action
- an active metabolite loading period of several months may be required before reaching steady-state tissue concentrations
- life-threatening arrhythmias: IV loading often is starting to establish initial plasma levels.

Measuring amiodarone plasma concentrations is not useful
- Plasma concentrations >2.5 mg/L have been associated with an increased risk of toxicity
- optimal dose of amiodarone has not been well characterized
- differences in dose requirements for therapy of supraventricular and ventricular arrhythmias

Oral administration for a typical adult
- a loading regimen of 80 to 1600 mg/d (in two or three doses) for 10 days
- 600 to 800 mg/d for 4 to 6 weeks
- and then maintenance doses of 200 to 600 mg/d.

for acute therapy in an adult (IV):
- 150 mg given over 10 minutes
- followed first by a secondary loading infusion of 60 mg/h for 6 hours
- and then by a maintenance infusion of 30 mg/h to achieve a 1000 mg/d dosing

Electrophysiology
- Complex and incompletely understood
- produces all four effects according to the Vaughan Williams classification
- use-dependent class I activity, inhibition of the inward sodium currents, and class II activity
- Depresses SA node automaticity, which slows the heart rate and conduction and increases refractoriness of the AV node, properties useful in managing supraventricular arrhythmias

Indications
- primary indication: ventricular tachycardia or fibrillation refractory to other therapy
- most efficacious agent for reducing ventricular arrhythmias
- suppresses the incidence of post-MI sudden death
- effective in converting atrial fibrillation to sinus rhythm

- Its class III activity results in increases in atrial and ventricular refractoriness and in prolongation of the QTc interval
- effects of oral amiodarone on SA and AV nodal function are maximal within 2 weeks
- effects on VT and ventricular refractoriness emerge more gradually during oral therapy, becoming maximal after 10 weeks or more
Side Effects

- Occur with long-term oral administration and have not been associated with acute IV administration
- Most serious is pulmonary toxicity
- Some case series: an increased risk of marked bradycardia and hypotension immediately after cardiac surgery in patients already on amiodarone at the time of surgery

Ventricular Tachyarrhythmias

- IV amiodarone is approved for rapid control of recurrent VT or VF
- One study compared three doses of IV amiodarone: 525, 1050, and 2100 mg/d
  - No statistically significant difference in the number of patients without VT/VF recurrence during the 1-day study period: 32 of 86 (37%), 36 of 92 (45%), and 42 of 92 (53%) for the low-, medium-, and high-dose groups,

- The third study compared two IV amiodarone doses (125 and 1000 mg/d) with bretylium (2500 mg/d).
  - No significant difference in the primary outcome

IV amiodarone (1 g/d) is moderately effective during a 24-hour period against VT and VF.
- Most effective and rapid treatment of any hemodynamically unstable sustained ventricular tachyarrhythmia is electrical cardioversion or defibrillation
- IV antiarrhythmic drugs: if the VT is hemodynamically stable
The Guidelines 2000 for Emergency Cardiovascular Care

- at least three shocks and epinephrine or vasopressin before any antiarrhythmic drug
- removed the former recommendation of lidocaine and adenosine use in stable wide QRS tachycardia
- labeled as "acceptable" but not primarily recommended (lidocaine) or not recommended (adenosine)
- amiodarone is also considered acceptable

ARREST study

- The Amiodarone in the Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachycardia (ARREST) study
- randomized, double-blind, and placebo-controlled
- 504 patients
- amiodarone 300 mg administered in a single IV bolus significantly improves survival to hospital admission in cardiac arrest still in VT or VF after three direct-current shocks (44% versus 34%; p < .03)

Dorian randomized trial

- out-of-hospital Vf resistant to three shocks, intravenous epinephrine, and a further shock or if they had recurrent Vf after initially successful defibrillation
- receive IV amiodarone plus lidocaine placebo or IV lidocaine plus amiodarone placebo
- 347 patients (mean age 67 ± 14 years)
- 22.8% of 180 patients survived to hospital admission compared with 12.0% of 167 patients treated with lidocaine (p = .009).

Supraventricular Arrhythmias

- any tachyarrhythmia that requires atrial or atrioventricular junctional tissue for initiation and maintenance
- may arise from reentry caused by unidirectional conduction block in one region of the heart and slow conduction in another
- enhanced automaticity
- triggered activity
- atrial fibrillation, atrial flutter, atrial tachycardia, AV reentrant tachycardia, and AV nodal reentrant tachycardia

Atrial Fibrillation

- common complication of cardiac surgery
- increases the length of stay in the hospital
- Advanced age, previous AF, and valvular heart operations are the most consistently identified risk factors
- current interests are directed at therapies to prevent postoperative AF
- Class III antiarrhythmic drugs (e.g., sotalol and ibutilide): torsades de pointes
- Newer promising intravenous agents (RSD1235)

Amiodarone is also an effective approach for prophylactic therapy of AF

Daoud:
- preoperative prophylaxis → oral amiodarone (64 patients) or placebo (60 patients) for a minimum of 7 days before elective cardiac surgery
- 600 mg qd for 7 days and then 200 mg/d until the day of discharge from the hospital
- Post-OP Af: 25% vs 53%
Guarnieri:
- 300 patients randomized in a double-blind
- IV amiodarone (1 g/d for 2 days) versus placebo immediately after open-heart surgery
- Post OP Af: 47% on placebo versus 35% on amiodarone ($p = .01$)

Summary of Af
- Many cases can be prevented with appropriate prophylactic therapy
- Beta-adrenergic blockers should be administered to most patients without contraindication
- Prophylactic amiodarone should be considered in patients at high risk for postoperative AF