Cardiovascular Drugs: Antidysrhythmic Drugs

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Classification of Antiarrhythmic Agents

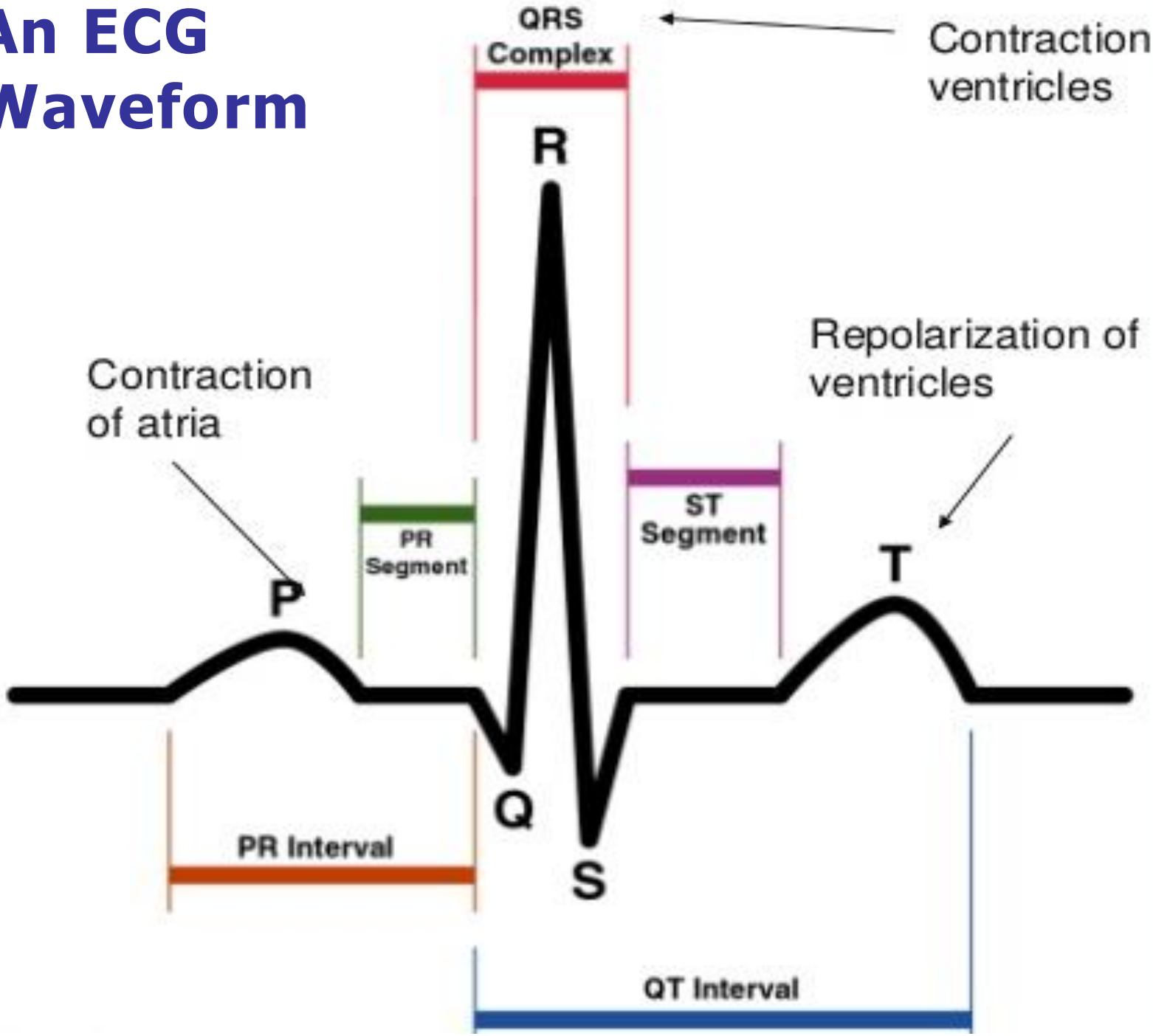
IA	Quinidine	IC	Flecainide
	Procainamide		Propafenone
	Disopyramide		Encainide
IB	Lidocaine	I?	Moricizine
	Mexiletine		
	Tocainide		

Classification of Antiarrhythmic Agents

II	Beta-adrenergic blockers	
III	Amiodarone	Ibutilide
	Dronedarone	Dofetilide
	Sotalol	Bretylium
IV	Calcium channel blockers	
	Diltiazem & Verapamil	

Generic	Brandname
Disopyramide	Norpace
Mexiletine	Mexitil
Flecainide	Tambocor
Propafenone	Rythmol
Amiodarone	Cordarone, Pacerone
Dronedarone	Multaq
Esmolol	Brevibloc
Sotalol	Betapace, Sorine
Ibutilide	Corvert
Dofetilide	Tikosyn
Digoxin	Lanoxin, Digitek
Adenosine	Adenocard

An ECG Waveform



CLASS I Antiarrhythmic drugs

- Class I drugs widen QRS complex
  - IA Prolong QT
  - IB Shorten QT
  - IC Prolong QRS (They have no effect on action potential duration)

Toxicity of CLASS I Antiarrhythmic drugs

- At toxic doses, patients will demonstrate increased Q-T and QRS intervals.

- Hypotension in type IA intoxication is caused by depressed myocardial contractility from the Na^+ channel blockade and peripheral vasodilation from the K^+ channel blockade.

CLASS IA: QUINIDINE

- Depresses rapid action potential upstroke and decreases conduction velocity (Na+ channel blockade)
- significantly prolongs repolarization (K+ channel blockade).
- Indicated for atrial fibrillation and ventricular tachycardias.

Quinidine adverse effects

- GI irritation
- Bitter taste
- Hepatitis & other hepatic conditions
- Rash & drug fever
- Thrombocytopenia
- Cinchonism
  - Tinnitus
  - Blurred vision
  - Headaches
  - Dizziness

Quinidine

- **Different salts**
  - **Sulfate (83%)**
  - **Gluconate (62%)**
- **Hepatically eliminated ($t_{1/2}$ ~6-8 hr)**
- Metabolized by CYP 3A4; Inhibits CYP 2D6
- **Increases digoxin & warfarin levels**
- **IV dosage form – hemodynamic instability**
- **Some concern when IV verapamil or diltiazem is given to a patient on**

Quinidine

- The Na^+ channel blockade of quinidine and probably the other type IA agents has been demonstrated to increase in acidotic environments and worsen its toxicity.

CLASS IA: Procainamide

- **Short half-life (~3 hours)**
- **6-h & 12-h sustained release dosage forms once existed**
- **50% hepatically metabolized, mostly to N-acetyl procainamide (NAPA) (fast/slow acetylators)**
- **NAPA is renally eliminated**
- **Causes drug-induced SLE**

Procainamide adverse effects

- Gastrointestinal
- CNS
- Fever
- Rash
- Blood dyscrasias
- Some negative inotropic properties
- Hypotension occurs mainly with IV infusions that exceed 20 mg/min.

Procainamide

- **Dosing**
  - **Acute: 17 mg/kg @ 20 mg/min (50 mg/min, if urgent)**
  - **Infusion: 1-4 mg/min (depends on renal function)**
- **Metabolism**
  - **NAPA produced (a renally eliminated active metabolite of procainamide)**
  - **Toxicity if NAPA levels exceed 20 mg/L**

Disopyramide

- **Concentration-dependent plasma protein binding.**
- **An increase in dosage rate results in an increase in the percentage of disopyramide that is unbound.**
- **Increased unbound drug allows for enhanced clearance.**
- **As a result, increasing the dosage rate results in a less than proportional increase in total drug concentration**
- **Elimination (~50% hepatic, ~50% renal)**

Disopyramide

- **Therefore, total drug concentrations have a limited role in assisting on how much to adjust the dosage of disopyramide due to its concentration-dependent plasma protein binding**

- **Total drug concentrations can be used to document a patient's "effective" drug concentration once efficacy has been demonstrated**

Disopyramide adverse effects

- Gastrointestinal
- Negative inotrope
- Anticholinergic adverse effects
  - Dry mouth
  - Blurred vision
  - Constipation
  - Urinary hesitation

Class IA intoxication

- The most serious manifestations of type IA intoxication are primarily cardiovascular.

- Almost any dysrhythmia can occur in more serious cases, but the most common ones are QRS and Q-T interval prolongation, bundle branch blocks, ventricular tachycardia (often polymorphic), and ventricular fibrillation.

Treatment of Class IA intoxication

- Cardiac Conduction Delays:

NaHCO3 1–2 mEq/kg IV boluses. Maintain arterial pH at 7.4 to 7.5.

- Hypotension:

0.9% NaCl 200–500 mL bolus infusions to correct hypovolemia.

NaHCO3 1–2 mEq/kg IV boluses. If still hypotensive, consider a pressor agent (Dopamine, norepinephrine, or epinephrine).

Treatment of Class IA intoxication

- Dysrhythmias:

Bradydysrhythmias—isoproterenol or epinephrine infusion.

Polymorphic ventricular tachycardia (torsades de pointes):

Magnesium, 2 g IV bolus. May repeat in 5–15 minutes.

Isoproterenol or overdrive cardiac pacing

Treatment of Class IA intoxication

- Other:

Consider hemodialysis or hemoperfusion in patients with procainamide intoxication and large ingestions, high plasma concentrations, presence of circulatory collapse, or renal insufficiency.

CLASS IB: LIDOCAINE

- Half Life
  - Initially, 1.5 hours; but increases to 3.0 hours 2-3 days into therapy
    - Lidocaine reduces its own rate of metabolism

    Why? (homework)

LIDOCAINE

- Toxicity most often manifested by:

Nausea	Dizziness
Drowsiness	Confusion
Tremors	Facial numbness
Paresthesias	Peripheral numbness
Altered speech	Seizures

LIDOCAINE

- **Dosing**
  - 1.0-1.5 mg/kg IVP over 1-2 min; repeat every 5-10 min with 0.5-0.75 mg/kg, as needed, until 3 mg/kg total dose
  - Typical maintenance dose: 1.0-4.0 mg/min
    - Use lower rate with CHF

CLASS IB: Mexiletine

<u>Adverse Effects</u>

- *Extremely* GI irritating
- Altered CNS functioning

- Hepatically metabolized
  - Half-life: 6-12 hours

CLASS IB toxicity

- Severe intoxications can inhibit the Na^+ channel in even normal cardiac tissue and will be similar to quinidine toxicity with a widened QRS complex and a diminished cardiac output.
- Mexiletine and tocainide intoxications are similar in presentation.

Treatment of Class IB intoxication

- General supportive care and control of the seizures is done first.
- Repetitive seizures should be controlled with IV doses of lorazepam. Phenytoin acts as a class IB antidysrhythmic and should not be used.
- After airway management and seizure control, appropriate gastric decontamination with activated charcoal can be used.
- Hypotension should be treated first with a normal saline bolus, then with a vasopressor.

Treatment of Class IB intoxication

- Theoretically, $NaHCO_3$ should be efficacious, but it has not been used clinically or studied experimentally.

- The experience of treating tocainide and mexiletine intoxications is limited but should be similar to that of lidocaine.

CLASS III: AMIODARONE, SOTALOL, BRETYLIUM

- The toxicities of this group of Antidysrhythmics cannot be predicted or explained by K^+ channel blockade alone.
- A pure K+ blocker would slow the action potential's return to baseline and reset the myocardial cell at a higher level that would make it more prone to ventricular irritability.

CLASS III toxicity

- Amiodarone has well-documented chronic toxicities (pulmonary fibrosis, Q-T prolongation, and thyroid abnormalities) but little acute toxicity because of its poor absorption. The prolonged period of absorption allows the logical use of late gastrointestinal decontamination

CLASS III toxicity

- Sotalol is rapidly and completely absorbed and demonstrates toxicity within an hour of ingestion. In addition to the K^+ channel blockade, it also has a significant β-adrenergic receptor antagonist effect that explains most of the hemodynamic changes in overdose.

CLASS III toxicity

- Bretylium is only available in intravenous form, and intoxication is usually iatrogenic. In addition to its type III antidysrhythmic properties, bretylium affects the autonomic nervous system. The severe coma caused by bretylium remains unexplained.

Treatment of CLASS III Drug toxicity

- The slow absorption of amiodarone allows for late GIT cleaning. Activated charcoal is effective in binding amiodarone .
- Cholestyramine binds amiodarone in the gastrointestinal tract as well as reduces the elimination half-life of absorbed drug, but its role in this ingestion is currently unclear.
- Intravenous potassium should be given slowly to increase the serum potassium to greater than 4.5 mmol/L.

Treatment of CLASS III Drug toxicity

- Sotalol ingestions resemble β-blocker intoxications. The initial treatment includes appropriate GIT cleaning, cardiac monitoring, and K^+ repletion. Hypotension has been successfully treated with isoproterenol (to increase myocardial rate), dopamine, and cardiac pacing. Glucagon, commonly employed in β-blocker intoxications, is a logical choice in a patient refractory to other pressors.

Treatment of CLASS III Drug toxicity

- The treatment of bretylium intoxication includes airway management and other supportive measures. Coma may be prolonged and can resemble brain death.

In addition, hypotension may require vasopressors or extracorporeal cardiac support.