Katzung pharmacology
Lec: 1 & 2

Summary

DRUG SUMMARY TABLE: Antiarrhythmic Drugs

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Group 1A				
Procainamide	Use- and state-dependent block of I_{Na} channels • some block of I_K channels. Slowed conduction velocity and pacemaker activity • prolonged action potential duration and refractory period	Atrial and ventricular arrhythmias, especially after myocardial infarction	Oral and parenteral • oral slow-release forms available • Duration: 2–3 h	Increased arrhythmias including torsades, hypotension, lupus-like syndrome
Disopyramide: similar to procainamide but longer duration of action; toxicity includes antimuscarinic effects and heart failure				
Quinidine: similar to procainamide but greater toxicity, including cinchonism (tinnitus, vertigo, headache), gastrointestinal disturbance, and thrombocytopenia				
Group 1B				
Lidocaine	Highly selective use- and state-dependent I_{Na} block; minimal effect in normal tissue; no effect on I_K	Ventricular arrhythmias post-myocardial infarction and digitalis-induced arrhythmias	IV and IM Duration: 1–2 h	Central nervous system (CNS) sedation or excitation
Mexiletine: similar to lidocaine but oral activity and longer duration of action; also used in neuropathic pain				
Group 1C				
Flecainide	Selective use- and state-dependent block of I_{Na}; slowed conduction velocity and pacemaker activity	Refractory arrhythmias	Oral	Increased arrhythmias • CNS excitation
Group 2				
Propranolol	Block of β receptors; slowed pacemaker activity	Postmyocardial infarction as prophylaxis against sudden death ventricular fibrillation; thyrotoxicosis	Oral, parenteral Duration: 4–6 h	Bronchospasm • cardiac depression, atrioventricular (AV) block, hypotension (see Chapter 10)
Metoprolol: similar to propranolol but β_1-selective				
Esmolol: selective β_1-receptor blockade; IV only, 10-min duration. Used in perioperative and thyrotoxicosis arrhythmias				

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Group 3				
Amiodarone	Strong I_K block produces marked prolongation of action potential and refractory period. Group 1 activity slows conduction velocity • groups 2 and 4 activity confer additional antiarrhythmic activity	Refractory arrhythmias • used off-label in many arrhythmias (broad spectrum antiarrhythmic action)	Oral, parenteral Half-life and duration of action: 1–10 wk	Thyroid abnormalities, deposits in skin and cornea, pulmonary fibrosis, optic neuritis • torsades is rare with amiodarone
Sotalol	I_K block and β-adrenoceptor block	Ventricular arrhythmias and atrial fibrillation	Oral Duration: 7 h	Dose-related torsades de pointes • cardiac depression
Ibutilide	Selective I_K block • prolonged action potential and QT interval	Treatment of acute atrial fibrillation	Ibutilide is IV only Duration: 6 h	Torsades de pointes
Dofetilide	Like ibutilide	Treatment and prophylaxis of atrial fibrillation	Oral Duration: 7 h	Torsades de pointes
Group 4				
Verapamil	State- and use-dependent I_{Ca} block slows conduction in AV node and pacemaker activity • PR interval prolongation	AV nodal arrhythmias, especially in prophylaxis	Oral, parenteral Duration: 7 h	Cardiac depression, constipation, hypotension
Diltiazem	Like verapamil	Rate control in atrial fibrillation	Oral, parenteral Duration: 6 h	Like verapamil
Dihydropyridines: calcium channel blockers but not useful in arrhythmias; sometimes precipitate them				
Miscellaneous				
Adenosine	Increase in diastolic I_K of AV node that causes marked hyperpolarization and conduction block • reduced I_{Ca}	Acute nodal tachycardias	IV only Duration: 10–15 s	Flushing, bronchospasm, chest pain, headache
Potassium ion	Increase in all K currents, decreased automaticity, decreased digitalis toxicity	Digitalis toxicity and other arrhythmias if serum K is low	Oral or IV	Both hypokalemia and hyperkalemia are associated with arrhythmogenesis. Severe hyperkalemia causes cardiac arrest
Magnesium ion	Poorly understood, possible increase in Na^+/K^+ ATPase activity	Digitalis arrhythmias and other arrhythmias if serum Mg is low	IV	Muscle weakness • severe hypermagnesemia can cause respiratory paralysis

Q & A

Questions 1 and 2. A 76-year-old patient with rheumatoid arthritis and chronic heart disease is being considered for treatment with procainamide. She is already receiving digoxin, hydrochlorothiazide, and potassium supplements for her cardiac condition.

1. In deciding on a treatment regimen with procainamide for this patient, which of the following statements is *most* correct?
   (A) A possible drug interaction with digoxin suggests that digoxin blood levels should be obtained before and after starting procainamide
   (B) Hyperkalemia should be avoided to reduce the likelihood of procainamide toxicity
   (C) Procainamide cannot be used if the patient has asthma because it has a β-blocking effect
   (D) Procainamide cannot be used if the patient has angina because it has a β-agonist effect
   (E) Procainamide is not active by the oral route

2. If this patient should take an overdose and manifest severe acute procainamide toxicity with markedly prolonged QRS, which of the following should be given immediately?
   (A) A calcium chelator such as EDTA
   (B) Digitalis
   (C) Nitroprusside
   (D) Potassium chloride
   (E) Sodium lactate

Answers

1. Hyperkalemia facilitates procainamide toxicity. Procainamide is active by the oral route and has a duration of action of 2–4 h (in the prompt-release form). Procainamide has no significant documented interaction with digoxin and no significant β-agonist or β-blocking action. The answer is **B**.
2. The most effective therapy for procainamide toxicity appears to be concentrated sodium lactate. This drug may (1) increase sodium current by increasing the sodium ion gradient and (2) reduce drug-receptor binding by alkalinizing the tissue. The answer is **E**.

3. A 57-year-old man is admitted to the emergency department with chest pain and a fast irregular heart rhythm. The ECG shows an inferior myocardial infarction and ventricular tachycardia. Lidocaine is ordered. When used as an antiarrhythmic drug, lidocaine typically

(A) Increases action potential duration
(B) Increases contractility
(C) Increases PR interval
(D) Reduces abnormal automaticity
(E) Reduces resting potential

4. A 36-year-old woman with a history of poorly controlled thyrotoxicosis has recurrent episodes of tachycardia with severe shortness of breath. When she is admitted to the emergency department with one of these episodes, which of the following drugs would be *most* suitable?

(A) Amiodarone
(B) Disopyramide
(C) Esmolol
(D) Quinidine
(E) Verapamil

Answers

3. Lidocaine reduces automaticity in the ventricles; the drug does not alter resting potential or AP duration and does not increase contractility. The answer is **D**.

4. Beta blockers are the most effective agents in acute thyrotoxic arrhythmias. Esmolol is a parenteral, rapid-acting β blocker (see Chapter 10). The answer is **C**.

5. A 16-year-old girl has paroxysmal attacks of rapid heart rate with palpitations and shortness of breath. These episodes occasionally terminate spontaneously but often require a visit to the emergency department of the local hospital. Her ECG during these episodes reveals an AV nodal tachycardia. The antiarrhythmic of choice in most cases of acute AV nodal tachycardia is

(A) Adenosine
(B) Amiodarone
(C) Flecainide
(D) Propranolol
(E) Verapamil

6. A 55-year-old man is admitted to the emergency department and is found to have an abnormal ECG. Overdose of an antiarrhythmic drug is considered. Which of the following drugs is correctly paired with its ECG effects?

(A) Quinidine: Increased PR and decreased QT intervals
(B) Flecainide: Increased PR, QRS, and QT intervals
(C) Verapamil: Increased PR interval
(D) Lidocaine: Decreased QRS and PR interval
(E) Metoprolol: Increased QRS duration

Answers

5. Calcium channel blockers are effective in supraventricular AV nodal tachycardias. However, adenosine is just as effective in most acute nodal tachycardias and is less toxic because of its extremely short duration of action. The answer is **A**.

6. All the associations listed are incorrect except verapamil (see Table 14–1). Because calcium blockers slow AV conduction, group 4 drugs such as verapamil and diltiazem increase PR interval and have little effect on the other ECG variables. The answer is **C**.

7. A 60-year-old man comes to the emergency department with severe chest pain. ECG reveals ventricular tachycardia with occasional normal sinus beats, and ST-segment changes suggestive of ischemia. A diagnosis of myocardial infarction is made, and the man is admitted to the cardiac intensive care unit. His arrhythmia should be treated immediately with

(A) Adenosine
(B) Digoxin
(C) Lidocaine
(D) Quinidine
(E) Verapamil

8. Which of the following drugs slows conduction through the AV node and has its primary action directly on L-type calcium channels?

(A) Adenosine
(B) Amiodarone
(C) Diltiazem
(D) Esmolol
(E) Flecainide
(F) Lidocaine
(G) Mexiletine
(H) Procainamide
(I) Quinidine

Answers

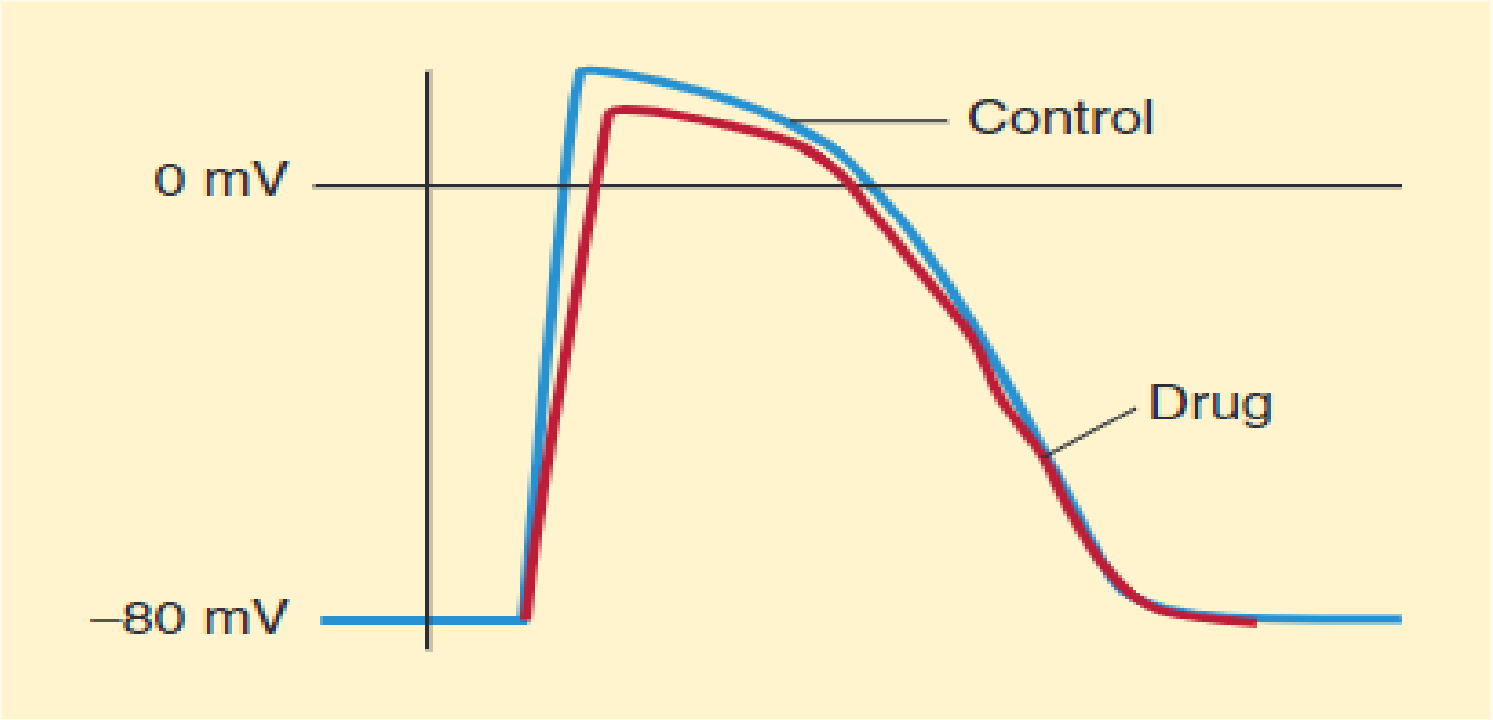
7. Lidocaine has limited applications as an antiarrhythmic drug, but emergency treatment of myocardial infarction arrhythmias is one of the most important. Lidocaine is also useful in digoxin-induced arrhythmias. After recovery from the acute phase of a myocardial infarction, β blockers are used for 2 yr or more to prevent sudden death arrhythmias. The answer is **C**.

8. Diltiazem is the calcium channel blocker in this list. (Beta blockers also slow AV conduction but have much smaller effects on calcium channels.) The answer is **C**.

9. When working in outlying areas, this 62-year-old rancher is away from his house for 12–14 h at a time. He has an arrhythmia that requires chronic therapy. Which of the following has the longest half-life of all antiarrhythmic drugs?

(A) Adenosine
(B) Amiodarone
(C) Disopyramide
(D) Esmolol
(E) Flecainide
(F) Lidocaine
(G) Mexiletine
(H) Procainamide
(I) Quinidine
(J) Verapamil

10. A drug was tested in the electrophysiology laboratory to determine its effects on the cardiac action potential in normal ventricular cells. The results are shown in the diagram.



Which of the following drugs does this agent most resemble?

(A) Adenosine
(B) Flecainide
(C) Mexiletine
(D) Procainamide
(E) Verapamil

Answers

9. Amiodarone has the longest half-life of all the antiarrhythmics (weeks). The answer is **B**.

10. The drug effect shown in the diagram includes slowing of the upstroke of the AP but no significant change in repolarization or AP duration. This is most typical of group 1C drugs. The answer is **B**, flecainide.

END