Lecture 5
Cardiovascular Medication Intoxication

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Editing File

Color Index : Red : important ,Green: doctor`s note

Beta Blockers

Mechanism of Action of Beta Blockers

- Inhibit endogenous catecholamines such as epinephrine at the beta-receptor.
- Rapidly absorbed after oral ingestion
- Peak effect of normal-release preparations occurs in **1 to 4 hours**. If came and no symptoms then patient is fine
- Hepatic metabolism on first pass results in significantly less bioavailability after oral dosing the with IV injection (1 : 40 for propranolol).
- Volume of distribution for various beta-blockers general exceeds 1 L/kg, meaning tissue concentrations exceed those of serum (high concentration in the tissue = hard to remove the drug from the body = hemodialysis is ineffective).
- Hemodialysis is not efficacious for most beta-blockers
- Protein binding varies from 0% for sotalol to 93% for propranolol. But it is high so it can't be dialyzed easily
- Elimination half-lives vary from 8 to 9 minutes for esmolol to as long as 24 hours for nadolol and others.

Beta Blockers

Selected Characteristics of Common Beta-Blockers

	V_D (L/KG)	ISA	ELIMINATION HALF-LIFE (HR)	LIPOPHILIC	PROTEIN BINDING (%)	MSE	COMMENTS
Nonselective Beta-Blockers							
Propranolol	4	0	4	+	93	+	Most fatalities
Nadolol	1.9	0	10–20	0	20	0	Dialyzable
Timolol	1.4–3.5	0	3–5	+	10	0	Dialyzable
Pindolol	3–6	+	3–4	+	51	+	
Labetalol	10	0	4–6	0	50	+	Alpha-blockade also
Oxprenolol	1.3	+	2	+	78	+	
Sotalol	1.6–2.4	0	7–18	+	0	0	Class III and class II antidysrhythmic; torsades de pointes; dialyzable
Carvedilol	1.5–2	0	6–10	+	95	0	
Selective Beta-Blockers							
Metoprolol	5.5	0	3–4	+	12	0	
Atenolol	0.7	0	5–8	0	5	0	Dialyzable
Esmolol	2	0	0.13	0	55	0	
Acebutolol	1.2	+	2–4	+	26	+	QT prolongation, VT
Practolol	1.6	+	10–11	+		0	
Bisoprolol	2.9	0	10–12	0	30	0	
Betaxolol	5–13	0	12–22	0	55	0	

ISA, intrinsic sympathomimetic activity; MSE, membrane-stabilizing effect; V_d, volume of distribution; VT, ventricular tachy

Highest fatality from **propranolol** (non-selective beta blocker) and it's the only one that causes tachycardia in case of toxicity unlike others

Manifestation of overdose

1. Bradycardia (65/90 cases)
2. Hypotension (64/90)

Most common

3. Unconsciousness (50/90)
4. Respiratory arrest or insufficiency (34/90)
5. Hypoglycemia (uncommon in adults)
6. Seizures (common only with propranolol, 16/90)
7. Symptomatic bronchospasm (uncommon)
8. VT or VF (6/90)
9. Mild hyperkalemia (uncommon)
10. Hepatotoxicity, mesenteric ischemia, renal failure (rare or single case reports)

*Intoxication with beta-sympatholytics.
VF, ventricular fibrillation; VT, ventricular tachycardia.

Diagnostic Strategies

Depend on the clinical picture, there is no blood levels

Hypoglycemia is common in children

Beta Blockers

Management B blokcers intoxication

- **IV fluids,** Oxygen, Monitoring of cardiac rhythm and respirations.
- **Activated charcoal is unproven treatment.**
- Multiple-dose charcoal without supporting evidence for an improvement in outcome.
- Absence of symptoms **4 hours** after ingestion implies a **low risk** for subsequent morbidity *unless* a **delayed-release preparation** is involved (so you need to know exactly in each case which type of beta blocker the patient took and in what form)

First step in beta blocker overdose:

- Atropine
- Glucagon
- Crystalloid Fluid

Phase I (Resuscitation)
Boluses of atropine, glucagon, fluids

Phase II (Stabilization)
Infusions of
- Glucagon
- Insulin-glucose
- Catecholamines (epinephrine, norepinephrine, isoproterenol, dobutamine, dopamine, metaraminol)
- Phosphodiesterase inhibitors (amrinone)

Early cardiac pacing if no prompt response to chronotropic or dromotropic drugs

Peripheral arterial and pulmonary artery catheter monitoring if refractory hypotension

Consider hemodialysis of hydrophilic beta-blockers with low protein binding and low V_d

V_d, volume of distribution.

Beta Blockers

If patient is hypotensive:

- 20 to 40 ml/kg normal saline or ringer lactate solution is infused, if hypotension persist cardioactive drugs indicated (dopamine or epinephrine)
- Other catecholamines include norepinephrine, dobutamine, and phenylephrine.
- Often, norepinephrine or dopamine is added to beta-agonists such as **isoproterenol** that lack vasopressor activity.

Disposition

Patients who remain completely asymptomatic for **6 hours** after an oral overdose of normal-release preparations can be safely referred for psychiatric evaluation, with medical consultation for the first 24 hours.

Ca Channel Blockers

Most fatalities occur with **Verapamil**

Ca Channel Blockers Mechanism of Action

- They block the slow calcium channels in the myocardium and vascular smooth muscle, leading to coronary and peripheral vasodilation.
- Reduce cardiac contractility
- Depress SA nodal activity
- Slow AV conduction.
- Both verapamil and diltiazem act on the heart and blood vessels, whereas nifedipine causes primarily vasodilation.

In the pancreas, calcium channel blockade inhibits insulin release, resulting in hyperglycemia.

As with beta-blockers, selectivity is lost in cases of overdose

All calcium channel blockers are rapidly absorbed

Onset of action and toxicity ranges from less than 30 minutes to 60 minutes

Peak effect of nifedipine can occur as early as 20 minutes after ingestion,

High protein binding and V_d greater than 1 to 2 L/kg make hemodialysis or hemoperfusion ineffective.

Fortunately (except with sustained-release preparations), their half-lives are relatively short, limiting toxicity to 24 to 36 hours.

Ca Channel Blockers

Selected Characteristics of Common Calcium channel -Blockers

	V_D (L/KG)	HALF-LIFE (HR)	PROTEIN BINDING (%)	COMMENTS
Verapamil	4	3–12	90	Most fatalities; impairs contractility and cardiac conduction more than most other calcium antagonists
Diltiazem	1.7–5.3	3–7.9	70–80	Suppression of atrioventricular node similar to verapamil; myocardial depression otherwise less
Nifedipine	1.4–2.2	1–5	92–98	Vasodilation greatest effect
Nicardipine	0.64	8–9	95	Vasodilation
Nimodipine	0.94–2.3	1–2	95	No reports of oral overdosage (2005 *PDR*)
Amlodipine	21	30–50	98	Vasodilation
Bepridil	8	33–42	99	Class I as well as class IV antidysrhythmic; prolongs QT: torsades de pointes
Felodipine	10	10	99	Vasodilation
Isradipine	3	1.9–16	95	Vasodilation
Nisoldipine	4–5	7–12	99	Vasodilation

V_d volume of distribution.

Manifestation of Ca Channel poisoning

Cardiovascular: Hypotension, sinus bradycardia, sinus arrest, AV block, AV dissociation, junctional rhythm, asystole; ventricular dysrhythmias uncommon except with bepridil
Pulmonary: Respiratory depression, apnea; pulmonary edema; adult respiratory distress syndrome
Gastrointestinal: Nausea, vomiting, bowel infarction (rare)
Neurologic: Lethargy, confusion, slurred speech, coma; seizures (uncommon); cerebral infarction (rare)
Metabolic: Metabolic (lactic) acidosis; hyperglycemia (mild); hyperkalemia (mild)
Dermatologic: Flushing, diaphoresis, pallor, peripheral cyanosis

AV, atrioventricular.

Ca Channel Blockers

Diagnostic Strategies

- Serum Ca antagonists are not availble
- Glucose and Electrolytes (including Ca & Mg)
- Hyperglycemia secondary to insulin inhibition occurs occasionally but mild and short-lived
- Lactic Acidosis occurs with hypotension and hypoperfusion
- ECG, a prolonged QRS or QT interval suggest bedpril or a co-ingested cardiac toxin such as TCA

Disposition

- Because the peak effect occurs in 90 minutes to 6 hours, patients who are totally asymptomatic for 6 hours can be safely discharged

- For delayed-release preparations should be admitted for at least **24 hours** of continuous cardiac monitoring.

Management Ca Channel Blocker intoxication

IV, Oxygen, Cardiac Monitoring,

No evidence for activated charcoal

Phase 1
Boluses of atropine, calcium, fluids

Phase 2
Catecholamine infusions
Calcium infusion
Insulin glucose infusion
Glucagon infusion
Phosphodiesterase infusion
Transcutaneous or transvenous cardiac pacing
Invasive monitoring

Phase 3
Consider intra-aortic balloon counterpulsation, cardiac bypass

Nitrates & Nitrites

Mechanism of Acrtion

- Widely used as **vasodilators** in the treatment of heart failure and ischemic heart disease.
- augment coronary blood flow as well as reduce myocardial oxygen consumption by reducing afterload.
- At lower doses nitrates primarily **dilate veins**
- At higher doses they also **dilate arteries**.

Hypotension is a common complication, usually transient, but responds to supine positioning, IV fluids, and reduction of dose.

Low-dose pressors are occasionally needed, but it is best to avoid them in the setting of acute coronary syndromes.

Digitalis

Mechanism of Action

It has two effects:

1. increasing the force of myocardial contraction to increase cardiac output in patients with heart failure.
2. decreasing **atrioventricular (AV)** conduction to slow the ventricular rate in atrial fibrillation.

It inhibits membrane sodium-potassium adenosine triphosphatase (ATPase), which increases intracellular sodium and calcium and increases extracellular potassium.

Therapeutic Dose

- At therapeutic doses, the effects on serum electrolyte levels are minimal.
- At therapeutic levels, digitalis indirectly increases **vagal activity** and decreases **sympathetic activity**.

Toxic Dose

- With toxic levels, digitalis paralyzes the **Na-K pump**, potassium cannot be transported into cells, and serum potassium can rise as high as 13.5 mEq/L.
- At toxic levels, digitalis can directly halt the generation of impulses in the SA node, depress conduction through the AV node, and increase the sensitivity of the SA and AV nodes to **catecholamines**.

Digitalis

Because significant protein binding and large volume of distribution suggest that hemodialysis, hemoperfusion, and exchange transfusion are ineffective

DYSRHYTHMIAS ASSOCIATED WITH DIGITALIS TOXICITY

Nonspecific
PVCs, especially bigeminal and multiform
First-, second- (Wenckebach's), and third-degree AV block
Sinus bradycardia
Sinus tachycardia
Sinoatrial block or arrest
Atrial fibrillation with slow ventricular response
Atrial tachycardia
Junctional (escape) rhythm
AV dissociation
Ventricular bigeminy and trigeminy
Ventricular tachycardia
Torsades de pointes
Ventricular fibrillation

More Specific, but Not Pathognomonic
Atrial fibrillation with slow, regular ventricular rate (AV dissociation)
Nonparoxysmal junctional tachycardia (rate 70–130 beats/min)
Atrial tachycardia with block (atrial rate usually 150–200 beats/min)
Bidirectional ventricular tachycardia

AV, atrioventricular; PVC, premature ventricular contraction.

KEY CONCEPTS

Digitalis

- Consider digoxin intoxication in any patient with gastrointestinal or visual disturbance and a new dysrhythmia or conduction disturbance.
- Dose digitalis Fab antibody fragments by body load of digitalis, not by body weight of the patient.
- Use digitalis Fab fragments before pacing or other antidysrhythmic drugs.
- Hyperkalemia in digitalis toxicity is best treated with Fab fragments. Conventional treatment with sodium bicarbonate, insulin, and glucose as well as with calcium is also appropriate, especially when Fab fragment preparations are not immediately available.

Beta-Adrenergic Blockers

- Beta-blocker intoxication usually causes bradydysrhythmias and occasionally AV block.
- Noncardiac symptoms such as obtundation, seizures, and hypoglycemia may predominate, especially early in the course and particularly with propranolol.
- Volume expansion, atropine, calcium, and glucagon are early treatment measures, but absent a response, begin a high-dose insulin/glucose infusion.

Calcium Channel Blockers

- Signs and symptoms of calcium channel blocker intoxication occur early after overdose.
- CNS depression is common; seizures are not.
- AV block and bradydysrhythmias predominate, except with bepridil.
- Volume expansion, calcium, and vasopressors have been the mainstays of treatment, but high-dose insulin/glucose infusion probably offers the most therapeutic benefit in cases of severe intoxication.

Nitrates and Nitrites

- Hypotension and methemoglobinemia are common presentations.

You always need to know

- Time of ingestion
- Specific name of the medication
- Number of pills ingested
- Formulatio (i.e., immediate release vs. sustained release)
- Dose per tablet
- Co-ingestants
- Chronic medications taken as prescribed
- Alcohol, or illicit drugs