Cardiovascular drugs

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Objectives:

- Not mentioned in the lecture but the doctor said MCQ will be from what we have discussed in the lecture so we focused on what doctor said only.

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Beta-blockers

Mechanism of action:

- 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 Patient came in this period and no symptoms, then the patient is fine. Absence of symptoms 4 hours after ingestion implies a low risk for subsequent morbidity unless a delayed-release preparation is involved.
- Hepatic metabolism on first pass results in significantly less bioavailability after oral dosing than 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[1]).
- Protein binding varies from 0% for sotalol to 93% for propranolol. But if 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

Selected Characteristics of Common Beta-Blockers All I want you to know in this table is propranolol

	VD (UKG)	ISA	ELIMINATION HALF-LIFE (HR)	LIPOPHILIC	PROTEIN BINDING (%)	MSE	comments
Nonselective Beta-Blockers							
Propranolol	4	0	4	+	93	+	most fatalities
Nadolol	4	0	10-20	0	20	0	dialyzable
Timolol	1.9	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	

[1] Hemodialysis or hemoperfusion may be beneficial for atenolol, nadolol, sotalol, and timolol, the beta blockers with lower Vd, lower protein binding, and greater hydrophilicity (after you try every other management option)

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	

Important questions:

what is the most common presentation of b-blockers intoxication ? bradycardia

what could happen with bradycardia ? hypernatremia (uncommon)

- Propranolol can present with wide complex tachycardia (in the majority of the cases, it is due to propranolol). Treated with sodium bicarbonate
- Why propranolol ?

1-Most fatalities

2- it has different MOA, by blocking sodium channels so it increases the sympathetic drive .. and the NA blockage will lead to prolonged QRS ..

- Both propranolol and TCA present with wide complex tachys and seizure.. how to differentiate? Really we don't need to differentiate since the treatment is the same. 'Supportive' by IV sodium bicarbonate .. drug levels might help in TCA but we don't usually do it.

MANIFESTATIONS OF OVERDOSE: IMPORTANT

1. Bradycardia
2. Hypotension
3. Unconsciousness
4. Respiratory arrest or insufficiency
5. Hypoglycemia (uncommon in adults)
6. Seizures (common only with propranolol) like other Na channel blockers
7. Symptomatic bronchospasm (uncommon)
8. VT or VF (VF, ventricular fibrillation; VT, ventricular tachycardia).
9. Mild hyperkalemia (uncommon)
10. Hepatotoxicity, mesenteric ischemia, renal failure (rare or single case reports)

Diagnostic Strategies

- Depend on the clinical picture. (Toxidrome; you can't diagnose it by toxicology screen; it's diagnosed clinically)
- Hypoglycemia is common in children

Management

- Crystalloid IV fluids (normal saline or lactated Ringer's), Oxygen, Monitoring of cardiac rhythm and respirations.
- Activated charcoal and Multiple-dose charcoal is unproven treatment. Why it's unproven? Charcot use should be 1-in the FIRST hour 2-with conscious patients 3-in cases when you're 100% sure the airway is secured 4-with very high lethal dose of b blocker مرره صعب تتوافق جميع هذه الشروط فعشان كذا ما نعتبره من التريتمنت
- In case of Hypotension, Bradycardia, and Atrioventricular Block, start IV fluid and Catecholamines (epinephrine, norepinephrine, and dopamine)
- Atropine and Glucagon.
- Sodium bicarbonate is indicated in QRS complex widening.
- High-Dose Insulin Euglycemia (HDIE)Therapy. Insulin has inotropic effect, but is given with dextrose to prevent further hypoglycemia.
- Refractory cases of bradycardia may respond to an external or transvenous pacemaker.

To summarize: The first step in the treatment of beta-blocker overdose is:

1- atropine 'first line'

2- if fails glucagon ' some inotropic effect, a well known antidote, but not the first because of nausea, vomiting and hyperglycemia.

3- crystalloid fluids

4-Calcium is a good inotrope but only used as a last resort

- Note: Some start with 500ml to 1 L fluid, if it didn't work we add another bolus of fluid and atropine.. Others start with atropine immediately .

Disposition

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

calcium channel blockers

Most fatalities occur with verapamil

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 acts on blood vessels, thus primarily causes 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 Vd 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

Selected Characteristics

	VD (UKG)	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

Manifestation of 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.
- They usually are hyperglycemic.
- seizures and unconsciousness (uncommon)with CCB, it more commonly happens with Propranolol toxicity.
- It is difficult to differentiate between CCBs and beta blockers intoxication; the best way is to do it by Hx. Anyways management is almost the same but in CCBs intoxication be more generous in using ca.

Diagnostic Strategies

- Serum levels Ca antagonists are not available.
- Glucose and Electrolytes (including Ca & Mg)
- Hyperglycemia secondary to insulin inhibition occurs occasionally but mild and short-lived no treatment is needed
- 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

Management

CCBs intoxication management is the same as beta blockers management, except in CCBs we give calcium salts and that is being in form of Ca chloride and and Ca gluconate.

Vomiting is a powerful vagal stimulus that can exacerbate bradycardia and heart block. If you wanna intubate the pt, make sure to sedate him, because intubating him will stimulate the vagus and result in severe nausea and vomiting

- IV fluid, Oxygen, Cardiac Monitoring.
- No evidence for activated charcoal.
- If there is Hypotension and Bradycardia:
    - Atropine
    - IV calcium
    - Epinephrine, norepinephrine, and dobutamine have also led to successful outcomes

- If symptomatic bradycardia or heart block persists, the next step is a pacemaker

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.

Nitrates & Nitrites

If a patient comes with MI and he is taking Viagra (phosphodiesterase PDE inhibitor).. NEVER give nitrates !! It might kill the patient.

Mechanism of action:

- Nitrates toxicity is usually iatrogenic. They are widely used as vasodilators in the treatment of heart failure and ischemic heart disease. They 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
- Nitrites are also oxidizing agents that convert hemoglobin to methemoglobin "methemoglobinemia", impairing oxygen delivery. When methemoglobin levels exceed 15%, a venous blood sample appears chocolate brown, and the skin appears blue even while patients look remarkably comfortable.
- Unlike most cases of cyanosis, supplemental oxygen Even with 100% o2 does not improve the patient's color.
- 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.

Management

- IV fluid. usually good response
- IV methylene blue, but this antidote is usually not needed unless methemoglobinemia approaches 30%.

Digitalis (digoxin)

Mechanism of action:

It has two effects:

- Increasing the force of myocardial contraction to increase cardiac output in patients with heart failure.
- 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.

At therapeutic doses:

- The effect on serum electrolyte levels is minimal.
- At therapeutic levels, digitalis indirectly increases vagal activity and decreases sympathetic activity.

At toxic doses:

- Digitalis paralyzes the Na-K pump, potassium cannot be transported into cells, and serum potassium can rise as high as 13.5 mEq/L. (Hyperkalemia) MCQ
- It 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 can produce virtually any dysrhythmia or conduction block, and bradycardias are as common as tachycardias.

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
- Torsade's 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

TYPICALLY (it's digoxin toxicity unless proven otherwise):
1-SLOW ATRIAL Fib (<30 bpm)
2-BIDIRECTIONAL VENTRICULAR TACHYCARDIA

NONCARDIAC SYMPTOMS OF DIGITALIS INTOXICATION IN ADULTS AND CHILDREN

A very wide spectrum. Most important effects are GI (nausea and vomiting) and blurred or colored vision, as well as neurological symptoms.

Diagnostic Strategies

- Serum digoxin levels The only drug in this lecture that we depends on its level. (peak in 1.5 to 2 hours)
- The ideal serum digoxin concentration for patients with heart failure is 0.7 to 1.1 ng/mL.
- In acute poisoning, serum potassium may begin to rise rapidly within 1 to 2 hours of ingestion, potassium should be withheld, even if mild hypokalemia is measured initially. i.e. even if there was hypokalemia we don't give K because it's trapped inside the cells, unless very severe.

Management:

1- supportive (avoid inotropes as much as you can)

2- Antidote: **digibind** (Fab Fragments). severe hyperkalemia is indication for treatment with antidote

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

KEY CONCEPTS

Digitalis

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

Beta-adrenergic Blockers

- Beta-blocker intoxication usually causes AV block and brady dysrhythmias
- 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 measures used to restore normal heart rate and cardiac output. Absent a response, begin insulin-glucose infusion and titrate rapidly up to 1 unit/kg/ hour as needed.

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 brady dysrhythmias predominate, except with bepridil
- Volume expansion, calcium and vasopressors have been the mainstays of treatment, but insulin-glucose infusion probably offers the most therapeutic benefit in cases of severe intoxication

Nitrates and Nitrites

- Hypotension and methemoglobinemia are common presentations

MCQ's

Q1) 40-year-old male was brought to the hospital and his wife reports that he took about 40 tablets of immediate-release Metoprolol three hours ago in an attempt to end his life. He is lethargic but arousable. His blood pressure is 90/45 mmHg, his heart rate is 45 beats/minute. Which therapy will you try first?

A. Start him on activated charcoal
B. Insert transvenous pacemaker
C. IV atropine
D. IV fluid with dextrose

Q2) which of the following make calcium channel blockers considered as the most likely diagnosis ?

A. diarrhea with nausea and vomiting
B. hypotension ,bradycardia and lethargy
C. dry skin and tachycardia
D. extrapyramidal involuntary movement

Q3) What is the most effective treatment modality in digoxin toxicity?

A. Activated charcoal
B. Potassium replacement
C. Fab fragments
D. Catecholamine

Q4) which of the following has the highest fatality rate among beta blocker overdose ?

A. Sotalol
B. Metabrolol
C. Propronalol
D. Atenolol

Q5) What is the most common presentation of nitrate intoxication?

A. Severe bradycardia
B. Carboxyhemoglobinemia
C. Hypotension
D. Seizures

Q6) One of the complications of BB is hypoglycemia, which one of the following patient groups are at high risk for this complication?

A- Adults

B-Children

C-Men over 70 year of age

D-Women over 60 year of age

Q7) Which of the following is the appropriate antidote for beta-blocker overdose?

A. Glucagon

B. IV potassium

C. IV magnesium

D. Metoprolol

Answers : Q1:C -Q 2:B - Q3:C - Q4:C - Q5:C - Q6:B - Q7:A