Forensic & Toxicology Team

MED 433

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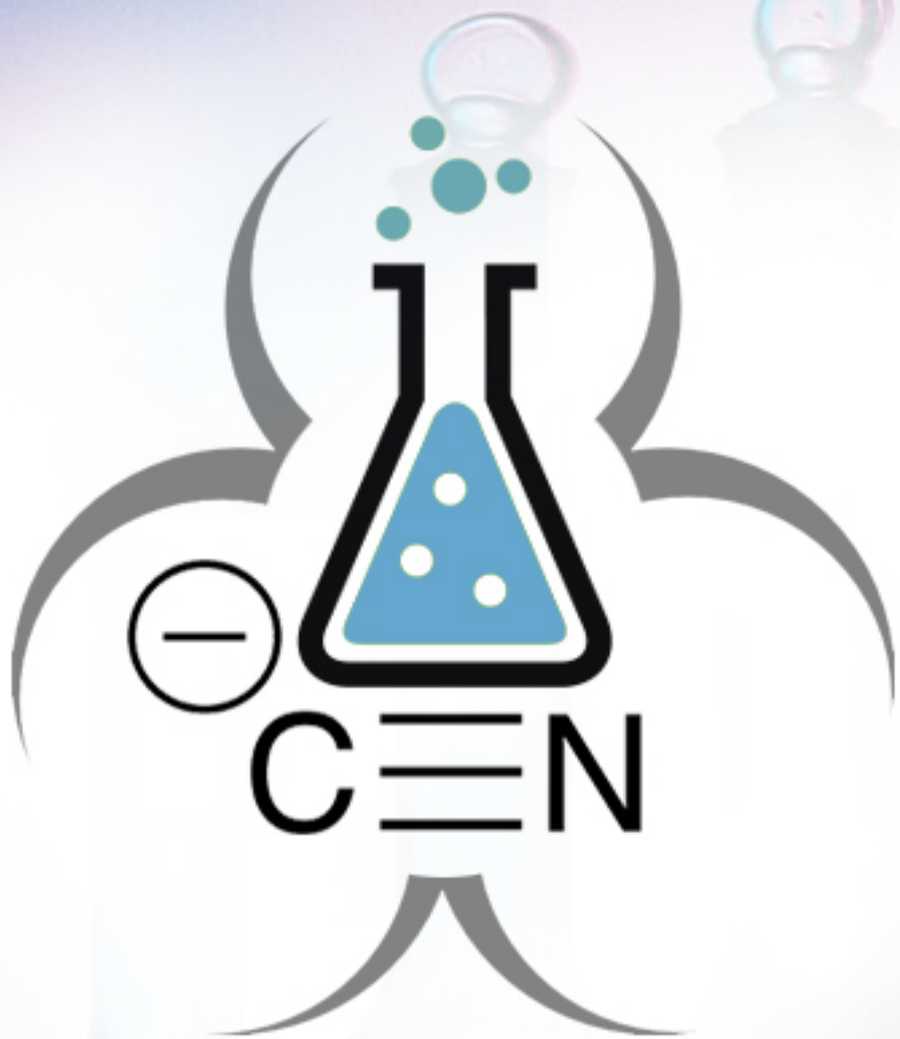


Lecture5 : Cardiovascular drugs Intoxication

➢ β-Blockers

- They inhibit endogenous catecholamines such as epinephrine at the beta-receptors.

	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	

Characteristics of different types of β-blockers
(For reading)

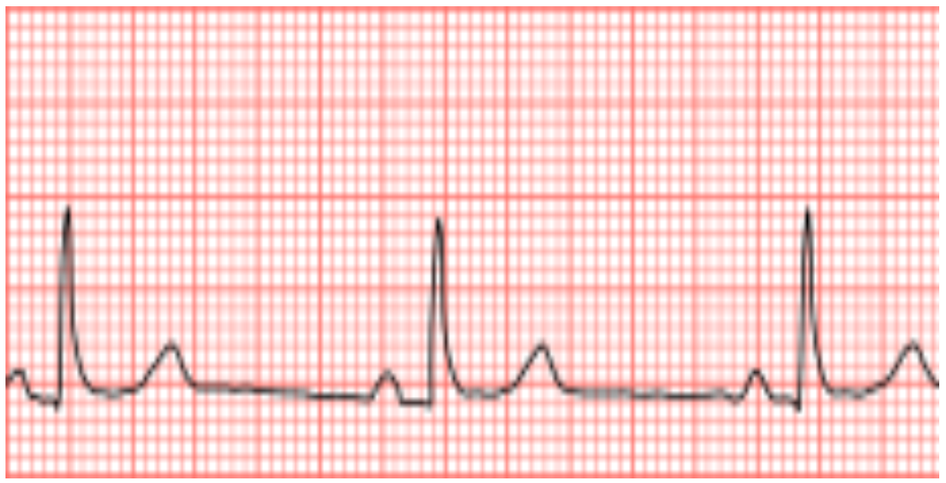
Pharmacokinetics

Beta-blockers are rapidly absorbed after oral ingestion and the peak effect normally is within 1 to 4 hours of ingestion.

- Hepatic first pass metabolism results in significantly less bioavailability after oral dosing than with IV injection (1:40 for propranolol) That means IV injection produce 40 times effect of oral ingestion
- Volume of distribution for various beta-blockers generally exceeds 1 L/kg, meaning tissue concentrations exceed those of serum. Most of what we ingest goes to body tissues instead of being in the serum and Hemodialysis is not efficient for most beta-blockers
- Protein binding varies from 0% for Sotalol to 93% for propranolol.
- Elimination half-lives ($t_{1/2}$) vary from 8 to 9 minutes for Esmolol to as long as 24 hours for Nadolol and others

Manifestations and complications

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



Diagnosis and management

- Diagnosis of β-blockers overdose depends on the clinical picture of the patient
- In children with β-blockers overdose, Hypoglycemia is common.

First step management:

I. IV fluids (To correct the severe hypotension)
II. Oxygen (since many patients develop respiratory insufficiency)
III. Monitoring of card for rhythm and respirations.

- Activated charcoal is not a proven treatment.
- Multiple-dose charcoal can be used. However, there's no supporting evidence for an improvement in outcome.

Always remember, Onset of toxicity is early, so the absence of symptoms 4 hours after ingestion indicates a low risk for subsequent morbidity unless a delayed-release preparation of β-blockers is involved.

* Ventricular tachycardia or ventricular fibrillation

Management of β-blockers toxicity

- To reverse the effect of toxicity, chronotropic, dromotropic, **inotropic and vasopressor agents** should be given.
- Main goal is to correct **HYPOTENSION – BRADYCARDIA – AV BLOCK**
- Usually a combination of agents are given because one agent is not sufficient to work against all the effects of β-blockers.

1/ Atropine

- A dose of atropine may quickly wear off or be ineffective, so infusion of more potent drugs or cardiac pacing is usually necessary.
- Atropine (0.5 mg for adults, 0.02 mg/kg for children, minimum 0.10 mg) **should be given before vagal stimuli such as tracheal or gastric intubation.**

2/ Glucagon

- **Does not depend on beta-receptors for its action, has both inotropic and chronotropic effects.**
- **It helps to counteract the hypoglycemia induced by beta-blocker overdose.**
- Initially is given as a 5- to 10-mg IV bolus and Because of its short (20-minute) half-life, an infusion of 2 to 5 mg/hour (or for children, 0.05–0.1 mg/kg bolus, then 0.05–0.1 mg/kg/hour) should be started immediately after the bolus.
- With cumulative large doses, glucagon should be diluted in 5% glucose in water for constant infusion.
- Side effects include nausea and vomiting in most patients, mild hyperglycemia, hypokalemia, and allergic reactions.
- The response to glucagon alone is often inadequate.

3/ Sodium bicarbonate

- Sodium channel blockade, manifested by QRS widening, occasionally occurs with beta-blocker intoxication and may respond to infusion of sodium bicarbonate.

4/ Crystalloid fluids

In hypotensive patients, 20 to 40 mL/kg of normal saline or Ringer's lactate solution can be infused and repeated.

If hypotension or bradycardia persists, other cardioactive drugs are indicated such as dopamine, or epinephrine and other catecholamines including norepinephrine, dobutamine, and phenylephrine. Often, norepinephrine or dopamine is added to beta-agonists like isoproterenol that lack vasopressor activity (Isoproterenol has no effect on α receptors)

Cont'd: Management of β-blockers toxicity

5/ High-Dose Insulin Euglycemia (HIDE)

- There are no randomized controlled human trials. However, some observational studies showed multiple case reports of a hemodynamic improvement after institution of HDIE.
- High-dose (0.5–1 unit/kg/hour) insulin infusion for hemodynamically significant toxicity is often given.
- Beta-blocker toxicity shifts myocardial energy preferences from free fatty acids to carbohydrates, and insulin increases myocardial carbohydrate uptake.

Recent canine (dogs) and porcine (Pigs) models showed the benefit of insulin infusion up to 10 units/kg/hr.

IMPORTANT :

- ✓ Glucose, usually in 5 to 10% solutions, is infused to maintain a serum glucose of approximately 100 mg/dl.
- ✓ The combination of glucose and high-dose insulin augments myocardial contraction independent of beta-receptors.
- ✓ Glucose and potassium should be monitored frequently during infusion and supplemented as needed to maintain euglycemia and eukalemia.

6/ Refractory cases of bradycardia may respond to an external or trans-venous pacemaker.

7/ Calcium

- Because deleterious effects on calcium transport may contribute to beta-blocker toxicity, IV calcium salts have been suggested for treating hypotension.
- Calcium should be given cautiously and less aggressively than for cases of calcium channel blocker overdose.
- Constant infusions are safer than boluses.
- Give 1 to 2 g over 5 to 10 minutes, monitoring closely for effect.

8/Cardioversion and defibrillation

- Are indicated for ventricular tachycardia and ventricular fibrillation following Beta-blocker toxicity, respectively, following American Heart Association guidelines.

(Toxic amounts of β-blockers cause cardiac arrhythmias because of the ECG changes they produce due to Na and Ca blockage effects)

- Pulsatile ventricular tachycardia or frequent ventricular ectopy can most safely be treated with lidocaine.

Management of β-blockers toxicity

9/Hemodialysis or hemoperfusion

- may be beneficial for atenolol, Nadolol, Sotalol, and Timolol, and other beta-blockers with lower volume of distribution, lower protein binding, and greater hydrophilicity (water preference).
- They can be lifesaving in cases of refractory hypotension.

However, such measures must be done before prolonged hypotension leads to multi-organ ischemic injury.

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

➢Calcium channel blockers (CCBs)

- Most fatalities occur with verapamil, but generally severe toxicity and death have been reported for most drugs of this class.
- It produces its toxic effects by blocking the slow calcium channels in the myocardium and vascular smooth muscle leading to :

I. coronary and peripheral vasodilation.
II. Reduction in cardiac contractility
III. Depression of SA nodal activity
IV. slow AV conduction

- Both verapamil and diltiazem act on the heart and blood vessels, whereas Nifedipine causes primarily vasodilation.

- As with beta-blockers, selectivity is lost in cases of overdose, thus they act systemically (e.g. Hyperglycemia due to calcium blockade in the pancreas)

Pharmacokinetics

- 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.
- Peak effect of sustained-release verapamil can be delayed for many hours.
- High protein binding and volume of distribution greater than 1 to 2 L/kg make hemodialysis or hemoperfusion ineffective.
- Fortunately (except with sustained-release preparations), their half-lives are relatively short, So toxicity only persist for 24 to 36 hours.

	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

Characteristics of different types of β-blockers (For reading)

Manifestations and complications

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

Diagnosis:

- Serum levels of calcium antagonists are not available
- Glucose and Electrolytes (including calcium and magnesium).
- Hyperglycemia secondary to insulin inhibition occurs occasionally, but mild and short-lived requires no treatment. - Lactic acidosis occurs with hypotension and hypoperfusion.
- ECG is necessary, A prolonged QRS or QT interval suggests Bepridil ingestion or a co-ingested cardiac toxin such as a Tricyclic antidepressant (TCA).

Management:

- IV fluids
- Oxygen supplement
- Cardiac monitoring

Important: If symptomatic bradycardia or heart block persists, the next step is a pacemaker or chronotropic agent such as isoproterenol.

- Vomiting is a powerful vagal stimulus that can exacerbate bradycardia and heart block.
- Atropine (0.5–1 mg, up to 3 mg for adults, and 0.02 mg/kg for children, minimum 0.1 mg).
- Intravenous calcium (have considerable effect on contractility but their effect on bradycardia, AV block, and peripheral vasodilation is often poor)
- Epinephrine, norepinephrine, and dobutamine.
- Glucagon has also been used for its inotropic and chronotropic effects.
- Insulin (0.5–1 iu/kg/hr) Its proposed mechanism of action is by improving calcium use in the myocytes, although the exact mechanism is unclear, (but giving insulin alone is not enough since the patient may develop hypoglycemia), so we give Glucose (5–10% solutions usually suffice), hence the name (High-Dose Insulin Euglycemia) (HDIE).

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

Nitrates and Nitrites :

- Widely used as vasodilators in the treatment of heart failure and ischemic heart disease.
- At lower doses nitrates primarily dilate veins
- At higher doses they also dilate arteries.
- Hypotension is a common complication, but usually responds to supine positioning, IV fluids, and reduction of dose, usually transient.
- Nitrites are also oxidizing agents that convert hemoglobin to methemoglobin ⟹ impairing oxygen delivery.

❖ Note : When methemoglobin levels exceed 15%, a venous blood sample appears chocolate brown, and the skin appears blue even while patients look remarkably comfortable.

- Treatment :

- IV methylene blue, but this antidote is usually not needed unless methemoglobinemia approaches 30%.
- The usual dose of methylene blue in adults is 1 to 2 mg IV over 5 minutes.

Digitalis Intoxication :

- Pathophysiology:

In therapeutic doses	In toxic doses
Increasing the force of myocardial contraction to increase cardiac output in patients with heart failure.	Paralyzes the Na-K pump, potassium cannot be transported into cells, and serum potassium can rise as high as 13.5 mEq/L.
Decreasing atrioventricular (AV) conduction to slow the ventricular rate in atrial fibrillation.	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.
It inhibits membrane sodium-potassium adenosine triphosphatase (ATPase), which increases intracellular sodium and calcium and increases extracellular potassium.	Can produce virtually any dysrhythmia or conduction block, and bradycardias are as common as tachycardias.
Digitalis indirectly increases vagal activity and decreases sympathetic activity.	

❖Note: The significant protein binding and large volume of distribution suggest that hemodialysis, hemoperfusion, and exchange transfusion are ineffective.

Diagnostic Strategies :

- ## Serum digoxin levels

- It is the steady state, rather than peak level, that correlates with tissue toxicity and is used to calculate antidote dosages.
- Peak levels after an oral dose of digoxin occur in 1.5 to 2 hours (the best time to measure it is between 0.5 to 6 hours) .
- Steady-state serum concentrations are not achieved until after distribution, or 6 to 8 hours after a dose or overdose, and may be only one fourth to one fifth of the peak level.
- Patients with heart failure should have serum digoxin level with a range of 0.7 to 1.1 ng/mL.
- Patients taking digitalis therapeutically often take diuretics as well, and they often have low serum and total body potassium levels. The acutely poisoned patient, in contrast, may have life-threatening hyperkalemia.*normally we give diuretics along with digoxin, but in overdose of digoxin even if we give diuretics to the patient, he may develop cardiac arrest .

Management :

Electrolyte Correction

K:

In cases of chronic intoxication, often exacerbated by hypokalemia, raising the serum potassium level to 3.5 to 4 mEq/L is an important early treatment. 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.

Cont.

- Potassium can be administered orally (which is safer) or intravenously (IV) although a rate more rapid than 10 to 40 mEq/hour is dangerous.
- A serum potassium level greater than 5 mEq/L warrants consideration of digitalis antibody (ovine Fab fragment) treatment.
- If digitalis antibodies are not immediately available, severe hyperkalemia should be treated with IV glucose, insulin, and sodium bicarbonate.

Mg

- Many patients on diuretic therapy are also magnesium-depleted, even when the measured serum magnesium level is normal.
- If significant magnesium depletion is suggested, 1 to 2 g of magnesium sulfate can be given over 10 to 20 minutes (child: 25 mg/kg), followed by a constant infusion of 1 to 2 g/hour.

Atropine

- Atropine is generally used for severe bradycardia and advanced AV block, with mixed results. Generally, an external or trans-venous pacemaker should be prepared when bradycardia or AV block appears.

Pacing

- Cardioversion and defibrillation can cause asystole after attempts to treat tachydysrhythmias.
- Lower energy settings, such as 25 to 50 J, may be less hazardous.

Cont.

Fab Fragments (Digibind or Digifab)

- **Digitalis antibodies are derived from sheep immunized with digoxin.**
- Side Effects : - erythema, urticaria, and facial edema
  - Hypokalemia
  - Exacerbation of congestive heart failure
  - Increase in ventricular rate with atrial fibrillation.
- Indicated for serious cardiovascular toxicity, Not for prophylactic administration of higher than expected serum levels.
- The primary indication for antibody treatment in cases of acute poisoning is hyperkalemia with a serum potassium level greater than 5.5 mEq/L or ECG changes.
- Fab fragment therapy should be used before transvenous pacing, which carries significant risk.

IMPORTANT

TREATMENT OF CCB INTOXICATION :

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

FACTORS ASSOCIATED WITH INCREASED RISK OF DIGITALIS TOXICITY :

- Renal insufficiency
- Heart disease
  - Congenital heart disease
  - Ischemic heart disease
  - Congestive heart failure
  - Myocarditis
- Electrolyte imbalance
  - Hypokalemia or hyperkalemia
  - Hypomagnesemia
  - Hypercalcemia
- Alkalosis
- Hypothyroidism
- Sympathomimetic drugs
- Cardiotoxic co-ingestants
  - Beta-blockers
  - Calcium channel blockers
  - Tricyclic antidepressants
- Drug interactions
  - Quinidine, amiodarone
  - Erythromycin
  - Verapamil, diltiazem, nifedipine
  - Captopril
- Elderly woman

Cont.

NONCARDIAC SYMPTOMS OF DIGITALIS INTOXICATION IN ADULTS AND CHILDREN :

General
Weakness
Fatigue
Malaise

Gastrointestinal
Nausea and vomiting
Anorexia
Abdominal pain
Diarrhea

Ophthalmologic
Blurred or snowy vision
Photophobia
Yellow-green chromatopsia (also red, brown, blue)
Transient amblyopia, diplopia, scotomata, blindness

Neurologic
Dizziness
Headache
Confusion, disorientation, delirium
Visual and auditory hallucinations
Paranoid ideation, acute psychosis
Somnolence
Abnormal dreams
Paresthesias and neuralgia
Aphasia
Seizures

RECOMMENDATIONS FOR ADMINISTRATION OF DIGITALIS ANTIBODY FRAGMENTS :

Adults
1. Severe ventricular dysrhythmias
2. Progressive and hemodynamically significant bradydysrhythmias unresponsive to atropine
3. Serum potassium greater than 5 mEq/L
4. Rapidly progressive rhythm disturbances or rising serum potassium level
5. Co-ingestion of cardiotoxic drugs such as beta-blockers, calcium channel blockers, or tricyclic antidepressants
6. Ingestion of plant known to contain cardiac glycosides *plus* severe dysrhythmias (rare)
7. Acute ingestion greater than 10 mg *plus* any one of factors 1 through 6 above
8. Steady-state serum digoxin greater than 6 ng/mL *plus* any one of factors 1 through 6 above

Children
1. Ingestion of greater than 0.1–0.3 mg/kg or steady-state digoxin greater than 5 ng/mL *plus* rapidly progressive symptoms or signs of digitalis intoxication *or* potentially life-threatening dysrhythmias or conduction blocks *or* serum potassium greater than 6 mEq/L
2. Co-ingestion of other cardiotoxic drugs with additive or synergistic toxicity
3. Ingestion of plant known to contain cardiac glycosides *plus* severe dysrhythmias (rare)

MCQs:

1) Which of the following CCB has the most serious side effect in case of overdose?

A. Diltazam
B. Verapamil
C. Nifedipine
D. Amlodipine

2) 55 year old gentleman with HTN and DM took an overdose of BB, after 6 hours he had no symptoms. What's is the next to do to manage this patient?

A. Keep monitoring for 24 hrs
B. Discharge him
C. Refer to psychiatric
D. Start immediately with atropine, glucgone and IV fluids

3) Seizure is only common with which of the following drugs?

A. Propanolol
B. Dilatazam
C. Nifedipine
D. Verapamil

4) All of these agents are used initially in case of beta-blocker overdose but:

A- Atropine
B- Crystalloid fluids
C- Catecholamines
D- Glucagon

5) All of these mechanism are the effect of CCB except:

A. Reduce cardiac contractility
B. Slow AV conduction
C. Reduce the action of Na/K pump
D. Depress SA nodal activity

6) What is the antidote for Nitrates toxicity?

A. Methylene blue
B. Methemoglobin
C. O2
D. Flumazenil

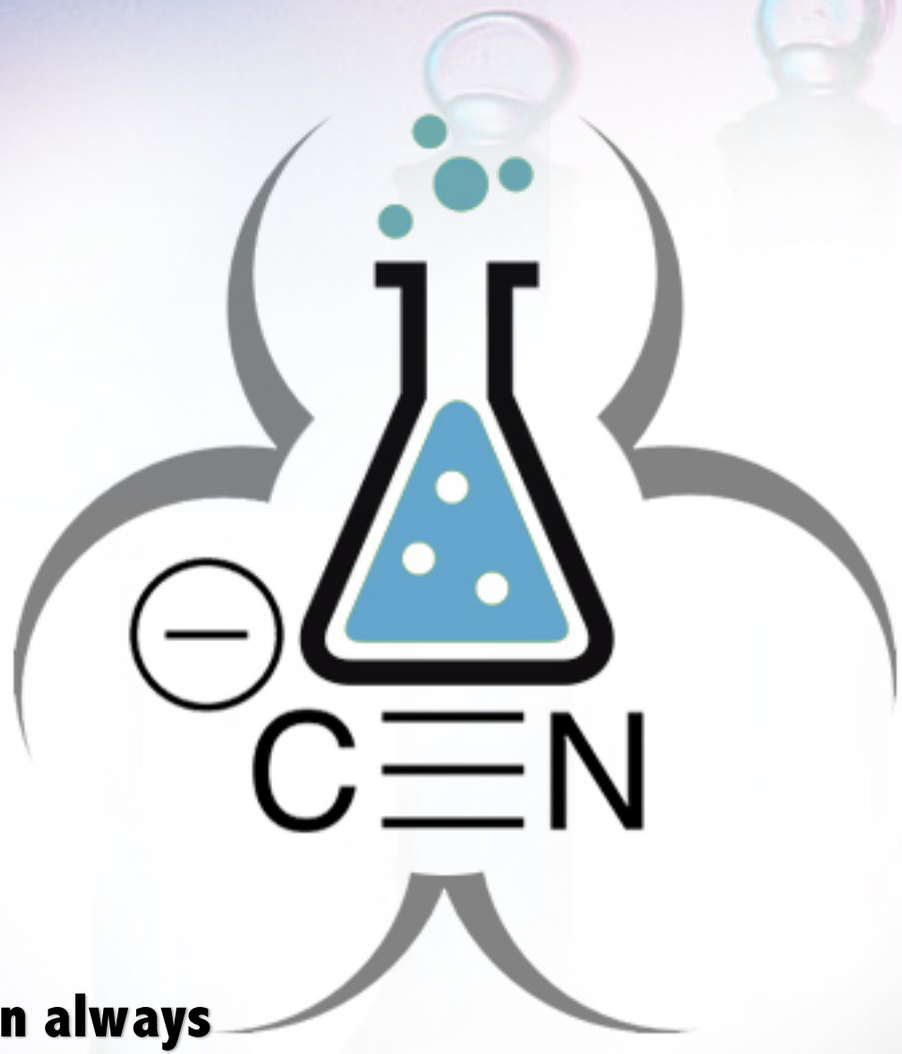
7) All of these factors increase risk of Digitalis toxicity except:

A. Hypercalcemia
B. Captopril
C. Alkalosis
D. Hypermagnesaemia

8) The most common cause of hyperkalemia is:

A. Liver failure
B. Digitalis toxicity
C. Renal failure
D. CCBs

Answers: 1-B, 2-A, 3-A, 4-C, 5-C, 6-A, 7-D, 8-C



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