



Episode 152 (Ch. 147 9th) – Cardiovascular Drugs

Episode Overview:

Cardioactive steroids = e.g. digitalis and plants

1. How does digoxin work (mechanism of action)?
2. How does digoxin toxicity present clinically?
3. Compare acute vs chronic digoxin toxicity
4. What are the risk factors for chronic digoxin toxicity?
5. What types of ECG findings are associated with digoxin toxicity? (List 3 dysrhythmias specific to digoxin toxicity).
6. Describe the management priorities in digoxin toxicity
 - a. List 5 indications for DigiFab
 - b. List 3 dosing strategies for DigiFab
7. What other treatments should be considered in patients with digoxin toxicity?

Beta adrenergic blockers

1. Which β blockers have membrane stabilizing activity? Why is this important?
2. Why is propranolol the most lethal β blocker?
3. Describe the stepwise management of β blocker toxicity
4. Which β blockers can be dialysed?

Calcium Channel Blockers

1. Describe the different mechanism of action of Dihydropyridines and Non-dihydropyridines. How is this relevant to toxicology?
2. Describe the stepwise management of CCB toxicity

Clonidine

1. How does clonidine work?
2. How does clonidine toxicity present and how is it managed?

Nitrates, Nitrites

1. What are 2 common clinical presentations of Nitrate/Nitrite toxicity?
2. How is nitrite poisoning managed?

Wisecracks

1. List 6 differential diagnoses for the “slow + low” patient
2. List 6 non-cardiac symptoms of cardioactive steroid intoxication
3. List three plants containing cardiac glycosides
4. Contrast adult vs. pediatric age differences in digoxin intoxication
5. What are the clinical differences in presentation between β blocker, CCB and digoxin toxicity?



Welcome! This episode we'll be covering five major groups of cardiovascular drugs:

- Cardioactive steroids = e.g. digitalis and plants
- Beta adrenergic blockers
- CCB's
- Clonidine
- Nitrates, Nitrites

KEY CONCEPTS

Cardioactive Steroids

- Digoxin toxicity is often occult and should be considered in any patient who is on digoxin and presents with gastrointestinal or visual disturbance and a new dysrhythmia or conduction disturbance.
- Digi Fab is the specific antidote for digoxin toxicity and is dosed by body load of digoxin, not by body weight of the patient.
- Indications for digitalis Fab are summarized in the episode (so stay tuned), and Fab should be used before pacing or antidysrhythmic drugs.
- Hyperkalemia in acute digitalis toxicity is best treated with Fab fragments. Conventional treatment as for any other cause of hyperkalemia is also appropriate 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 occur
- Volume expansion, atropine, calcium, and glucagon, HDI/glucose infusion, pressors
- When using HDI/glucose infusions, concentrate glucose solutions to avoid fluid overload.

Calcium Channel Blockers

- Signs and symptoms of calcium channel blocker intoxication often occur early after overdose but may be significantly delayed with sustained release products.
- AV block and bradydysrhythmias predominate with verapamil and diltiazem; dihydropyridine calcium channel blockers may present with tachycardia.

Clonidine

- Clonidine poisoning may mimic opioid poisoning and is best treated with crystalloid fluids followed by an infusion of norepinephrine and narcan.

Nitrates, Nitrites, and Methemoglobinemia

- Nitrates are contraindicated in patients who have recently taken phosphodiesterase inhibitors for erectile dysfunction / pulmonary HTN.
- Patients with a methemoglobin concentration of 25% and/or symptoms of anemia should be treated with methylene blue.



Core questions:

- **Cardioactive steroids = e.g. digitalis and plants**

Digoxin is derived from the Balkan foxglove plant, *Digitalis lanata*.

- ❑ *Despite centuries of experience with digitalis, chronic and acute poisonings still occur.*
- ❑ *Medication errors and toxic effects account for the most common causes (44%) of preventable iatrogenic cardiac arrests.*

1. How does digoxin work (mechanism of action)?

- **Increases inotropy** (*inhibition of membrane sodium-potassium-adenosine triphosphatase (Na⁺, K⁺ -ATPase), which increases intracellular sodium and extracellular potassium concentrations. This increase in intracellular sodium concentration results in dysfunction of the sodium-calcium ion exchanger, which normally extrudes intracellular calcium after systole. This subsequent increase in intracellular calcium concentration results in a larger amount of calcium pumped into the sarcoplasmic reticulum so that on calcium-induced calcium release during subsequent action potentials, a larger amount of calcium is released into the cell, causing a more powerful contraction and thus increased cardiac output.*)
 - Increase in intracellular Na⁺ and Calcium
- **Decreases SA and AV nodal conduction**
 - *At toxic concentrations, digoxin can directly block 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*
 - **In toxicity gives tachy-brady/AV block syndromes**
- **Purkinje effects:**
 - *decreased resting potential, resulting in slowed phase 0 depolarization and conduction velocity; (2) decreased action potential duration, which increases sensitivity of muscle fibers to electrical stimuli; and (3) enhanced automaticity resulting from increased rate of phase 4 repolarization and delayed after-depolarizations.*
 - *These mechanisms account for an increase in premature ventricular contractions, which is the most common electrocardiographic manifestation of digoxin toxicity. At extremes of toxicity, these effects result in a dangerous sensitivity to mechanical and electrical stimulation. Interventions with pacemaker wires, catheters, and cardioversion can result in asystole, ventricular tachycardia, and ventricular fibrillation.*

2. How does digoxin toxicity present clinically?



- **Chronic = nonspecific symptoms (see wisecracks)**
- **Acute:**
 - No sign or symptom, including dysrhythmia, is unique to digoxin poisoning, so the differential diagnosis is broad.
 - **More likely Low and Slow**
 - **Gastrointestinal symptoms - N/V and abdominal pain**

Non cardiac symptoms include:

- General weakness
- Headache
- Dizziness
- ALOC
- Blurred “snowy” vision
- Yellow-green halos
- Scotomas
- N/V/D
- Abdominal Pain
- Anorexia

3. Compare acute vs chronic digoxin toxicity

See Table 147.1 in Rosen’s 9th Edition.

Chronic	Acute
Higher Mortality (LL50 6ng/ml)	Lower mortality
Ventricular Dysrhythmias more common	Bradycardia and AV block more common
Elderly	Younger
Underlying heart disease increases morbidity and mortality	Absence of heart disease decreases morbidity and mortality

- The LL50 for acute intoxication is not known, but it is much higher, especially in children.
- The association of hyperkalemia with acute toxicity is obvious given the mechanism of digoxin; either hypokalemia or hyperkalemia may occur with chronic toxicity
- Children with healthy hearts can tolerate massive acute oral ingestions without Fab treatment. This excludes therapeutic errors, children who are taking digoxin therapeutically, and children with heart disease. Dosage calculation and administration errors account for more pediatric digoxin intoxication and death than accidental oral ingestion.

4. What are the risk factors for chronic digoxin toxicity?



These factors decrease elimination, and alter the pharmacodynamics of the drugs.

- Renal Insufficiency
- Heart Disease
 - Congenital
 - Ischemic
 - CHF
 - Myocarditis
- Electrolyte Imbalance
 - Hypo/HyperK
 - HypoMg
 - HyperCa
- Alkalosis
- Hypothyroidism
- Sympathomimetic Drugs
- Cardiotoxic Co-ingestants
 - Beta-Blockers
 - CCBs
 - TCAs
- Drug Interactions
 - Quinidine, Amiodarone
 - Verapamil, diltiazem, nifedipine
 - Erythromycin
 - Captopril
- Elderly woman

5. What types of EKG findings are associated with digoxin toxicity? (List 3 dysrhythmias specific to digoxin toxicity).

Digoxin can produce virtually any dysrhythmia or conduction block, and bradycardias are as common as tachycardias (Box 147.1).

*However, none is unique to digoxin, and because they can all occur in the setting of ischemic and other heart disease, **digoxin toxicity remains a clinical rather than an electrocardiographic diagnosis.***

What rhythm is NOT associated with Dig toxicity = rapidly conducted SVTs (e.g. rapid a. fib).

The specific ones!

- Afib with AV dissociation (slow ventricular rate)
 - Atrial tachycardia with a block
 - Bidirectional VT
 - Junctional Tachycardia
-



6. Describe the management priorities in digoxin toxicity

The treatment of significant digoxin poisoning is the administration of digoxin-specific fragment antigen-binding (Fab) antibodies (DigiFab); all other interventions are considered complementary.

- a. a. List 5 indications for DigiFab

In acute poisoning:

- History:
 - Other cardiac toxic drug ingestion - CCB, BB, TCA with shock
 - Acute ingestion > 10 mg plus clinical toxicity
 - Ingestion of plant containing cardioactive steroids plus dysrhythmias
- Physical:
 - Too fast and deadly: unstable ventricular dysrhythmias (not PVCs)
 - Too slow and deadly: unstable dysrhythmias (hemodynamic compromise) such as symptomatic sinus bradycardia, or second- or third-degree heart block unresponsive to atropine.
 - Cardiac arrest
- Labs: serum potassium level above 5.0 mEq/L (acute ingestion)
 - Acute steady state > 13 nmol/L and one clinical sign
 - Any serum level > 19 nmol/L (this is not a steady state level, will change after drug distributes)

Fab fragment therapy should be used before transvenous pacing, because the latter is believed to carry risk of ventricular dysrhythmia, although the evidence for this is mixed.

The peak level at 2 hrs is usually MUCH higher than the actual steady state level (suggest false toxicity).

**Diagnosis and management rely heavily on serum digoxin concentrations, but it is the steady state (6-8 hrs after the dose/overdose), rather than peak concentration, that correlates with tissue toxicity and is used to calculate antidote dosages.*

- b. b. List 3 dosing strategies for DigiFab

- **Empirically in the setting of cardiovascular collapse / arrest - give 10-20 (logistically restrained) vials**
- **Based on steady-state digitoxin concentration**
- **Based on ingested dose of digoxin or digitoxin**

See Boxes 147.5 and 147.7 for sample calculations.

Reactions:

- Sheep-derived digoxin antibodies, so people can develop:



- Allergic reactions (esp. asthmatics)
- Erythema, urticaria
- Hypokalemia
- CHF exacerbation
- Increase ventricular rate/atrial fibrillation

7. What other treatments should be considered in patients with digoxin toxicity?

Here are the big points:

1. Temporize bradycardia with atropine
2. Watch the K⁺ (helps guide acute Fab treatment or chronic OD's need repletion)
3. Correct the Mg⁺

Temporizing measures while waiting for DigiFab

4. Consider pacing and cardioversion (avoid if possible!)
5. Consider Phenytoin or lidocaine for tachydysrhythmias

- *We recommend using atropine as a temporizing measure for patients with shock while Fab fragments are being administered. We also recommend atropine for bradycardia refractory to Fab fragments. Standard dosing (0.02 mg/kg in children with a minimum of 0.1 mg; 1 mg IV in adults) should be used. Doses can be repeated every 3 to 5 minutes. In general, an external or transvenous pacemaker should be readied once atropine has been administered.*
- *Significant magnesium depletion is present or suspected (eg, electrocardiographic changes such as QTc prolongation are present), 1 to 2 g of magnesium sulfate should be administered over 10 to 20 minutes (child: 25 mg/kg), followed by a constant infusion of 1 to 2 g/hr until magnesium concentrations are normal (careful in renal failure; and NO in bradydysrhythmias)*
- *Maintain K⁺ at 3.5-4 mmol/L (only in chronic toxicity)*
- *Digoxin immune Fab fragments are the preferred therapy for dysrhythmias, but a dysrhythmia may require intervention while Fab fragments are readied, or to begin to show effect after infusion.*

Transvenous pacing has been a mainstay of treatment for several decades; however, there is some evidence that the catheter may induce ventricular tachydysrhythmias in a myocardium made irritable by digoxin, although convincing studies on this question are lacking.

Iatrogenic accidents of cardiac pacing are frequent (36%) in one study and can be fatal (up to 13%). Transvenous pacing should be used only if external pacing fails. Pacing usually is required only temporarily while waiting for Fab fragments to take clinical effect.

Cardioversion in the setting of digoxin poisoning should be reserved for life-threatening dysrhythmias such as tachydysrhythmias with profound refractory hypotension, unstable ventricular tachycardia, or ventricular fibrillation.



Because most assays measure both bound and unbound drug, digoxin concentrations will be elevated for up to 1 week after Fab fragments administration, with values often greater than 100 ng/mL once Fab fragments have been administered.

The significant protein binding and large volumes of distribution of digoxin suggest that hemodialysis, hemoperfusion, and exchange transfusion are ineffective. The long half-lives have therapeutic implications for temporizing measures such as pacemakers, atropine, and antidysrhythmic drugs compared to the more definitive treatment of Fab fragments.

Plants with Digoxin in them!

1) Common oleander 2) yellow oleander 3) Lily of the valley 4) Red squill 5) Foxglove 6) dog's bane 7) Milkweed

Beta adrenergic blockers

Have B1 effects:

Competitively inhibit endogenous catecholamines such as epinephrine at beta-adrenergic receptors, blocking the catecholamine effects of inotropy (increased myocardial contraction), dromotropy (enhanced cardiac conduction), and chronotropy (increased heart rate).

Have B2 effects:

Complex β_2 effects include vascular (smooth muscle relaxation and vasodilation), liver (glycogenolysis, gluconeogenesis), lung (bronchodilation), adipose tissue (release of free fatty acids), and uterus (smooth muscle relaxation) effects.

Which β blockers have intrinsic sympathomimetic activity? Why is this important?

The intrinsic sympathomimetic activity of some beta-blockers such as pindolol, oxprenolol, acebutolol, and carteolol can lead to some unusual manifestations such as ventricular dysrhythmias and sinus tachycardia instead of bradycardia.

- Can produce:
 - torsades de pointes (Sotalol)
 - QT prolongation, VT (Acebutolol)

The first two on the “SANTA” mnemonic

1. Which β blockers have membrane stabilizing activity? Why is this important?

Propranolol, nadolol, and acebutolol have a membrane-stabilizing effect that impairs SA and AV node function and leads to bradycardia and AV block. Ventricular conduction is also depressed, leading to QRS widening, occasional ventricular dysrhythmias such as ventricular tachycardia and ventricular fibrillation, and cardiogenic shock.



SAID simply....they BLOCK Na channels!

2. Why is propranolol the most lethal β B?

Much of propranolol's unique toxicity derives from its:

- **Lipophilic nature** which allows it to penetrate the CNS, causing obtundation, respiratory depression, and—with large overdoses—seizures.
 - **Seizures** probably result from a combination of hypotension, hypoglycemia, hypoxia, and direct CNS toxicity including sodium-channel blockade.

Other beta-blockers are not lipophilic and do not have these effects. Of note, bronchospasm is rarely a problem in cases of beta-blocker overdose, even with nonselective beta-blockers. The few cases of symptomatic bronchospasm respond to the usual bronchodilator nebulizations.

Highly protein bound and lipophilic (can't be dialysed).

3. Describe the stepwise management of β B toxicity

Immediate measures include IV fluids, supplemental oxygen, and monitoring of cardiac rhythm and respirations.

Resuscitation sequence:

- AC not recommended by Rosen's (Jesse says this: AC may or may not be appropriate, consult your local toxicologist)
- In hypotensive patients, bolus 20 to 40 mL/kg of normal saline or lactated Ringer's
- Temporize with IV atropine if HR < 50 bpm
- Give 3-6 g Calcium Gluconate over ~15 mins for bradycardia and hypotension
- Consider Glucagon:
 - *Glucagon has **both inotropic and chronotropic effects** and does not depend on beta-adrenergic receptors for its action; therefore, it has long been used for beta-blocker toxicity. It **stimulates the production of intracellular cyclic adenosine monophosphate independently of the beta-adrenergic receptor.** Furthermore, it helps counteract the hypoglycemia induced by beta-blocker overdose. Although not well studied, the initial **dose of glucagon is a 5- to 10-mg IV bolus (0.05 to 0.1 mg/kg for children).** If a response occurs to glucagon, specifically if heart rate, blood pressure, or symptom improvement is observed, the "response dose" should be started as an infusion at a rate of the response dose administered over 1 hour.*
 - **Can consider glucagon for patients with bradycardia or hypotension not responsive to crystalloid fluids, atropine, and an initial bolus of calcium.**
 - Usually an infusion is needed due to the 20 min half-life
 - *thought to be a transient bridge to HDI therapy*
- High dose insulin therapy:



- *Despite glucagon's longer history for treatment of beta-blocker toxicity, HDI is a superior therapy. HDI is not a vasopressor; it is a profound inotrope with vasodilating properties.* *The mechanism for HDI is not fully elucidated but probably involves both optimization of the use of carbohydrates for fuel by cardiac myocytes and modulation of intracellular calcium. HDI improves cardiac output significantly in beta-blocker toxicity from an increase in stroke volume more than heart rate.*
- Dose range: **0.5 - 10 U/Kg/hr**
 - *One “amp” of D50 should be administered followed by 1 U/kg of regular insulin as a loading dose. An infusion of 25 g/hr of concentrated glucose should be initiated in addition to an infusion of insulin at 1 U/kg/hr. The insulin infusion should be increased by 2 U/kg/hr every 10 minutes until hypotension resolved or a maximum rate of 10 U/kg/hr is reached.*
- **Requires frequent glucose measurements (use dextrose to keep glucose > 12)**
- **Replace K⁺ because of insulin shifting**
- *We recommend HDI for patients experiencing hypotension despite crystalloid fluid, atropine, and a single bolus of calcium and glucagon. We also recommend a central venous catheter and an arterial catheter be placed immediately upon the decision to initiate HDI.*
- **Catecholamines (norepinephrine is preferred 1st line, then vasopressin)** are indicated when mean arterial pressure (MAP) cannot be maintained at 60 mm Hg or above, despite use of crystalloid infusion, calcium, atropine, glucagon, and HDI. A single catecholamine of choice after HDI and glucagon has not emerged.
- **Pacemaker** for refractory cases of bradycardia. A pacemaker is particularly useful when cardiac contractility is vigorous but bradycardia is Persistent.
- **Intralipid:** *IFE is a reasonable therapy in beta-blocker overdose in patients with shock refractory to conventional treatments. We recommend IFE in patients with persistent bradycardia or hypotension not responding to IV fluids, calcium, HDI, and at least three vasopressors or inotropes at maximum recommended infusion rates. Dosing for IFE is also not universally agreed upon. We recommend an initial bolus of 1.5 mL/kg of 20% lipid solution given over 2 to 3 minutes, followed immediately by an infusion of 0.25 mL/kg/min.*
- **ECMO:** *We recommend ECMO in cases where patients have hypotension refractory to HDI, at least three catecholamines, and IFE, or in cases with bradycardia unresponsive to inotropes and a pacemaker.*
- Specific cases:
 - **PROPRANOLOL:**
 - Bicarbonate should be dosed at 1 to 2 mEq/kg IV as a bolus repeated every 3 to 5 minutes until the QRS narrows to less than 120 ms.
 - **SOTALOL:**



- Pulsatile ventricular tachycardia can most safely be treated with lidocaine.
- Pulseless VT = defibrillation
- Overdrive pacing with isoproterenol or a pacemaker and magnesium sulfate are specific therapies for torsades de pointes.

4. Which β blockers can be dialysed?

SANTA can't pee.....

- Sotalol
- Atenolol
- Timolol
- Acebutolol
- Nadolol

Hemodialysis or hemoperfusion may be beneficial for beta-blockers with lower Vd, lower protein binding, and greater hydrophilicity.

CCB's

1. Describe the different mechanism of action of Dihydropyridines and Non-dihydropyridines. How is this relevant to toxicology?

Dihydropyridines:

- Amlodipine
- Nifedipine
- Other “-pines”

Non-dihydropyridines:

- Verapamil
- Diltiazem

Calcium channel antagonists block the slow L-type calcium channels in the myocardium and vascular smooth muscle, leading to coronary and peripheral vasodilation. They also reduce cardiac contractility, depress SA nodal activity, and slow AV conduction.

In cases of overdose, verapamil has the deadliest profile, combining severe myocardial depression and peripheral vasodilation. Both verapamil and diltiazem act on the heart and blood vessels, whereas dihydropyridine calcium channel blockers (such as nifedipine) cause primarily vasodilation and subsequent reflex tachycardia.

IN TOXICOLOGY THIS DIFFERENTIATION IS NOT AS PRONOUNCED

As with beta-blockers, selectivity is lost after overdose, and toxicity is fourfold; the calcium antagonists have negative effects on heart rate, contractility, conduction, and vascular tone.



with the exception of dihydropyridine calcium channel blockers, which tend to result in tachycardia even in severe toxicity.

2. Describe the stepwise management of CCB toxicity

Very rapidly absorbed (usually within 30 mins)

Flowsteps:

1. MOVIE
2. Fluid bolus for hypotension
3. Temporizing measures:
 - a. Atropine
 - i. For symptomatic bradycardia < 50 bpm
 - b. IV calcium
 - i. 3-6 g Calcium Gluconate over 15 mins; may be repeated
4. High insulin glucose therapy
 - a. Dose range: **0.5 - 10 U/Kg/hr**
 - i. *One “amp” of D50 should be administered (if glucose <11) followed by 1 U/kg of regular insulin as a loading dose. An infusion of 25 g/hr of concentrated glucose should be initiated in addition to an infusion of insulin at 1 U/kg/hr. The insulin infusion should be increased by 2 U/kg/hr every 10 minutes until hypotension resolves or a maximum rate of 10 U/kg/hr is reached.*
5. Vasopressors
6. Stop-gap therapies:
 - a. Methylene blue
 - i. *Inhibits the enzyme guanylyl cyclase, resulting in decreased production of cyclic guanosine monophosphate (cGMP) and inhibition of endothelial smooth muscle relaxation, causing an increase in systemic vascular resistance.*
 - ii. *Especially helpful for amlodipine toxicity*
 - iii. *Consider use of methylene blue only as an alternative salvage therapy to ECMO when HDI, catecholamines, and IFE have failed. Dosing involves a 1- to 2-mg/kg bolus of a 1% methylene blue solution followed by an infusion of 1 mg/kg for up to 6 hours.*
 - b. Intralipid:
 - i. *Animal evidence exists that IFE may be effective especially for the treatment of verapamil toxicity. Human case reports exist of successful resuscitation of toxicity from diltiazem and verapamil. Dosing and indications are identical to those for beta-blocker toxicity. We recommend that IFE be used in patients with hypotension refractory to calcium, HDI, and three vasopressors.*
 - c. ECMO



Things NOT recommended:

- *Do not recommend glucagon in calcium channel blocker poisoning. It has no mechanistic advantage over epinephrine, and no good evidence exists to support its use in calcium channel blocker poisoning*

High protein binding and Vd greater than 1 to 2 L/kg make **hemodialysis or hemoperfusion ineffective**. With sustained-release preparations, their half-lives are relatively short, generally limiting toxicity to 24 to 36 hours.

Clonidine

1. How does clonidine work?

*Clonidine is a **centrally acting α_2 -adrenergic** agonist (its a sympatholytic) and imidazoline agonist initially approved by the FDA as a treatment for hypertension in 1974. Since that time, its use has expanded to treat conditions such as attention-deficit/hyperactivity disorder (ADHD), pheochromocytoma, and withdrawal from opioids, ethanol, and nicotine. It is also used in spinal and epidural anesthesia. **Based on its mechanism of action, it mimics clinical features of both opioid poisoning and poisoning from digoxin, beta-blockers, or calcium channel blockers.***

2. How does clonidine toxicity present and how is it managed?

Binding to pre-synaptic α_2 -adrenergic receptors in the brain:

- Less norepinephrine release =
 - Bradycardia, hypotension, decreased mental status, miosis, and occasionally hypothermia.

Supportive care is the mainstay of management:

- Generous IV fluid boluses for hypotension
- Vasopressors - ideally norepinephrine for hypotension
- **Naloxone:**
 - *Recommend escalating doses of naloxone of 0.1 mg, 0.4 mg, 2 mg, and 10 mg. Naloxone is indicated solely if the patient is obtunded or has an unprotected airway, and it should be administered in parallel with any necessary IV fluids or catecholamines.*

Clonidine's peak effects occur 2 to 4 hours post-ingestion. Its half-life is between 5 and 13 hours. Therefore patients with normal vital signs and mental status 4 hours post-ingestion may be discharged home or to an appropriate psychiatric facility.



Nitrates, Nitrites

Nitrates (nitroglycerin, isosorbide mononitrate, and dinitrate) are widely used as vasodilators in the treatment of heart failure and ischemic heart disease.

Other exposures:

- *Young adults, usually male, who inhale various alkyl nitrites (amyl, butyl, isobutyl, or ethyl nitrite) in the hope of enhancing or prolonging sexual pleasure aka “poppers”.*
- *Nitrates are occasionally found in rural well water contaminated by livestock or fertilizer runoff. Oral nitrates may be converted to nitrites in the gastrointestinal tract, especially in infants up to 4 months old.*

Methemoglobin is incapable of carrying oxygen, thus it alters the shape of the hemoglobin-dissociation curve shifting it to the left, causing functional anemia via impaired oxygen delivery.

1. What are 2 common clinical presentations of Nitrate/Nitrite toxicity?

Hypotension (due to vasodilation) - with reflex tachycardia and headache

Low SpO₂ & cyanosis occurs commonly if the percentage of methemoglobin exceeds 10%.

Higher concentrations of methemoglobin may result in fatigue, dyspnea, weakness, dizziness, drowsiness, coma, seizures, and death.

How to confirm the diagnosis:

1. **Pt. has a low SpO₂ (usually in the 75-85% range)*****
 - a. **Trial of the High flow oxygen test - 15 lpm via NRB**
 - b. **= no improvement of cyanosis → think MetHgb.**
2. **Blood CO-oximetry**
 - a. **MetHgb > 10% usually causes symptoms**

*****[clinical pearl]**

Clinicians should be wary of interpreting pulse-oximetry in the setting of methemoglobinemia. Pulse oximeters function by reading the absorbance of light at wavelengths of 660 and 940 nm, which are selected to separate oxy and deoxyhemoglobin. Methemoglobin absorbs light at both these wavelengths more than either oxy or deoxyhemoglobin. This results in unreliable pulse oximetry that typically reads between 75% and 85%, regardless of the patient's oxygenation status.

Blood upon venipuncture reveals “**chocolate-colored**”

2. How is nitrite poisoning managed?



In the case of the too-high IV nitro infusion for sympathetic crashing acute pulmonary edema (SCAPE) = Nitrate poisoning usually responds to supine positioning, IV fluids, and reduction of dose or removal of the offending agent.

In the case of nitrate/nitrite induced methemoglobinemia =

1. **supportive care such as supplemental oxygen and IV fluids.**
2. **severely poisoned patients (symptomatic and MetHgb levels on co-oximetry >20-25%) should be treated with IV methylene blue.**
3. **An intravenous dose of 1–2 mg/ kg (max dose 24hrs 7mg/kg) of 1% methylene blue solution for patients with a methemoglobin concentration greater than 25% and any symptoms of functional anemia.**

The infusion should be given over 5 minutes to reduce pain at the IV site. A clinical response should occur within minutes of infusion. If cyanosis does not resolve in 1 hour, a second infusion of 1 mg/kg can be repeated.

Wisecracks

1. **List 6 differential diagnoses for the “Slow + Low” patient (bradycardia and hypotension)**
 - CCB OD
 - BB OD
 - Digoxin OD
 - Cardiac glycoside plant / animal ingestion
 - tizanidine or imidazoline receptor agonists such as tetrahydrozoline and oxymetazoline
 - sedative-hypnotic drug overdose,
 - hypoglycemic drug ingestion,
 - opioid overdose,
 - CNS injury or infection, endocrine-metabolic disorder, sepsis, and acute myocardial infarction.
2. **List 6 non-cardiac symptoms of cardioactive steroid intoxication**
 - General
 - Weakness
 - Fatigue
 - Malaise
 - GI
 - NV
 - Anorexia
 - AP
 - Diarrhea



- Ophth
 - Blurred vision
 - Photophobia
 - Chromatopsia
 - Transient amblyopia, diplopia, scotomas, blindness
- Neurologic
 - Dizziness
 - HA
 - Confusion
 - Visual or auditory hallucinations
 - Paranoid ideations/psychosis
 - Somnolence
 - Abn Dreams
 - Paresthesias and neuralgias
 - Aphasia
 - Seizures

Those “classic” (but actually not pathognomonic) features:

- **Gastroenteritis symptoms**
- **Chromatopsia**

Methanol, metformin, ethambutol, ethyl chloride, quinine, and other antimalarial medications are all capable of producing visual disturbances. Gastrointestinal disturbances are common and nonspecific and may be misdiagnosed as gastritis, enteritis, or colitis.

3. List three plants containing cardiac glycosides

Paralyzes the Na^+, K^+ -ATPase pump, potassium cannot be transported into the cell = serum potassium rise.

- Digoxin is derived from the Balkan **foxglove plant**, *Digitalis lanata*
- **Oleander** (*Nerium oleander*), common to much of the Southern United States, contains oleandrin, a cardiac glycoside.
 - Can be yellow, white, pink
 - **Importantly: this is a drug overdose where activated charcoal has shown a mortality benefit if given early!**
- **Lily-of-the-Valley** (*Convallaria majalis*), found in much of the Northern Hemisphere, contains convallatoxin, a cardiac glycoside.

Monkshood toxicity may mimic it! Many other plants may contain similar toxins that affect cardiac sodium and potassium channels (but not digitoxin)



Purple foxglove aka digitalis purpurea



Balkan Foxglove



Oleander



Lily of the Valley

Plants with Digoxin in them!

- 1) Common oleander 2) yellow oleander 3) Lily of the valley 4) Red squill 5) Foxglove 6) dog's bane 7) Milkweed

4. Contrast adult vs. pediatric age differences in digoxin intoxication

Children with healthy hearts can tolerate massive acute oral ingestions without Fab treatment. This excludes therapeutic errors, children who are taking digoxin therapeutically, and children with heart disease. Dosage calculation and administration errors account for more pediatric digoxin intoxication and death than accidental oral ingestion.

Adult	Pediatric
Toxic at lower concentrations	Asymptomatic at higher concentrations
Nausea, fatigue, and visual changes	Obtundation and vomiting more common
Tachydysrhythmias as common as blocks and brady's	Bradydysrhythmias and blocks most common
Allergic reactions to Fab uncommon	Allergic reactions extremely rare
Vd less variable	Vd more variable

5. What are the clinical differences in presentation b/n β blocker, CCB and digoxin toxicity?

Beta blocker	Calcium channel blocker	Digoxin toxicity >99% of cases are from chronic toxicity
Acute toxicity	Acute toxicity	
<ul style="list-style-type: none"> ● Rapid onset < 30 mins (unless delayed release form) 	<ul style="list-style-type: none"> ● Rapid onset < 30 mins (unless delayed release form) 	<ul style="list-style-type: none"> ● More gradual onset, vague symptoms
<ul style="list-style-type: none"> ● Bradycardia 	<ul style="list-style-type: none"> ● Bradycardia 	<ul style="list-style-type: none"> ● Cardiac:



<ul style="list-style-type: none"> ● Hypotension ● <u>Unconsciousness</u> ● Seizures* ● Hypoglycemia (especially in children) 	<ul style="list-style-type: none"> ● Hypotension ● Consciousness normal ● Hyperglycemia ● non-cardiogenic pulmonary edema, respiratory distress, and apnea 	<ul style="list-style-type: none"> ○ tachy/brady dysrhythmias ○ Less hypotension ● Non-cardiac sxt <ul style="list-style-type: none"> ○ GI distress ○ Malaise ○ Weakness ○ Dizziness ○ Confusion ○ Altered LOC ○ Visual changes
<p>Special concerns:</p> <ul style="list-style-type: none"> ● Propranolol, nadolol, betaxolol, sotalol and acebutolol = leading to QRS widening, occasional ventricular dysrhythmias such as ventricular tachycardia and ventricular fibrillation, and cardiogenic shock 	<p>Special concerns:</p> <ul style="list-style-type: none"> ● Amlodipine: can cause a reflex tachycardia and hypotension ● Calcium influx into the pancreas is blocked = leading to hyperglycemia ● Pediatrics: Nifedipine, verapamil, and probably other drugs in its class join the short list of medications that can kill a child with ingestion of a single tablet. Seizures may be more common in children than in adults and should be treated with diazepam, lorazepam, or phenobarbital. 	<p>Special notes:</p> <ul style="list-style-type: none"> ● Has a rapidly acting antidote! ● Can present with any dysrhythmia other than A fib. With RVR ● Acute toxicity is rare ● Inquire re: cardiac glycoside containing plants ● Myocardium is irritable