Emergency Medicine Approach to Toxicology

HSM CHIEF OF MEDICINE GRAND ROUNDS

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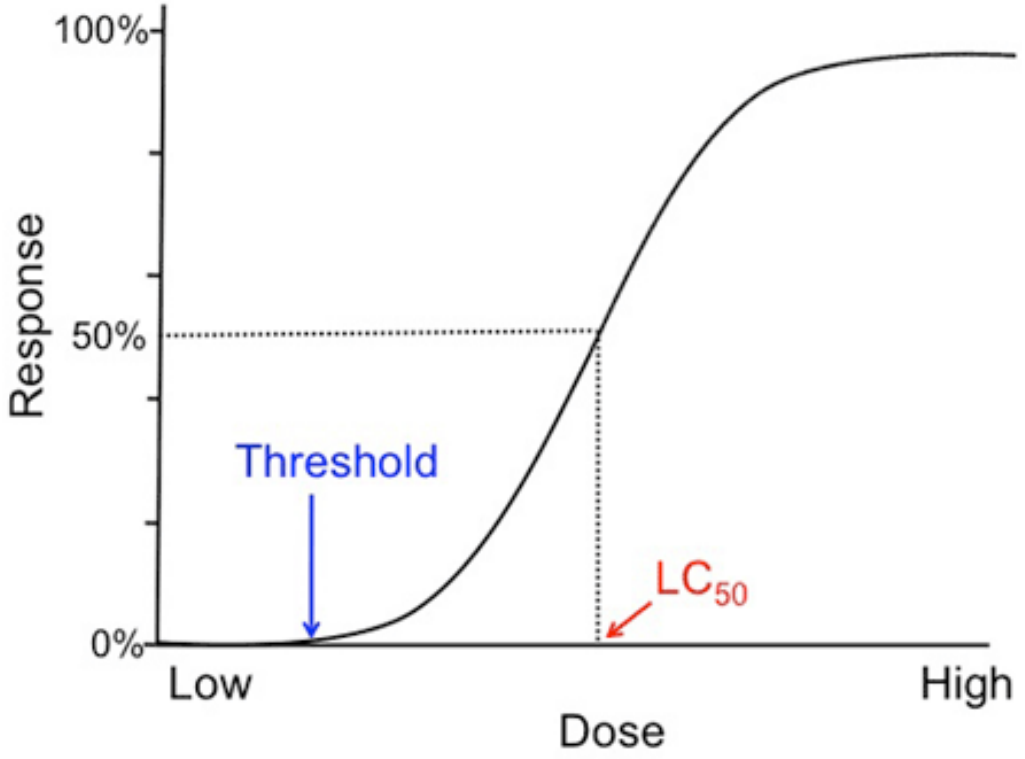
Objectives

- General principles of toxicology
- Recognizing and treating common poisonings
- Differentiating between similar toxidromes
- Learning what resources are available

What is a Poison?

- All substances are poisons; there is none that is not a poison.
- The right dose differentiates a poison and a remedy.

  Paracelsus (1493-1541)



Toxicology pathophysiology

Exposure + Hazard = Risk

All substances can be a poison

Depends on the:

- Substance, the pathway, dose, duration & frequency of exposure
- Absorption, Distribution, Metabolism & Excretion
- Concentration of the active compound at its site of action over time
- Bioactivation: compounds to reactive metabolites
- Individual variation will affect toxicity: LD50

LD50 Comparison

Chemical	LD_{50} (mg/kg)
Ethyl Alcohol	10,000
Sodium Chloride	4,000
Ferrous Sulfate	1,500
Morphine Sulfate	900
Strychnine Sulfate	150
Nicotine	1
Black Widow	0.55
Curare	0.50
Rattle Snake	0.24
Dioxin (TCDD)	0.001
Botulinum toxin	0.0001

Principles of Toxicology: management

Give supportive care

Poison Control
1-800-222-1222

Know when to intervene

Antidotes

Reduce absorption
(Ipecac/ gastric lavage rarely used), Activated charcoal

Increase elimination
Repeated Charcoal/sorbitol,
Dialysis

Reduce exposure
Decontamination
Remove bottles

Toxicology and Emergency Medicine

Challenges

- Decontamination of any clothing/skin
- Quickly differentiating between similar presentations which may be treated differently
- Not forgetting potential co-ingestions
- Quickly treating without harming

Patient #1

65 yo male brought in by ambulance after collapsing in his garage.

Wife says he goes out to the garage to work on his car and drink

VS BP 130/78, HR 101, RR 30, Afebrile

Appears intoxicated and tachypneic

Breathalyzer = 0.00

Labs return:

- Na 145, Cl 99, HCO3 16
- BUN 28, Glucose 180, ETOH 0
- Lactate 3.0
- Measured Osmols 330

Toxic alcohols (cont'd): tools

Na 145, Cl 99, HCO3 16
BUN 28, Glucose 180, ETOH 0
Measured Osmols 330

- **What kind of poisoning gives this chemistry result?**

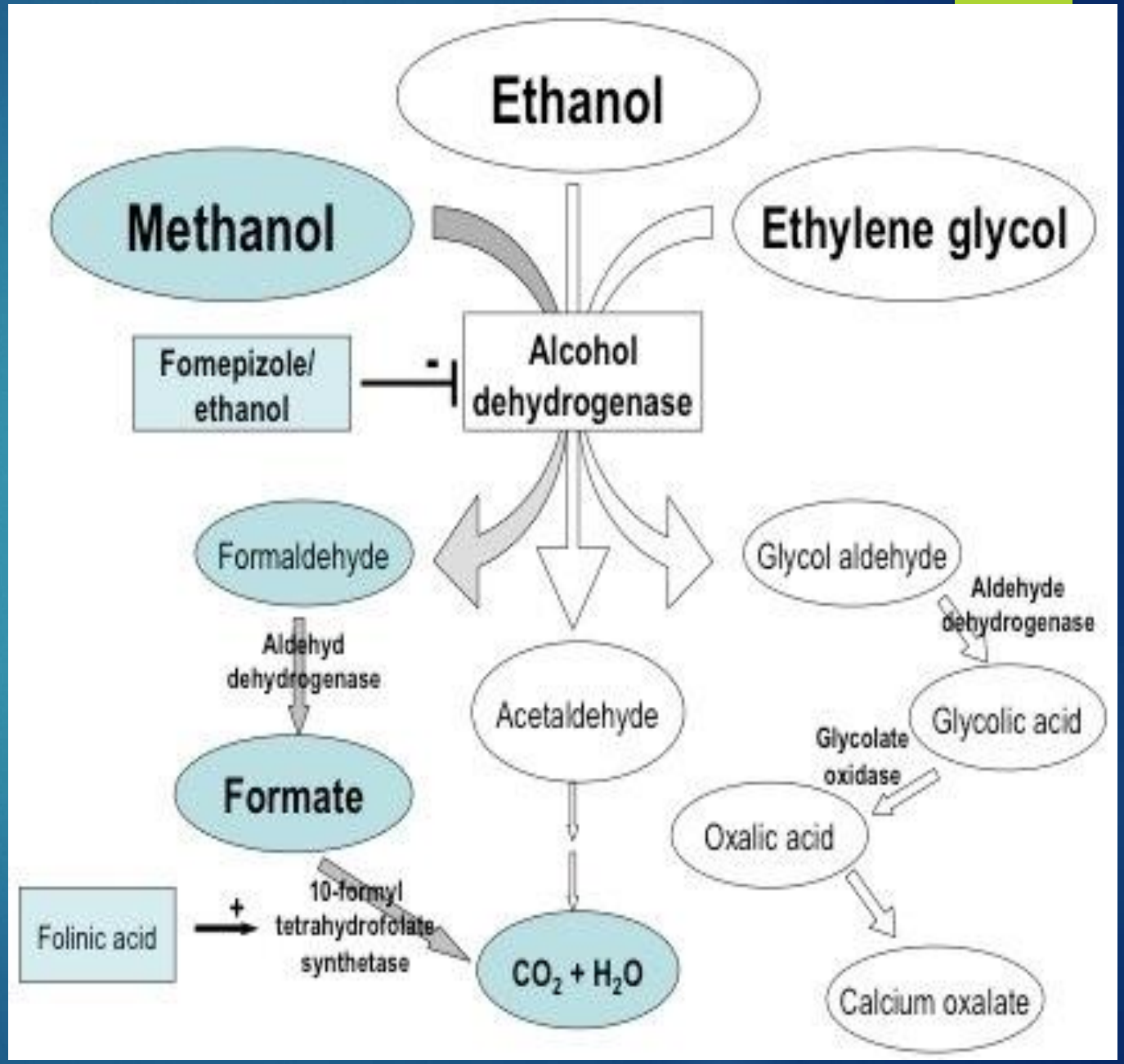
Anion gap

- Measured AG less calculated AG: (Na) less (bicarb + chloride): Na 145 – (Cl 99, HCO3 16) = AG of **30**. (nl 4-16)
- Normal AG is **4-16**.
- Therefore, pt has elevated AG acidosis

Osmolar gap

- Measured osmols less calculated osmols: [2 x (Na)] +(glucose / 18) + (urea / 2.8)+(ethanol/4.1)
- In this case it is 2x145 + 180/18 + 28/2.8 = **310**. Measured Osmals of **330** gives gap of **20**.
- Normal osm. gap is **10** or less

Toxic alcohols (cont'd): tools



Lab Abnormalities

Anion Gap

- Very early an anion gap metabolic acidosis may not have had time to develop
- Absence of an anion gap metabolic does not rule out toxic alcohol poisoning.
  - Ethylene glycol and methanol contribute to the Anion Gap

Creatinine

- **Ethylene glycol** may cause renal failure with an **elevated creatinine**

Lactate

- **Methanol** and **ethylene glycol** may cause an **elevated lactate**.

Osmolar gap

- **Isopropyl (rubbing) alcohol** metabolizes to acetone. Both increase the **osmolar** gap.
- Acetone is NOT an acid and does *not* contribute to the anion gap

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- Breathalyzer = 0.00
- Labs return

  Na 145, Cl 99, HCO3 16

  BUN 28, Glucose 180, ETOH 0

  Measured Osmols 330

  Summary:

  AG of 30

  OG of 20

  Pt vomits and has nystagmus

  What does this suggest?

Toxidrome: alcohols

- Methanol and ethylene glycol
  - Impressive anion gap metabolic acidosis
- Ethanol and isopropyl alcohol
  - Generally don't cause a big anion gap metabolic acidosis
- Early signs are similar-- GI upset (potentially nausea and vomiting), inebriation, slurred speech, nystagmus
- Methanol: '*Snowstorm' vision*, **blurry vision** and ultimately **blindness** with fixed dilated pupils
- Ethylene glycol: The finding of **extraocular movement paralysis** is a very late finding and rarely seen in the ED.
- **Pearl:** The triad of acidosis, high osmolality and low or zero ethanol level is highly suspicious for a toxic alcohol ingestion
- Must consider if pt is **not sobering up** as expected

Toxic alcohols: treatment summary

Prevent toxic metabolites: Competitively inhibit alcohol dehydrogenase

- **Fomepizole** started within 30 minutes. If one does not have access to fomepizole, consider **ethanol**.
  - **Dosing:** loading dose of 15mg/kg, then 10mg/kg q12h for the first 48 hours, after which the dose is increased to 15mg/kg q12h
- **Ethanol dosing:** oral ethanol q1h to a target serum ethanol level = 22-23 mmol/L.
  - Note that if the patient comes in having co-ingested ethanol, they will not require fomepizole or ethanol as long as their serum ethanol remains above 22-23 mmol/L.
- Not needed for **isopropyl alcohol**

Consider bicarb, Replenish cofactors and Consider hemodialysis

- IV **Bicarb** for pH less than 7.2
- **Folic acid** (50mg IV q4-6h) or folinic acid (1-2mg/kg IV q4-6h) for **methanol**;
- **Thiamine** (100mg IV q6h) and pyridoxine (100mg IV q6h) for **ethylene glycol**
- **Dialysis** is usually required for **methanol** –it is eliminated too slowly for antidote alone to be effective.
- **Dialysis** MAY NOT BE required for ethylene glycol if fomepizole in begun early and there is no acidemia or renal dysfunction

Hemodialysis: general principles

Efficacy — HD is most useful in removing toxins with the following characteristics:

- Low molecular weight (<500 daltons)
- Small volume of distribution (<1 L/kg)
- Low degree of protein-binding
- High water solubility
- Low endogenous clearance (<4 mL/min per kg)
- High dialysis clearance relative to total body clearance

Specific drugs/poisoning amenable to HD includes toxic alcohols

- Barbiturates
- Bromides
- Alcohols:
  - Ethanol
  - Isopropanol
  - Acetone
  - Methanol
  - Ethylene glycol
  - Propylene glycol
- Lithium
- Procainamide
- Theophylline
- Salicylates
- Heavy metals (possible)
- Trichloroethanol/Chloral hydrate
- Atenolol
- Sotalol
- Biguanides (eg, metformin) when associated with lactic acidosis

Patient #1

65 yo male brought in by ambulance after collapsing in his garage.

Wife says he goes out to the garage to work on his car and drink

Wife arrives, says pt keeps leftover antifreeze in coke cans on the window sill.

UA returns calcium oxalate crystals

Highly suggestive of ethylene glycol poisoning

- Pt treated with fomepizole, no longer "drunk" and renal function/bicarb returned to normal.
- Discharged the following day
- No longer stores chemicals in coke cans

Patient #2

- 28 y/o man was brought by police after he called stating people were trying to break into his apartment and rob him
- Per EMS, he presented paranoid, complaining of a "panic attack" and was picking at his skin
- Temp 102 F, HR 125/min, BP 170/100, exam shows dilated pupils, agitation, diaphoresis

Differential Diagnosis

- Sympathomimetics
- Anticholinergics
- Organic psychiatric disease
- Delirium
- Other

Toxidrome: sympathomimetics

Substances: Cocaine, methamphetamine, MDMA (ecstasy), pseudoephedrine

Physiology

Typically affect CNS and CV systems	Release catecholamines from the presynaptic terminals	Act on peripheral a- and β adrenergic receptors	May block reuptake of dopamine increasing postsynaptic dopamine concentrations	May inhibit GABAergic neurons

Example: Crystal meth

--Widely available

--5 percent in US has used it; 500,000 in last 30 days

---meth synthesis carries significant risk of explosion or toxic exposure and is responsible for exposing many children to profoundly toxic products

Sympathomimetics: Presentation

- Diaphoresis
- CNS signs (early): hypervigilance, akathisia

  May progress to agitated delirium, paranoia, delusion, hallucination, SI/HI, psychosis, seizure
- Tachycardia, hypertension, can progress to hyperthermia
- Excoriations from formication: "crank bugs"
- Look for chronic users: malnourished, disheveled, agitated, poor dentition
- Distinguish from serotonergic symptoms of lower extremity tremors and clonus.
  - However, MDMA can cause both

Sympathomimetics

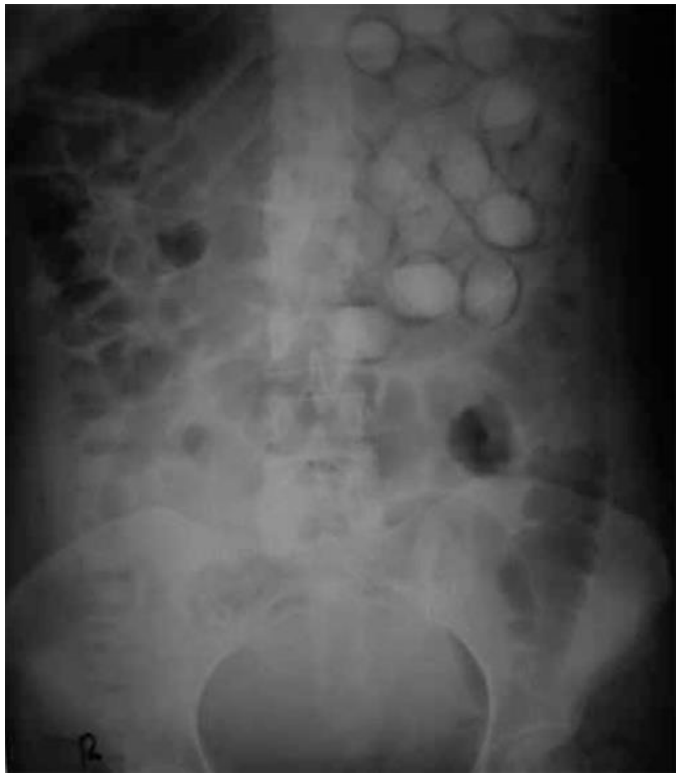
Amphetamine effects are indistinguishable from those of **cocaine** except for the duration of action, which is longer and around 24 h for amphetamine

Compared to other amphetamines, **MDMA** causes a greater release of serotonin as compared to dopamine

This may explain its relatively more prominent psychoactive effects

Sympathomimetics: Treatment

- Evaluate for AMI, stroke, seizure, rhabdomyolysis, delirium
  - Most chest pain is non-cardiac but need to consider cardiac chest pain with cocaine
- Treatment
  - Reduce stimulation
  - Cooling if needed
  - Benzodiazepines
  - Avoid beta blocker—this can lead to unopposed a-stimulation
    - Can cause hypertension, ischemia, vasoconstriction
  - Body Packers: whole bowel irrigation



Patient #3

- 33 y/o woman brought by friend for new confusion, agitation, and c/o needing to urinate but being unable
- VS: HR 120, T 101
- Clinical evaluation showed she had many of these findings:
  - Tachycardia
  - Flushed
  - Dry mouth, dry skin
  - Agitated
  - Urinary retention

Anticholinergic Toxidrome

Red as a beet

Dry as a bone

Blind as a bat

Mad as a hatter

Hot as a hare

Full as a flask

Anticholinergic Poisoning: Some Sources

- OTC "sleeping pills"
- Lomotil (diphenoxylate-atropine)
- Scopolamine patches
- Cyclopentolate (mydriatic/cycloplegic)
- Jimson weed
- Tricyclic antidepressants (TCAs):
  - Nortriptyline
  - Amoxapine
  - Desipramine (Norpramin)
  - Doxepin
  - Imipramine (Tofranil)
  - Nortriptyline (Pamelor)
  - Protriptyline (Vivactil)
  - Trimipramine (Surmontil)

Management - Anticholinergics

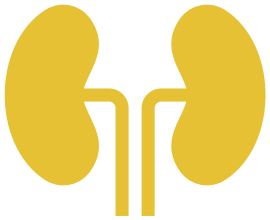
ABCs, IV, O2 (if hypoxic), Monitor

- ECG to look for QTc prolongation

Management:

- Reduce hyperthermia
- Urinary catheter for urinary retention

TCA OVERDOSE – Specific Concerns



Management:

ABCs

Bicarbonate IV until QRS shortens

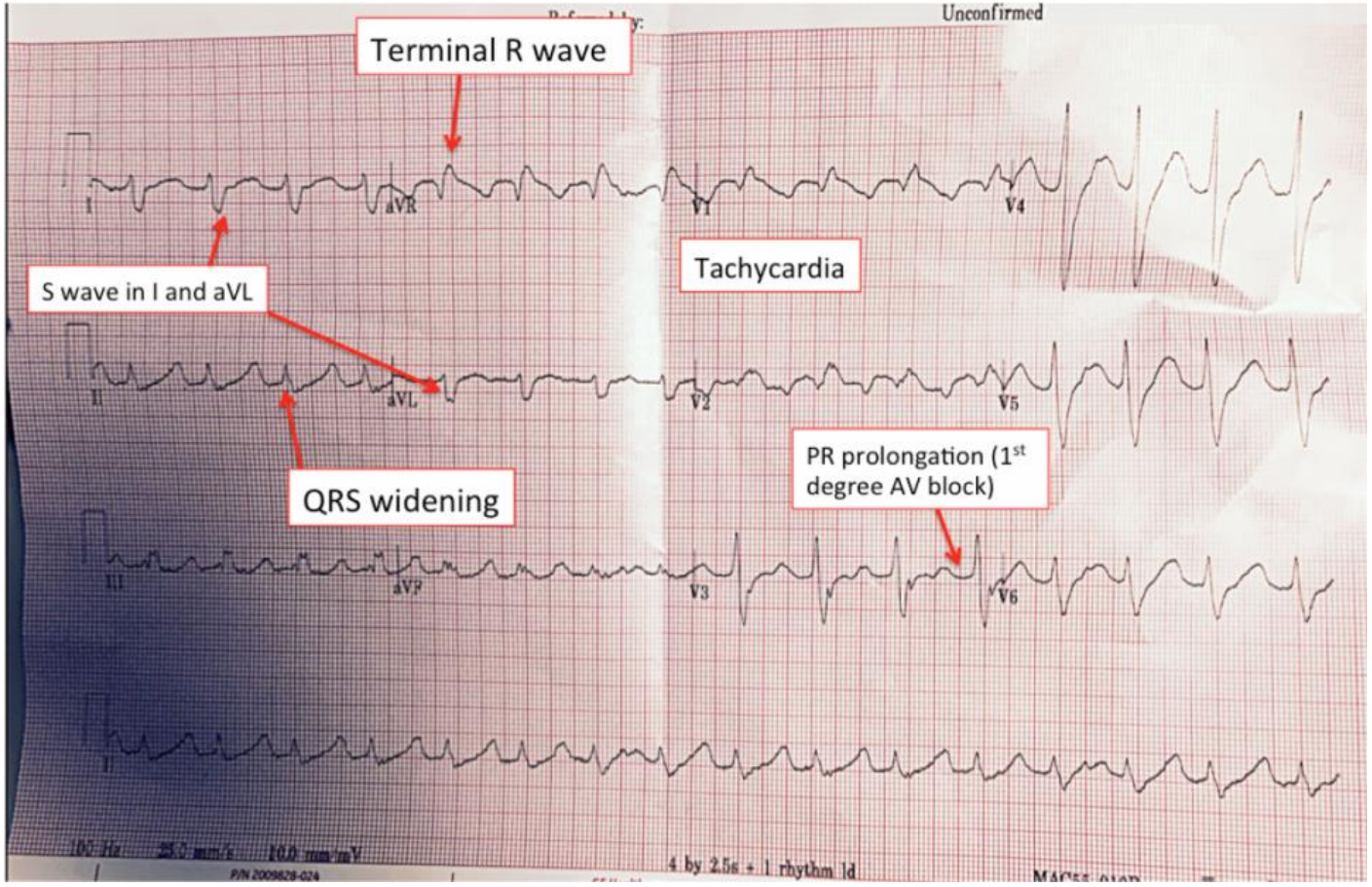
Activated charcoal

Charcoal hemoperfusion

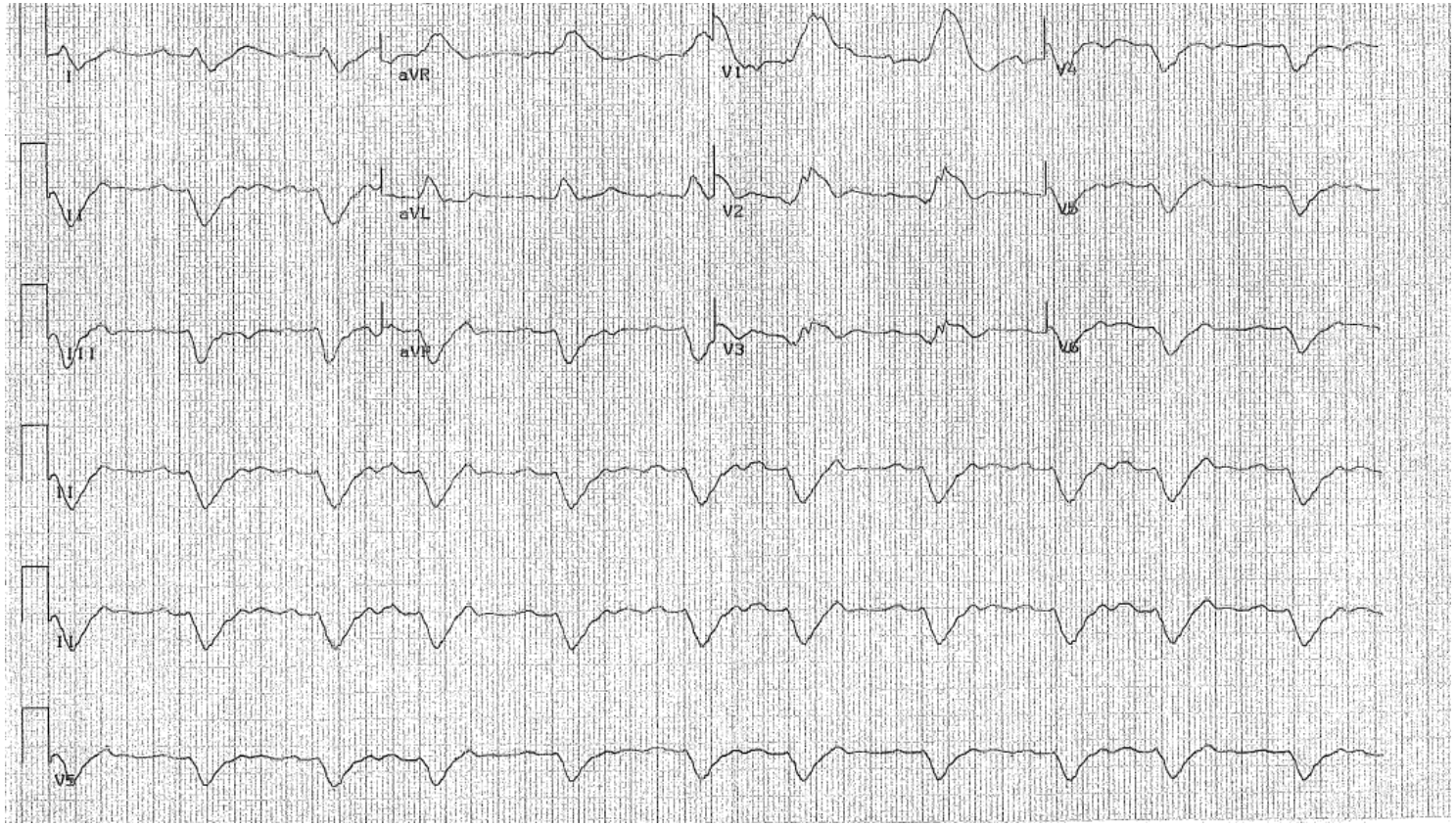
Monitoring of QRS:

QRS of > 100 ms is predictive of risk for seizures

QRS of > 160 ms is predictive of ventricular arrhythmia


Unconfirmed
Terminal R wave
S wave in I and aVL
QRS widening
Tachycardia
PR prolongation (1st degree AV block)
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
4 by 2.5s + 1 rhythm ld

EKG changes



Late EKG changes

Management - Anticholinergics

- Medications
  - Activated Charcoal
    - Shown to reduce absorption* even > 1 hour after ingestion due to delayed gastric emptying
  - Benzodiazepines
    - First line for management of agitation
  - Consider physostigmine
    - Inhibits acetylcholinesterase
      - Indications: Seizure, coma, arrhythmia
      - Do **not** use in TCA overdose (asystole)

*Int J Clin Pharmacol Ther Toxicol. 1984 Aug;22(8):395-400. **Activated charcoal adsorption of diphenhydramine.** Guay DR, Meatherall RC, Macaulay PA, Yeung C

Poisoning: Role and Limits of Urine Drug Screens

- Tox screen at VA called UDAS
- Limited to amphetamine, benzos, cannabinoids, opioids, ethanol, oxycodone, and methadone and metabolites
- Can show compliance with prescribed opioids and methadone
- Shows exposure, not intoxication, so needs clinical correlation
- False positives and negatives common

Think Co-Ingestants, Esp. Acetaminophen Overdose

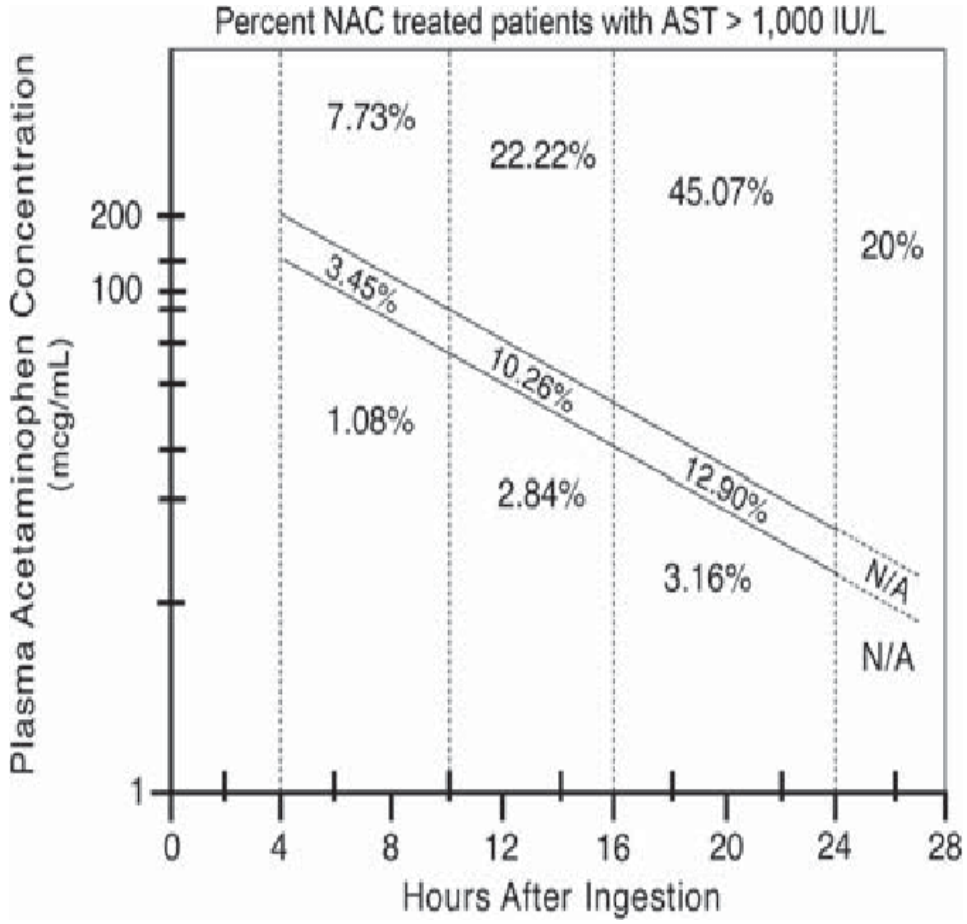
- Example: the tragedy of missing acetaminophen overdose
  - Over 600 drugs containing acetaminophen including many OTC sleeping medications
  - Suicidal patients may not be forthcoming
  - Not on routine tox screens
  - Treatment after 24 hrs—reduced effectiveness
  - Latency period prior to hepatic and renal toxicity

Management of Acetaminophen Overdose

- Suicide precautions
- Activated charcoal
- Urine tox to evaluate for co-ingestants
- Ask for the bottle if available
- Check 4- hour acetaminophen level
- Suspect in any drug with "-cet" in the name, eg Darvocet, Percocet, Oxicet, paracetamol, etc.)

Management of Acetaminophen Overdose (con't'd)

- Check 4- hour acetaminophen level
  - Rumack-Matthew nomogram
    - Cannot rely 100% on nomogram—must treat with any GI symptoms
    - May underestimate risk
      - Chronic alcoholism
      - Malnutrition
      - P-450 (CYP2E1) inducing drugs
      - Delayed gastric emptying
        - Tylenol PM
      - Tylenol ER
    - If concern for acute ingestion and initial level is below the toxicity line, recheck at eight to ten hours



Acetaminophen Treatment

- There is a 100% effective antidote
  - N-Acetyl cysteine (NAC): IV and PO protocols
    - IV
      - Loading dose 150 mg/kg over 60 minutes; Maintenance dose 50 mg/kg over 4 hours then 100 mg/kg over 16 hours
      - Watch for anaphylactoid reactions
    - PO
      - 140 mg/kg followed by 17 doses at 70 mg/kg q 4 hours (72 hrs)
    - Continue until
      - Undetectable acetaminophen concentration
      - Improving hepatic aminotransferases
      - Improving prognostic markers
    - Works despite activated charcoal
    - May need to adjust dose for morbidly obese patients massive overdose

Activated charcoal

- No standard of care for its use
- Direct binding, using 1-2 mg/kg or about 10:1 ratio of charcoal to ingestant
- Poorly binds alcohols, hydrocarbons, iron, lithium, caustics, alkali, acid
- Multidose: repeat Q 4 hrs
- Useful as "gut dialysis" for sustained release drugs and those with enterohepatic circulation:
  - Theophylline, phenobarbital, salicylates, carbamazepine, chlorpropamide, quinine, and phenytoin
- Contraindications: somnolence (aspiration), need for urgent EGD (blocks view of bowel)

Opioid OD: Fentanyl vs Oxycodone

Patient #4

- 79 yo male, h/o hypertension, CAD, brought in to Triage by his wife due to low blood pressure at home and seeming depressed
- VS BP 79/36, HR 38, RR 16, O2 sat 96%, Afebrile

Differential Diagnosis

- Overdose
  - Beta blocker
  - Calcium channel blocker
  - Clonidine
- Hypovolemia
- Sepsis

Patient #4

- 79 yo male, h/o hypertension, CAD, brought in to Triage by his wife due to low blood pressure at home and seeming depressed
- VS BP 79/36, HR 38, RR 16, O2 sat 96%, Afebrile
- Seems slightly lethargic; FSBS 55

Beta-blocker vs Calcium Channel Blocker (CCB) Overdose

Beta-blocker	Altered mental status Bronchospasm Hypoglycemia
Calcium-blocker	Hyperglycemia

Beta-blockers

Lipophilic vs lipophobic

- Most are moderately lipophilic - propranolol

Hepatic vs renal excretion

- Mostly hepatic except for atenolol, labetalol and sotalol

Normal peak absorption within 1-4 hours (except for sustained-release)

Beta- Blocker Overdose Presentation

Hypotension, bradycardia	Pathways dependent on circulating catecholamine
Hypoglycemia	Inhibition of glycogenolysis and gluconeogenesis
Most symptoms/findings occur within 2 hours (except Sotalol and Sustained release)	
Patients may need intubation due to obtundation	

Beta-blocker Effects- Special considerations

Sustained release beta-blockers

- May have different timing of symptoms and may require monitoring for longer
  - Symptom onset may not be for 6-12 hours

Propanolol

- Sodium channel blockade ("membrane stabilizing"), QRS widening
- Most lipophilic – can cross the blood-brain barrier, may cause seizures in OD
  - Study of 58 Betablocker poisonings, of those who ingested Propranolol > 2 g, 2/3 had seizures

Sotalol

- Potassium efflux blockade, QT prolongation -> monitor for torsades
- May be risk of toxicity up to 20 hours after ingestionQTc prolongation may last 3-4 days
- QTc prolongation may last 3-4 days

David M. Reith, Andrew H. Dawson, Ian M. Whyte, Nicholas A. Buckley & Geoffrey P. Sayer (1996) Relative Toxicity of Beta Blockers in Overdose, Journal of Toxicology: Clinical Toxicology, 34:3, 273-278, DOI: 10.3109/15563659609013789

Ca-Channel Blockers

Lipophilic vs lipophobic

- Lipophilic

Hepatic vs Renal

- All undergo hepatic first-pass metabolism

Normal peak absorption within 1-4 hours (except for sustained-release)

Affect the L-type calcium channels – prevent intracellular influx of Ca+

- SA chronotropy – Sinus bradycardia
- AV nodes – Negative dromotropy - Conduction delays
- Myocardial contraction – negative inotropy
- Suppression of Insulin secretion

Large volume of distribution

Ca-Channel Blocker Classes

Phenylalkylamines

- Verapamil
  - Suppresses cardiac contractility, SA node automaticity, AV node conduction and causes vasodilatation

Benzothiazepines

- Diltiazem
  - Similar to above with less vasodilatation but more effect on conduction

Dihydropyridines

- Nifedipine, amlodipine, felodipine, nicardipine, nimodipine
  - Mostly vasodilatory effect

Ca-Channel Blocker Overdose

Both **verapamil** and **diltiazem** have similar effects of bradycardia, hypotension and conduction abnormalities

Nifedipine causes hypotension and ***reflex tachycardia***

In massive overdose, selectivity may be lost

Effects from Sustained Release formulations may be delayed 12-16 hours with peak at 24 hours

Reduced insulin secretion -> hyperglycemia

Conduction delays (AV blocks, bundle branch blocks, QT prolongation)

Metabolic acidosis

Few reports of non-cardiogenic pulmonary edema

Treatment of Beta-blocker and CCB Overdoses

ABC, IV x 2 large bore, O2 (if indicated), Monitor with pacing pads

Intubation if necessary to protect the patient's airway

Consider atropine pre-treatment to prevent vagally mediated worsened bradycardia

IV fluid resuscitation

Call Poison control

Treatment of Beta-blocker and Ca-Channel Blocker Overdoses (2)

Charcoal

- If less than 1 hour since ingestion or per Poison Control

Atropine for bradycardia

- May be ineffective in severe CCB overdose

Vasopressors

- Consider need for inotropic support vs low systemic vascular resistance

Calcium administration (VAPSHCS has Calcium Chloride (diluted)

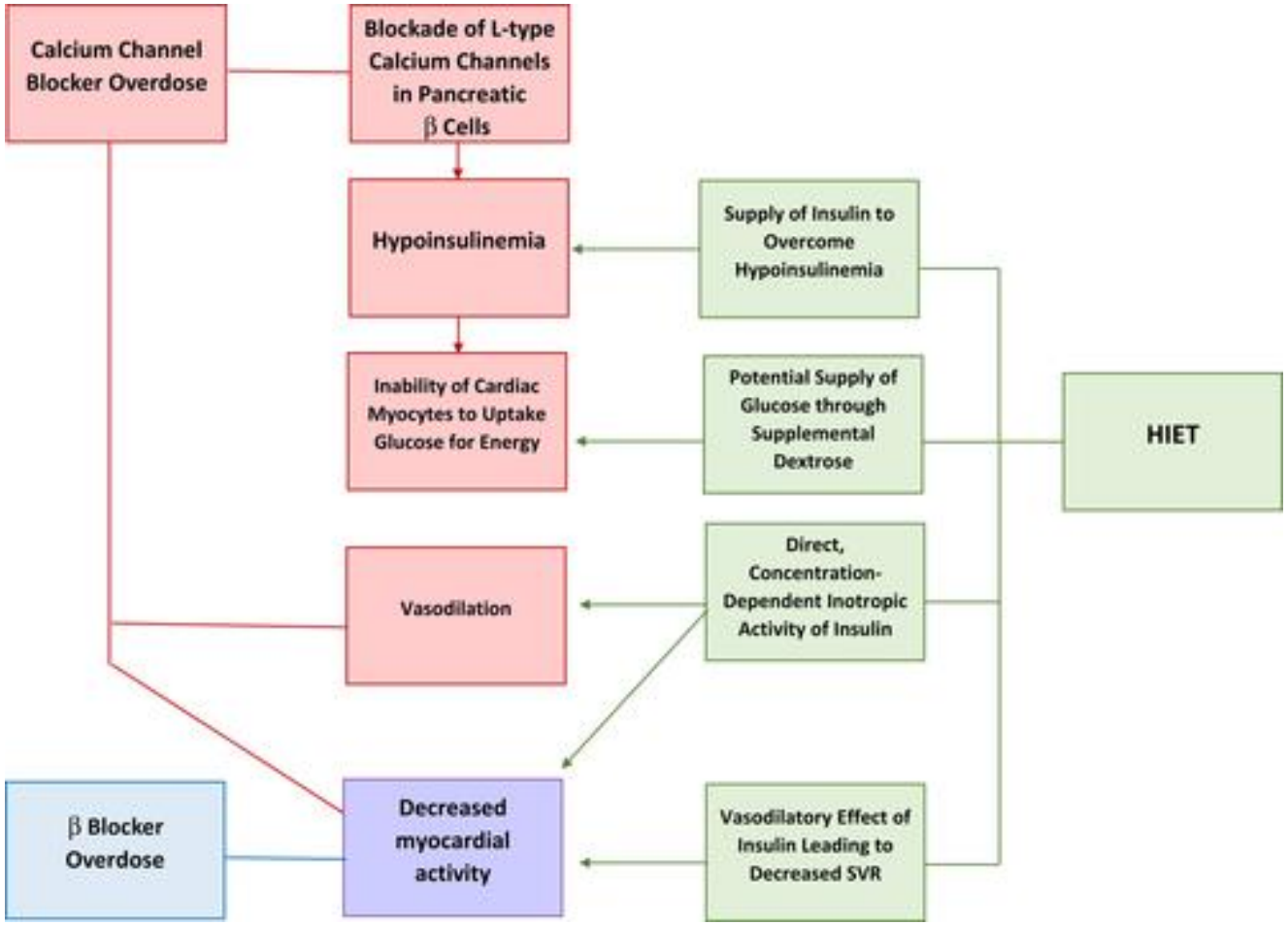
- CCB overdose - may improve hypotension and conduction but may not help bradycardia
- Beta-blocker overdose - may help, especially if concern of concommitant Ca-channel blocker ingestion
- You can give too much (calciphylaxis – ATN, splenic infarcts, etc)

Treatment of Beta-blocker and Ca-Channel Blocker Overdoses (3)

- Bicarb for QTc prolongation
- Glucagon (give with an antiemetic)
  - Unclear support from literature, mostly animals
  - Initial study in 1998 – the glucagon that was used also contained insulin
- Hyperinsulinemic euglycemia (HIE) (more evidence with CCB overdoses)
- ECMO
- Consults: Cardiology
- Dispo: ICU

Scott Weingart. EMCrit Podcast 27 – Calcium Channel Blocker Overdose. EMCrit Blog. Published on June 29, 2010. Accessed on November 1st 2019. Available at [https://emcrit.org/emcrit/calcium-channel-blocker-od/].

HIE Therapy in Calcium Channel Blocker and Beta-blocker Overdose



Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, Volume: 38, Issue: 11, Page:
First published: 23 August 2018, DOI: (10.1002/phar.2177)

Hyperinsulinemic Euglycemia (HIE)

- May increase cardiac output without increasing myocardial oxygen demand (insulin may have a positive inotropic effect)
- May be helpful in cases refractory to IVF, atropine and glucagon
- May cause hypokalemia and hypoglycemia, may need repletion first
  - Before initiating, check glucose (> 200 mg/kL) and K+ (>2.5 mEq/L)
- May need initial vasopressor support due to delayed effects of HIE of 15-60 minutes

Kristin M. Engebretsen, Kathleen M. Kaczmarek, Jenifer Morgan & Joel S. Holger (2011) High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning, Clinical Toxicology, 49:4, 277-283, DOI: 10.3109/15563650.2011.582471

Hyperinsulinemic Euglycemia (HIE)

- When to use
  - Symptomatic patients & potentially toxic doses
    - Hypotension and/or bradycardia
      - Goal BP >= 90 mm Hg and HR >= 50 bpm
    - Altered mental status
    - EKG abnormalities
  - Needing increased myocardial function

Krenz, J. R. and Kaakeh, Y. (2018), An Overview of Hyperinsulinemic-Euglycemic Therapy in Calcium Channel Blocker and β-blocker Overdose. Pharmacotherapy, 38: 1130-1142. doi:10.1002/phar.2177

Hyperinsulinemic Euglycemia (HIE)

- Regular insulin 1 unit/kg bolus + dextrose 0.5 g/kg IV
  - Monitor glucose every 30 minutes (don't start dextrose if FSBS > 400)
    - Insulin infusion of 0.5-1 units/kg/hr (Max 10 units/kg/hr)
    - Goal to maintain euglycemia (glucose between 100 mg/dL – 200 mg/dL)
      - Use D10 infusion and D50 boluses as needed
  - Monitor potassium every 30-60 minutes then 1-2 hours once stable
- Duration – until stable + slowly taper over several hours
  - May need to continue dextrose for several hours to prevent hypoglycemia
  - Watch for rebound hyperkalemia

Krenz, J. R. and Kaakeh, Y. (2018), An Overview of Hyperinsulinemic-Euglycemic Therapy in Calcium Channel Blocker and β-blocker Overdose. Pharmacotherapy, 38: 1130-1142. doi:10.1002/phar.2177

Specific Treatment for Beta-blocker Overdoses

- Consult Nephrology
  - Hemodialysis (if it is one of the renal excreted beta-blockers)

Specific Treatment for CCB Overdoses

- Refractory cases/last ditch effort
  - Intravenous Lipid Emulsion therapy
  - Methylene blue
  - ECMO
- Monitor at least 12 hours for IR; 24 hours for sustained release

Pitfalls in the Management of Overdoses

- Not consulting poison control
- Not considering co-ingestions
- Not recognizing occult acetaminophen overdose
- Not considering toxic alcohols in an intoxicated appearing patient
- Not recognizing QTC prolongation in anticholinergic overdose
- Not recognizing a TCA overdose
- Not considering sustained release medications

Poisoning: Summary

- Goals: How to recognize and treat poisonings which may present similarly
- General principles of toxicology: Decontamination, reduce absorption, recognize toxidrome, antidote, supportive care
- Toxidromes
- Resources available:
  - Poison Control
    - 1 800 222 1222 (separate number for animal poisonings)

Thank you—questions?