Brigham and Women's Hospital
Founding Member, Mass General Brigham

An approach to the poisoned patient

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- Clinical Focus: Emergency medicine, medical toxicology
- Research Focus: Ingestible electronics, wastewater epidemiology and translational drug/device research

DISCLOSURES

- Research grants from NIH, ARPA-H and Bill and Melinda Gates Foundation

- Dr. Chai has equity stake in Biobot Analytics, a wastewater based epidemiology company and is a consultant for Syntis Bio, Pfizer

OBJECTIVES

- Recognize a constellation of symptoms that correspond with a specific toxidrome(s) or poisoning
- Identify management techniques and appropriate antidotes based on toxidrome identification

CASE PRESENTATION

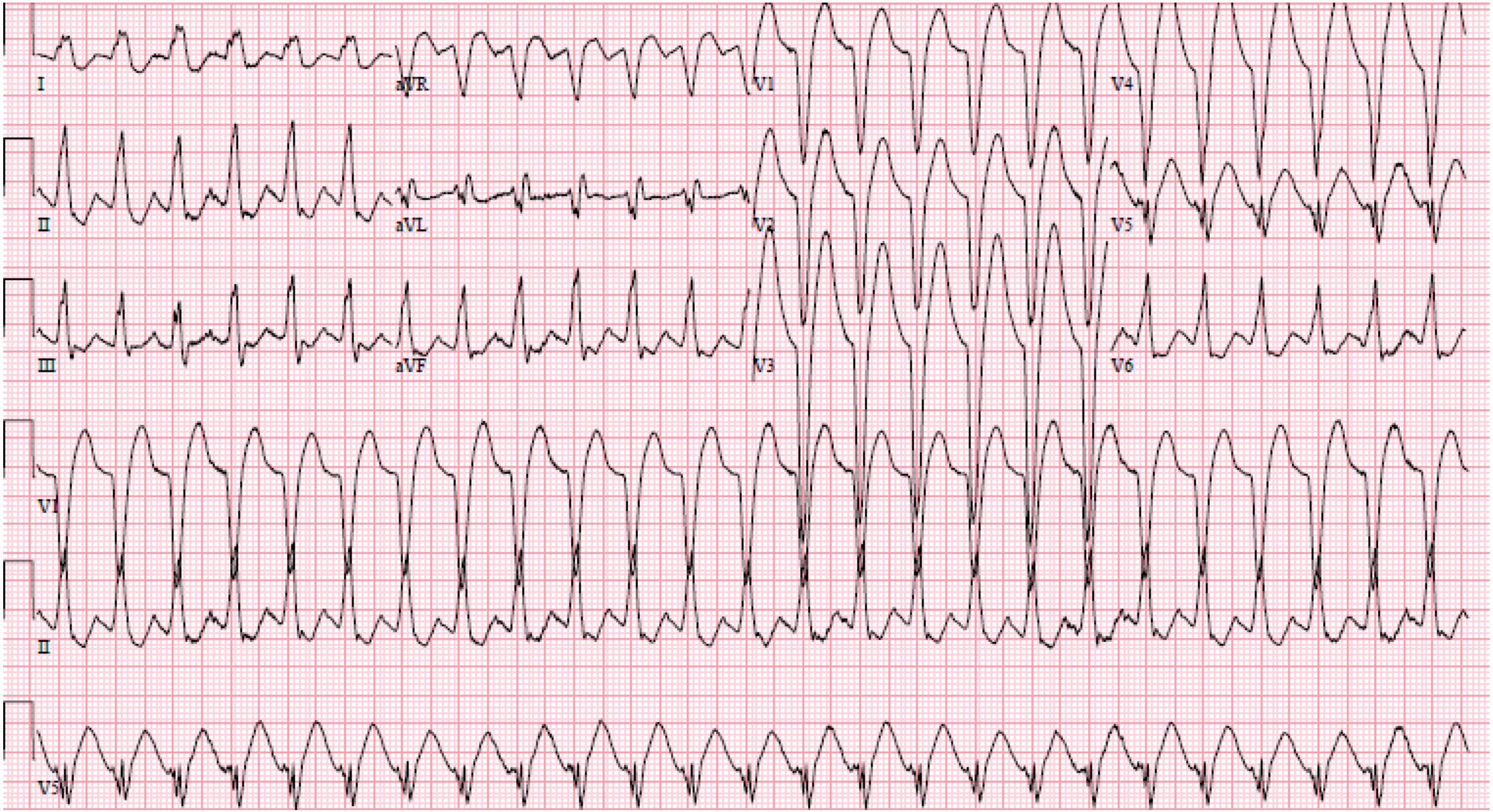
28yo male presents to the ED feeling unwell. Has a tonic clonic seizure in the waiting room.

Initial vitals:

- HR 150, RR 30, Temp 98.6, BP 170/90, O2: 100% on 2LNC

Exam:

- Bilateral lower extremity clonus, flushed and moist skin, pupils 9mm
- Intubated given inability to protect airway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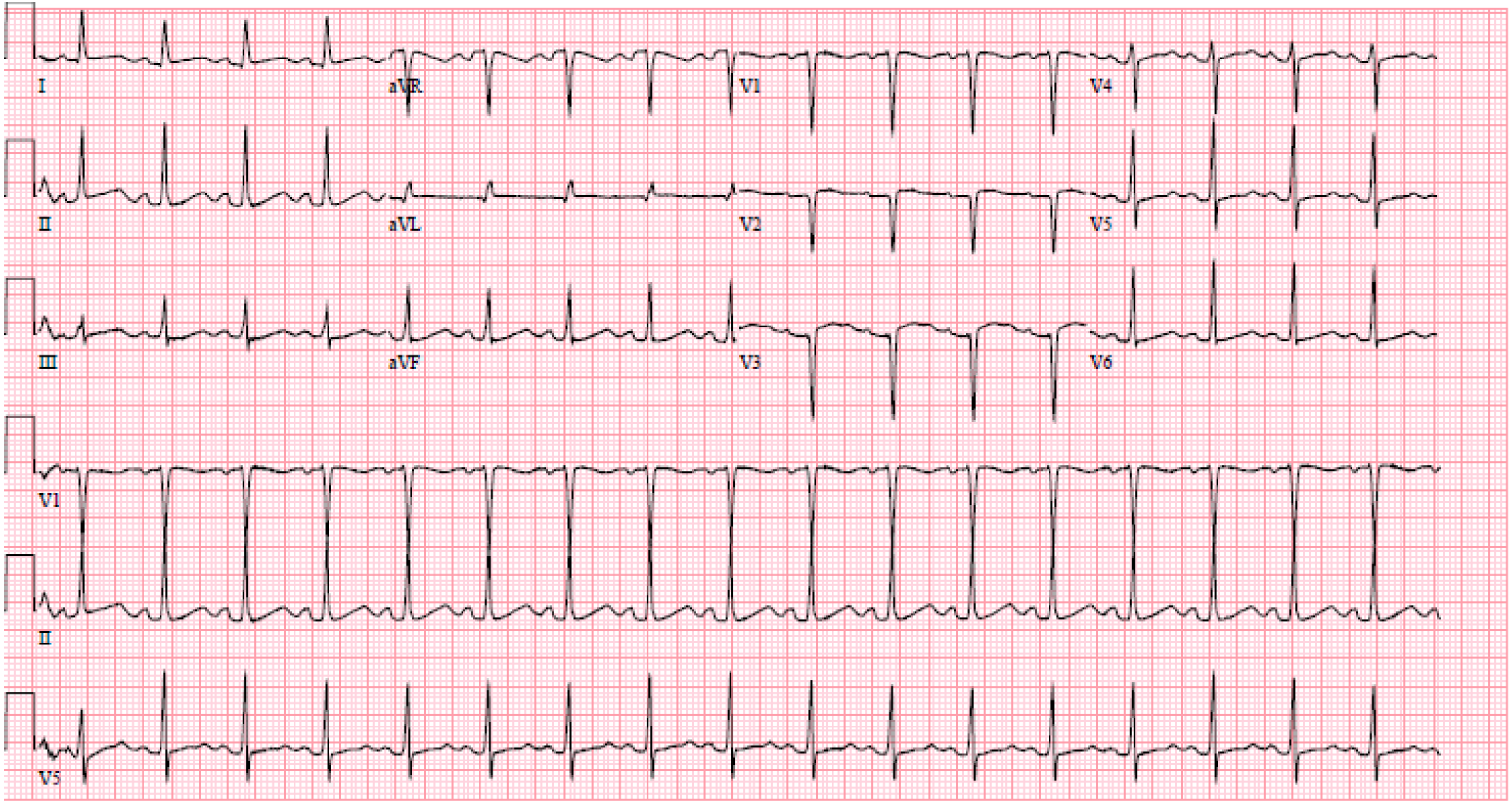
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ICU COURSE

- Maintained on sodium bicarbonate infusion for the next 24 hours
- No further seizure activity
- Extubated, sodium bicarbonate discontinued

Admits to intentional overdose, venlafaxine

TOXIDROMES

- We don’t know what they took, or when they took it.
- What findings point to a potential ingestion?
- What are the symptoms that best correlate with a poisoning?
- Identification of the specific agent (in most cases) may not change the clinical management.

HISTORICAL ELEMENTS

When was the ingestion?

What did they take?

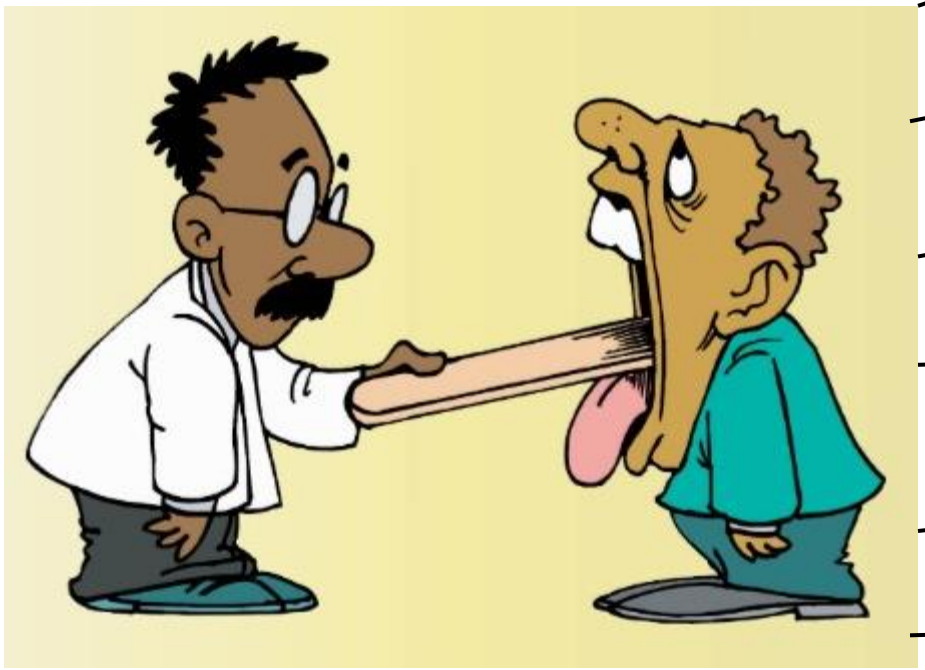
Co-ingestants?

Medications they have access to?

How did they get to the hospital?

History of prior attempts?

PHYSICAL EXAM



Mental Status

Pupils

Mucous Membranes

Bowel Sounds

Bladder

Clonus, reflexes

DIAGNOSTICS

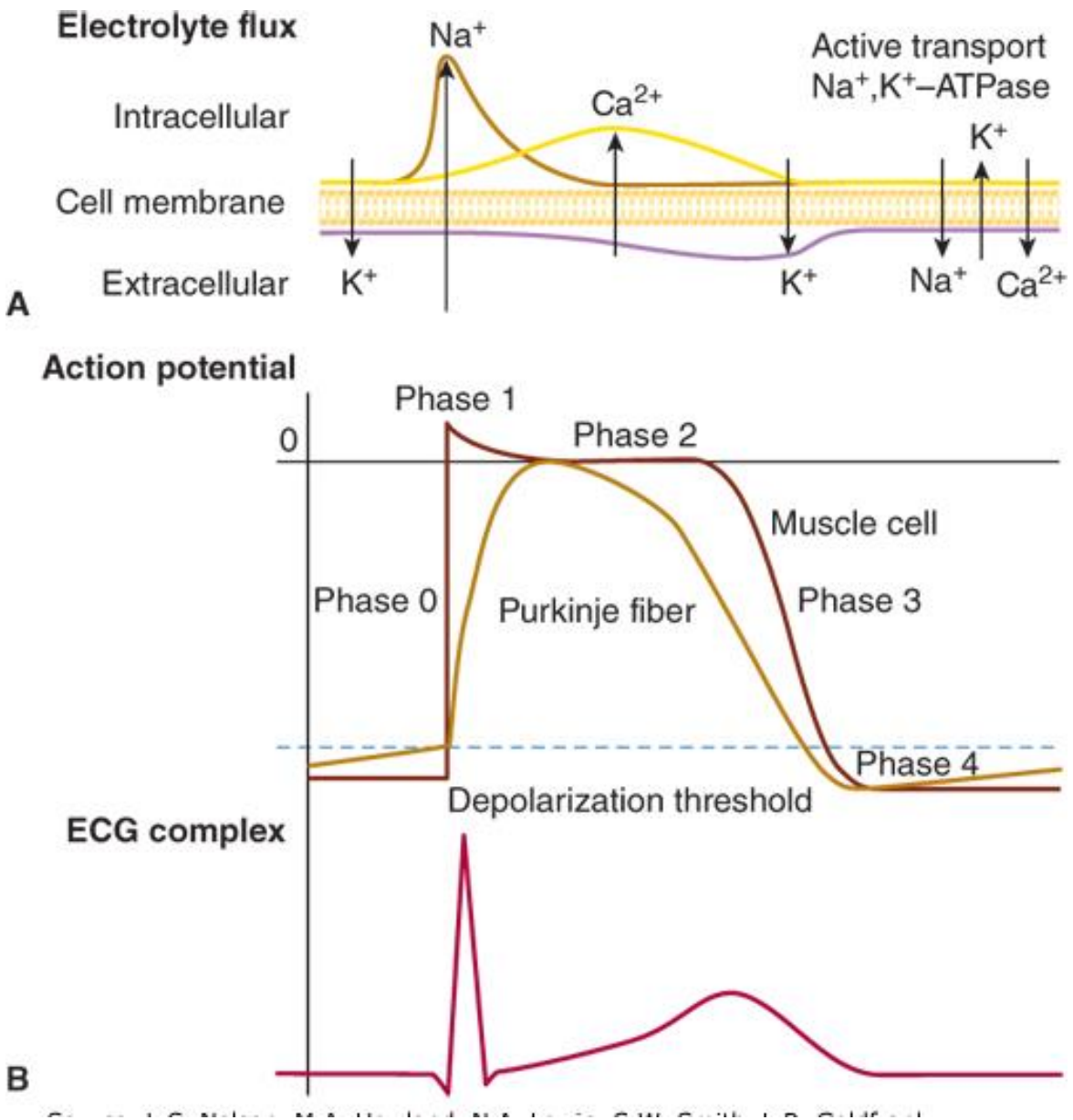
- CBC
- Chemistry
- Liver function
- Salicylates
- Acetaminophen
- Ethanol
- Ucg

- Fingerstick glucose
- EKG (rate, intervals)

THE TOXIC EKG

Na Channel: **QRS Complex**
- Antiarrythmic agents
- Tricyclic antidepressants
- Sympathomimetics (cocaine)
- Cathinones
- Hydroxychloroquine

Ca Channel: **QTc**
- SSRI/SnRI
- Calcium channel blockers
- Antipsychotics
- Antibiotics (macrolides, fluoroquinolones, penicillin combinations)
- Antiemetics



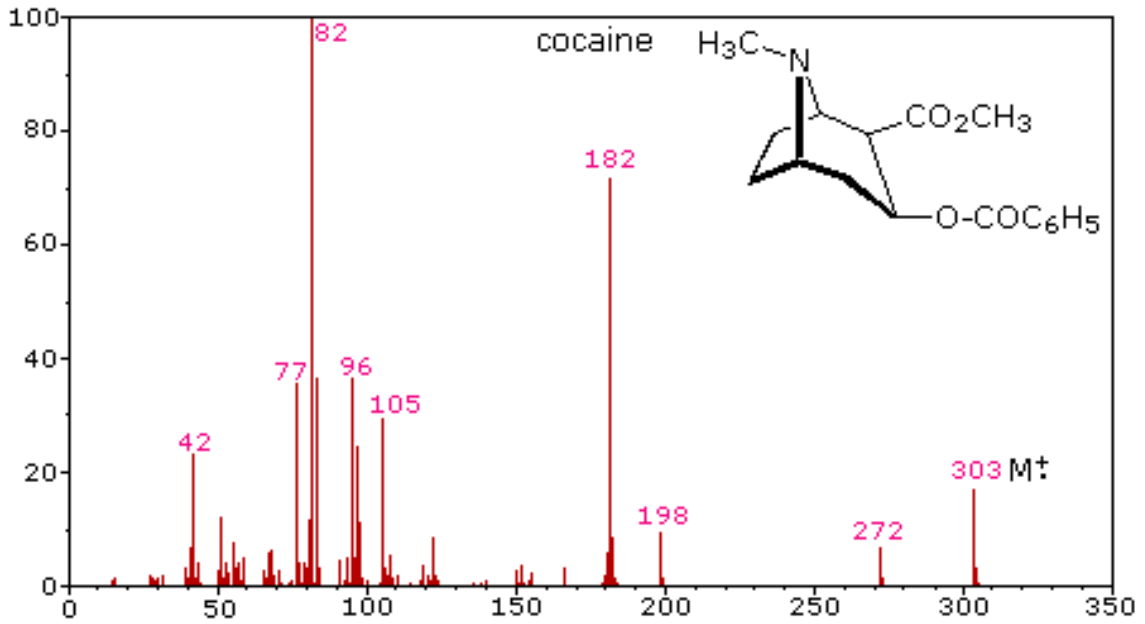
Nelson et al. Goldfranks Toxicologic Emergencies. 11ed. Chapter 15: Cardiologic principles. 2019.

DRUG SCREENING

- Drugs of abuse screening rarely changes clinical management
- Know the matrix you are testing
- Know the analytical technique and its limitations
  - Immunoassay (drugs of abuse screen, urine tox)
  - Confirmatory screening (GC/LC-MS/MS)

URINE DRUGS OF ABUSE

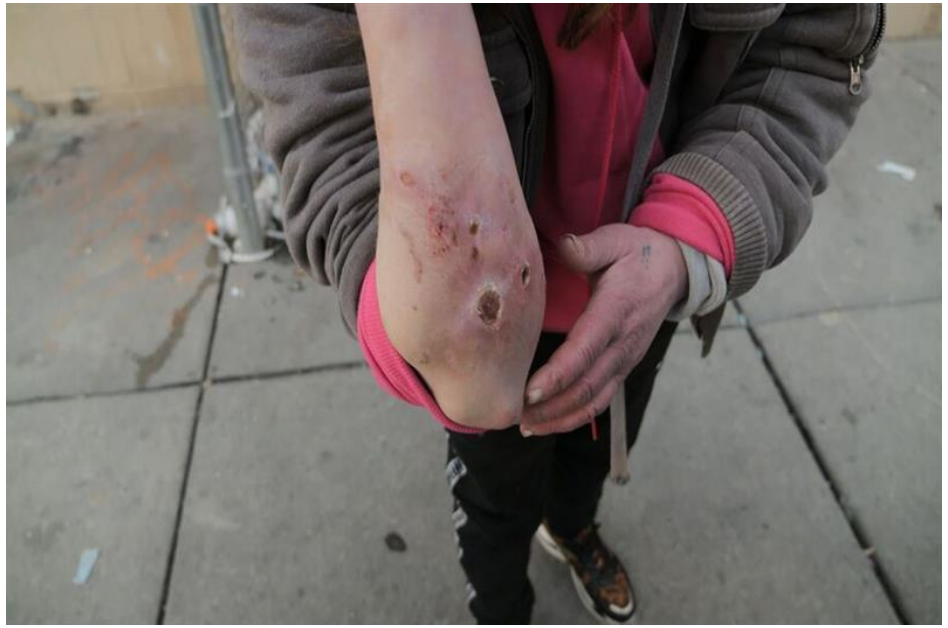
Initial Test Analyte	Federal Cutoff Concentrations (ng/mL)
Marijuana metabolites	50
Cocaine metabolites	150
Opiate metabolites (codeine/morphine[1])	2,000
6-Acetylmorphine (6-AM)	10
Amphetamines[2] (Amphetamine /methamphetamine)	500
Phencyclidine (PCP)	25
Methylenedioxymethamphetamine (MDMA)	500



US Department of Health and Human Services. Technical Assistance Publication Series: Clinical Drug Testing in Primary Care. 2012

CASE 1

- Patient being admitted to ICU with respiratory depression and poor GCS
- Found down, unable to get history
- Exam:
  - VS: afebrile, HR 60, RR 5, O2 93% on 4LNC, BP 110/75
  - Pinpoint pupils, cool skin, rash on arms



OPIOID TOXIDROME

- Coma, Respiratory depression, PINPOINT PUPILS, apnea (opioid receptor agonism)

- Antidote: Naloxone
  - Indications: RR<10 + clinical signs of opioid poisoning or loss of airway
  - Goal: restore respiratory drive

CASE 2

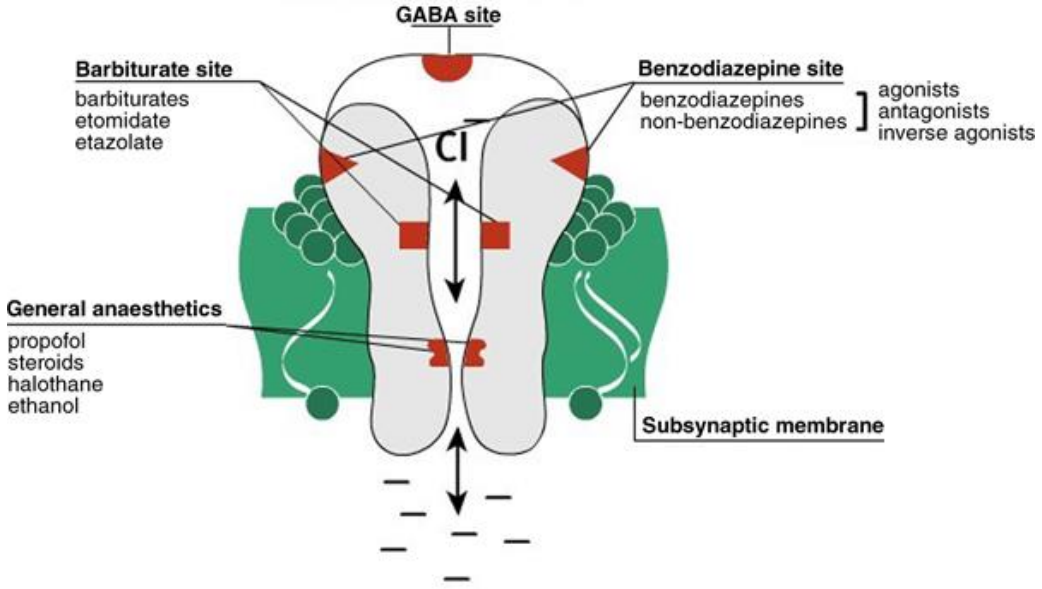
- 80yo patient admitted to inpatient medicine service is unarousable
- Sonorous respirations, new medication for sleep prescribed

- Exam:
  - VS: afebrile, HR 80, BP 110/75, RR 12, O2 93% 4L NC
  - Pupils 4mm, reactive, skin cool

SEDATIVE HYPNOTIC TOXIDROME

- Coma, Respiratory depression, NORMAL PUPILS, apnea

- Treatment: supportive care
  - Flumazenil: benzodiazepine antagonist
    - AE: seizures, dysrhythmias
    - Short half life and AE profile makes flumazenil suboptimal



Penninga et al. Adverse Events Associated with Flumazenil Treatment for the Management of Suspected Benzodiazepine Intoxication – A Systematic Review with Meta-Analyses of Randomised Trials. Basic and Clinical Pharmacology and Toxicology. 2015.

CASE 3

- 20yo male brought to ED by police
- Agitated, combative, restrained

- Exam:
  - VS: temp 105, hr 140, BP 180/90, RR 25, O2 Sat 100% RA
  - Pupils 8mm
  - Flushed skin, diaphoretic
  - Hyper-reflexia

SYMPATHOMIMETIC TOXIDROME

- Surge in sympathetic system: massive release of Dopamine, norepinephrine, epinephrine
- Amphetamines, cocaine, cathinones, ecstacy
- Fever, agitation, tachycardia, **ABSENCE OF CLONUS**

Treatment: Supportive care

- Active cooling (ice water)
- Benzodiazepines
- Manage rhabodmyolysis
- Anticipate washout syndrome

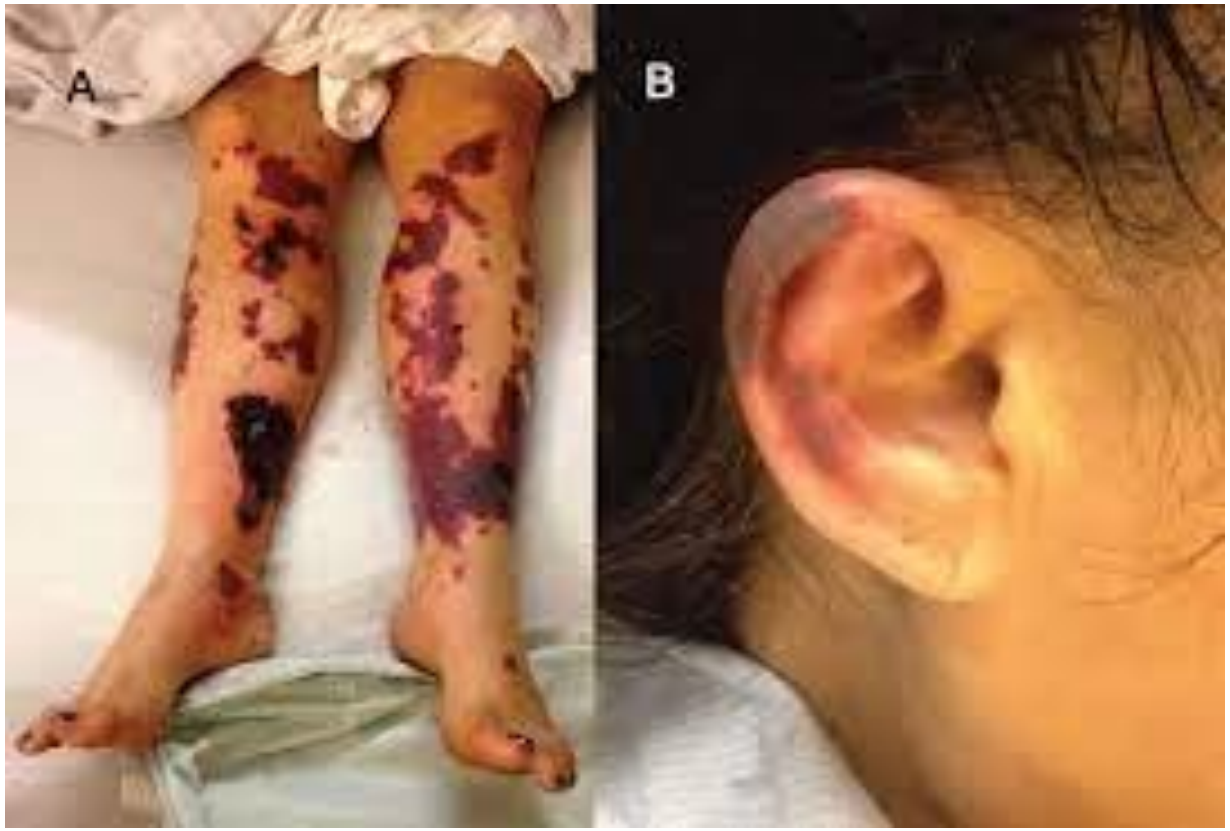
Laskowski et al. Ice water submersion for rapid cooling in severe drug-induced hyperthermia. Clinical Toxicology. 2016.

ASSOCIATED SYMPATHOMIMETIC

- Patient treated in ICU for sympathomimetic toxidrome
- Painful rash on admission
- Neutropenic, agranulocytosis

LEVAMISOLE INDUCED VASCULITIS

- Common adulterant in cocaine
- Anti-helmithnic
- Levamisole- dopaminergic
- Metabolite: Aminorex (amphetamine-like)



Hahn et al. Levamisole-induced vasculitis in a cocaine user. Journal of Rheumatology. 2015

CASE 4

- 20yo male brought to ED by police
- Confused, mumbling, picking at things in the air
- Exam:
  - VS: temp 100.9, hr 140, BP 180/90, RR 25, O2 Sat 100% RA
  - Pupils 8mm
  - Dry skin
  - Hyper-reflexia, distended bladder

ANTICHOLINERGIC TOXIDROME

- “anticholinergic delirium”

- Diphenhydramine, TCAs, antipsychotics
- Fever, agitation, **DRY SKIN**, **ABSENCE OF CLONUS**

Treatment: Supportive care
- Benzodiazepines
- Physostigmine (adverse event: seizures)

CASE 5

- 20yo male brought to ED after a suicide attempt
- History of depression, prior suicide attempts
- Diaphoretic, confused
- Exam:
  - VS: temp 98.6, hr 140, BP 180/90, RR 25, O2 Sat 100% RA
  - Pupils 8mm
  - Flushed, diaphoretic
  - Clonus

SEROTONIN SYNDROME

- Seven different subtypes of Serotonin receptors
- 5-HT 2A is most implicated in serotonin syndrome (ondansetron: 5HT3)
- SSRI/SnRI/psilocybin
- Antibiotics (linezolid, isoniazid, ritonavir)
- Opioids (meperidine, tramadol, fentanyl)
- dextromethorphan
- agitation, **DIAPHORESIS**, **CLONUS**

Treatment: Supportive care

- Benzodiazepines
- Fevers/severe agitation: paralysis
- Antidote: Cyproheptadine

CASE 6

- 50yo male history of schizophrenia admitted to medicine service for pneumonia
- Develops fevers, tremors. No other clear source other than his pneumonia

- Exam:
  - VS: temp 102, hr 120, BP 180/90, RR 20, O2 Sat 100% RA
  - Rigidity in extremities (lead pipe)
  - Upper and lower extremity tremors
  - Labs- WBC 30

NEUROLEPTIC MALIGNANT SYNDROME

- **Addition or withdrawal** of dopaminergic agents
- Patients with mental health, Parkinson's, dementia
- Rigidity (vs clonus), tachycardia, hyperthermia

Treatment: Supportive care

- Reintroduce inciting agent

CASE 7

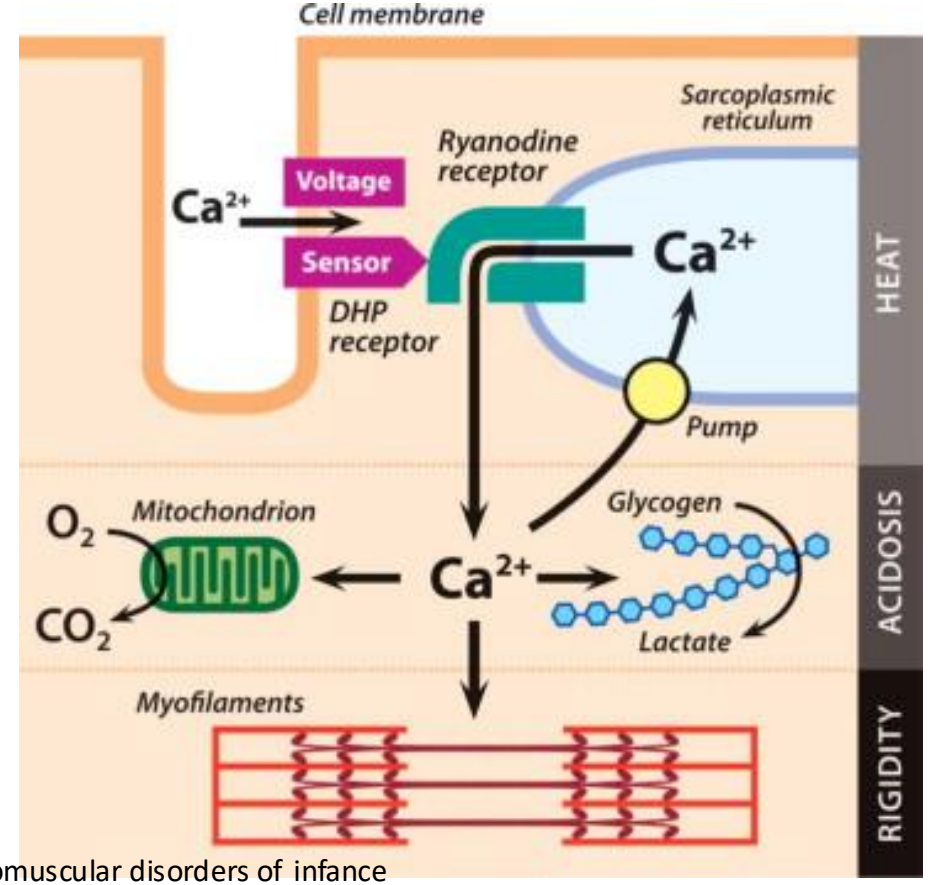
- 30yo female post op from uncomplicated cholecystectomy
- Family history of adverse reaction to anesthesia
- fevers

- Exam:
  - VS: temp 108, hr 120, BP 180/90, RR 20, O2 Sat 100% RA
  - Labs- WBC 30

MALIGNANT HYPERTHERMIA

- **Postoperative malignant fevers**
- Mutation in ryanodine receptor → prevents calcium influx into myosin
- Isometric muscle contractions leading to rhabomyolysis and fevers

Treatment: Supportive care
- Antidote: Dantrolene



Klinger et al. Malignant hyperthermia: an inherited disorder of muscle calcium metabolism. Neuromuscular disorders of infance

CASE 8

- 44yo male transfer from outside hospital, respiratory failure of unknown etiology
- Noted became acutely diaphoretic and nauseous, multiple episodes of emesis
- Brought to outside hospital, intubated
- Pre-intubation exam:
  - VS temp 98.6, hr 40, BP 150/90, RR 5, O2 Sat 100% 14L face mask
  - Flaccid extremities
  - Diaphoretic, pupils 4mm

CHOLINERGIC TOXIDROME

- Permanent blocking of acetylcholinesterase resulting in increased cholinergic tone
- Cholinergic agents (organophosphorous, weaponized OPs- sarin, VX, novichok) cause irreversible covalent bonding at acetylcholesterage
- Can also produce cardiotoxicity and delayed neurologic complications (OP-induced delayed neuropathy)

Treatment: Atropine, benzodiazepine, oximes

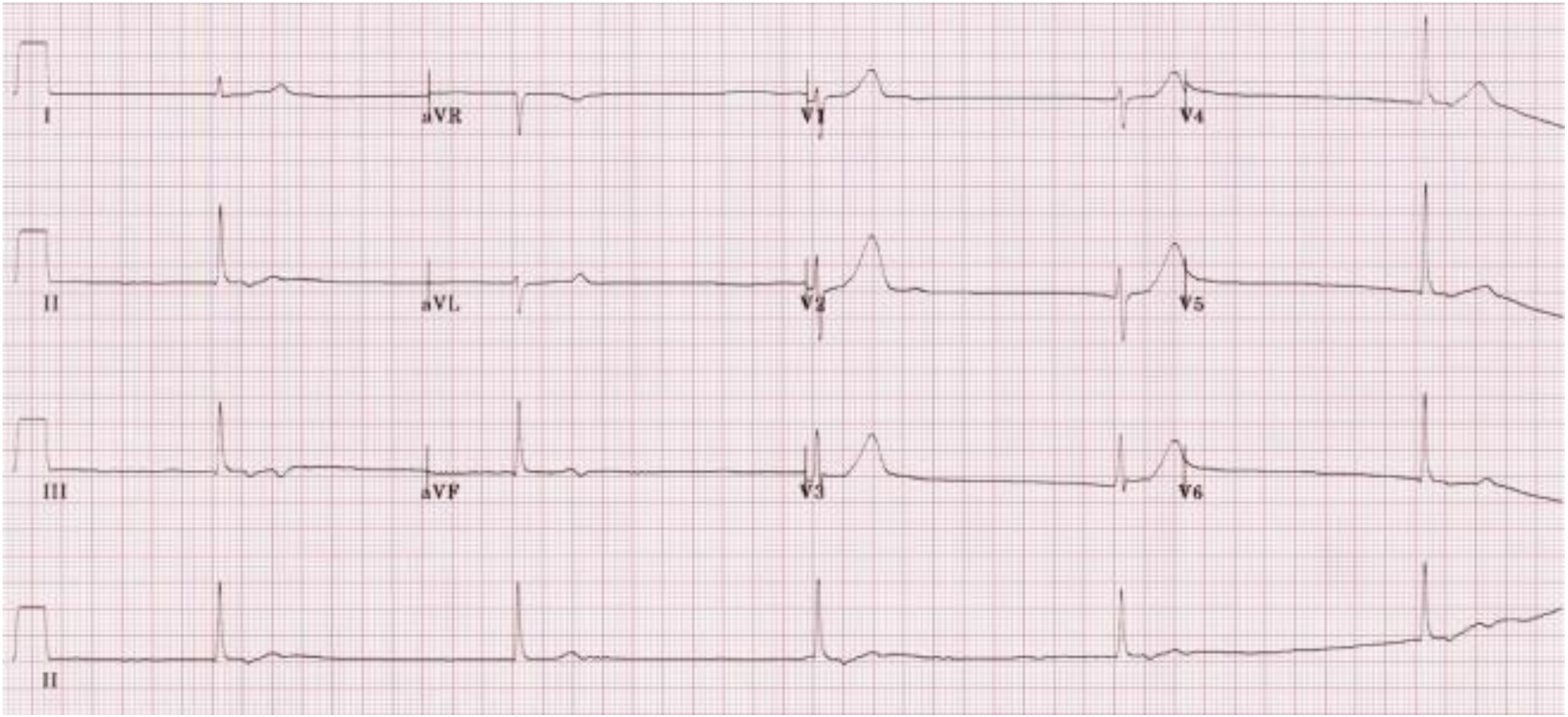
- Atropine: reverse bradycardia, dec secretions
- Benzos: antiepileptic
- Oximes: Prevent the aging process– must be given prior to onset of aging process

Steiindl et al. Novichok nerve agent poisoning. Lancet. 2021.

CASE 9

- 35yo male presents after a suicide attempt.
- Otherwise healthy, no medical problems.
- Calling because patient has developed bradycardia in ED

- Exam:
  - VS temp 98.6, hr 30, BP 150/90, RR 18, O2 Sat 100% RA
  - Awake, oriented x3, tearful about attempt
  - Strong peripheral pulses
  - Bedside blood glucose: 150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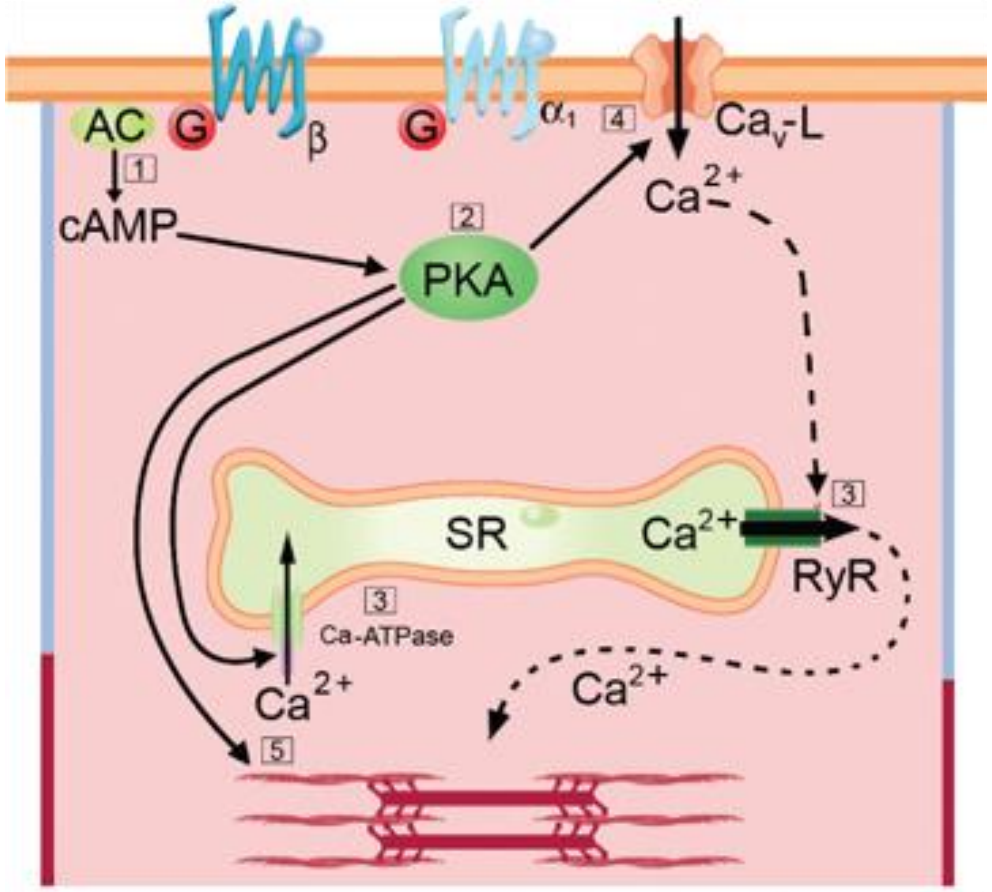
CALCIUM CHANNEL BLOCKER TOXICITY

- Recognize a toxidrome of cardiovascular toxins (calcium channel versus beta blocker)

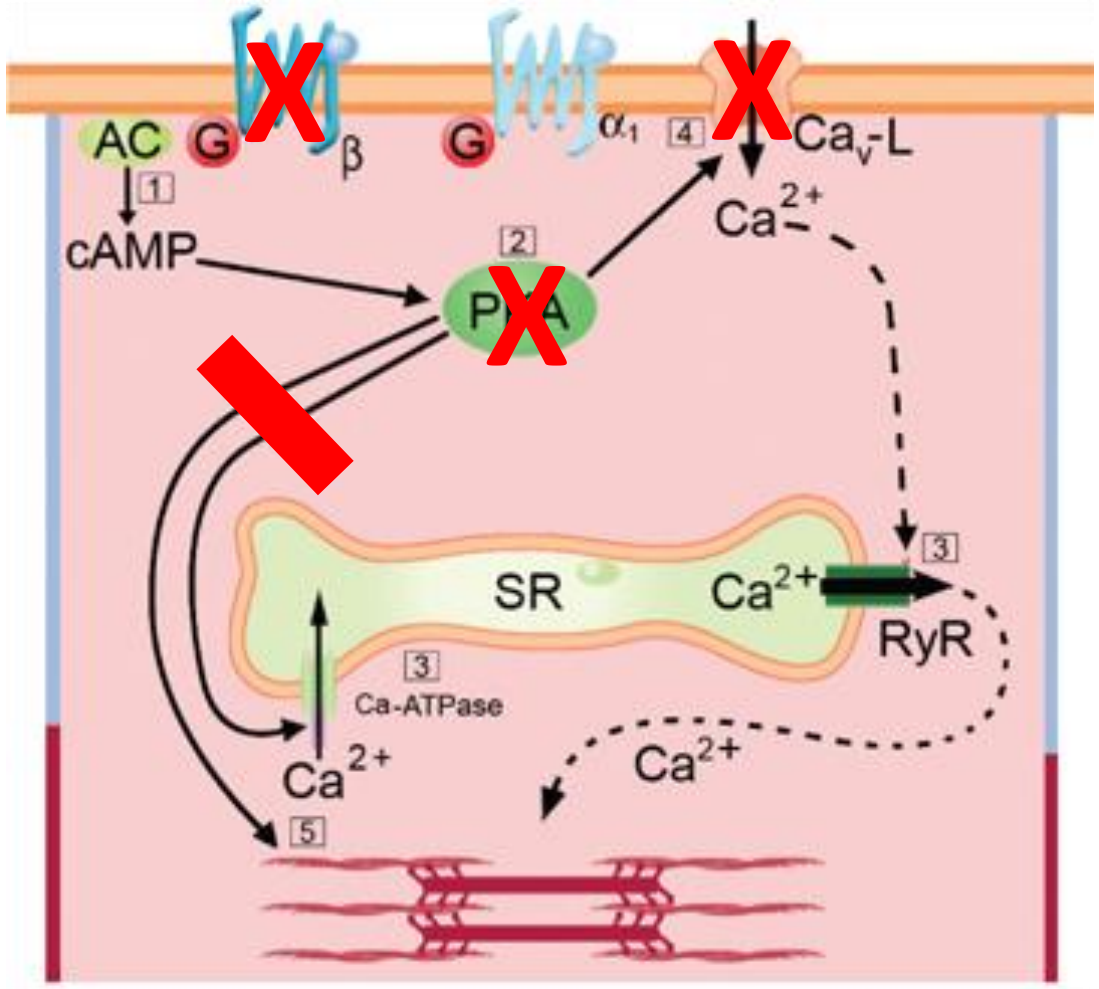


- Blunt ionotropy
- Decrease contractility
- Slow SA node discharge
- Blocks free fatty acid mobilization from fat cells

Goldfranks Toxicologic Emergencies 10th ed. Beta Adrenergic Antagonists.

CARDIOVASCULAR POISONS TOXICITY

- Blockade of beta receptor of Ca channel results in similar presentations



BRADYcardia

HYPOtension

Reliant on sympathetic tone to maintain above

HYPOglycemia (BB)

HYPERglycemia (CCB)

Goldfranks Toxicologic Emergencies 10th ed. Beta Adrenergic Antagonists.

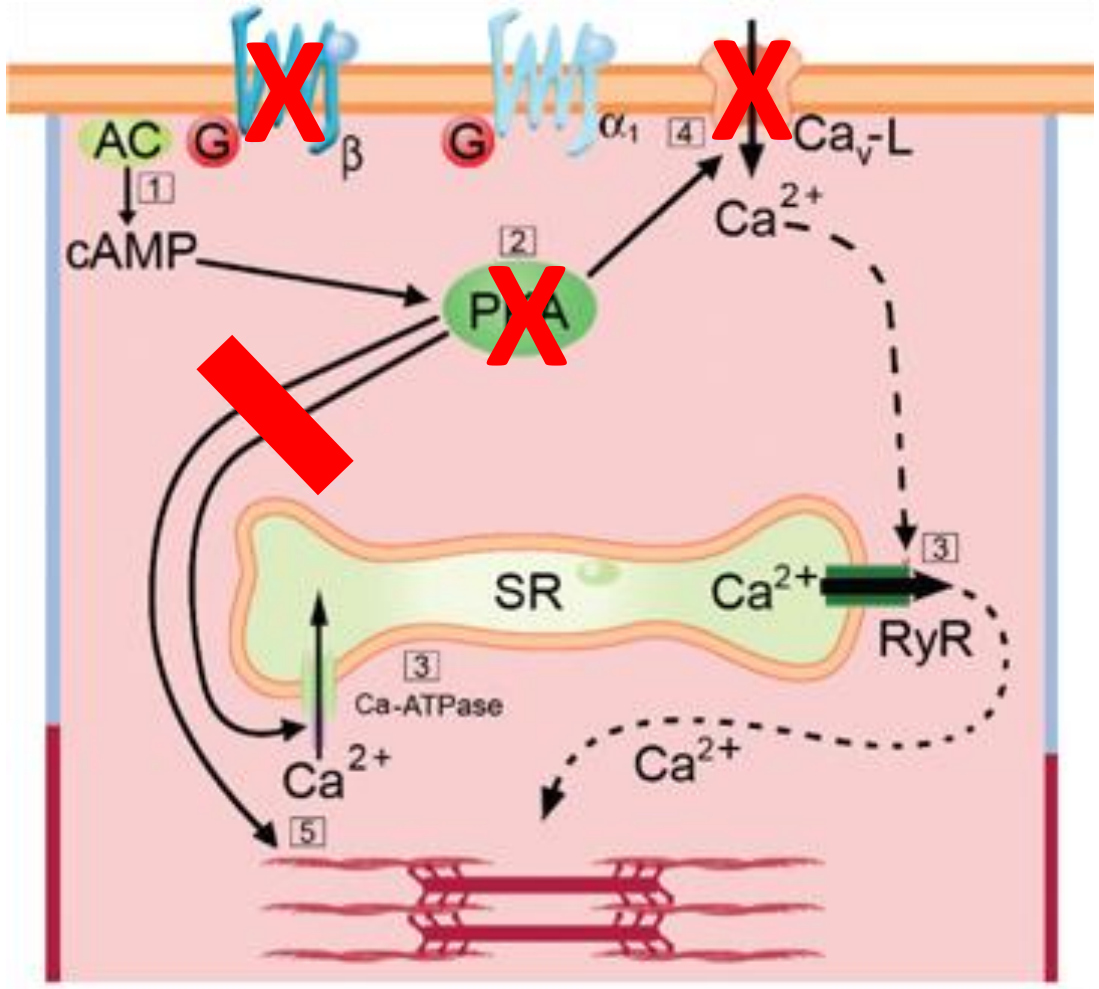
CARDIOVASCULAR POISONS TOXICITY

- Physical exam, bedside glucose

	Heart Rate	Blood Pressure	Mental Status	Blood Glucose
Calcium Channel	Decreased	Decreased	Normal	Hyperglycemia
Beta Blocker	Decreased	Decreased	Depressed, altered	Hypoglycemia

CARDIOVASCULAR POISONS TOXICITY

- Blockade of beta receptor of Ca channel results in similar presentations



- Calcium salts (overwhelm beta blockade)
- Intravenous lipid emulsion (free fatty acid energy source)
- High dose insulin euglycemia
- Mechanical support (ECMO)

Goldfranks Toxicologic Emergencies 10th ed. Beta Adrenergic Antagonists.

TAKE HOME MESSAGES

- Learn to recognize a constellation of symptoms and exam findings that lead to a toxidrome. Confirmatory testing is rarely needed or clinically useful.

- Bedside testing (EKG and glucose) can help differentiate between different xenobiotics.

TAKE HOME MESSAGES

	Heart rate	Resp rate	Blood pressure	Mental status	Skin	Reflexes
Opioid	Nml	Low	Nml	Dec	Nml	Nml
Sedative/hypnotic	Nml	Low	Low/nml	Dec	Nml	Nml
Sympathomimetic	High	High	High	Agitated	Diaphoresis	+
Anticholinergic	High	Nml	Nml	Altered	Dry	+
Serotonin Syndrome	High	Nml	Nml	Altered	Diaphoresis	+ (clonus)
NMS	High	High	Nml	Altered	Nml	Rigidity
Malignant Hyperthermia	Nml	Nml	Nml	Nml	Flushed	rigidity
Cholinergic	Low	Nml	Nml	Seizures	diaphoresis	Nml
Ion Channel (BB)	Low	Nml	Low	Sedated	Nml	Nml
Ion Channel (CCB)	Low	Nml	Low	Alert	Nml	Nml

Test your knowledge!

1) A patient is admitted to the ICU on a naloxone drip after a suspected opioid overdose. He presented with hypopnea and pinpoint pupils. His urine drugs of abuse screen returns negative for opiates. Describe the most likely reason:

a) The patient did not overdose on opioids, the presentation is more consistent with benzodiazepine overdose.
b) Naloxone neutralizes opioids on the urine drug of abuse screen.
c) The patient overdosed on opioids that do not react with the opiate immunoassay.
d) Another drug is the primary cause of the overdose.

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d) Another drug is the primary cause of the overdose.

Rationale: Opioid immunoassays test for metabolites of natural opiates (morphine derivatives). Remember to treat the presenting toxidrome given limitations of the laboratory test.

Test your knowledge!

2) A patient presents with bradycardia and hypotension after an intentional overdose. She is oriented, remorseful. On exam, she has strong radial pulses and a fingerstick of 250. EKG demonstrates junctional bradycardia. What is the causative agent and antidotal therapy?

a) Digoxin, DIGIFab
b) Beta blocker, glucagon
c) Calcium Channel blocker, hyperinsulinemia euglycemia therapy
d) Cocaine, benzodiazepines

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b) Beta blocker, glucagon

c) Calcium Channel blocker, hyperinsulinemia euglycemia therapy

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Rationale: This is clearly poisoning from a cardiovascular toxin. Remember the differentiation between calcium channel and beta blocker toxicity based on physical exam: strong pulses, preserved mental status and hyperglycemia in the setting of bradycardia and hypotension suggest calcium channel blockers.

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