Topics in Toxicology 2007

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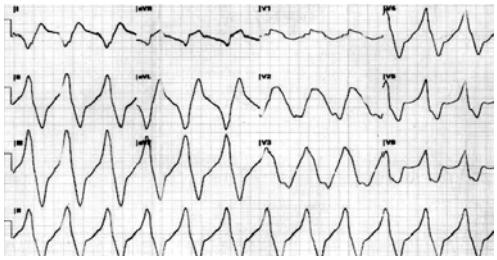
California Poison Control System

Case 1

- 74 yo female w/ dizziness, nausea
- PMHx: atrial fibrillation, hypertension
- Meds:
  - Digoxin
  - Fosinopril
  - Spironolactone
  - Hydrochlorothiazide
  - Recently added ibuprofen for joint pain
- BP 130/90 HR 75/min

ECG #1



(ECG from Parham WA et al Tex Heart Inst J 2006; 33:40-7)

You suspect: (choose one)

1. Acute myocardial infarction
2. Ventricular tachycardia
3. Hyperkalemia
4. Hypokalemia

Serum K = 7.4 mEq/L

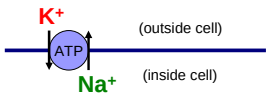
1. Acute myocardial infarction
2. Ventricular tachycardia
3. **Hyperkalemia**
4. Hypokalemia

Med list review

- Digoxin
- Fosinopril
- Spironolactone
- Hydrochlorothiazide
- Ibuprofen

Digoxin

- Vagotonic effects
  - Sinus bradycardia, AV block
  - Slows ventricular rate in atrial fibrillation
- Inhibits Na^+-K^+-ATPase pump
  - ↑ **extracellular K^+**



Fosinopril

- ACE inhibitor
- Reduces conversion of angiotension I → angiotension II
  - ↓ vasoconstriction
  - ↓ **aldosterone** – leads to ↓ **K^+ excretion**

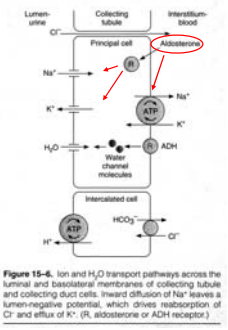


Figure 15–6. Ion and H_2O transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells. Inward diffusion of Na^+ leaves a lumen-negative potential, which drives reabsorption of Cl^- and efflux of K^+. (R, aldosterone or ADH receptor.)

Spironolactone

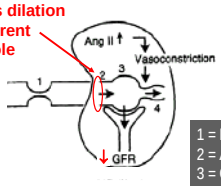
- Aldosterone inhibitor
  - ↑ reabsorption of K^+, excretion of Na^+
  - **Hyperkalemia**

Hydrochlorothiazide

- Diuretic, acting on distal convoluted tubule
  - Na^+ loss – accompanied by water (volume)
  - Some Na^+ reabsorbed in collecting tubule in exchange for K^+ excretion, *assuming aldosterone is functional*

Ibuprofen

blocks dilation of afferent arteriole



1 = Renal artery stenosis
2 = Afferent arteriole
3 = Glomerulus
4 = Efferent arteriole

NSAIDs block Prostaglandin E2 (which dilates #2) - ↓GFR

Summary – Meds and K^+

- Digoxin ↑K^+
- Fosinopril ↑K^+
- Spironolactone ↑K^+
- HCTZ decreases volume
- NSAID decreases GFR ↑K^+

Hyperkalemia and the heart

- Peaked T waves
- Reduced conduction speed
  - ↑ PR interval
  - ↑ QRS interval
- Depressed pacemaker activity
  - Loss of P waves
  - Asystole

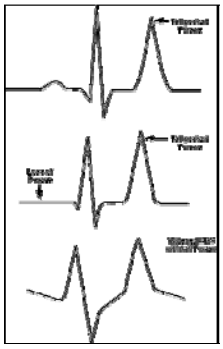
NOTE: poor correlation of ↑K^+ with ECG changes; low sensitivity / specificity
Ann Emerg Med 1991; 20:1229

ECG changes with ↑K^+

bad

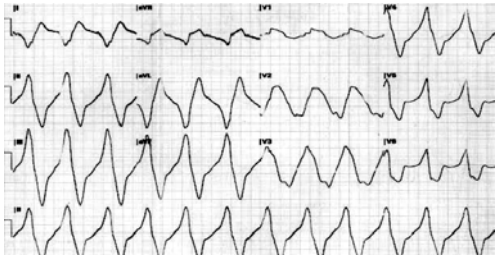
badder

baddest



From AFP 2006; 73:283

Another look at ECG #1



(ECG from Parham WA et al Tex Heart Inst J 2006; 33:40-7)

Case, continued

- Na^+ = 132
- K^+ = 7.4
- Cl^- = 100
- HCO_3 = 20
- BUN = 64
- Cr = 2.6

Treatment: first drug?

1. Kayexalate™
2. Sodium bicarbonate
3. Insulin + glucose
4. Calcium

Treatment: <u>first</u> drug?

1. Kayexalate™ – slowly removes K^+
2. Bicarbonate – redistribution (slow)
3. Insulin+glucose – redistribution (slow)
4. **<u>Calcium</u> – rapid physiological effect**

Calcium immediate benefits:

- Improves conduction in Purkinje system
- Restores pacemaker activity

Note: Ca^{++} does not remove K from the extracellular space or from the body

Case, continued

- You are about to give the calcium, when the lab calls: **serum digoxin = 3.2 ng/mL**

Does this change your plans?

1. Cancel the Ca^{++} order
2. Give the Ca^{++}

Okay, I should have added #3:

1. Cancel the Ca^{++} order
2. Give the Ca^{++}
3. **Give digoxin antibodies**

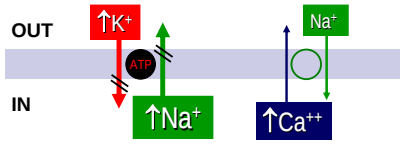
The Ca^{++} "stone heart" controversy

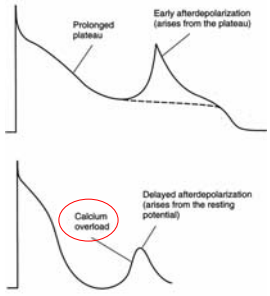
". . .in the presence of digitalis poisoning calcium may be disastrous, as intracellular hypercalcemia is already present."
[Goldfrank's Toxicologic Emergencies]

". . .any extra calcium will cause such an intense contraction that the heart will never relax (this is called 'stone heart')."
[Introduction to Emergency Medicine]

Digitalis glycosides

- Block Na^+/K^+-ATPase pump
- Increased intracellular Na+ reduces the driving force for the Na^+/Ca^{++} exchanger
- Ca^{++} accumulates inside of cell
  - Increased inotropic effect
  - Too much intracellular Ca^{++} can cause ventricular fibrillation, and possibly excessive actin-myosin contraction





Origin of "the controversy"?

JAMA 1936; 106:1151-3

THE ADDITIVE EFFECT OF CALCIUM AND DIGITALIS

A WARNING, WITH A REPORT OF TWO DEATHS

J. O. BOWER, M.D.
AND
H. A. K. MENGLE, M.D.
PHILADELPHIA

Bower's cases

- 32 yo F admitted with acute cholecystitis
  - Two days after surgery BP 90/50 and HR 100 with "extrasystoles" – digalen started
  - Day 6 post-op HR 120, "rapid and weak"
  - Two min after 10 cc IV Ca-gluconate she had a cardiopulmonary arrest
  - No reported K^+ or Ca^{++} levels

Bower's 2nd case

- 55 yo M w/ suspected hyperparathyroidism
  - R thyroidectomy – no PTH tumor found
  - Digalen "140 minims" given over 20 hrs [why?]
  - Two days post-op he developed tremor "diagnosed as beginning tetany"
  - Given Ca-chloride 10% IV --- 50 cc's !!
  - "Cardiac collapse," unable to resuscitate, no further info provided

What we DO know: (from animal studies)

- Very, very high calcium levels are bad
  - eg, serum levels 30-65 mg/dL
  - Ventricular fibrillation
  - Lowers the fatal digitalis dose
- Moderate hypercalcemia probably not bad
  - eg, serum levels up to 25 mg/dL
  - No difference in fatal digitalis dose compared with normocalcemic animals
- Low potassium levels increase risk of v. fib.

More recent animal studies

- *Acad Emerg Med 1999; 6:378*
  - No increase in the rate of dysrhythmias or mortality in guinea pigs treated with intravenous calcium for digoxin-induced hyperkalemia
- *Clin Toxicol 2004; 40:337*
  - No hastening of the time to asystole in pigs given a lethal dose of digoxin followed by calcium chloride 10 mg/kg (versus saline)

And where are all the case reports?

- *Ann Emerg Med 1997; 29:695*
  - 30-year Medline review unable to find any report of adverse effects after the administration of calcium to hyperkalemic patients with possible digoxin poisoning

Was the myth busted in 1939?

"Our experiments suggest that the danger of injecting calcium into the digitalized patient is simply that of injecting calcium into any patient with cardiac disease . . . certainly this danger cannot be great in practice, considering the widespread use of calcium intravenously. . ."

Smith PK: Arch Intern Med 1939; 64:322

To sum up:

- Calcium is *theoretically* dangerous in digitalis-intoxicated patients
  - But animal studies show danger only with extremely high Ca^{++} concentrations
  - 2 Human case reports lack details, unconvincing
- Calcium is the treatment of choice for severe *hyperkalemia* with serious ECG changes
  - *Give it if the patient has wide QRS, no P waves*
  - Some advise slower admin (eg, over a few min)

Another case

- 32 yo man ingests a large number of his antidepressant tablets and has a seizure
- Is lethargic in the ED
- HR 100/min BP 110/80
- ECG: normal QRS
- Tox screen (+) for amphetamines

Which one of the following is most likely involved?

1. Amitriptyline (Elavil™)
2. Sertraline (Zoloft™)
3. Methamphetamine (generic)
4. Bupropion (Wellbutrin™)

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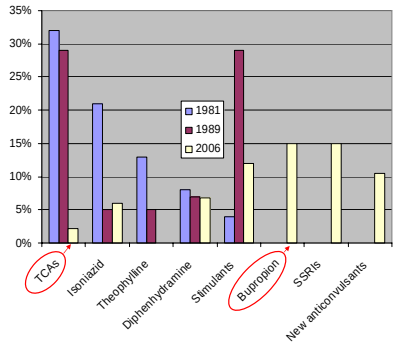
Bupropion

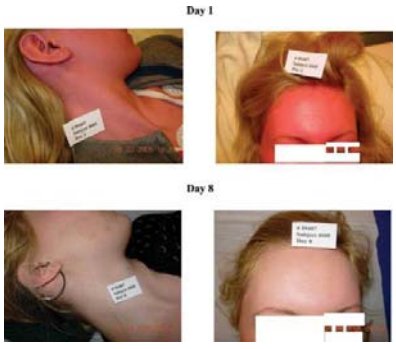
- Neurotransmitter effects similar to TCAs
  - Inhibits reuptake of NE, dopamine
  - No effects on serotonin reuptake
  - Not cardiotoxic (no QRS effects)
- Seizures common
- False positive tox for amphetamines

Calls to SF Poison Center about Drug-related Convulsions



Something Red

- 24 yo woman rescued from a smoke-filled apartment
- Lethargic
- HR 120/min BP 90/p RR 24/min
- Treated with 100% oxygen and a new antidote



from Clin Toxicol 2006; 14.17

The antidote was probably:

1. Hydroxocobalamin
2. Hyperbaric oxygen
3. Niacin
4. Leucovorin

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1. **Hydroxocobalamin**
2. Hyperbaric oxygen
3. Niacin
4. Leucovorin

Hydroxocobalamin (Cyanokit™)

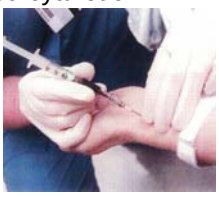
- Vitamin B12a
- Combines rapidly with cyanide to form cyanocobalamin = Vitamin B12
- Side effects
  - Red skin and body fluids ~ 2-7 days
  - Nausea, vomiting
  - Occasional hypertension, muscle twitching

Something Blue

- 69 yo woman undergoing transesophageal echocardiography for evaluation of cardiac thrombus prior to cardioversion
- PMHx: ASCVD, HTN, Type II DM, hyperlipidemia, obesity, and atrial fib.
- Meds: amiodarone, ASA, enoxaparin, glyburide, T4, metoprolol, niacin, rabeprazole, simvastatin, and warfarin

Case, cont.

- During the procedure oxygen saturation was measured at 90%
- After the procedure her pulse ox fell further and she appeared cyanotic despite 100% O2
- ABG: pO2 293



J Am Osteopathic Soc 2005; 105:381

What is the antidote?

1. 100% oxygen
2. Octreotide
3. Methylene blue
4. Naloxone

What is the antidote?

1. 100% oxygen
2. Octreotide
3. **Methylene blue**
4. Naloxone

Methemoglobinemia

- Oxidized form of hemoglobin
  - Unable to carry oxygen efficiently
  - Blood appears “chocolate brown”
- pO2 is normal (dissolved O2 unaffected)
- Pulse oximetry often 88-90%, even with severe MetHgb (eg, 50%)
- Treatment: ***methylene blue***

Causes of Methemoglobinema

- Many poisons and drugs
  - Any oxidant is a potential cause
  - Drugs: dapsone; sulfonamides; nitrites; phenazopyridine (Pyridium™); and some local anesthetics
- The patient had been treated with a topical anesthetic spray containing benzocaine

Case

- A 34 year old man is found unconscious, with resp. depression and pinpoint pupils
- He awakens rapidly after injection of IV naloxone 0.4 mg
- UTox “drugs of abuse” screen negative

Which of the following is likely to give a negative opiate UTox?

1. Codeine
2. Heroin
3. Morphine
4. Oxycodone

Which of the following drugs is likely to give a negative UTox?

1. Codeine
2. Heroin
3. Morphine
4. **Oxycodone**

Opiates vs. Opioids

- Opiates = derivatives of opium
  - Morphine
  - Heroin
  - Codeine
- Opioids = synthetic agonists at opioid receptors
  - Fentanyl, Dilaudid™, oxycodone, methadone

Opioids, cont.

- Methadone
  - Long half-life (20-30 hrs!)
  - Can see relapse 1-2 hrs after naloxone

Note: <u>some</u> urine drugs of abuse tox screens <u>will</u> include a special analysis for methadone . . . ask your lab

New Opioid

- Buprenorphine (Subutex™, Suboxone™)
  - Used in Rx of opioid-dependent patients
  - Longer duration of action
- Partial agonist and antagonist effects
  - Lower "ceiling" effect makes it less prone to abuse and safer in OD
  - Can cause <u>acute opioid withdrawal</u> Sx

See http://buprenorphine.samhsa.gov