Better Living Through Chemistry

Kurt C. Kleinschmidt, M.D.
Associate Professor of Surgery
Division of Emergency Medicine
Faculty, Section of Toxicology
University of Texas Southwestern Medical Center
Associate Medical Director, Emergency Department
Parkland Memorial Hospital
Dallas, Texas
The Plan

• Case based
  – Presentation
  – Pathophysiology
  – Diagnosis
  – Management

• Some of the common
Emergency Medicine Approach to a Patient

Chief Complaint → History → Physical → Ancillary tests → Differential Diagnosis → Treatment

Chest Pain

Heart Attack
Aortic Dissection
Pulmonary Embolism
Pneumonia
Pericarditis
Muscle strain

Pneumonia
Pericarditis
Muscle strain
Pulmonary Embolism
Heart Attack
Aortic Dissection

Muscle Strain
Emergency Medicine Approach to a Patient

• **How sure am I of my diagnosis?**
  – History 80%
  – Physical 90%
  – Ancillary tests 95%

• **EM providers are pessimists**

• **Sometimes we are given the diagnosis…**
  then must know what to do with it
Case 1

- **History:** 16 y/o male brought by his parents. Chief complaint is weakness; especially in his legs. Can’t stand up. Began this morning. Not feeling ill o/w.

- **PMH:** None

- **Medications:** None

- **Social History:** ∅ alcohol, tobacco, other drugs

Differential Diagnosis

- Muscle infection
- Stroke
- Trauma
- Thyroid problem

- Electrolyte
- Botulism
- Peripheral nerve
- Spinal cord problem
Case 1

- **Physical Exam**
  - HR 80 (60-100) RR 16 (16-20)
  - BP 110/70 Temp 97°F
  - Oxygen Saturation 98% (> 95%)
  - Diffusely weak with 3/5 strength
  - Facial muscles are normal strength
  - Coordination intact
  - Sensation intact
  - Muscles are non-tender
So then we got mom and dad out of the room... and talked some more

...and the rest of the story

- Sniffer
- Been doing more over recent weeks
- Last night was a big night...

Thus, suspect he is hypokalemic (Low potassium)

Potassium 2.4
Bicarbonate 15
Hypokalemic Periodic Paralysis

- Condition associated with low potassium
- Weakness is the usual presentation
- Toluene...a classic cause...
  - Common hydrocarbon solvent
  - Replaced benzene (ass with leukemia)
  - Paints, varnishes, glues
Toluene

- Highly fat soluble
- Highly volatile
- Stimulates gamma aminobutyric acid (GABA)…the primary CNS inhibitory neurotransmitter
- Inhibits glutamate NMDA receptors (a stimulatory neurotransmitter)
- Renal tubular effects
  - Acidosis
  - Loss of potassium
  - Chronic use causes leukoencephalopathy
Case 1 Conclusion

- Ensured he was breathing OK (ABC’s!!!)
- Admitted to hospital
- Potassium supplementation by intravenous route
- Good news…strength improved to normal
- Bad news…grounded for life
Case 2

- 17 y/o male comes home from an “evening out” with his buddies. He is agitated and confused. The buddies leave quickly and without explanation. Parental units bring him to the ER.
- PMH: None
- Medications: None
- Social History: Has used alcohol; Denies drugs
Case 2

Physical Exam

- Wide-eyed and agitated
- Confused, Hyper-religious
- Skin: Diaphoretic and warm
- HR 140
- RR 30
  - BP 220/120
  - Temp: 105°F
- Pupils: 6 mm (3-4 mm)
- Strength: Godzilla-like with all extremities

Differential Diagnosis

- Cocaine
- Theophylline
- Hypoglycemic
- Amphetamines
- Cold pills
- Psychodelics
- Caffeine
- Hallucinogens
Case 1

Impression

- Suspect drugs
  - Cough & Cold medicine abuse
  - Amphetamine-like (Ecstasy)
  - Cocaine
  - Doubt caffeine or theophylline
- Check glucose level
- Complications of the sympathomimetic state
  - Hyperthermia
  - Rhabdomyolysis
    - (Muscle breakdown → Myoglobin release → Kidney failure)
  - Seizures
  - Stroke
Epinephrine
Norepinephrine
first messenger
receptor
transducer amplifier
second messenger

Postsynaptic Membrane
Monoamine Receptor

G protein
adenylate cyclase
cAMP
Phenylethylamine Structures

- Phenylethylamine
- Epinephrine (Adrenaline)
- Amphetamine
- Ephedrine
- 3,4 methylenedioxymethamphetamine (MDMA) (Ecstasy)
- Phenylpropanolamine
Alpha
Vasoconstriction
↑ Urethral tone
Mydriasis
Diaphoresis

Beta
Vasodilation
Intestinal Relaxation
Uterus Relaxation
Bronchodilation
Glycogenolysis
Tachycardia
Heart Contractility
Lipolysis
The Limbic System of the Brain

- **Components:**
  - Limbic lobes w/ Diencephalon, hemispheres
  - Ant. Nucleus of thalamus
    - Amygdaloid nucleus
    - Hypothalamus (Temperature Regulation)

- **Effects:**
  - Emotions (Fear, Excitement, Anger, etc)
  - Memory
  - Visceral brain (autonomic effects)
The Limbic System
Effects: Emotions (Fear, Excitement, Anger, etc) & Psychosis

Dopaminergic  Cholinergic

The desired balance...

Dopaminergic  Cholinergic

Dopa (Monoamine) Excess…
...Psychosis…
...like Schizophrenia

Dopaminergic  Cholinergic

Dopamine much less
…Anti-Psychotic Med effect
…Parkinson’s Syndrome
Cocaine

- Not a monoamine
- Pathophysiology
  - Uptake ↓ of monoamine neurotransmitters
  - → ↑ Dopamine → Psychostimulant
  - Vasoconstrictor
  - CNS stimulation
  - Excitatory amino acids i.e. glutamate
- Clinical Effects
  - Sympathomimetic effects
  - Agitation (↑ Temperature)
  - Muscle damage (Rhabdomyolysis)
Amphetamines

- Phenylethylamine derivatives
- Pathophysiology
  - Monamine Release ↑
  - Monoamine Reuptake ↓
  - Limbic effects prominent
- “Designer” Amphetamines big in 1980s
  - First done to avoid the law
  - MDMA / Adam / Ecstasy now a “rave” favorite
- Methamphetamine
  - Easy to make; Low cost
  - Most common illicit drug made in “labs” in the US
  - “Ice” is a high purity, crystalline form
MDMA (Ectasy, Adam)

ICE (Pure Methamphetamine)
Dextromethorphan

- D-isomer of codeine analog
- Anti-tussive in many OTC cough medications
- No analgesic or CNS effects at therapeutic doses
- Other effects…
  - ↑ serotonin (a monoamine) release
  - Affects NMDA receptor at PCP site
    - Hallucinations
  - Sigma receptor → Psychotomimetic symptoms
    (hallucinations, Delusions, Dysphoria, Depersonalization, Emotion lability)
- Toxicity: Hyperexcitable, lethargy, ataxia, seizures, diaphoresis, HTN, nystagmus, dystonia,
Cold Medicines

- **“Decongestants”**
  - Pseudoephedrine; phenylpropanolamine
  - Not commonly done

- **Antihistamines “Allergy” meds**
  - Older antihistamines are in the “combination” cough and cold medicines
  - Anticholinergic effects
    - Delerium
    - Dry skin (Can **not** sweat)
Cough and Cold Medications
• 17 y/o male
• Wide-eyed and agitated
• Confused, Hyper-religious
• Skin: Diaphoretic and warm
• HR 140 RR 30
  BP 220/120 Temp: 105°F
• Pupils: 6 mm (3-4 mm)
• Strength: Godzilla-like with all extremities

With all the different drug possibilities…
how do I know which one is the problem, and
thus how to treat him?
Case 2  Diagnosis: Drug Screens

- **Gas Chromatography / Mass Spectrometry**
  - Detailed to the very specific drug
  - Expensive
  - Long time to do…

- **Urine “Tox Screen”**
  - Common
  - Relatively inexpensive
  - Tells if a drug “class” is present
  - Limited “sensitivity” and “specificity”
  - Still takes an hour to do!!!
Case 2   Treatment

It does not matter exactly which drug it is!!!

Treat...

• **Symptoms**
  – Agitation
  – Sympathetic
    • Fast Heart Rate
    • Hypertension

• **Complications**
  – Hyperthermia
  – Muscle breakdown → Renal Failure
Case 2  Treatment

• Hyperthermia
  – Stop new heat production (Agitation)
  – Cool him off…
    • Ice baths
    • Fans
    • Not acetaminophen or aspirin
    • Avoid medicines that affect body temperature regulation

• Muscle Breakdown
  – Aggressive IV fluids to keep urine output up
Case 2     Treatment

Benzodiazepines (i.e. Valium)

- Affects CNS (which → periphery)
- Mechanism: ↑ Gamma-aminobutyric acid (the #1 CNS Inhibitory neurotransmitter)
- Decreases
  - Agitation
  - Heart Rate
  - Blood Pressure
- Aggressive use i.e. every five minutes until patient’s agitation is stopped
- If overuse, can make patient stop breathing
Case 2  Closure

- Agitation resolved and temperature decreased
- Patient awoke and was normal
- The rest of the story...
  - Had been to a “little party”
  - Used Ecstasy
  - Promises he’ll never do it again
  - Grows up and becomes…?
Case 3

- 15 y/o girl brought in after overdosing on Tylenol. Took a bottle. Occurred 8 hours ago. She has no complaints.
- PMH: Nothing
- Medications: Nothing
- Physical Exam:
  - Awake and alert
  - Vital signs are normal
  - Abdomen is normal
Acetaminophen

- Most commonly used analgesic medicine
  - Effective
  - Safe when used properly
- Common overdose
  - Available
  - Danger of it are not well known
- More hospitalizations with it than any other agent
- Liver toxin in overdose
  - Liver failure
  - #1 cause of need for liver transplant
  - Death
Acetaminophen

P450 Metabolism

Acetaminophen Urine (5%)
Acetaminophen Glucuronidation (45%)
Acetaminophen Sulfation (45%)

Glucuronidation
Sulfation

NAPQI (5%)

Glutathione

Non-toxic Metabolites

Liver Toxicity

Overdose

Acetaminophen Metabolism

Overwhelm the glucuronidation and sulfation pathways.

NAPQI production increased

Glutathione is rapidly depleted

Liver toxicity occurs
Acetaminophen Treatment

• Get it out of the stomach
• Get it through the intestines so fast that little is absorbed
• Decrease the absorption into the body from the intestines
• Prevent the effects
• Heal the injury that already exist
Acetaminophen Treatment

- Get it out of the stomach
  - Syrup of Ipecac → Vomit
  - Gastric Emptying (Hose down into stomach)
  - But...these have not been shown to change clinical outcomes (deaths, hospital length of stay)
- Get it through the intestines fast; little is absorbed
  - Sorbitol; Magnesium Citrate
  - No change in clinical outcomes
Acetaminophen Treatment

- Decrease the absorption into the body (Charcoal)
  - Decreases absorption a statistically significant amount
  - But no change in clinical outcomes
  - It has its own complications (Risk / Benefit Ratio)
    - Aspiration
      - Turn a benign OD into a 3 week hospital stay
    - Could absorb an antidote
- Our approach
  - Using much less than we used to
  - Educate other physicians as to our concerns
Acetaminophen Treatment

- Prevent the effects
- Heal the injury that already exist

An Antidote
Antidotes

- Very few exist
- Most “poisonings” are treated with supportive care
- Some antidotes more dangerous than the “poison”
- Ideal Antidote
  - Safe
  - Effective
  - Inexpensive
  - Easy to use by the nurses
  - Easy to take by the patient
Acetaminophen Antidote

N-Acetylcysteine (NAC)

- Safe ✓
- Effective ✓
- Inexpensive ✓
- Easy to use by the nurses ✓
- Easy to take by the patient ±
Acetaminophen metabolism and treatment:

- **P450 Metabolism**

- **Glucuronidation (45%)**

- **Sulfation (45%)**

- **NAPQI (5%)**

- **Liver Toxicity**

- **NAC**

- **Glutathione**

- **Urine (5%)**

- **Non-toxic Metabolites**

- **N-Acetylcysteine (Sulfur containing)**

Acetaminophen treatment with NAC (N-Acetylcysteine) for liver toxicity.
Does Every Acetaminophen Overdose Get NAC?

- No... Decision is based on...
  - Time of presentation
  - Acetaminophen Level in the blood
  - Single exposure of over a period of time (Chronic)
The Acetaminophen Nomogram

Single, acute overdose
Original Work:
200 was “toxic” at 4 hrs
USA: Fudge Factor
(150 is “toxic”)

Our patient’s 8 hour level
175 mcg/mL
Case 3

- Started NAC therapy while in the ER
- Checked Liver function tests
- Admit to hospital
- Psychiatric evaluation