Drops, Ointments, Creams, and Patches: Be Careful!

Most clinicians are unaware of the potential toxicity of pharmaceutical agents delivered by non-traditional pathways. This presentation will highlight some of the more dangerous products (e.g. drops, salves, ointments, and patches) available that have proven toxicity in children.

OBJECTIVES
- Identify the toxicity of pharmaceutical agents administered topically
- Recognize the symptoms and signs of these agents and their antidotes if appropriate

3/24/2015
9:00 AM-9:30 AM
Grand Ballroom
TU-2

DISCLOSURES:
(+) No significant financial relationships to disclose
Drops, Ointments, Creams, and Patches: Be Careful!
(as if we didn’t have enough to worry about!)

Richard M. Cantor, MD FAAP/FACEP
Professor of Pediatrics and Emergency Medicine
Director, Pediatric Emergency Services
Medical Director, CNY Poison Control Center
Golisano Children’s Hospital
Syracuse NY

Children Keep Poison Centers BUSY!

Children account for 65% of all calls to Poison Centers

BUT luckily only represent 6.9% fatalities

Top 5 Substances in Less Than 5 Year Olds

- Cosmetics/Personal Care Products
- Analgesics
- Household Cleaning Substances
- Foreign Body/Toys
- Topical Preparations
ONE Dose IS Enough!

- Oral hypoglycemics
  - Sulfonylureas & “Glitinides”
- TCA’s
- Clonidine
- Opioids
- Methylsalicylate
- Visine

- Calcium Channel Blockers
- Beta Blockers
- Antidysrhythmics
- Ethylene glycol
- Methanol


Keep The Cap On Please
Case

- 18 month old found by parent with an opened tube of Dibucaine 1% Ointment
  - 30 gram previously used tube
  - Approximately half of the tube remains
  - Estimated dose 12-13 mg/kg
- 45 minutes later began seizing


Upon ED Arrival

- Unresponsive
- No further seizure activity
- Vital signs
  - Temp 97 F (rectally)
  - HR 100
  - BP 103/50
  - Fingerstick 214 mg/dL
- Physical Exam
  - Non-contributory
  - No cyanosis
Therapeutic Interventions
- Sodium bicarbonate boluses 1 mEq/kg x 3 given
- Sodium bicarbonate infusion started
- Magnesium 50 mg/kg IV given for prolonged QTc

Repeat ECG
- QRS complex narrowed
Amide Local Anesthetics

- Sodium channel blockers preventing neurons from reaching threshold
  - Class Ia
- Well described CNS and Cardiovascular toxicity
  - Seizures
  - Conduction delays
  - Wide QRS complex
  - Vasodilatory effect
Dibucaine

- Considered one of the most potent and toxic amides
- Injectable form removed by the FDA due to toxicity
- Available as an over-the-counter topical preparation
- Toxic human doses not well defined


Reported Dibucaine Fatalities

- 18 month old estimated ingestion of 150 mg (15 mg/kg) of 1% ointment
  - Seizures; wide-complex bradycardia; hypotension; ventricular tachycardia; asystole
  - Died 7 hours after ingestion

- 2 year old male unknown quantity of 0.5% cream
  - Seizures; supraventricular tachycardia
  - Died 1 hours after arrival to ED

- 21 month old female ingested ¾ of 1-ounce tube (19 mg/kg) of 1% ointment
  - Seizures; Wide-Complex bradycardia; hypotension; cardiac arrest (resuscitated); ventricular fibrillation
  - Died 3 hours after ingestion

Treatment

- Benzodiazepines
- Sodium Bicarbonate
- Lidocaine?
- **20% Fatty Acid Emulsion**

Lipid Emulsion

  Cardiac arrest after bupivacaine; failed ACLS for 20 minutes; successfully resuscitated after intralipid

- Litz et al Anaesthesia. 2006 Aug;61(8):800-1
  Cardiac arrest after ropivacaine; drowsiness and dizziness followed by cardiovascular collapse; failed ACLS for 10 minutes; successfully resuscitated after intralipid

- Whiteside J. Anaesthesia 2008; 62:203-204
  Seizures after lumbar plexus block with bupivacaine; Intralipid administered with seizure termination almost immediately
Lipid Emulsion

- When and How?
  - Cardiotoxicity (?CNS toxicity) from local anesthetics
  - Refractory cardiovascular collapse
    - Lipophilic toxin
    - Sodium Channel Blocking agents
    - Calcium Channel Blocking agents

- 100 mL of 20% intralipid BOLUS (1-2 minutes)
- 0.25-0.5 mL/kg/min of 20% intralipid for 2 hours

Case Continued

- Patient remained hemodynamically stable
- Was transferred to PICU
- Was extubated within 8 hours and following commands
- Discharged to home < 24 hours after presentation
Just Under The Radar

History

- A 6 month old infant arrives with a chief complaint of *gradual onset of ashen color over 1 day*

- Has been well of late without fever, intercurrent illness or exposures

- Insignificant PMH

- No one is ill at home
Physical Examination

- Vital Signs
  - T 37°C, HR 140, RR 60, BP 90/46
  - OSAT 87% (in Room Air)

- General
  - Plump, drooling, cyanotic infant

- Chest
  - Lungs clear
  - No murmur

- Neck
  - Supple

- Chest
  - PMI normal, no murmur
  - Clear lungs

- Abdomen
  - Hyperactive bowel sounds

- Rectal
  - Watery guaiac neg stool
Physical Examination

- Pulses
  - *Fair*
- Extremities
  - Full ROM
- Neurologic
  - Non focal lethargy
- Skin
  - *Cap refill < 2 seconds*

Define the symptom complex

- Hypoxia
- Ashen color
- Good perfusion
- No real PMH
Establish a Framework for Investigation

- Cyanotic presentation?
- Cardiac studies
- Pulmonary workup
- Other

Intervention/Response

- OSAT 87% in room air
  - 87% in 100% O2
- CBC, U/A, CXR normal
- ABG in 100% O2
  - pH 7.33 pCO2 35 \(\text{pO2 300 (OSAT 88%)}\)
Blood On The Tracks

What is Methemoglobinemia?

- The conversion (oxidation) of iron in the heme moiety from ferrous to ferric state, rendering it incapable of binding oxygen
  - Fe++ → Fe+++
Etiologies of Methemoglobinemia

- Nitrates
  - Amyl Nitrate
  - Nitroglycerin
  - *Infectious Diarrhea* *(beware of rotavirus!)*
- Benzocaine/Lidocaine
- Quinone
- Sulfonamides
- Napthalene

Treatment

- Mild cases: Remove offending agents + supplemental oxygen
- Level >30%: *Methylene blue*
  - Intravenous: 1-2 mg/kg over 5 minutes
  - May repeat dose within one hour
  - *Contraindicated* in G6PD Deficiency
Case Progression

- Methemoglobin level = 30
- Received mehylene blue over 8 hours
- **Offending agent**

A Case of Misdirection
Case 4

- 5 year old male is found unresponsive by his father
- On arrival to the ED, the patient was cyanotic, apneic and asystolic
- Aggressive PALS protocol
- Had 3-4 episodes of asystole at outside facility
- ECG after resuscitation
  - Sinus rhythm
  - QTc prolonged

HPI

- Usual state of health
- Nondiscript viral illness the day or two prior
- Went to the park at 4pm with friends
- Took a 4 hour nap that evening
- Woke up and was very sleepy; ate a ‘few french fries’ and went back to bed for the night
- Found the next morning unresponsive and had wet the bed
- Grandmother had used lindane either the night prior or two nights prior
Case Progression

- Transferred to PICU
- On arrival to the PICU
  - Intubated
    - unresponsive and not requiring sedation
  - Vitals: HR 130 bpm; SBP 70 mmHg
  - Fixed and dilated pupils
  - Retinal hemorrhages

Case Progression

- Laboratory Results
  - At outside facility
    - pH 6.00/30/120 (during cardiac arrest)
    - Urine toxicology: negative
    - APAP/ASA/EtOH: negative
  - At PICU
    - VBG: 7.28/46/26
    - 144/3.5/101/18/34/1.4; gluc 281; Ionized Ca 1.03
    - Lactate 7.7 mmol/L
    - ALT 574; AST 760; INR 2.31; CK 4472
Case Progression

- Head CT: Excessive cerebral and cerebellar edema with uncal herniation
- Support withdrawn; patient expired at 1630 on day of presentation

Lindane

- Organic chlorine pesticide
- Topical scabicide
- Kwell®
- Well absorbed dermally
- GABA Antagonists
  - Seizures are generally self-limiting
Case Continued

- Autopsy Results
  - *Fentanyl level = 10 mcg/L*

Welcome to Patch World
Patches: An Innovative Drug Delivery System

- **Fentanyl** (Duragesic®)
- Lidocaine (Lidoderm®)
- **Clonidine** (Catapress®)
- Methylphenidate (Daytrana®)
- Rivastigmine (Exelon®)
- **Nicotine**
- Scopolamine
- Nitroglycerin
- Granisetron (Sancuso®)

Diagram:
- Reservoir patch has polyester backing film
- Drug reservoir: fentanyl, alcohol, hydroxyethyl cellulose gel
- Delivery membrane
- Silicone adhesive layer also contains fentanyl
- Matrix patch
- Drug matrix is within silicone adhesive layer
- Only two layers once applied to skin, the backing film overlying the adhesive/drug matrix
- Kinetics, drug levels, onset and offset are similar to reservoir patch
- Matrix patch smaller, thinner
Patch Science

- Drug delivery is constant per unit time and proportional to the surface area of the patch
- There may be wide variations in time to peak drug levels of absorption
  - May be 13 hours in fentanyl
- Absorption continues even after patch is removed

“Used” Fentanyl Patches

- Hospice patients
  - 28 – 84% of fentanyl remained in patches after 3 days use
- Cancer patients
  - 41 – 58% of fentanyl remained in patches after 3 days use

Ann Pharm 29:969 1995
A Drop In The Bucket?

Case

- A 2 year old is found with an open bottle of Visine Eye Drops
- She is sleepy and barely responsive
- Her skin is cool and clammy
- An ambulance is called........
Case PE

- Pertinent Physical Findings
  - CNS Depression
  - Pinpoint Pupils
  - Bradycardia

Visine
Is this Clonidine?

- Imidazoline compound
- Presynaptic $\alpha_2$-adrenergic agonist
  - Decrease sympathetic outflow
- First studied as a nasal decongestant
- Subsequently used as an anti-hypertensive
- Widespread use
- ADHD Indications

Other Drugs to Consider

- Intuniv® (Extended Release Guanfacine)
  - FDA Indication for ADHD
- Tenex® (Guanfacine)
- Kapvay® (Extended release Clonidine)
  - FDA Indication for ADHD
- Zanaflex® (Tizanidine)
- Precedex® (Dexmedetomidine)
  - IV administration/inpatient use
Pathophysiology

- Stimulation of $\alpha$-adrenergic receptors in the brain
  - Decreases heart rate, vascular tone and blood pressure
- In overdose, peripheral $\alpha$-adrenergic agonism can occur
  - Vasoconstriction and hypertension
- Imidazoline binding sites in the brain

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In Overdose…

- CNS depression
- Bradycardia
- Hypotension
- Respiratory depression
- Sinus bradycardia
- Pinpoint pupils

When ACLS may not be Enough

- Naloxone
  - $\alpha_2$ and $\mu$ receptors are coupled to inhibitory G proteins and open K+ channels
  - Variable Response
  - Higher Doses
  - Continuous infusions
- Atropine
- Patient Stimulation

Case 5 (cont)

- Child continued to improve after stimulation
- Naloxone 2 mg dose increments up to 10 mg done
  - Very little response
- Improved over next 12 hours and discharged the next day

Who Has The Breath Mints?
A 3 year old presents with a three day history of fever, progressive sleepiness, and respiratory distress.

Previously healthy, his parents report that he developed a fever (101) at first, for which they gave Tylenol.

His behavior has become that of a lethargic and irritable child, with what the parents describe as a “funny, fast breathing pattern”.

No rash, URI, nausea, vomiting or diarrhea is described.
Physical Examination

- **Vital Signs**
  - T 40°C, HR 140, RR 70 and deep, BP 140/70
- **General**
  - Sleepy toddler, responding to mother’s voice
- **HEENT**
  - Normal pupils, Pharynx dry
- **Neck**
  - Supple

- **Chest**
  - PMI normal, no murmur
  - Clear lungs
- **Abdomen**
  - Soft, No mass
  - Bowel sounds normal
Physical Examination

- Pulses
  - Normal
- Extremities
  - Full ROM
- Neurologic
  - Non focal lethargy
- Skin
  - Medicinal smell

Primary and Secondary Survey

- ABC’ S intact
- Chemstrip 100
  - Nonfocal lethargy
- Pupils normal
- Supple neck
- Clear chest
- Negative PMH, medications, allergies
Initial Problem List

- Fever
- Lethargy
- *Hyperpnea*

Toxins that cause HYPERVENTILATION

- P.A.N.T.
  - P  PCP, Pneumonitis (chemical)
  - A  ASA (central CNS stimulation)
  - N  Non cardiogenic pulmonary edema
  - T  Toxic metabolic acidosis
Initial differential

- Sepsis
- Pneumonia
- Meningitis

Investigations

- CBC/diff normal
- Electrolytes = Anion Gap 30
- CXR normal
- ABG (room air)
  - pH 7.50  PCO2 20  PO2 100  BE -15

Primary Respiratory Alkalosis  Primary Metabolic Acidosis
Toxins that cause ANION GAP ACIDOSIS

- M Methanol
- U Uremia
- D DKA
- P Phen (met) formin
- I Iron, INH
- L Lactate
- E Ethanol, Ethylene glycol
- S Salicylates

Lab results

- Serum Osmolarity= 280
- Calculated Osmolarity= 288
- Ethanol= 0
- BUN= 8
- Salicylates= 66mg/dL
The osmolal gap

- The difference between **serum and calculated osmolarities (should be < 10-15)**

- **Serum** osmolarity: measured by freezing point depression in the lab

- **Calculated** osmolarity: 2XNa + BUN/2.8 + Glucose/18

Agents associated with an elevated osmolal gap

- Methanol (dry gas, windshield washer fluid)
- Ethanol
- Ethylene Glycol (antifreeze)
- Isopropyl Alcohol (rubbing alcohol)
- Mannitol
- Glycerol
- Paraldehyde
Salicylates

- **Central stimulation** of the respiratory center = primary respiratory alkalosis and insensible fluid losses

- Uncouples oxidative phosphorylation and interrupts glucose metabolism (**primary metabolic acidosis**) 

- Alter platelet function and bleeding time

Toxic dose

- Therapeutic dose = 10-15 mg/kg

- Toxic acute dose is > 140 mg/kg

- Severe intoxication seen with 300-500 mg/kg
Clinical manifestations

- Vomiting, **hyperpnea**, tinnitus, and lethargy
- Severe intoxication
  - coma
  - seizures
  - hypoglycemia
  - hyperthermia
  - pulmonary edema

Diagnosis

- History and ASA level
- Anion gap metabolic acidosis
- Initial respiratory alkalosis, dissipates with general clinical deterioration
- Abdominal x-rays may demonstrate **radiopaque** enteric-coated or sustained-release tablets
Sodium bicarbonate

- *Increases urine pH, ion trapping ASA*

- Initial dose at 1-2 meq/kg

- Drip of 3 amps in 850 cc D5W at 1.5 - 2 times maintenance

- Attempt to keep urine pH over 7.5

- *Hemodialysis* is also very effective

Diagnosis

- Oil of Wintergreen Linament
  - 30 grams ASA/15cc
Thanks!