Overdose stories that might SURPRISE you...in a bad way!

Debra A. Kent, Pharm.D.
Clinical Supervisor
B.C. Drug and Poison Information Centre, BCCDC
Clinical Professor, Faculty of Pharmaceutical Sciences, UBC
kent@dpic.ca
17 March 2017
Presenter Disclosure

- Debra Kent, presenter
- I have no current or past relationships with commercial entities
- I have received a speaker’s fee from CHSP for this learning activity
Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization
Goals & Objectives

- Discuss overdoses that may be associated with surprisingly rapid deterioration in clinical status.

- Discuss current approach to managing these overdoses that may be unexpected and perhaps not anticipated.
Case: Bupropion

- Young adult female brought to ER approximately 3 hours after ingesting 60 tablets of 150 mg bupropion XL.
  - HR 95/min, normotensive
  - ECG: NSR, QRS, QTc normal

- 9 hours post ingestion - ICU
  - Developed multiple seizures
  - Controlled with lorazepam & propofol
  - Intubated, ventilated
  - HR 150/min, BP 150/90 mmHg, pupils 8 mm
Case: Bupropion

- 12 hours post ingestion
  - BP 90/60 mmHg
  - BP began dropping despite norepinephrine, phenylephrine, vasopressin

- Pt developed idioventricular rhythm
  - Followed by pulseless, wide-complex rhythm
  - QRS 0.154 sec (normal < 0.1)
  - Then v. tach and v. fib
  - Received: defibrillations, epi, Mg, sodium bicarbonate boluses over 15 min
  - Circulation sustained for 20 minutes

- PEA with wide-complex recurred
  - Patient couldn’t be resuscitated
  - Pt expired approximately 16 hours post ingestion
Bupropion

**Mechanism:**
- Structurally similar to amphetamines
- Inhibits dopamine >> norepinephrine
- Sodium channel blockade with large doses

**Toxicity**
- *Typical:* Sinus tachycardia, hypertension, agitation, tremor, seizures
- *Severe:* Hypotension, QRS prolongation, cardiac arrest
Bupropion

- Toxic dose
  - Adults: seizures common with > 2.5 g; seen with as little as 600 – 1,000 mg
  - > 300 mg in a child
- Onset delayed due to SR, XL formulation
  - Consider activated charcoal several hours post ingestion
- Monitor VS, ECG for 18-24 hrs.
- Aggressive supportive care
  - BDZ ++++, propofol as needed for seizures
  - Sodium bicarbonate for QRS prolongation
  - Vasopressors for hypotension
  - Lipid emulsion for severe cardiac toxicity
Intravenous lipid emulsion (ILE)

- Effective in reversing LAST (local anesthetic systemic toxicity)
- Consider for drug-induced cardiotoxicity not responding to standard resuscitative measures
  - Bupropion
  - TCAs, CCBs, beta blockers
- Proposed mechanism(s) still not clear.
  - Lipid sink
  - Metabolic effect (free fatty acid uptake)
  - Membrane effect (Na, Ca channels)
Intravenous lipid emulsion (ILE)

- **Dose:** (lipidrescue.org)
  - Bolus: 1.5 mL/kg of 20% lipid emulsion over 1 min (~100 mL)
  - Followed by: 0.25-0.5 mL/kg/min (~18-36 mL/min)
  - Continue for 10 minutes after recovery
  - Upper dose limit: 10 mL/kg over first 30 minutes

- **Case reports of ADRs**
  - Pancreatitis
  - Analytical interferences
Pitfalls in Managing Bupropion

- Monitoring for only several hours.
- Forgetting that sedating co-ingestants may wear off as bupropion effects begin.
- Underestimating cardiovascular toxicity of large doses.
- Not realizing how quickly patients can deteriorate from seizures to cardiovascular collapse.
- Failure to aggressively dose sodium bicarbonate.
- Not considering lipid emulsion for asystole.
Case: Colchicine Overdose

- Male in his 20’s had fight with girlfriend and took handful of his colchicine at 02:00 hrs
- Vomited at 07:00 hrs
- Presented to ED 20 hrs post ingestion with gastrointestinal sxs
- Labs (on admission):
  - WBC 36.9, INR 1.7
  - Creatinine 143 µmol/L, Urea 8.1 mmol/L, lactate 3.6 mmol/L
  - CK 408 µmol/L
Case: Course

- **Treatment included:**
  - Ondansetron, activated charcoal, IV fluids
  - Transfer to higher level of care (out of small hospital)

- **Course over next 24 hrs**
  - Increasing trops, SCr, urea, CK, INR, WBC
  - VS stable, intermittent diarrhea & vomiting, decreasing urine output
24 hrs post admission
  ◦ Required intubation/ventilation
  ◦ BP dropped to 60/20 mmHg
  ◦ BP 131/94 mmHg with epi, levo, dopamine, vasopressin

72 hrs post ingestion
  ◦ pH 7.05, trops 27.9, SCr 417 µmol/L
  ◦ ALT 1570 U/L, CK 9883 µmol/L
  ◦ Pt expired
Colchicine

- Plant alkaloid found in autumn crocus
- Available in 0.6, 1.0 mg tabs for gout & Familial Mediterranean Fever (FMF)
- Multi-system poison
  - Inhibits microtubule formation & function
  - Interferes with cellular mitosis & shape
  - Rapidly dividing cells & those with high density of microtubules most affected
Dose

- Therapeutic dose:
  - Gout, acute: 1.2 mg/day
  - FMF: 1.2-2.4 mg/day

- Toxic dose:
  - > 0.5 mg/kg → high fatality rate
  - Lowest reported fatal dose: 7-26 mg
Kinetics

- Rapid oral absorption
- Peak in 0.5-2 hrs
- Widely distributed; highly lipid soluble
- Primarily metabolized via CYP 3A4
  - Lots of drug interactions (Clarithromycin strong inhibitor of 3A4)
- Cycled enterohepatically
- Also excreted renally
- Half-life:
  - 2-30 hrs
  - can remain in tissues up to 10 days
Clinical Effects - 3 phases

- *Gastrointestinal phase: 10-24 hrs*
  - N, V, D, hypovolemia, leukocytosis

- *Multi-organ phase: 1-7 days*
  - Respiratory distress syndrome
  - Dysrhythmias, cardiac failure, death
  - Encephalopathy, convulsions
  - Renal failure, liver failure
  - DIC, bone marrow suppression, pancytopenia
  - Electrolyte imbalance

- *Recovery phase: 7-21 days*
  - Alopecia, resolution of organ derangements, rebound leukocytosis
Treatment

- No specific antidote
- Aggressive GI decontamination
  - Lavage, if early presentation
  - Activated charcoal, even if several hours post ingestion
  - Multi-dose charcoal should be considered
- Symptomatic/supportive
  - IV fluids, electrolytes, vasopressors
  - Antibiotics, blood products
  - G-CSF
Pitfalls in Managing Colchicine

- Lack of familiarity with potential toxicity.
- Failure to initiate early aggressive gastrointestinal decontamination.
- Failure to provide aggressive, supportive care.
Case: Acetaminophen massive ingestion

- Elderly woman brought to ER when found unresponsive in independent care facility. Blister packed meds (none missing):
  - Zopiclone, risperidone, lithium, levothyroxine, felodipine, bisoprolol, aripiprazole

- On admission:
  - pH 7.20, anion gap 24, lactate 6.1 mmol/L
  - AST 8 U/L, INR 1.0, creatinine 62 µmol/L
  - Acetaminophen 2646 µmol/L, lithium 0.5 mmol/L
Case: Acetaminophen massive ingestion

- Next day (day 1)
  - Intubated, ventilated
  - BP dropped
  - pH 6.97, HCO₃⁻ 5 mmol/L, MeHb 11.7%
  - Lactate 12.8 mmol/L, Anion gap 34
  - Acetaminophen 3173 µmol/L
  - AST 44 U/L, INR 1.3

- Current therapies
  - Vasopressors
  - IV N-acetylcysteine
Acetaminophen

- Most common cause of acute liver failure
- 5-15% dose metabolized by CYP2E1 to toxic intermediate (NAPQI)
- Toxicity can occur with acute overdose or chronic supratherapeutic dosing
- Risk increased in
  - chronic alcoholics, malnourished, chronic isoniazid
- N-acetylcysteine: antidote
  - Effective in both early & late presentation
  - Safe, inexpensive
  - Indications:
    - Acetaminophen level > treatment line, if acute
    - Signs, sxs of hepatic injury, regardless of level
Acetaminophen Toxicity—
typical progression

- **Initial**
  - Nonspecific GI symptoms

- **Within 24-30 hours**
  - AST/ALT & INR rises later

- **3-5 days post ingestion, in severe cases**
  - AST, ALT in 10,000’s
  - Coagulopathies, bleeding
  - Coma
  - Hepatorenal syndrome, lactic acidosis

- **Can progress to death from**
  - Hepatic failure, cerebral edema, multi-organ failure
Acetaminophen Toxicity—rare cases of massive overdose

- Early onset of:
  - Lactic acidosis
  - Coma
  - Hypotension
  - Liver enzymes and INR near normal

- “Mitochondrial inhibition”
  - Glutathione depletion produces cascade of events including mitochondrial oxidative stress
  - Inhibition of mitochondrial respiration results in increased production of lactate.

  *Note*: late onset lactic acidosis after liver toxicity is a different mechanism
Early acidosis

- **Approach to therapy**
  - IV N-acetylcysteine (NAC)
  - Consider hemodialysis
    - Acetaminophen is rapidly removed
      - Reduces body burden, serum levels
    - Corrects acidemia
    - Also removes NAC
      - Double NAC rate
      - Consider additional half-load when dialysis > 6 hours
Methemoglobinemia with acetaminophen overdose

- ? secondary to oxidant effect of massive dose
- ? related to ↑ NADPH glutathione reductase activity
  - *Note:* MeHb commonly seen in cats following acetaminophen administration

- Hemolytic anemia and hemolysis reported in G6PD-deficient patients following acute acetaminophen overdose.
Case: Acetaminophen massive ingestion

- Day 2
  - Pt intubated, ventilated, on vasopressors, IV NAC
  - Not transferred for dialysis
  - Methylene blue not given
  - Acetaminophen 5152 µmol/L
  - pH 7.10, HCO₃ 8 mmol/L, MeHB 10.4%
  - Lactate 14.5 mmol/L, anion gap 36
  - AST 386 U/L, Creatinine 120 µmol/L, INR 2.9
Case: Acetaminophen massive ingestion

- **Day 3**
  - Acetaminophen 4140 µmol/L
  - pH 7.10, HCO₃ 8 mmol/L, MeHB 7.8%
  - Lactate 15 mmol/L, AG 36
  - AST 935 U/L, Creatinine 191 µmol/L, INR 7.4

- **Day 4**
  - pH 7.25, HCO₃ 12 mmol/L, MeHB 4.8%
  - INR >10, lactate 18.9 mmol/L
  - Pt expired late evening
Pitfalls in Managing *Early Lactic Acidosis* from Acetaminophen

- Unfamiliar with this being related to acetaminophen, especially when LFTs are normal.
- Failure to aggressively manage & consider hemodialysis.
- Failure to increase NAC dose during dialysis.
Case: Shatter

- 20-year-old male presented to ER with hallucinations & agitation.
- Friends said he smoked “shatter”.
  - They did as well but they were fine.
“Shatter” refers to concentrated cannabis.

- “Dab” is a dose of cannabis concentrate, usually referring to butane hash oil (BHO)
- Term “dab” has grown to include other forms including shatter, wax, budder
- Solvent extracted with butane or alcohol
  - Home labs have exploded
  - Can purchase from dispensaries
Marijuana

- Dried flower bud
- Female plant
- THC content 5-20%
Hash/Hash oil

- Hashish
  - Pressed resin from trichomes
  - THC: 20-60%

- Hash oil
  - Hashish heated and pressed to produce oil
  - THC: 30-80%
Shatter & Wax

- **Shatter**: clear-like substance, breaks into pieces, smoked in special bong or vape pen
- **BHO (butane hash oil)**: smoked in vape pens or on cig paper
- **Wax (budder, crumble)**: “bowl topping”
- Concentrates can be up to 90% THC
Heated on hot surface & smoked or vaporized
Case: Course

- 6 hrs later
  - Pt tachycardic, agitated, confused, screaming
  - Afebrile on admission, now 37.6 C
  - Labs: normal; Urine + only for THC
  - So far: 60 mg lorazepam & 20 mg loxapine

- 14 hrs: still requiring sedation for agitation

- 24 hrs:
  - Awake, drowsy from sedation
  - Remembers smoking shatter from a bong, his first time; friends are regular users
  - Now anxious & worried
Other Stimulant Hallucinogens

- **Phenethylamines** - includes methamphetamine, MDMA
  - Designer substitutions alter serotonin vs stimulant properties
  - 2 C-substitutes
  - NBOMe
  - Cathinones/mephedrone/others (‘bath salts’)

- **Piperazines**
  - BZP
  - TFMPP

- **Tryptamines**
  - LSD, psilocybin
  - DMT-Ayahuasca
  - AMT (α-methyltryptamine)
  - Foxy methoxy (5-MeO-DIPT)

- **Synthetic cannabinoids** (‘spice’, JWH-018 & others)
“N-Bomb, legal acid”
(images of powder bought in BC)

- N-2-methoxybenzyl analogs of 2C-substituted family of phenethylamines
- Potent 5HT\textsubscript{2A} analog
- Sold as powders or blotters
- Case: 15 y.o. male ingested 25-I-NBOMe and mushrooms
  - Began to vomit, seize, became unresponsive
  - Resuscitation efforts were unsuccessful
  - Died 3 days later of multi-organ failure
NBOMe & 2C substituted phenethylamine exposures in UK


- 2 year period: 341 cases (148 NBOMe; 193 2C)

- Common clinical effects with both
  - Tachycardia
  - Agitation/irritability
  - Hallucinations/ delusions
  - Confusion
  - Hypertension

- NBOMe: higher rates of seizures, hallucinations
- Death: 2.3%; no difference between groups
- Treatment:
  - IV fluids, benzodiazepines, supportive care
Case: Designer Benzodiazepine

- 17 y.o. male brought to ER by police
- VS stable, GCS 14, slurring, drooling
- Took 2-3 tabs of 0.25 mg flubromazolam a few hours earlier (purchased off internet)
- No co-ingestants
- Symptomatic care
- 14 hrs post ingestion, still too drowsy to talk coherently
Designer Benzodiazepines

“For research use only, not for human or veterinary use.”

- Flubromazolam/flubromazepam
  - Unlicensed benzodiazepine
  - Available on internet
    - Pills, powders, blotters
  - Marketed as ultrapotent
  - May have longer half-life
  - Case in literature: (ClinTox 2016;54:66.)
    - Deep coma, ↓ RR, ↓ BP
    - Utox positive for BDZ
    - Woke up with flumazenil
  - Treatment: symptomatic, supportive
Case: Opioids

- 29-year-old female brought to ER by ambulance.
- Found unresponsive, cyanotic, agonal respirations, RR 4/min, sats 60%, pinpoint pupils
- Given 5 mg naloxone; only response was slight twitch.

- **Question to poison centre:**
  - *How much naloxone can be given?*
FENTANYL
CAN BE DEADLY WHEN CUT WITH THE DRUGS YOU'RE TAKING

KNOW YOUR SOURCE? BE DRUG SMART
KNOWYOURSOURCE.CA
Fentanyl

- Increasing % of opioid deaths in Canada have fentanyl detected
- Powder being sold as heroin/cocaine
- Fake oxycodone (“green pills”)
- 50-100 times more potent than morphine
- Negative on opioid Utox
- Urine screen for fentanyl available
Novel synthetic opioids

- Carfentanil
  - 4-carbomethoxy-fentanyl
  - Analog of fentanyl
  - 100 times more potent opioid than fentanyl
  - 10,000 times more potent than morphine or heroin

- U-47700 (“U4”)
  - Non-fentanyl-based synthetic μ-opioid agonist
  - Developed in 1970’s
  - Sold on internet as “research chemical”
  - Found in pills/powders
  - 7-8 times more potent than morphine
W-18

• Developed in 1981 as possible analgesic (W-series compounds)
• Identified along with other synthetic opioids in pills/powders in Canada
• No evidence that W-18 has any agonist activity at opioid receptor
• Reports of toxicity on its own are speculative
Naloxone

- **Indications:**
  - RR < 10/min or
  - sats < 92% on room air, inability to protect airway, or fentanyl-induced chest wall rigidity

- **Dose:**
  - Initial: 0.1 mg IV/IO or 0.4 mg IM/SC/IN
  - Subsequent: every 2 min IV or every 3 min IM
    - 0.4 mg, 0.4 mg, 2.0 mg, 4.0 mg, 10 mg
    - Consider 15 mg as a final dose
  - Repeat dosing or an infusion may be required

- **Monitoring period:**
  - 6 hrs after last naloxone dose, or
  - 12 hrs after naloxone infusion stopped
  - Methadone: Observe 12 hrs after methadone & at least 12 hrs after last naloxone dose or discontinuation of infusion
Case: Opioids

- Naloxone was repeated and when given 15 mg, she sat up in bed & responded.
- Observed for 12 hours longer.
- No further doses required.
- Discharged with RR 18, sats 97%, alert and oriented without verbal or physical stimulation.
- She thought she was using heroin.
Summary- Key Points

- Surprises can be...
  - Unexpected serious toxicity
  - Rapid deterioration of clinical status
  - Unusual treatments that may be helpful

- By anticipating these situations, pharmacists can...
  - Focus recommendations
  - Improve outcomes
Discussion & Questions
Selected References

- **Bupropion:**

- **Intravenous Lipid Emulsion (ILE):**
Selected References

- **Colchicine:**

- **Acetaminophen-massive ingestion:**
Selected References

• **Street Drugs:**