Poisonings and Intoxications: A Focus on Extracorporeal Therapies

MITCHELL H. ROSNER, MD
DIVISION OF NEPHROLOGY
UNIVERSITY OF VIRGINIA
ASN BOARD REVIEW AND UPDATE COURSE 2015

Objectives

- Learn how to approach the poisoned/intoxicated patient
- Understand the common methods available to treat the poisoned/intoxicated patient
  - Specific antidotes
  - Extracorporeal techniques (hemodialysis, hemofiltration, hemoperfusion, plasmapheresis)
- Review the principles behind effective extracorporeal removal of toxins
- Discuss the care of patients poisoned/intoxicated by specific agents:
  - Toxic alcohols (ethanol, methanol, ethylene glycol, isopropyl alcohol)
  - Salicylates
  - Lithium
  - Bath salts

Epidemiology

2010 Annual Report of the American Association of Poison Control Centers’ National Poison Data System

- 2010: 2,384,825 reported exposures (stable over last 10 years)
- Unintentional exposures account for 81%
- 25% require management in a healthcare facility (4% in an ICU)
- 2010: 1,146 fatalities (92% occur in adults > 20 years)
- 40.3% of cases treated by decontamination only (majority charcoal)
- 9.9% of cases treated by a therapeutic intervention
- 32.8% of cases treated by decontamination and intervention
- Hemodialysis in 2162 cases (0.09%)
- Hemoperfusion in 22 cases

Source: 2010 NPDS Annual Report
www.aapcc.org/dnn/NPDSPoisonData/NPDSAnnualreports.aspx

Most common poisonings-2010
Adults age > 20 years

<table>
<thead>
<tr>
<th>Poison Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>12.96</td>
</tr>
<tr>
<td>Sedative/hypnotics/antipsychotics</td>
<td>11.18</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>6.19</td>
</tr>
<tr>
<td>Cleaning substances</td>
<td>6.01</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>5.48</td>
</tr>
<tr>
<td>Alcohols</td>
<td>4.69</td>
</tr>
<tr>
<td>Bites/envenomations</td>
<td>3.86</td>
</tr>
<tr>
<td>Pesticides</td>
<td>3.70</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>2.92</td>
</tr>
</tbody>
</table>

Source: 2010 NPDS Annual Report
www.aapcc.org/dnn/NPDSPoisonData/NPDSAnnualreports.aspx
## Initial Approach

- **Brief history and focused physical examination**
  - What was taken? How much? How long ago?
  - Other medications? Other medical conditions?
  - Assess need for critical care
    - Vital signs include pulse oximetry and finger stick glucose
    - Mental status/airway protection
    - Pupil size/skin exam (toxidromes)
    - ECG/cardiac monitoring
  - IV access
  - Naloxone 0.4 to 2 mg IV for suspicion of opioid intoxication
  - 50% dextrose in water for hypoglyemia
  - IV thiamine 100 mg
  - IV flumazenil variable doses for benzodiazepine intoxication

## Initial Studies: Unknown Toxin

- Arterial blood gas
- CO-oximetry for carboxyhemoglobin and methemoglobinemia
- Comprehensive metabolic profile, magnesium, phosphorus (determine anion gap)
- Lactate, ketones
- Serum osmolality (determine osmolal gap)
- Urine and serum toxicology screen
- When applicable, levels for specific toxins:
  - Toxic alcohols, lithium, valproic acid, salicylates, acetaminophen, digoxin

## Decontamination

- **Prevention of further absorption**
  - Gastrointestinal lavage (whole bowel irrigation): best for toxins poorly absorbed by charcoal such as lithium
  - Activated charcoal: useful for agents such as salicylates, phenobarbital, theophylline, digoxin, phenytoin, carbamazepine and sustained-release drugs as well as drugs that slow GI motility such as anticholinergics.
    - Administered orally or by nasogastric tube
    - Interrupts enterohepatic circulation
    - Effective for drugs with low protein binding, small volume of distribution
    - Not effective for tricyclic antidepressants

## Forced Diuresis/Urine Alkalization

- **Urinary alkalization:**
  - Promotes elimination of weak acids (pKa of 3 to 7.5)
  - Change in intraluminal pH promotes formation of a higher fraction of ionized drug (ion trapping)
  - For example:
    - At a urine pH of 5 the ratio of salicylate to salicylic acid is 100:1
    - At a urine pH of 7.0, this ratio is 10,000:1
  - Furthermore, by increasing urine flow rate, the concentration of toxins in the tubular fluid is reduced and this reduces the gradient for uptake/reabsorption into tubular cells
  - Most useful for enhancing the elimination of salicylates or barbiturates
Urinary Alkalinization

- Goal urine pH ≥ 7.5
- Technique:
  - Bolus: 8.4% sodium bicarbonate IV at 1-2 meq/kg (1-2 amp)
  - Infusion: 1 liter of D5W with 150 meq sodium bicarbonate per liter at a rate of 100-250 ml/hour
- Monitoring:
  - Systemic pH should not rise above 7.60
  - Serum potassium, ionized calcium
  - Drug levels as appropriate
  - Urine pH
  - Volume status

Antidotes

- Available for a limited number of poisons/intoxications
- Timing of administration is critical and requires rapid recognition of the specific poisoning

<table>
<thead>
<tr>
<th>Poison</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Hyperbaric oxygen</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Sodium thiosulfate</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Specific Fab fragments</td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Methanol</td>
<td>4-methylpyrazole</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Flumazenil</td>
</tr>
<tr>
<td>Opiates</td>
<td>Naloxone</td>
</tr>
</tbody>
</table>

Drug or Toxin Removal by Extracorporeal Therapies

To determine the ability of a toxin to be removed by a specific extracorporeal technique:

- Drug-Related Factors
  - Molecular weight: one of the most reliable predictors of drug removal by dialysis. As MW > 5000 D, need high flux dialysis membrane with a high Qb and Qd
  - Charge: more highly charged substances have lower clearances
  - Membrane binding: some clearance may be due to binding of the drug to the membrane
  - Protein binding: highly protein-bound substances are not cleared well (to be removed binding should be < 80%)
  - Volume of distribution: removal best when Vd < 1 L/kg
  - Lipid or water solubility: water soluble drugs have higher removal rates
  - Rebound: movement of drug from peripheral storage compartments into blood. Characteristic of lithium which distributes predominantly in cells and repeated dialysis sessions may be required

Bayliss G. Hemodial Int 2010; 14: 158-167

Drugs or Toxin Removal by Extracorporeal Therapies

- Dialysis related factors
  - Membrane type/flux
  - Dialyzer surface area
  - Dialysate composition
  - Blood flow rate
  - Dialysate flow rate
- Toxin removal is primarily through diffusion with a smaller, variable contribution from convection (more important as MW increases)
- Overall clearance of the toxin can be increased by increasing surface area, blood flow rate and ultrafiltration rate
Indications for Extracorporeal Therapy

- Progressive deterioration despite appropriate therapy
- Normal routes of elimination/detoxification of the toxin are impaired (renal/liver failure)
- Ingestions that are associated with serious morbidity/mortality and which have been shown to be removed by extracorporeal means (lithium, methanol, etc)
- Severe central nervous system depression leading to hypoventilation, hypotension and hypothermia
- Patients presenting with overt signs and symptoms of toxicity
- Patients presenting with toxic levels of toxic agents that are effectively removed through extracorporeal means
- Extracorporeal therapy with add significantly to total body elimination (> 30% increase in clearance)

Removable by Hemodialysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>MW (daltons)</th>
<th>Vd (L/kg)</th>
<th>% bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylate</td>
<td>138</td>
<td>0.2</td>
<td>80-90 but falls with toxic levels</td>
</tr>
<tr>
<td>Lithium</td>
<td>7</td>
<td>0.6-0.9</td>
<td>0</td>
</tr>
<tr>
<td>Methanol</td>
<td>32</td>
<td>0.6-0.7</td>
<td>0</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>62</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>60</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Theophylline</td>
<td>180</td>
<td>0.5</td>
<td>50-60</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>144</td>
<td>0.1-0.2</td>
<td>&gt;90% but falls with higher levels</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>454</td>
<td>0.4-0.8</td>
<td>50</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>232</td>
<td>0.5</td>
<td>20-30</td>
</tr>
<tr>
<td>Metformin</td>
<td>165</td>
<td>&gt; 3 (variable)</td>
<td>0-10</td>
</tr>
</tbody>
</table>

Bayliss G. Hemodial Int 2010; 14: 158-167

Hemoperfusion

- Cartridge contains charcoal coated with an ultra-thin porous coating which decreases direct contact between blood and charcoal (platelets are most vulnerable and levels fall about 30%)
- Drug removal by adsorption
  - Vd < 1 L/kg
  - Water soluble
  - Low endogenous clearance (.4 ml/min/kg)
- System contains a filter in the venous line to remove loosened charcoal particles before return to the blood stream
- Does not address electrolyte or acid-base abnormalities
- Hypocalcemia common
- Rarely utilized and not widely available (in 2009 used 26 times)

Drug removal by Hemoperfusion

- Barbiturates
- Phenytoin
- Theophylline
- Amanita mushrooms
- Carbamezepine (most common indication)
- Valproic acid
- Chloral hydrate
- Dapsone
- Methotrexate
Continuous Renal Replacement

- Due to low clearance rates, inefficient in rapid removal
- Benefit in decreasing post-treatment rebound for compounds such as lithium and can be used as an adjunct to hemodialysis
- Adjunctive benefit in patients that are hemodynamically unstable
- Should NOT be considered a first-line therapy for toxin removal

Plasma Exchange

- Ability to rapidly remove toxins for the blood compartment that is independent of toxin’s size, charge or protein-binding characteristics
- Replacement with plasma may be beneficial in some circumstances (cholinesterase with organophosphate poisonings)
- Does not correct acid-base or electrolyte abnormalities
- Removes toxins exclusively from the plasma (thus, requires a Vd < 1 L/kg)
- Exchange of 1-2 plasma volumes

Removal by Plasma Exchange

- Amanita mushroom (category II indication)
- Digoxin
- Snake envenomation (removal of toxin and inflammatory mediators): pit vipers
- Cisplatin
- Biological agents
  ○ Natalizumab (antibody against α4 chain of VLA-4 used for treatment of multiple sclerosis)
- NO category I indications

Specific Cases: Case I

A 42 y/o man with a history of bipolar disorder treated with lithium was brought to the ED by his nursing home with altered mental status. He has a history of stage 3 CKD with a baseline serum creatinine of 1.4 mg/dL. Exam reveals normal vital signs, an agitated delirium, nystagmus and ataxia. A head CT reveals mild atrophy. Labs reveal:

Ca 9.2
Mg 3.4
Lithium level 4.3 mmol/L

EGC: slightly prolonged QT interval
**Audience Response Question**

Which one of the following would be your next step in the treatment of this patient?

- A. Intravenous saline with serial lithium levels
- B. Gastric lavage to remove any unabsorbed lithium tablets
- C. Hemodialysis for 4 hours
- D. Hemodialysis for 2 hours
- D. Continuous renal replacement therapy until lithium level is < 1.0 mmol/L

---

**Lithium**

- Small molecule – 7 Da
- The most dialyzable toxin known (small, VD 0.6-0.9), <10% protein-bound
- Renal elimination – Li excretion and reabsorption generally follows Na
  - Sodium-avid states (e.g., vol depletion, CHF) increase lithium reabsorption
- Elimination half-life 12-27 hours in normal kidney function
- Normal renal clearance: 10-40 mL/min
- Clearance with hemodialysis: 70 to 170 mL/min
- Clearance with CVVHDF 48 ml/min (dialysate flow rate of 1 L/h) and 62 ml/min (dialysate flow rate of 2 L/h)


---

**Symptoms and Signs of Lithium Toxicity**

- Temperature dysregulation (hypo- or hyperthermia)
- Mental status changes ranging from confusion to coma
- Nausea, vomiting, diarrhea
- Xerostomia, delirium, nephrosis
- Dizziness, ataxia
- Seizures, increased deep tendon reflexes: potential for permanent neurological dysfunction
- Hypercalcemia, increased TSH, leukocytosis
- Decreased anion gap
- Abnormal ECG (prolonged QT, ST depression, inverted T waves, sinus node dysfunction)


---

**Treatment of Lithium Toxicity**

- Indications for hemodialysis
  - Lithium level >4-6 mmol/L (some debate)
  - Lithium level 2.5 to 4 mmol/L if:
    - Severe neurologic symptoms
    - Impaired renal excretion
    - Hemodynamically unstable (may be role for CRRT)
    - If levels not decreasing in first 12 hours with IV fluids
  - Lithium level <2.5 mmol/L if:
    - ESRD patient
    - Rising Lithium level
- Rebound after hemodialysis
- Repeat dialysis may be required 6 to 8 hours after initial treatment
- Critical to continuously measure levels
ARS: Case II

A 52 y/o disheveled man, a known alcoholic, presents to the ED after being found in the street by the police. He is confused and not answering questions. Exam: T 36, HR 120, BP 82/45, RR 30; cachectic man who is minimally responsive, dilated pupils poorly responsive to light. A head CT reveals swelling and changes of the putamen. Labs reveal:

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>149</td>
<td>111</td>
<td>9</td>
<td>168</td>
</tr>
<tr>
<td>4.8</td>
<td>&lt;5</td>
<td>1.1</td>
<td></td>
</tr>
</tbody>
</table>

Serum osmolality 413 Lactic Acid 1.8 ABG 7.02 / 12 / 142

The most likely toxic ingestion is:
- a. Isopropyl alcohol
- b. Ethanol
- c. Methanol
- d. Ethylene glycol

ARS Question

- In addition to fomepizole, which of the following other therapies would you employ in this patient?
  - a. Plasma exchange
  - b. Hemodialysis with heparin anticoagulation
  - c. Hemodialysis no anticoagulation
  - d. No additional therapy is needed except for fomepizole
  - e. CVVHD

A word about the osmolal gap

- Osmolal gap is the difference between measured and calculated plasma osmolality
- Calculated plasma osmolality:
  \[ P_{\text{osmol}} = 2 \times [Na^+] + \frac{\text{BUN}}{2.8} + \text{[glucose]} + \text{[ethanol]} \]
- Abnormal gap > 10-15 mOsm/kg
- Cautions:
  - POOR screening tool unless markedly elevated
  - Both positive and negative predictive value are low
  - Unidentified osmoles are present in keto- and lactic acidosis, renal failure
  - Osmolal gap may normalize as anion gap develops
  - Threshold of > 20 mOsm/kg more specific for alcohol ingestion

Changes in the anion gap and osmolal gap

Initiate HD alone if HAGA present and methanol levels <10 mg/dl or no osmolal gap but strong suspicion of ingestion

Toxic Alcohols: Metabolism to Toxic Metabolites

Alcohol dehydrogenase is the critical enzymatic step in the conversion of alcohols to more toxic metabolites.


Toxic Alcohols: Comparison

<table>
<thead>
<tr>
<th></th>
<th>Alcoholic ketoacidosis</th>
<th>Methanol</th>
<th>Ethylene glycol</th>
<th>Isopropyl alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Osmolar gap</td>
<td>Present (lactate)</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Anion gap</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Serum/urine ketones</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>AKI / calcium oxalate stones</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Reduced vision</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

ARS Question

The following was seen on a urinalysis of a patient presenting with intoxication, a high osmolal gap and severe metabolic acidosis:

Which one of the following is the likely cause of this finding?

- a. Ethanol
- b. Ethylene glycol
- c. Methanol
- d. Propylene Glycol

Treatment: Inhibition of Alcohol Dehydrogenase

- Ethanol
  - Need to maintain blood level ≥100 mg/dL
  - Requires frequent monitoring of levels
  - Sedating, intoxicating
- Fomepizole (4-methylpyrazole)
  - Affinity 8x that of ethanol
  - Non-sedating
  - Much more expensive than ethanol
  - Requires less monitoring of levels than ethanol
  - Dose needs to be supplemented during hemodialysis
  - Loading dose of 15 mg/kg body wt
  - Maintenance dose of 10-15 mg/kg every 12 hours
Methanol Intoxication: Treatment

- Inhibition of alcohol dehydrogenase (ADH)
  - Fomepizole or ethanol
- Cofactor therapy
  - Folic acid 50 mg IV q6h x 24 hours
  - Increases metabolism of formate to CO2 and H2O
- Indications for Hemodialysis:
  - The American Academy of Clinical Toxicology recommends that hemodialysis be considered in the presence of metabolic acidosis (blood pH 7.25 to 7.30), visual abnormalities, renal failure, or electrolyte imbalance unresponsive to conventional therapy and/or serum methanol concentration of >50 mg/dL
  - However, fomepizole therapy, in some cases, has completely eliminated the need for dialysis even with very high presenting levels


Ethylene Glycol Intoxication: Treatment

- Inhibition of alcohol dehydrogenase
  - Fomepizole or IV ethanol
- Cofactor therapy
  - Pyridoxine (100 mg IV qd) may increase metabolism of glyoxylate to hippuric acid
  - Thiamine (100 mg IV qd) may increase metabolism of glyoxylate to α-(OH)β-keto adipic acid
- Indications for Hemodialysis
  - Severe metabolic acidosis (pH <7.30)
  - Acute kidney injury
  - In absence of fomepizole:
    - Ethylene glycol level >50 mg/dL
    - Continue until level <20 mg/dL
  - With fomepizole inhibition:
    - No specific threshold for starting HD
    - HD may shorten duration of treatment


ARS: Case

A 42-year-old woman came to the ED several hours after taking up to 100 full-strength aspirin pills. She promptly vomited multiple pill fragments after arrival. Activated charcoal was administered shortly after arrival. Exam notable for T 37, HR 90, BP 130/70, RR 32; she is tachypneic but conversant, complaining of tinnitus, nausea, abdominal pain and has epigastric tenderness, otherwise exam is unremarkable.

<table>
<thead>
<tr>
<th>138</th>
<th>92</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>17</td>
<td>0.8</td>
</tr>
</tbody>
</table>

ABG  pH 7.47   pCO2 18   pO2 100   Ca 8.6   Ab 4.0
Salicylate level 65 mg/dL

What is the most appropriate treatment at this time?

A. Emergent hemodialysis
B. Urinary alkalinization
C. CRRT
D. Repeated activated charcoal administration
E. Forced diuresis with IV normal saline

Salicylate Toxicity

- Management
  - Gut decontamination
  - Plasma acid-base status
    - Acidemia increases CNS salicylate toxicity
    - Target blood pH is 7.50-7.59
    - If ventilatory support necessary, care must be provided to maintain a high minute ventilation and maintain elevated blood pH
  - Glucose supplementation
    - CNS glucose may be depressed despite normal serum glucose
  - Correction of electrolyte disturbances
  - Urinary alkalinization
    - Urinary alkalinization increases excretion
    - Bicarbonate infusion to maintain urine pH >7.5
ARS Question

• TRUE OR FALSE

• Acetazolamide can be used to cause an alkaline urine in patients with salicylate intoxication

Extracorporeal Therapy for Salicylate Toxicity

• Extracorporeal therapy
  • Hemodialysis (even though protein binding is very high, with toxic levels this binding decreases)
  • Indications
    • Altered mental status / seizures / cerebral edema
    • Non-cardiogenic pulmonary edema
    • Renal failure interfering with excretion
    • Fluid overload prohibiting administration of sodium bicarbonate / uncontrolled metabolic acidosis
    • Plasma salicylate level > 80 to 100 mg/dL
    • Clinical deterioration despite aggressive supportive care

A new intoxication: Bath Salts

• A 25-year-old man was transported to the emergency department (ED) by police after exhibiting unusual behavior. The patient was found with marked agitation and altered mental status. His girlfriend reported that he had injected bath salts and was subsequently found running wildly throughout the local neighborhood, markedly combative and foaming at the mouth.

• His initial examination revealed blood pressure 148/66 mm Hg, pulse rate 175 beats/min, respiratory rate 18 breaths/min, temperature 41.3°C (106.3°F) rectally, and transcutaneous oxygen saturations 100%. The examination was significant for the following: mydriasis, rightward deviation of the eyes, calor, and combative requiring restraint by multiple staff members.

• Initial laboratory values were significant for the following: WBC count 17,000/mm3, potassium 5.1 mEq/L, serum bicarbonate 14 mEq/L, creatinine 2.88 mg/dL, glucose 45 mg/dL, aspartate aminotransferase 201 U/L, alanine aminotransferase 334 U/L, creatine kinase 2,334 U/L, troponin 3.24 ng/mL, and lactate 7 mg/dL.

• Slowly recovered over 18 days in the hospital and required dialysis for 1 month before renal recovery.

Borek HA, Holstege CP. Annal Emerg Med 2012; epub
Bath Salts

- Bath salts and other Internet-acquirable synthetic substances are emerging drugs of abuse. These products are sold under a variety of unassuming brand names, such as Ivory Wave, Ocean Burst, TranQuility, Vanilla Sky, and White Lightning. Various products often have written warnings stating “not for human consumption” on the packages.
- Typical bath salt products contain a white powder that is abused by inhalation, ingestion, or injection. Bath salts can be purchased through a number of venues, such as on the Internet, in head shops, in convenience stores, or in certain tobacco shops. Analytic testing of some of these products has found 3,4-methylenedioxypyrovalerone (MDPV).
- Mechanism of organ toxicity not clear

Borek HA, Holstege CP. Ann Emerg Med 2012; epub

Bath Salts

Synthetic Marijuana (Cannabinoids)


In March 2012, the Wyoming Department of Health was notified by Natrona County public health officials regarding three patients hospitalized for unexplained acute kidney injury (AKI), all of whom reported recent use of synthetic cannabinoids (SCs), sometimes referred to as "synthetic marijuana."

- SCs are designer drugs of abuse typically dissolved in a solvent, applied to dried plant material, and smoked as an alternative to marijuana.
- After the Wyoming Department of Health launched an investigation and issued an alert, a total of 16 cases of AKI after SC use were reported in six states

Synthetic Cannabinoid-Induced AKI

- Renal biopsy in 3 cases: acute tubular necrosis
- Spontaneous resolution in all cases
- Other side effects:
  - Psychosis
  - Seizures
  - Hypokalemia
  - Hypertension
  - Acute myocardial infarction (?)


Investigation for the Cause of AKI

- The results of the investigation determined that no single SC brand or compound explained all 16 cases.
- Toxicologic analysis of product samples and clinical specimens (available from seven cases) identified a fluorinated SC previously unreported in synthetic marijuana products: (1-(5-fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl) methanone, also known as XLR-11

Ecstasy

- Synthetic drug synthesized in 1914 (appetite suppressant)
- Recreational drug use began in 1970s and has grown significantly.
- Most commonly used in night clubs or rave parties
- 39% of college students have reported use
- Mood enhancing causing energy, empathy, euphoria.
- Toxicity is NOT related to overdose and most individuals use the drug without harm
- Risk of death in first time users is 1:2000 to 1:50,000


Ecstasy

- Amphetamine derivative and causes release of serotonin, dopamine and norepinephrine
- Also leads to release of vasopressin, cortisol and prolactin
- Metabolized by CYP2D6 pathway and polymorphisms are associated with toxicity
- Drugs lead to numerous clinical syndromes:
  - Hypertension, tachycardia, arrhythmias, sudden death
  - Liver failure
  - Acute kidney injury (rhabdomyolysis)
  - Hyponatremia
Ecstasy-Induced Hyponatremia
- One of the more common toxicities
- Dilutional in nature and due to combination of non-osmotic vasopressin release in setting of large intake of water during parties
- Almost all cases are in females
- Recent study at a rave party conclusively demonstrated MDMA-induced hyponatremia
- Treatment with hypertonic saline for symptomatic patients

Van Dijken GD et al. Nephrol Dial Transplant 2013

Other Items to Know About
- Anabolic steroids associated with podocyte toxicity and focal segmental glomerulosclerosis in long-term abusers
- An adulterant of cocaine, levamisole, is associated with ANCA-like vasculitis
  - Serologically, almost all patients are MPO-ANCA positive
  - At least 50% will also be PR3-ANCA positive
  - Low-level positivity to other auto-immune antigens


Metformin and Lactic Acidosis
- Metformin, a dimethylbiguanide, is a widely used oral antihyperglycaemic drug used in the long term treatment of type 2 diabetes mellitus.
- A potential complication of metformin is the development of type B (non-hypoxic) lactic acidosis. Although metformin associated lactic acidosis is a rare condition, with an estimated prevalence of one to five cases per 100,000 population, it has a reported mortality of 30-50%
- Ninety percent of metformin is excreted unchanged by the kidneys
- While initial recommendations were to avoid in patients with CKD (< 30 ml/min), this has been relaxed in recent years

Metformin and Lactic Acidosis

- Bicarbonate therapy alone along with loop diuretics can be effective in some patients with milder presentations.
- Metformin is a small molecule (165 kDa) with a 50% oral bioavailability; it does not undergo hepatic metabolism and the main route of elimination is renal tubular secretion.
- Metformin is not bound to proteins and its apparent volume of distribution is usually reported to be higher than 3 L/kg (63 to 646 L in total) attesting to the predominance of the intracellular location.
- Considering these data, metformin can theoretically be extracted from blood by hemodialysis if dialysis is conducted for long enough to mobilize the intracellular form.

Dabigatran-associated bleeding

- Limited data suggests that dialysis is at least partially effective in removing dabigatran in those patients who develop bleeding complications.
- Clearance of dabigatran via continuous veno-venous hemodiafiltration was calculated by Chiew et al., using both the recovery and A-V pair methods, with a mean clearance of 58.1 and 31.9 ml/h, respectively, and a calculated mean extraction ratio of 0.2. Large rebound though.
- Another study:
  - Dabigatran concentrations decreased by 52%-77% during intermittent hemodialysis but rebounded up to 87% within 2 hours after completion of dialysis. Initiation of continuous renal replacement therapy after intermittent hemodialysis attenuated the rebound effect in one patient and contributed to a reduction in dabigatran concentrations of 81% over 30 hours.

Rivaroxaban and apixaban may not be dialysable due to a high degree of protein binding.

- Rivaroxaban concentrations decreased by 52%-77% during intermittent hemodialysis but rebounded up to 87% within 2 hours after completion of dialysis. Initiation of continuous renal replacement therapy after intermittent hemodialysis attenuated the rebound effect in one patient and contributed to a reduction in rivaroxaban concentrations of 81% over 30 hours.

Summary

- Early and rapid recognition of toxic ingestions is critical.
- Specific antidotes if available need to be given rapidly.
- Extracorporeal therapies are effective in selective cases.