Management of Poisonings: Core Curriculum 2010

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INTRODUCTION

Nephrologists frequently are asked to consult in the treatment of intoxicated patients. Poisonings and ingestions can result in acute kidney injury or electrolyte or acid-base disorders, and some patients may require extracorporeal drug removal. The American Association of Poison Control Centers reported approximately 2.5 million human poison exposures in the United States in 2008, resulting in more than 1,750 deaths. In the course of the year, more than 1.5 million exposures required some form of decontamination. Although most reported exposures are not referred to health care facilities, 598,048 exposures were managed in health care facilities, with 2,235 patients requiring extracorporeal treatment (hemodialysis in 2,177 and hemoperfusion/other in 58).

In this article, we outline initial supportive care and specific treatment, such as decontamination, antidotes, enhanced elimination, and principles and techniques of dialysis and other methods of blood purification. Treatment of common intoxicants also is addressed briefly. Finally, consideration is given to dialyzer drug removal and practicalities such as coding and reimbursement.

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BASIC MANAGEMENT

Enteric Decontamination

- An essential part of management given that ingestion is the route of exposure in most poisonings (almost 80% in 2008)
  - Unconscious patients and patients with impaired reflex airway protection should not undergo enteric decontamination without prior endotracheal intubation to prevent aspiration pneumonitis
- Decontamination involves measures to remove and prevent absorption of toxins from the gastrointestinal (GI) system and includes the use of ipecac or other emetics, gastric lavage, activated charcoal or other oral sorbents, cathartics, and whole-bowel irrigation

Emetics

- Induction of emesis with syrup of ipecac is not recommended for routine practice in poisoning
  - Uncertain efficacy
  - Poor drug recovery
  - Interference with other efficacious treatments
- Induced emesis may have an occasional role in "out-of-center" poisoning when benefit is determined to outweigh risk
- Should never be used after ingestion of acids, alkalis, or hydrocarbons because of the risk of further mucosal injury or pneumonitis

Gastric Lavage

- Associated with significant risk and minimal drug recovery by 2 hours after ingestion and is not routinely recommended
- May increase drug transit into the intestine
- Although it has been advocated for toxins that delay gastric emptying (eg, tricyclic antidepressants [TCAs]), there is no evidence of clinical benefit compared or combined with activated charcoal

- Should never be used after ingestion of acids, alkalis, or hydrocarbons because of the risk of further mucosal injury or pneumonitis

Activated Charcoal

- In single or multiple doses, adsorbs a variety of toxins and may prevent gastrointestinal absorption if administered within 1 hour after ingestion
- Clinical benefit has not been clearly shown, but charcoal is associated with minimal risk and should be considered on initial presentation

Whole-Bowel Irrigation

- Although unproved, irrigation with saline or polyethylene glycol may have a role in ingestions of sustained-release/enteric-coated drugs, iron preparations, and narcotic packets
  - However, it is not recommended routinely and is contraindicated in patients with bowel perforation, obstruction, or ileus
- Sodium polystyrene sulfonate (Kayexalate [Sanofi-Aventis]) is an enteric cation exchange resin that decreases the half-life ($t_{½}$) and increases the elimination of lithium after acute and long-term ingestion
  - Because hypokalemia also may result, serum potassium levels should be monitored and repleted as necessary

Antidotes

- After initial supportive care, antidotes should be considered for known or suspected poisonings
- Emergency stocking recommendations and indications vary
- Poisoning antidotes have been reviewed extensively and nephrologists should be familiar with their use
  - Naloxone, a μ-receptor antagonist, to reverse central nervous system (CNS) and respiratory depression of opiates and opioids
  - Flumazenil for benzodiazepine overdose
    - Not routinely recommended due to seizure risk
  - *N*-Acetylcysteine (NAC) for acetaminophen poisoning
    - Increases glutathione stores; prevents toxicity of *N*-acetyl-*p*-benzoquinone imine (NAPQI)
  - Fomepizole and ethanol to inhibit alcohol dehydrogenase (ADH) and prevent the formation of toxic metabolites in methanol and ethylene glycol poisoning
  - Sodium bicarbonate for TCA and salicylate (see Ion Trapping) poisoning
  - Digoxin immune Fab (Digibind [GlaxoSmithKline]) for cardiac glycoside overdose
    - Immunopharmacologic treatment
    - Large digoxin-antibody complexes may not be eliminated in patients without kidney function or using hemodialysis
    - Recrudescence of digoxin poisoning has been reported 24-48 hours after receiving Fab antibodies in patients with kidney failure
  - Physostigmine for anticholinergic poisoning (atropine/belladonna and *Datura* species)
  - Atropine and pralidoxime (2-PAM) for procholinergic manifestations of organophosphate poisoning
  - Chelation with deferoxamine, EDTA, dimercaprol (BAL), penicillamine, 2,3-dimercaptosuccinic acid (DMSA or succimer) for various metal intoxications (lead, aluminum, etc)
  - Hydroxocobalamin, amyl nitrite, sodium nitrite, and sodium thiosulfate for cyanide poisoning
  - Glucagon for β-blocker overdose
  - Methylene blue as a reducing agent for the treatment of methemoglobinemia, as well as carbon monoxide and cyanide toxicity
  - Phytonadione for warfarin overdose
  - Pyridoxine for isoniazid (INH) and ethylene glycol poisoning
  - Octreotide for oral hypoglycemic overdose
  - Botulism antitoxin
  - Snake, spider, and other antivenoms

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DRUG METABOLISM AND PHARMACOKINETICS (TOXICOKINETICS)

Overview

- Although many drugs are excreted unchanged through the kidney, many more are metabolized and drug action eventually ceases by a variety of mechanisms
  - Formation of hydrophilic derivatives that are excreted by the kidney
  - Decreased tubular reabsorption of ionic compounds (the principle used in "ion trapping")
  - Bioinactivation of drugs by alteration of chemical structure (sulfation, methylation, glucuronidation, oxidation, or hydrolysis)
- Formation of active metabolites, prodrugs, and toxification also may occur
  - Bioactivation of imipramine to desipramine
  - Bioactivation of sulindac to sulindac sulfide

Considerations in Patients With Reduced Kidney Function

- In the presence of decreased glomerular filtration rate (GFR), accumulation of drug or metabolite may occur and produce toxic effects on the kidney or other organs
  - Aminoglycoside accumulation
  - Prolonged sedation/coma from midazolam
  - Formation of normeperidine from meperidine as a toxic convulsant in kidney failure
- Drug interactions also may pose problems
  - Alterations in the cytochrome P-450 enzyme system
  - Inhibition of xanthine oxidase activity by allopurinol, leading to 6-mercaptopurine toxicity in patients receiving concomitant azathioprine
- As GFR decreases, drug dosages or time between each dose must be altered to avoid accumulation
  - Timing and adjustment of dosage follows rigorous pharmacokinetic principles concerning elimination

- Drug dosage is based on the principle that rate out = rate replaced

Basic Principles of Pharmacokinetic Elimination

- Elimination rate constant (K_{el}) of a drug describes drug removal
  - Most drugs are eliminated using first-order kinetics
    - In other words, a constant fraction of the drug is removed per unit of time
    - Characterized by a straight line on a plot of drug concentrations on a log concentration/linear time scale
    - Enables calculation of the dosing interval between administrations (τ)
  - The $t_{½}$ of a drug (time taken for a 50% decrease in concentration) is closely linked to K_{el} ($t_{½} = 0.693/K_{el}$)
  - Clearance (Cl) of a drug (given in milliliters per minute) and its relationship to volume of distribution (V_d) is given by the equation $K_{el} = Cl/V_d$
    - Many drugs (eg, salicylate) are distributed in whole-body water
    - Many are not and distribute to an "apparent" volume (V_{dapp}) many times whole-body water (eg, digoxin and amitriptyline)
  - Certain drugs do not follow first-order kinetics in the "intoxicated" state
    - Zero order refers to a constant rate of drug removal per unit of time independent of concentration
    - In severe salicylate poisoning, several elimination pathways for the drug become saturated, and Cl becomes zero order
  - Many drugs do not fit a single-pool pharmacokinetic model, but fit a multicompartment model with 2 or more K_{el}s (eg, digoxin)
- When an extracorporeal device is added for treatment, the device will either add to body (endogenous) elimination or not
- Most publications showing decreased $t_{½}$ or increased K_{el} of a drug most often relate to elimination during the period of extracorporeal treatment; these revert to endogenous elimination rates when the procedure is discontinued
  - For 50-60 years, based on theoretical grounds by Schreiner and Maher, it has been recommended that for usefulness in poisoning, a 30%-40% increase over endogenous elimination should be achieved by an extracorporeal device
  - However, relatively few pharmacokinetic studies have been done in this area in poisoning

Ion Trapping

- Many drugs and toxins are weak acids or bases that diffuse back into tubular cells in their neutral form, but are poorly absorbed as anions or cations
- The dissociation constant (pK_a) of a drug determines ionization of a drug
- At urine pH that converts the drug to an ionized form, such a moiety is nonreabsorbable, leading to greater net excretion
  - This phenomenon is called ion or diffusion trapping
  - Anionic substances/weak acids (phenobarbital and salicylate) generally are excreted best at higher urine pH (>7)
    - Excretion of salicylate (pK_a for salicylic acid = 3.0) can be quadrupled if urinary pH is ≥7.5
    - At urine pH 6.0, a total of 99.9% of the salicylate should already be ionized and therefore not reabsorbed, suggesting that other mechanisms besides ion trapping may explain the enhanced salicylate excretion at higher urine pH
  - Cationic drugs (such as amphetamine) generally are excreted best at low urine pH (<5.5)
  - Clearance of many drugs and chemicals may not be increased substantially by ion trapping
    - Adjusting urine pH is effective only if V_d is low and altered urine pH has been shown to be effective in enhancing removal of the toxin

Forced Diuresis

- Complicated issue: desire to rid the body of toxin versus desire to avoid potential fluid overload
- Only 1 study has been performed to address this issue: Prescott et al showed that given

the same quantity of alkali (sodium bicarbonate), the same quantity of salicylate was recovered from urine whether 8 L (forced diuresis) or 4 L of saline solution was given to intoxicated patients
- Most now favor cautious use of alkalinization with fluid replacement to replace deficits already seen on presentation in salicylate poisoning

Osmolal Gaps

- Osmolal gap refers to the difference between measured osmolality (by depression of freezing point) and that calculated from plasma electrolyte, glucose, and blood urea nitrogen levels
  - This is useful in determining if there is another substance present contributing to measured osmolality
  - The most likely candidates in the setting of poisoning are alcohols: ethylene glycol, methanol, mannitol, and isopropanol

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EXTRACORPOREAL THERAPY

Peritoneal Dialysis

- Most efficient when long dialysate exchange times bring mesothelial transport to its maximum solute equilibrium (ie, dialysate–plasma [D/P] solute concentrations reach equilibrium, or D/P = 1)
  - Peritoneal clearance is considered too inefficient for crucial time-dependent reversal of drug intoxication; hence, peritoneal dialysis is reserved for particular treatments
    - For dialyzable poisons if the other methods are unavailable
    - To increase core temperature in hypothermic poisoned patients with preheated solutions

Hemodialysis

- Many factors affect drug removal in hemodialysis
  - Drug characteristics
    - Solute size
    - Lipid solubility
    - Protein binding
  - V_d
  - Concentration gradient between plasma and dialysate
  - Physical factors
    - Blood flow rate (Qb) through the dialyzer
    - Dialysate flow rate
    - Dialyzer surface area
    - Characteristics of the dialyzer membrane
  - An ideal dialyzeable drug has low molecular weight, is water soluble, and has low protein binding and low Vd (eg, lithium)
  - Drug removal is limited by membrane surface area × permeability
- Solute clearance from blood is determined by the product of Qb and the drug extraction ratio, or A – V/A, where A is arterial (inlet) concentration and V is venous (outlet) concentration of drug going through the dialyzer
- Modern dialyzers are constructed from synthetic porous membranes (polymers, such as polysulfone and polyacrylonitrile) that allow drugs to pass more readily than cellulosic dialyzers
  - In general, the higher the Qb, the higher the clearance of most drugs; dialysate blood flow rates more than 1.5 times the Qb do not achieve higher clearance
  - Using porous dialyzers, molecules up to about 11.8 kDa (β_2-microglobulin) theoretically can be dialyzed

- The various modifications of hemodialysis with large-pore membrane dialyzers (continuous arteriovenous hemofiltration [CAVH], continuous arteriovenous hemodialysis [CAVHD], continuous venovenous hemofiltration [CVVH], and continuous venovenous hemodialysis [CVVHD]) that rely on convection for solute and fluid removal are highly efficient at removing drugs
  - Highly porous membranes may obviate the need for hemoperfusion
  - Although continuous dialysis methods may achieve greater drug removal over time compared with standard hemodialysis, this may not be a desirable clinical goal if rapid reversal of a poison effect is necessary; eg, reversal of coma or hypotension as a result of barbiturate poisoning

Hemoperfusion

- Hemoperfusion is the method by which anticoagulated blood is passed through a column containing sorbent particles
  - Activated charcoal particles and resin beads (with or without ligands) contained in hemoperfusion devices have been used
    - Platelet depletion is the main side effect of uncoated charcoal (carbon) hemoperfusion; substantial improvement is achieved by coating the particle surface with a thin biocompatible membrane
    - Carbon is efficient at removing lipid- and water-soluble drugs
    - Certain resins are most effective for removal of lipid-soluble drugs
  - Antibody- or antigen-coated particle hemoperfusion devices have been constructed for the removal of specific toxins
- Clinically available hemoperfusion devices are: Gambro Adsorba, Asahi Hemosorba, Smith and Nephew Haemocol, and B Braun Hemoresin
- Hemoperfusion uses the physical process of drug adsorption, and in many instances, drug removal is superior to hemodialysis, peritoneal dialysis, or diuresis
- Water- and lipid-soluble substances with molecular weights ranging from 113-40,000 Da may be adsorbed

Using Hemodialysis or Hemoperfusion in Poisoning

- Supplementary Boxes S1 and S2 (available as online supplementary material associated with this article at www.ajkd.org) list representative drugs that have been reported to be removed using dialysis or hemoperfusion; in many cases, enhanced drug elimination and/or decreased coma time in response to treatment have been observed

Clinical Criteria for Dialysis or Hemoperfusion

- Progressive deterioration despite intensive care
- Severe intoxication with hypoventilation, hypothermia, and hypotension
- Predisposition to complications of coma (eg, chronic obstructive pulmonary disease)
- Impaired normal drug excretory function due to hepatic, cardiac, or renal insufficiency
- Poisoning with agents with metabolic and/or delayed effects, eg, methanol and ethylene glycol
- Intoxication with a drug or poison that can be extracted at a rate exceeding endogenous elimination

Pharmacokinetics

- Hemoperfusion or hemodialysis can augment drug elimination during the active procedure
  - Documented mostly in animals, but also in humans for acetaminophen, digoxin, theophylline, ethchlorvynol, doxorubicin (Adriamycin; Bedford laboratories, www.bedfordlabs.com), and perhaps paraquat
  - Enhanced elimination is calculated from changes in K_{el} and $t_{½}$ during the procedure
    - For theophylline poisoning, enhanced elimination after the procedure is discontinued may be a consequence of exposure of previously saturated binding sites, allowing normal drug metabolism to take place
    - Many drugs do not fit a single-pool pharmacokinetic model and rather fit a multicompartment model with 2 or more K_{el}s

- Example of drug with multicomponent pharmacokinetics is digoxin, in which the intercompartmental transfer rate coefficient governs transfer between a deep (muscle) and a superficial compartment (plasma); elimination can be augmented if a device enhances the intercompartmental removal rate of digoxin

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SPECIFIC INTOXICANTS

Salicylates

- Acute toxicity characterized by tinnitus/deafness, diaphoresis, vomiting, a mixed acid-base disorder, and eventual pulmonary edema and CNS dysfunction
- Decontamination should include administration of activated charcoal and enhanced elimination should be attempted with urinary alkalinization
- Hemodialysis is indicated for evidence of severe acidosis, CNS dysfunction, pulmonary edema, or levels >80 to 100 mg/dL
- Slow low-efficiency dialysis (SLED) and continuous venovenous hemodiafiltration (CVVHDF) also are efficacious for salicylate removal and correction of acid-base abnormalities

Barbiturates

- Overdose should be treated through initial supportive measures, decontamination with activated charcoal, and enhanced elimination with urinary alkalinization
- Hemodialysis (especially high flux) and hemoperfusion are both effective for extracorporeal drug clearance
- In less severe poisoning or as addition to hemodialysis, urine alkalinization to pH 8 will enhance phenobarbital removal

Theophylline

- May present with acute and/or chronic toxicity, principally characterized by arrhythmias and CNS disturbances
- Initial supportive measures should be followed by activated charcoal administration
- Cardiac and neurologic toxicity may require antiarrhythmic and anticonvulsant therapy, respectively (although it should be noted that seizures often occur at lower blood levels in long-term toxicity)
- Hemoperfusion is the preferred method of extracorporeal clearance and is recommended for rapidly increasing levels or those >60 mg/L
- Hemodialysis, although less effective than hemoperfusion, may be more readily available and associated with fewer complications

Lithium

- Although narrow therapeutic window, nonetheless frequently used for the treatment of bipolar affective disorder
- Acute toxicity involves progressive neurologic impairment, whereas log-term sequelae include nephrogenic diabetes insipidus, cystic interstitial nephritis, and nephrotic glomerulopathies
- Sodium polystyrene sulfonate can be used as exchange resin to enhance lithium elimination
- In patients with normal kidney function, clearance is increased with volume expansion, loop diuretics, and interruption of distal reabsorption with amiloride or triamterene
- Toxicity generally not evident with blood levels <1.3 mEq/L
- For levels >2.5 mEq/L, extracorporeal removal using hemodialysis (or hemofiltration) is indicated
- Levels may rebound after initial treatment and should be monitored carefully because repeated treatments may be necessary

Methanol

- Potentially fatal intoxicant that may be ingested, inhaled, or absorbed through the skin
- Initial signs of intoxication include inebriation and stupor, during which time a serum osmolar gap may be present
- Further toxicity follows a latent period of several hours
  - During this period, enzymatic biotransformation occurs in the liver and kidneys
    - ADH produces formaldehyde
    - Aldehyde dehydrogenase produces formic acid
  - Presence of anion gap metabolic acidosis indicates formate retention and the potential for retinal damage and blindness, cerebral hemorrhage and necrosis, Kussmaul respiration with apnea, coma, and death
- Due to rapid invasion (minutes), enteric decontamination is not possible
- Prevention of biotransformation and extracorporeal elimination of methanol and metabolites are the goals of treatment
  - Medical therapy involves folic or folinic acid to promote conversion of formate to water and carbon dioxide and ethanol or fomepizole (4-methyl pyrazole [4-MP]) to compete with ADH
    - Fomepizole is safer, but more expensive than ethanol
    - At methanol levels <20 mg/dL, fomepizole may be sufficient treatment, but requires prolonged (several days) infusion
  - Hemodialysis preferred for more severe intoxication
    - Clears methanol and formate and corrects metabolic acidosis
    - Indicated for acidosis, organ toxicity, or levels >50 mg/dL
    - Methanol levels may rebound and should be monitored accordingly
    - Because fomepizole and ethanol are dialyzable, dosage should be adjusted during dialysis

Ethylene Glycol

- Toxic alcohol with a sweet taste
- Often mixed with a fluorescein dye to aid in identification
- Ingestion is followed by absorption within an hour, subsequent inebriation, and stupor, with an evident serum osmolal gap
- As with methanol, toxicity and acidosis follow a latent period of biotransformation
  - ADH converts ethylene glycol to glycoaldehyde and eventually glycolic acid, glyoxylic acid, and oxalic acid
  - Anion gap metabolic acidosis then is evident, partly due to oxalate retention and lactic acidosis
  - Life-threatening CNS, cardiac, and kidney toxicity occur due to oxalate crystal deposition in blood vessels and tissues
  - Hypocalcemia and crystalluria also may be evident
- Treatment consists of inhibition of metabolism and extracorporeal elimination of ethylene glycol and metabolites
  - Medical therapy involves pyridoxine and thiamine to promote conversion of glyoxy-

lic acid to glycine rather than oxalate, and fomepizole or ethanol to competitively inhibit ADH
    - As with methanol, prolonged fomepizole infusion may be necessary when dialysis, the preferred treatment, is not used for more rapid clearance
  - Hemodialysis is indicated for organ toxicity, acidosis, and levels >50 mg/dL
    - There is potential for rebound, and repeated treatments may be necessary to maintain levels <20 mg/dL

Isopropyl Alcohol (isopropanol)

- An alcohol with toxic potential, readily available as a solvent or in "de-icing" and cleaning products
  - Often ingested by alcoholics in place of ethanol; for example, in-hospital hand sanitizer
  - Toxicity in children usually the result of misguided topical use by parents to reduce fever
- Toxicity may result from ingestion, inhalation, or dermal exposure
  - CNS depression may result in intoxication/stupor or coma
  - Hypotension/shock can result from myocardial and brainstem depression
  - Gastritis with hemorrhage and rhabdomyolysis also described
- Rapid invasion/absorption follows within several hours of ingestion
  - Increased serum osmolality (osmolal gap) evident
- Largely metabolized (80%) to acetone in the liver by ADH
  - Acetone may be identified by fruity odor on breath
  - Ketonemia/ketonuria is present without hyperglycemia
- Metabolic acidosis with increased anion gap may be evident, although rare
  - The result of lactate production from hypoperfusion, type A
- Treatment generally consists of appropriate supportive care
  - Fluid resuscitation and/or pressors, airway protection, and mechanical ventilation
- Although fomepizole effectively inhibits metabolism of isopropyl alcohol to acetone, toxic metabolites not of principal concern as with ethylene glycol and methanol
- Hemodialysis (standard intermittent or continuous) efficiently removes isopropyl alcohol and acetone
  - Recommended when evident hypotensive shock, respiratory failure, stupor, or coma and with isopropyl alcohol levels >400 mg/dL
- Hemodialysis is more efficient than peritoneal dialysis for clearance of isopropyl alcohol

Propylene Glycol

- An alcohol with low toxic potential used commercially as a coolant, in small quantities as a food or cosmetic additive, and as a medication solvent
  - Iatrogenic toxicity reported after intravenous administration of large and/or prolonged dosages of lorazepam; also possible with diazepam, phenytoin, phenobarbital, and etomidate
  - Oral toxicity unlikely unless large quantities in young children
  - Organ dysfunction (liver and kidney) and long-term ethanol abuse likely to increase toxicity
- Reported clinical effects include sepsis-like syndrome and acute kidney injury (possibly due to proximal acute tubular necrosis [ATN])
- Increased serum osmolality (osmolal gap) evident
- Metabolic acidosis with increased anion gap due to lactate accumulation may be evident
  - Metabolized in liver to lactate by ADH
- Treatment consists of cessation of medication infusion (if applicable) and appropriate supportive care
- Although fomepizole effectively inhibits metabolism to lactate, role in therapy uncertain and clinical judgment is necessary
- Hemodialysis effectively removes propylene glycol and lactate
  - Recommended for severe lactic acidosis

Metformin

- A biguanide oral antihyperglycemic medication used in the treatment of type 2 diabetes mellitus and "off-label" for polycystic ovary

syndrome and nonalcoholic fatty liver disease
- Rare but well-recognized toxicity with high mortality reported with both therapeutic use and overdose: metformin-associated lactic acidosis (MALA)
  - Toxic potential increased with acute or chronic kidney insufficiency
  - Frequent concern ahead of procedures with risk of acute kidney injury, eg, radiocontrast administration
- Clinical signs are insidious and include malaise, abdominal discomfort, nausea, and vomiting
- Severe acidemia (pH <7.0) and type B lactate acidosis with increased anion gap reported
  - Lactate production results from mitochondrial dysfunction and accelerated glycolysis
- Initial treatment involves supportive care and sodium bicarbonate infusion
- Hemodialysis efficiently removes metformin and lactate and corrects acidosis with volume-neutral bicarbonate delivery
- Peritoneal dialysis and hemofiltration with intravenous alkaline therapy also reported to be effective

Valproic Acid (valproate)

- A carboxylic acid used in bipolar disorder, seizures, and migraine with potential for overdose
  - Has become common exposure in United States, resulting in deaths
- Toxicity may result from ingestion
  - CNS depression varies in severity from cerebral edema to mild confusion
  - Also causes hypothermia, hypotension, nausea, vomiting, and diarrhea
  - Major cause of hepatotoxicity and hyperammonemia
  - Induces hypernatremia, hyperosmolality, hypocalcemia, and high-anion-gap acidosis
- Rapid absorption within several hours of ingestion
  - Plasma $t_{½}$ of 6-16 hours
  - Metabolized by conjugation in liver
  - Protein binding high (>85%) at therapeutic concentrations, but decreases with increasing concentrations (at 300 μg/mL, protein binding is 35%)
  - V_d is 0.1-0.5 L/kg, and molecular weight is 144 Da
- Treatment generally consists of appropriate supportive care
  - Fluid resuscitation and/or pressors, airway protection, and mechanical ventilation
  - L-Carnitine may be used for hyperammonemia, and naloxone may reverse CNS depression
  - Hemodialysis (standard intermittent or continuous) or hemoperfusion efficiently removes the unbound fraction of drug

Recommended when evident hypotensive shock, respiratory failure, stupor, or coma and with valproic acid (valproate; VPA) levels >150 μg/mL
- High-flux hemodialysis is more sustained than hemoperfusion (saturation of devices) for VPA clearance

Amanita Mushrooms

- A wild mushroom species (*Amanita phalloides*) ingested by mistake for edible mushrooms
  - Results in GI discomfort and delayed hepatic damage
  - Often seen in outbreaks, for example, after family picnics
- Reported clinical effects include diarrhea and vomiting progressing to hepatic cell death, coma, and renal tubule necrosis
- Increased levels of transaminases and creatinine evident
- Toxin is an octapeptide amanitin that is not destroyed in cooking process (or freezing and drying)
- Hemodialysis and hemoperfusion controversial because amanitin is not readily measured and Cl is unknown; anecdotal reports of recovery are positive and negative
  - Recent reports on the Molecular Adsorbents Recirculating System (MARS; uses resins and albumin to remove protein-bound toxins) have reported success in case series and case reports

- Liver transplant may be necessary

Methotrexate

- An inhibitor of dihydrofolate reductase; interrupts DNA synthesis of dividing cells
  - Widely used to treat oncologic diseases and autoimmune disorders and as an abortifacient
  - Inadvertent dosage errors and kidney failure are the major causes of methotrexate (MTX) intoxication
    - Dosage is calculated on a body-weight basis and is adjusted for kidney function (GFR)
    - With GFR in the reference range, the drug is 90% excreted by kidneys
- Manifestations of MTX toxicity are marrow suppression and its consequences and severe mucositis in the GI tract from mouth to intestinal mucosa; in addition, MTX may induce tumor lysis and has been shown to be teratogenic; may also induce hemorrhagic cystitis, which in the long term can cause bladder cancer
  - Toxic potential increases with acute or chronic kidney insufficiency
  - Bladder toxicity may be prevented by mesna pretreatment
  - Mucosal and bone marrow toxicity can be reversed somewhat by "leucovorin rescue"
- Clinical signs relate to effects on bone marrow: fever, leukopenia, diarrhea, GI bleed, hemorrhagic cystitis, and alopecia
- Initial treatment involves supportive care and leucovorin rescue
- It has been known for some time that MTX (molecular weight, 454 Da) is removable by hemodialysis (and its modifications CAVHD or CVVHD), multiple-exchange peritoneal dialysis, and hemoperfusion
  - High-flux hemodialysis efficiently removes MTX and may prevent toxicity, with Cl values around 70-143 mL/min

Procainamide

- Class 1a antiarrhythmic drug introduced in 1951; was used for atrial fibrillation and Wolf-Parkinson-White syndrome; rarely used now
- Molecular weight is 252 Da, with large V_d (1.4 L/kg)
- Its main metabolite, *N*-acetyl procainamide (NAPA), has twice the $t_{½}$ of the parent drug and is equipotent to procainamide (PA)
  - Toxic potential increased with acute or chronic kidney insufficiency
- Its main side effect is hypotension, but in overdose
  - Hypotension, lethargy, mental confusion
  - Rash, myalgia, fever, agranulocytosis, drug-induced lupus erythematosus, and torsades de pointes
- Hemodialysis (alone or combined with hemoperfusion) efficiently removes PA and NAPA; however, because the V_d is large, repeated treatment often is required to decrease their plasma concentrations
  - Reported Cl values
    - Hemodialysis, 88 mL/min
    - Hemoperfusion, 61 mL/min
    - Peritoneal dialysis, 3-5 mL/min
    - Combined hemoperfusion/hemodialysis, 135 mL/min

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CODING AND REIMBURSEMENT

Adverse Effect Codes

- When the drug was prescribed correctly and administered properly, the reaction plus the appropriate external cause (E) code, which ranges from E930-E949 (drugs, medicinal, and biological substances causing adverse effects in therapeutic use), should be coded

Poisoning Codes

- Poisoning includes *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 960-979 and encompasses a variety of situations
  - Error was made in drug prescription
  - Intentionally taken overdose of a drug
  - Nonprescribed drug taken with correctly prescribed and properly administered drug
  - Examples are wrong dose, wrong substance, wrong route of administration
- When coding a poisoning or reaction to the improper use of a medication, the poisoning code is sequenced first, followed by a code for the effect or result (eg, renal failure, delirium, respiratory failure)
  - If there also is a diagnosis of drug abuse or dependence to the substance, the abuse or dependence is coded as additional code
- E codes also should be assigned to indicate intent
  - Accidental
  - Intentional self-harm (suicide)
  - Assault
  - Undetermined (used when cannot be determined whether intent was accidental or intentional)

Drug Overdose by Unspecified Drug or Medicinal Substance

- Diagnosis code: 977.9 (ie, subcategory of poisoning by unspecified drug or medicinal substance)
- E code: E858.9 for accident, E950.5 for suicide attempt, E962.0 for assault, E980.5 for undetermined

Salicylate (acetylsalicylic acid)

- Diagnosis code: 965.1 (ie, subcategory of poisoning by analgesics, antipyretics, and antirheumatics)
- E code: E850.3 for accident, E950.0 for suicide attempt, E962.0 for assault, E980.0 for undetermined

Barbiturate

- Diagnosis code: 967.0 (ie, subcategory of poisoning by sedatives and hypnotics)
- E code: E851 for accident, E950.1 for suicide attempt, E962.0 for assault, E980.1 for undetermined

Theophylline

- Diagnosis code: 975.7 (ie, subcategory of poisoning by agents primarily acting on the smooth and skeletal muscles and respiratory system)
- E code: E858.6 for accident, E950.4 for suicide attempt, E962.0 for assault, E980.4 for undetermined

Toxic Effect Codes

- Toxic effect occurs when a harmful substance is ingested or comes in contact with a person
- Includes *ICD-9* codes 980-989
  - A toxic effect should be sequenced first, followed by the code(s) that identify the result of the toxic effect
  - E codes also should be assigned to indicate intent

Lithium

- Diagnosis code: 985.8 (ie, subcategory of toxic effect of other metals)
- E code: E866.4 for accident, E950.9 for suicide attempt, E962.1 for assault, E980.9 for undetermined

Methanol

- Diagnosis code: 980.1 (ie, subcategory of toxic effect of alcohol)
- E code: E860.2 for accident, E950.9 for suicide attempt, E962.1 for assault, E980.9 for undetermined

Ethylene Glycol

- Diagnosis code: 982.8 (ie, subcategory of toxic effect of solvents other than petroleum-based)
- E code: E862.4 for accident, E950.9 for suicide attempt, E962.1 for assault, E980.9 for undetermined

Current Procedural Terminology Codes for Hemodialysis or Hemoperfusion

Hemodialysis Services

- 90935 (hemodialysis procedure with single physician evaluation)
- 90937 (hemodialysis procedure requiring repeated evaluation[s] with or without revision of dialysis prescription)
- Subsequent hospital care codes 99231-99232 cannot be reported on the same day when *Current Procedural Terminology* (*CPT*) codes 90935 and 90937 are performed

Hemoperfusion

- 90997 (hemoperfusion [eg, with activated charcoal or resin])

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SUPPLEMENTARY MATERIALS

Box S1: Drugs and Chemicals Removed With Dialysis

Box S2: Drugs and Chemicals Removed With Hemoperfusion

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2010.05.014) is available at www.ajkd.org.