Fundaments of Toxicology—Approach to the Poisoned Patient

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Management of the poisoned patient begins with supportive care, assessment of organ function and dysfunction, and consideration of known or suspected poisons. The possibility of multiple ingestions should be considered with intentional exposures or suicide attempts. Enteric decontamination involves treatment to prevent the absorption of toxins from the gastrointestinal system and includes the use of activated charcoal. Poisoned patients may benefit from the use if antidotes are available, or enhanced elimination as with salicylate ion trapping during urinary alkalinization. The use of intravenous lipid therapy is of clinical benefit in poisoning from bupivacaine, amitriptyline, and bupropion. Hemodialysis is the most inexpensive, widely available, and most commonly used method of extracorporeal drug removal in the treatment of poisoning. Chelators with different chemical properties can bind toxic metals, providing an essential mechanism for detoxification, and may be used in combination with extracorporeal therapies such as DFO with HD for aluminum or iron, and DMSA or DMPS with HD to treat arsenic or mercury intoxication. The use of displacers with hemodialysis can be considered to augment clearance of protein-bound toxins.

Key Words: Activated charcoal, Antidotes, Urinary alkalinization, Hemodialysis, Chelation

Of the approximately 2.1 million human poison exposures in the United States reported in 2017, almost one-third were referred to or managed in health care facilities.[1] Management of the poisoned patient begins with supportive care, assessment of organ function and dysfunction, and consideration of known or suspected poisons. Patients with unstable presentation may require an established airway and ventilation, circulatory support, and/or advanced cardiac life support. Kidney function should be assessed, along with urine output and any electrolyte or acid-base derangements, as these may determine intervention. Investigation at presentation should include intake regarding the specific intoxicant(s), dose, and timing of exposure. The possibility of multiple ingestions should always be considered, particularly with intentional exposures or suicide attempts. When available, drug screens and levels should be measured; and the route of endogenous elimination of a poison or intoxicant should be established.

Nephrologists should be familiar with initial supportive care and more specific treatments such as decontamination, antidotes, and enhanced elimination. The application of extracorporeal therapies—hemodialysis, hemofiltration, and hemoperfusion—will also be reviewed, as useful adjuncts in the treatment of poisoning.[2]

ENTERIC DECONTAMINATION

For most poisonings, ingestion is the route of exposure. Enteric decontamination involves treatment to prevent the absorption of toxins from the gastrointestinal system and includes the use of activated charcoal, gastric lavage, cathartics, whole bowel irrigation, and ipecac or other emetics (Table 1). Many of these methods have no current role in poisoning treatment and are not recommended.

Unconscious patients and patients with impaired airway protection should not undergo enteric decontamination before endotracheal intubation due to the risk of aspiration and pneumonitis.

Activated charcoal (single or multiple dose) adsorbs a variety of toxins and may prevent absorption from the gastrointestinal tract, if administered within 1 hour of ingestion. Activated charcoal is associated with minimal risk and should be considered on presentation, despite a lack of outcome-based evidence.[3-5]

Gastric lavage is not recommended in the treatment of poisoning.[6] The procedure is associated with diminishing recovery of ingested poison or pills with time after ingestion; lack of demonstrable clinical benefit in illness severity, recovery time, or outcome; and significant risk of aspiration and pneumonitis, laryngospasm, and perforation of the stomach or esophagus (with mediastinal emphysema).[7] Although lavage has been advocated for some toxins (eg, paraquat) or drugs that slow gastrointestinal transit (eg, tricyclic antidepressants), there is no sufficient evidence of clinical benefit when compared with activated charcoal.[8] The use of gastric lavage in poisoning is so rarely employed that expertise is lacking and kits are largely unavailable. Lavage should only be attempted by experienced practitioners at the direction of a poison control center.

The use of cathartics is not recommended for enteric decontamination in the treatment of poisoning.[9] Catharsis with sorbitol or magnesium salts when attempted does increase gastrointestinal transit time, but without apparent clinical benefit in poisoning. In addition, when combined with activated charcoal, cathartics may increase rate of passage but do not appear to decrease absorption of the offending agent and in some studies can interfere with adsorption by activated charcoal.

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Financial Disclosure: The authors have no conflicts of interest or relationships to disclose.

Support: The authors are not supported by grants.

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1548-5595/$36.00

https://doi.org/10.1053/j.ackd.2019.12.001

Whole bowel irrigation with saline or polyethylene glycol can be considered in ingestions of sustained-release or enteric-coated drugs, particularly with presentation later (more than 2 hours after ingestion) than the window of benefit expected with activated charcoal. In addition, it is beneficial in cases with iron, lithium, or potassium tablets as well as ingested narcotic packets. Whole bowel irrigation is not routinely recommended; is contraindicated in patients with bowel perforation, obstruction, or ileus; and should not be used with activated charcoal.[10]

Induction of emesis with syrup of ipecac is not recommended for routine practice in poisoning owing to uncertain efficacy, poor drug recovery, and interference with other efficacious treatments.[11] Induced emesis may be of rare benefit in "out-of-center" poisoning.[12] Ipecac is now widely unavailable and only rarely used worldwide.[13]

Although not recommended in poisoning, it should be emphasized that induced emesis or gastric lavage should never be attempted after ingestion of caustic substances such as acids, alkalis, or hydrocarbons due to exacerbation of mucosal injury or pneumonitis.[14]

ANTIDOTES

Antidotes should be considered whenever available, and nephrologists should be familiar with their use.[15] For several poisonings, there are specific agents that can counteract toxicity, through a variety of mechanisms including competitive receptor antagonism, increased metabolism to less harmful compounds, inhibition of metabolism to harmful compounds, immune clearance, and other important molecular effects. Intraosseous route of administration is effective with many antidotes when intravenous access is not available.[16] Table 2 lists several important antidotes, although regularity of use and stocking recommendations may vary considerably.[17]

CLINICAL SUMMARY

- The approach to the poisoned patient includes supportive care, enteric decontamination, consideration of antidotes when available, enhanced elimination, and in some cases the use of extracorporeal therapies.
- In some cases of poisoning, intravenous lipid emulsion or the use of chelators may be of clinical benefit.

INTRAVENOUS LIPID EMULSION

The off-label use of intravenous lipid emulsion is recommended for severe poisoning with local anesthetics, in particular, cardiac arrest due to bupivacaine. Administration in severe and treatment refractory poisoning due to amitriptyline and bupropion is also recommended (Table 3).[18] Intralipid 20%®—a fat emulsion approved for parenteral nutrition—is the most frequently used formulation. Despite limited evidence, intravenous lipid emulsion has been administered for many drug intoxications. Caution, however, is advised owing to reported adverse effects with the poisoning regimen, including fat embolism, lung injury, lipid derangements, pancreatitis, and fat deposition and circulatory compromise during extracorporeal membrane oxygenation.[19]

ENHANCED ELIMINATION

Enhanced elimination describes measures to increase endogenous drug/toxin clearance in the urine through ion trapping by urinary pH modulation, diuresis, or forced diuresis. Of note, some authors also use the term broadly and inclusive of enteric decontamination and extracorporeal therapies.

Ion trapping involves modulation of urine pH to increase the excreted fraction of a drug by ensuring that it remains dissociated/ionized in the urinary lumen and, in turn, poorly reabsorbed. Many drugs and toxins are weak acids or bases, and the dissociation constant (pKa) of a drug determines ionization. Elimination of the anionic form of weak acids (such as salicylate) is increased at a higher or alkaline urine pH (>7.5), whereas cationic forms of weak bases (such as amphetamine) require low or acidic urine pH (<5.5). Although the clearance of many drugs is not substantially increased by this maneuver, salicylate (pKa 2.97) excretion is quadrupled with urinary pH > 7.5. Other mechanisms may explain the increase in salicylate elimination at alkaline urine pH, as the drug remains almost entirely ionized in physiologic urinary pH range. Complications of alkalinization include alkalosis with tetany and hypokalemia, and the procedure requires careful monitoring of blood and urine pH, and repletion of potassium as necessary.

Alkalinization of urine is recommended for the treatment of salicylate poisoning, of moderate severity, when dialysis is not indicated (Table 3). Alkaline diuresis is unnecessary and is not recommended. Alkaline diuresis and high urinary flow rates (>600 mL/hour) may be beneficial in patients with severe 2,4-dichlorophenoxyacetic acid and mecoprop poisoning. Alkalinization is not superior to multidose activated charcoal and is not recommended for treatment of barbiturate poisoning.[20]

Alkalinization is part of a combined prevention strategy (with glucarpidase and leucovorin) to increase elimination and prevent toxicity during treatment with high-dose methotrexate (pKa of 4.8 and 5.5), and the contribution of alkalinization may be significant.[21,22]

Urinary acidification to increase drug elimination has been attempted with ammonium chloride, ascorbic acid, and cranberry juice. Although acidification can increase the elimination of amphetamine and phencyclidine,[23] supportive care is usually sufficient and it is not recommended owing to potential exacerbation of myoglobinuric kidney injury due to rhabdomyolysis.

Forced diuresis has no current role in the treatment of poisoning, although a system of forced diuresis and matched hydration to maintain euvolemia may be an emerging preventative measure for contrast-induced acute kidney injury.[24]

Table 1. Enteric Decontamination

Unconscious patients should not undergo enteric decontamination, due to risk of aspiration
Activated charcoal prevents enteric absorption if given within one hour of toxic ingestion
Gastric lavage is not recommended for gastrointestinal decontamination
Use of cathartics is not recommended for gastric decontamination
Whole bowel irrigation can be considered with late presentation of ingestion of sustained release/enteric coated drugs—iron, lithium, potassium tablets ingestions, ingested narcotic packets.
Use of ipecac and induced emesis is not recommended for gastrointestinal decontamination

EXTRACORPOREAL THERAPY

The extracorporeal modality most frequently used in the treatment of poisoning is intermittent hemodialysis (with modern, high efficiency, high-flux synthetic membranes), with hemofiltration occasionally used, and hemoperfusion only rarely.[1]

The decision to use dialysis or another modality for detoxification is clinical and usually involves deterioration despite supportive treatment, with evident hypoventilation, hypothermia, hypotension, or mental status deterioration (progressive lethargy, stupor, or coma). The presence of acute kidney injury and electrolyte or acid base derangements should influence the decision to dialyze. Slow or continuous modalities may be required with significant hemodynamic instability, although slower clearance should be expected. The principles governing drug removal with each modality will be reviewed. Discrete indications for the use of dialysis to clear specific intoxicants will also be reviewed in another section, including treatment based on drug levels.

HEMODIALYSIS

Hemodialysis is the most inexpensive, widely available, and most commonly used method of extracorporeal drug removal in the treatment of poisoning.[25] Factors governing drug removal with hemodialysis are both drug related and dialysis related. Drugs with small size (molecular weight <500 Da), high water solubility, low degree of protein binding, small volume of distribution (<1 L/kg of body weight), and rapid equilibration to plasma from tissue will be more readily dialyzable. Dialysis factors include access type, blood and dialysate flow rates, and physical properties of the dialyzer (material, surface area, and pore size). As molecular weight increases, drug removal becomes less a function of diffusion than convection.[26] Historically, hemodialysis solely involved diffusive clearance, and increasing clearance of small drugs/solutes (<300 Da) can still be achieved with increasing blood and dialysate flow rates. As noted, high-efficiency, high-flux dialyzers and the option of convective fluid removal are now standard with modern conventional dialysis. Larger drugs/solutes (>300 Da) are less diffusible, and although clearance might be possible with the increased surface area and permeability of the modern dialyzers, true convection modalities such as hemofiltration or hemodiafiltration are theoretically superior for larger molecular weight intoxicants.

Hemodialysis is essential in the treatment of some cases of lithium, methanol, ethylene glycol, and salicylate poisoning. These toxidromes will be separately reviewed in other sections.

HEMOFILTRATION

As mentioned, convective modalities can clear larger molecules than dialysis. Molecular weight (up to 50,000 Da) and degree of plasma protein binding are the major determinants of membrane passage. The passage of a solute from plasma into the ultrafiltrate is described as the sieving coefficient—variable from 0 (negligible) to 1 (complete), with total clearance equal to the sieving coefficient multiplied by the ultrafiltration rate.

Intermittent hemofiltration or hemodiafiltration is used infrequently in the treatment of poisoning, seemingly limited by availability. Hemofiltration is usually employed continuously, such as continuous veno-venous hemofiltration (CVVH). In this setting, CVVH may be useful for the removal of large molecular weight drugs, with large volume of distribution, slow equilibration, or likelihood of rebound.[27] Hemodynamic instability, of course, provides an additional indication. Rapid detoxification in severe poisoning should not be attempted with CVVH at low blood flow rates, and overall, there are little data on the treatment of poisoning by hemofiltration.

HEMOPERFUSION

Hemoperfusion, although infrequently used in poisoning, involves adsorption of a drug or intoxicant from blood perfused over a large surface area column. Columns containing microporous activated charcoal (or carbon) remain the only approved devices in the United States, whereas engineered resin columns are available worldwide. Carbon columns can remove both lipid and water soluble drugs with molecular weight ranging from 100 to 40,000 Da.

The major disadvantage of hemoperfusion is that it can only provide clearance and not metabolic control. In addition, columns are more expensive than hemofilters and can become saturated during treatment with declining clearance. The procedure also requires systemic anticoagulation, and adverse effects are typical and include flushing and thrombocytopenia.

The standardization of high-flux membrane hemodialysis—and the ability to clear larger solutes with a more tolerable, available, and less expensive modality—has eliminated many indications for hemoperfusion.[28,29] Paraquat is one of the few poisonings for which hemoperfusion is superior to modern hemodialysis, although it may be the preferred modality for some lipid soluble drugs.

PERITONEAL DIALYSIS

Peritoneal dialysis cannot provide efficient time-dependent reversal of severe drug intoxication and should only be used in the treatment of poisoning of infants and

Table 2. Antidotes

Naloxone	For treatment of opiate and opioid overdose, μ-receptor antagonist; reverses CNS and respiratory depression. Available over-the-counter.
Anti-venom	Available treatment for snake (rattlesnake/*Crotalidae*, coral/*Micrurus fulvius*) spider (black widow/*Latrodectus mactans*), scorpion, and other envenomations.
Atropine and pralidoxime (2PAM)	For procholinergic manifestations of organophosphate poisoning.
Botulinum antitoxin	For treatment of botulism, in complement with supportive care. Trivalent and heptavalent equine immunoglobulin fragments are available for adults, whereas a divalent human immune globulin may be preferable in infants.
Diazepam	For chloroquine overdose in complement with supportive care, reduces mortality.
Digoxin immune Fab (Digibind®)	For digoxin/digitoxin overdose. Digoxin-ab complexes result in persistent drug levels and may not be clear without sufficient kidney function, even with hemodialysis; rebound poisoning/dissociation reported days after treatment in kidney failure patients. Also of clinical benefit with other cardiac glycosides, such as in poisoning due to oleander ingestion, and poisonous toad (*Bufo* species) encounters or venom containing Chinese medicine Chan Su or aphrodisiac compounds.
Flumazenil	For benzodiazepine overdose, not routinely recommended because of seizure risk.
Fomepizole/4MP	For methanol and ethylene glycol poisoning. As with ethanol, inhibits alcohol dehydrogenase, preventing the formation of toxic metabolites.
Glucagon	Treatment for ß-blocker overdose.
Glucarpidase	For methotrexate overdose or nephrotoxicity. Carboxypeptidase G2, provides enzymatic hydrolysis of methotrexate to metabolites, and nonrenal clearance.
Hydroxocobalamin, amyl nitrite, sodium nitrite, and sodium thiosulfate	For cyanide poisoning.
Methylene blue	For treatment of methemoglobinemia (Hgb-Fe3+) from oxidizing agents (eg, nitrates, sulfonamides, local anesthetics, rasburicase) and carbon monoxide and cyanide toxicity. Reducing agent.
NAC *N*-acetylcysteine	For acetaminophen overdose/poisoning. Increases glutathione stores, preventing toxicity of the *N*-acetyl-*p*-benzoquinone imine (NAPQI) metabolite.
Octreotide	For oral hypoglycemic overdose.
Phentolamine	For vasopressor extravasation treatment.
Physostigmine	For anticholinergic poisoning (atropine/*Belladonna* and *Datura).*
Phytonadione/VitK	For warfarin overdose.
Praxbind idarucizumab	For Pradaxa/dabigatran overdose. Monoclonal antibody, specific benefit only, not for overdose of other anticoagulants.
Prothrombin complex	For anticoagulant overdose. Can also give recombinant factor VIIa.
Pyridoxine	For isoniazid (INH) poisoning and a cofactor in the treatment of ethylene glycol poisoning.
Sodium bicarbonate	For tricyclic antidepressant (TCA) poisoning and ion trapping with salicylate poisoning.

small children or when other methods are unavailable.[30] In patients already receiving peritoneal dialysis, rapid exchanges can be performed to increase clearance of readily dialyzable drugs.[31] One advantage of peritoneal dialysis is the ability to provide active warming to increase core temperature in the hypothermic poisoned patient.

Table 3. Additional Therapy for Poisoning

Intravenous lipid emulsion recommended for severe poisoning with local anesthetics, such as cardiac arrest due to bupivacaine.
Intravenous lipid emulsion recommended for severe and treatment refractory poisoning due to amitriptyline and bupropion.
Alkalinization of urine (to pH > 7.5) effectively increases salicylate elimination and is recommended for the treatment of salicylate poisoning, of moderate severity, when dialysis is not indicated.
Alkaline diuresis and high urinary flow rates (>600 mL/hour) may be beneficial in poisoning with the herbicides 2,4-dichlorophenoxyacetic acid and mecoprop.
Urinary acidification and forced diuresis have no established role in the treatment of poisoning.

CHELATION THERAPY

Chelation therapy involves the use of compounds to treat poisoning due to metals. Chelators with different chemical properties can bind toxic metals (often with relative binding affinities) and promote excretion from the body, often providing an essential mechanism for detoxification.[32]

The most typical metal intoxications treated with chelation are arsenic, lead, and mercury, which are well-established neurotoxins.[33] Although many other metal intoxifications have been described, outcome of therapy is often uncertain, whereas chelators may deplete either essential or trace elements through bycatch.[34] Use of chelators should include prompt surveillance for copper, selenium, zinc, or magnesium deficiency.

The route of administration can be intravenous, intramuscular, or oral. Nephrologists should be familiar with several chelators, although they should be used with

Table 4. Chelators

Deferoxamine (DFO)	For iron removal in acute poisoning or chronic overload (hemochromatosis, transfusion-dependent thalassemia, or sickle cell anemia), also effective for aluminum toxicity.
Deferasirox & Deferiprone	Deferasirox and deferiprone are oral iron chelators.
Dimercaprol (BAL) or *British anti-Lewisite*	For **arsenic**, **lead**, and **mercury** poisoning.
2,3-dimercaptosuccinic acid (DMSA) or *succimer*	For **arsenic**, **lead**, and **mercury** poisoning. Safer derivative of BAL. Water soluble. For oral or intravenous use.
2,3-dimercapto propanesulfonic acid (DMPS)	For **arsenic**, **lead**, and **mercury** poisoning, may be the treatment of choice for arsenic poisoning. Water soluble. For oral or intravenous use. Not FDA approved, although under review.
Ethylenediaminetetraacetic acid (calcium EDTA)	For **lead** poisoning, although replaced by DMSA for most cases of lead poisoning.
Penicillamine	For **copper** toxicity, although tetrathiomolybdate has replaced its use in Wilson's disease.
Ferric ferrocyanide or *Prussian blue*	For **thallium** and **cesium** poisoning.

caution, as some can also be toxic. DMSA and DMPS (see below) are leading chelators for clinical toxicologic use (Table 4).

COMBINED CHELATION WITH EXTRACORPOREAL DETOXIFICATION

Extracorporeal therapies are not effective in the treatment of heavy metal poisoning. The addition of chelating agents can increase clearance of the metal-chelator complex, either through dialysis, filtration, or adsorption. The administration of DFO at the end of dialysis to chelate iron in overloaded dialysis patients is perhaps the most frequent application. Aluminum intoxication can also be treated with DFO used in combination with high-flux polysulfone membranes, with recovery exceeding DFO combined with charcoal hemoperfusion.[35]

The combination of DMSA or DMPS and dialysis in the treatment of heavy metal toxicity may be beneficial in the setting of decreased endogenous kidney function.[36] Complexes with arsenic, lead, methylmercury, or inorganic mercury would otherwise be typically filtered by the glomerulus and excreted in urine. Clearance and effective treatment of inorganic mercury poisoning with combined DMPS and CVVHDF has also been reported.[37]

CLEARANCE OF PROTEIN-BOUND TOXINS THROUGH DISPLACER-AUGMENTED HEMODIALYSIS

As outlined previously, dialysis does not efficiently remove highly protein-bound toxins. More recently, a novel technique using a competitive binding inhibitor to displace protein-bound substances was shown to increase the clearance of several prototypical uremic toxins (p-cresyl sulfate and indoxyl sulfate).[38] In the study of dialysis patients, infusion of ibuprofen into the arterial line of the hemofilter effectively displaced the protein-bound uremic toxins from albumin, increasing the fraction of the unbound toxin and augmenting clearance. This technique could also be applied to drug poisoning, to increase the dialytic clearance of highly protein-bound drugs. A modeling study has shown effective reduction in duration of high-flux dialysis time to until drug concentration reaches therapeutic level for the highly protein-bound (~86%) drug phenytoin using aspirin infusion (shared binding at Sudlow Site I), and for the less protein-bound (~73%) drug carbamazepine using ibuprofen infusion (shared binding on Sudlow Site II) (Maheshwari V, Unpublished data, 2019). Investigators have concluded that future use of displacer-augmented hemodialysis will require careful consideration of the displacer, including awareness of albumin binding sites, displacer half-life, expectation of entry in the fluid compartments of the patient, and timing of infusion for later in the treatment to coincide with lowest free drug concentrations.

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