Enhanced elimination of poisons

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INTRODUCTION

Management of the poisoned patient begins with a thorough evaluation, recognition that poisoning has occurred, identification of the agent(s) involved, assessment of severity, and prediction of toxicity. Therapy involves the provision of supportive care, prevention of poison absorption, and, when appropriate, the use of antidotes and other interventions to enhance elimination of the poison.

Methods to enhance the rate of elimination of poisons following a toxic ingestion are reviewed here. General issues regarding the management of toxic ingestions, specific issues related to gastrointestinal decontamination and gastric emptying, and the diagnosis and management of specific poisonings are discussed separately.

- General poisoning (See "General approach to drug poisoning in adults" and "Initial management of the critically ill adult with an unknown overdose" and "Approach to the child with occult toxic exposure".)
- Gastrointestinal decontamination (See "Gastrointestinal decontamination of the poisoned patient".)
- Select common poisonings (See "Acetaminophen (paracetamol) poisoning in adults: Treatment" and "Management of acetaminophen (paracetamol) poisoning in children and adolescents" and "Salicylate (aspirin) poisoning in adults" and "Salicylate poisoning in children and adolescents" and "Acute opioid intoxication in adults" and "Opioid intoxication in children and adolescents" and "Cocaine: Acute intoxication" and "Benzodiazepine poisoning and withdrawal" and "Carbon

monoxide poisoning" and "Methamphetamine: Acute intoxication" and "Selective serotonin reuptake inhibitor poisoning".)

GENERAL INDICATIONS AND CONTRAINDICATIONS

Enhanced elimination techniques can accelerate removal of a toxin, but few studies have investigated whether they actually shorten the duration of clinical toxicity and/or improve clinical outcomes. The main methods of enhancing the elimination of toxins are listed in the table (table 1).

General indications for enhanced elimination techniques include:

- Ingestion of a poison whose elimination can be enhanced.
- Failure of a patient to respond to maximal supportive care.
- The clinical course is predicted to be complicated based on the nature and/or concentration of the toxin, impaired clearance of the toxin, comorbid illness, concomitant severe electrolyte or other laboratory derangements that can be corrected with enhanced elimination, or some combination of these elements.

In all cases, the expected benefits of the use of an enhanced elimination technique must be carefully weighed against the risk of potential complications associated with the technique.

MULTIPLE-DOSE ACTIVATED CHARCOAL

Multiple-dose activated charcoal (MDAC) is a commonly used method for enhancing the elimination of toxins and may play an important role in specific poisonings. MDAC is discussed in detail separately. (See "Gastrointestinal decontamination of the poisoned patient", section on 'Multidose activated charcoal'.)

URINARY ALKALINIZATION

The urinary excretion of some drugs can be enhanced by altering the urine pH [1,2]. Altering the pH converts a lipid-soluble intact acid (HA) or base (BOH) in the tubular lumen into the charged salt (A- or B+):

HA <—> H+ + A-
BOH <—> B+ + OH-

The charged particle is lipid-insoluble and cannot easily move back across the renal epithelium. This leads to a marked increase in drug excretion.

Raising the urine pH to 7.5 to 8.0 in patients poisoned with weak acids (such as salicylates and phenobarbital) will drive the first reaction to the right, producing the desired increase in concentration of the charged salt (A-). Importantly, phenobarbital is the only barbiturate for which alkalinization is indicated, as short-acting barbiturates are metabolized in the liver, not eliminated via the kidney [3,4].

Urinary acidification (urine pH below 5.5) with ammonium chloride or ascorbic acid was used in the past to treat intoxications with weak bases such as amphetamines, quinidine, or phencyclidine. However, this practice has been abandoned, as efficacy has not been established and iatrogenic toxicity (from severe acidemia) can occur.

Indications and efficacy — Drugs that are likely to respond to urinary alkalinization usually meet four criteria [4,5]:

- They are predominantly eliminated unchanged by the kidney
- They are distributed primarily in the extracellular fluid compartment
- They are minimally protein-bound
- They are weak acids with pKa ranging from 3.0 to 7.5

Urinary alkalinization may be useful for the drugs listed in the following tables: (table 2 and table 3).

The clinical course of phenobarbital-poisoned patients may be improved by the use of urinary alkalinization [2,6]. One study of 16 phenobarbital-poisoned patients found that the concomitant use of both urinary alkalinization and MDAC doubled the rate of elimination and shortened the period of unconsciousness by up to 50 percent compared with patients receiving supportive care alone [2]. No comparable data exist showing improved clinical outcomes with the use of urinary alkalinization in other types of poisoning [5].

Urinary alkalinization is the most effective single method short of hemodialysis to enhance salicylate excretion, producing a mean elimination half-life of 5 hours versus half-lives of 8 and 19 hours in patients treated with isotonic saline solution diuresis or standard supportive care, respectively [7]. (See "Salicylate (aspirin) poisoning in adults" and "Salicylate poisoning in children and adolescents".)

Technique — The goal of urinary alkalinization is to achieve a urine pH of 7.5 or higher while maintaining a serum pH no higher than 7.55 to 7.60. This is generally done by administering an IV bolus of 1-2 mEq/kg of 8.4 percent sodium bicarbonate, followed by continuous infusion of sodium bicarbonate. The fluid for continuous infusion is mixed by placing 150 mEq of sodium bicarbonate into one liter of 5 percent dextrose in water (D5W). Prior to the initiation of therapy, baseline measurements of electrolytes, blood urea nitrogen, serum creatinine, glucose, systemic pH, urinary

pH, and serum drug concentrations should be performed. Placement of a Foley catheter is recommended to accurately measure urine output.

Adults — After initial fluid resuscitation with isotonic 0.9% saline or lactated Ringer's solution and intravenous bolus of sodium bicarbonate, the sodium bicarbonate continuous infusion should be administered at approximately 200 to 250 mL/hour. The rate should be titrated based on the urinary and systemic pH, which should be monitored throughout treatment. Intravenous fluid should be adjusted to maintain a urine pH ≥7.5 and serum pH <7.60.

Children — After initial fluid resuscitation with isotonic 0.9% saline or lactated Ringer's solution and intravenous bolus of sodium bicarbonate, the sodium bicarbonate continuous infusion should be administered at approximately 1.5 times maintenance fluids (see "Maintenance intravenous fluid therapy in children"). The rate should be titrated to maintain a urine pH ≥7.5. Increases in serum pH up to 7.60 are well tolerated in patients with normal renal function. Subsequent fluid administration should be based on urine output and ongoing losses. (See "Maintenance intravenous fluid therapy in children".)

Acetazolamide should **not** be used to alkalinize the urine. Acetazolamide raises urine pH by lowering systemic pH, which may cause clinical deterioration in some cases. Close monitoring of blood and urine pH, electrolytes, respiratory status, and urine output is important when diuresis and urinary alkalinization procedures are performed. (See "Salicylate (aspirin) poisoning in adults" and "Salicylate poisoning in children and adolescents".)

Contraindications — Urine alkalinization is contraindicated in patients with established or incipient renal failure, pulmonary edema, and cerebral edema. In addition, volume overload may complicate therapy in patients with preexisting cardiac disease [4].

Complications — Complications of alkalinization include hypokalemia, excessive alkalemia, and ionized hypocalcemia, which results from increased protein binding of calcium. The administration of 20 to 40 meq/L (mmol/L) potassium chloride may be required if the plasma potassium concentration falls during urinary alkalinization. Monitoring and repletion of ionized calcium is recommended to prevent a deterioration in cardiac function.

Extracorporeal treatment (ECTR) of poisonings entails the use of a heterogenous group of modalities to promote removal of a toxicant and to support or temporarily replace the function of a vital organ. ECTR modalities include hemodialysis, hemoperfusion, hemofiltration, hemodiafiltration, and therapeutic plasma exchange, exchange transfusion, and peritoneal dialysis. ECTR modalities are used in only 0.1 percent of poisonings [8,9].

HEMODIALYSIS AND HEMOPERFUSION

Although rarely necessary for the care of poisoned patients, hemodialysis (HD) is used in greater than 95 percent of patients in whom extracorporeal treatment (ECTR) is employed to enhance poison elimination [10-12]. During HD, up to 400 mL of blood per minute passes through an extracorporeal circuit in which toxic compounds in blood diffuse through a semipermeable membrane down a concentration gradient into a dialysate. Electrolyte disturbances and metabolic acidosis induced by certain drugs also can be readily corrected with this intervention. (See "Renal replacement therapy (dialysis) in acute kidney injury: Metabolic and hemodynamic considerations".)

Hemoperfusion refers to the circulation of blood through an extracorporeal circuit containing an adsorbent such as activated charcoal or polystyrene resin. In contrast to HD circuits, hemoperfusion devices contain thin, highly porous membranes and adsorbents that provide a large surface area to directly bind toxins [13]. Clearance rates are higher with hemoperfusion than HD if the adsorbent binds the ingested toxin; the extraction ratio for hemoperfusion approximates 1.0 for some poisons, and drug clearance rates approach the rate of blood flow through the hemoperfusion circuit. The use of HD or hemoperfusion for the treatment of specific poisonings is discussed in the topics devoted to those toxins.

Continuous renal replacement therapy (CRRT) has gained acceptance as an effective alternative treatment. It includes continuous veno-venous hemofiltration (CVVHF) and continuous veno-venous hemodiafiltration (CVVHDF) [14]. The evidence for these techniques is scant. In general, CRRT has lower clearance rates than conventional HD. It might offer some benefit in unstable or hypotensive patients [15].

Peritoneal dialysis is **much less effective** than HD or hemoperfusion, and is rarely if ever indicated in the care of poisoned patients.

Efficacy — HD is most useful in removing toxins with the following characteristics:

- Low molecular weight (<500 daltons)
- Small volume of distribution (<1 L/kg)
- Low degree of protein-binding
- High water solubility
- Low endogenous clearance (<4 mL/minute per kg)
- High dialysis clearance relative to total body clearance.

The utility of HD and hemoperfusion is limited when the drug is not concentrated in the extracellular fluid because of high lipid solubility and/or tight tissue binding. These characteristics are present with

tricyclic antidepressants, digoxin, and calcium channel blockers. (See "Tricyclic antidepressant poisoning" and "Digitalis (cardiac glycoside) poisoning" and "Calcium channel blocker poisoning".)

Hemodialysis removes the toxic metabolites of methanol and ethylene glycol, corrects acid-base abnormalities, and reduces end-organ sequelae and mortality associated with these poisonings [13,16-18]. Although HD clears ethylene glycol and methanol efficiently, HD is not commonly indicated when acidosis is not present, as fomepizole effectively blocks the activation of these alcohols to the toxic acidic species [19,20]. Treatment with HD early in the course of care may be prudent and cost effective for methanol-poisoned patients that present with high serum concentrations but no acidosis because endogenous clearance of methanol in those treated with fomepizole is slow. (See "Methanol and ethylene glycol poisoning: Pharmacology, clinical manifestations, and diagnosis".)

HD substantially increases the rate of elimination of isopropanol, salicylates, theophylline, and lithium, although data regarding clinical end points are sparse [13,21-24]. A 2015 systematic review supports the use of hemodialysis to remove metformin in cases of overdose [25]. (See "Isopropyl alcohol poisoning" and "Salicylate (aspirin) poisoning in adults" and "Theophylline poisoning" and "Lithium poisoning".)

Drugs adsorbed by activated charcoal can be extracted by hemoperfusion, and the rate of removal may exceed that achieved with hemodialysis. The extraction ratio of theophylline with hemodialysis, for example, is approximately 50 percent as compared with 99 percent at the beginning of hemoperfusion (before the cartridge becomes saturated). As the extraction ratio only reflects the percent removal of drug presented to the dialysis membrane or hemoperfusion cartridge; these techniques remove only a small fraction of body load of drugs with large stores. (See "Theophylline poisoning".)

High extraction ratios and clearance rates, however, do not necessarily predict improved clinical outcomes. No controlled clinical studies in poisoned patients have been performed to determine if hemoperfusion reduces morbidity or mortality as compared with supportive measures. Evidence of clinical effectiveness for hemoperfusion is based upon favorable pharmacokinetic data, animal studies, anecdotal case reports, case series, and uncontrolled retrospective studies. Three clinical studies have retrospectively compared hemoperfusion with supportive care for poisoning from a variety of drugs, but do not allow firm conclusions to be drawn regarding the relative efficacy of different management strategies [26-28].

Indications — When intoxication has occurred with a drug whose HD clearance is significantly greater than endogenous clearance, the use of HD may be necessary if the patient's condition

progressively deteriorates, or when measured drug concentrations are predictive of a poor outcome without HD [13]. Practically, HD is indicated for a limited number of poisonings (table 4).

Hemoperfusion may be considered for use in severe poisoning from the toxins listed in the following table (table 5). It is significantly more effective than HD in enhancing the clearance of theophylline but is associated with a higher complication rate and is not available at most medical centers [29]. If hemoperfusion is available, it is preferred over hemodialysis in these specific agents, but HD is an acceptable alternative.

Technique — HD and hemoperfusion require central venous access with a double lumen catheter. Acute vascular access for hemodialysis or hemoperfusion is best accomplished with femoral catheters, which can be rapidly and safely inserted. Subclavian catheterization can also be used; however, there is a risk of pneumothorax or hemothorax, and therapy may be delayed because of the necessity for radiographic confirmation of proper catheter placement. The duration of these procedures for poisoned patients is usually four to eight hours but should be governed by the clinical response and serum drug concentrations. (See "Central catheters for acute and chronic hemodialysis access" and "Dialysis-related factors that may influence recovery of renal function in acute kidney injury (acute renal failure)".)

Contraindications — HD and hemoperfusion normally require systemic anticoagulation with heparin, and patients with active hemorrhage, severe thrombocytopenia, or coagulopathy may not be candidates for these procedures. HD and hemoperfusion also may not be feasible in hypotensive patients. (See "Anticoagulation for the hemodialysis procedure" and "Intradialytic hypotension in an otherwise stable patient".)

Complications — Potential side effects of HD include hypotension, bleeding due to anticoagulation, hypothermia, air embolus, and complications that may result from obtaining central venous access (table 6). Hemoperfusion has these same complications, but also poses potential risks of charcoal embolization, hypocalcemia, hypoglycemia, leukopenia (10 percent reduction), and thrombocytopenia (30 percent reduction).

HEMOFILTRATION

There are limited data available on drug removal by continuous arteriovenous (CAVH) or venovenous (CVVH) hemofiltration. Hemofiltration has been used to enhance elimination of aminoglycosides, vancomycin, and metal chelate complexes, but the technique does not remove highly protein-bound drugs effectively [30]. It may also be of benefit for intoxications with drugs that have a large volume of distribution, tight tissue binding, or slow intercompartmental transfer (such as procainamide) [15]. (See "Drug removal in continuous renal replacement therapy".)

Blood may be pumped by the patient's own arterial (CAVH) or venous (CVVH) pressure, or by a hemodialysis machine entrained in the circuit (CAVHD, CVVHD). Blood that enters the hemofiltration circuit passes through filters (sheet membrane or hollow fiber) with large pores, and an ultrafiltrate forms which drags solutes with molecular weights up to 50,000 daltons (depending upon hemofilter pore size). Cells and solutes larger than the pore size remain in the blood and return to the circulation.

In contrast to HD or hemoperfusion, CAVH is driven by the patient's own blood pressure and can be run continuously. The rate of fluid removal, which is equivalent to the plasma clearance of drug, can exceed 100 mL/h; thus, fluid replacement is an essential component of the hemofiltration regimen.

Complications of hemofiltration include clotting of the filter and bleeding due to the requisite use of heparin. Fluid and electrolyte losses from the ultrafiltrate must be replaced continuously.

EXCHANGE TRANSFUSION

Exchange transfusion refers to the removal of a quantity of blood from a poisoned patient and its replacement with an identical quantity of whole blood; the process is usually repeated two to three times. Exchange transfusions are rarely indicated but may be useful in the treatment of massive hemolysis (eg, due to arsine or sodium chlorate poisoning), severe methemoglobinemia, severe sulfhemoglobinemia (eg, secondary to hydrogen sulfide exposure), or neonatal drug toxicity. Complications of the technique include transfusion reactions, ionized hypocalcemia, and hypothermia [31]. (See "Massive blood transfusion".)

Other methods of poison treatment that function, in part, to enhance elimination of toxicants include: whole-bowel irrigation, plasmapheresis, cerebrospinal fluid removal, hyperbaric oxygen therapy, chelation therapy, specific antibody-toxin binding, enterohepatic circulatory binding of toxins, cation exchanger binding in the intestinal tract, and intravenous lipid emulsion therapy (table 1).

Over the past decade, expert- and evidence-based consensus recommendations for extracorporeal treatment (ECTR) for a number of poisons have been published by the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup. This group of experts principally recommend hemodialysis (HD) as the preferred ECTR for severe poisoning from long-acting barbiturates, methanol, metformin, salicylate, theophylline, thallium, and valproic acid; and recommend against ECTR for poisoning from cyclic antidepressants and digoxin [25,32-45]. Per this workgroup, ECTR is suggested for select cases of severe carbamazepine and acetaminophen poisoning and may be reasonable for severe phenytoin toxicity [35,41,43,45]. Details about ECTR and other aspects of management for these toxicants are found in the UpToDate topics devoted to the poisoning in question.

ADDITIONAL RESOURCES

Regional poison control centers in the United States are available at all times for consultation on patients who are critically ill, require admission, or have clinical pictures that are unclear (1-800-222-1222). In addition, some hospitals have clinical and/or medical toxicologists available for bedside consultation and/or inpatient care. Whenever available, these are invaluable resources to help in the diagnosis and management of ingestions or overdoses. The World Health Organization provides a listing of international poison centers at its website: www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: General measures for acute poisoning treatment" and "Society guideline links: Treatment of acute poisoning caused by specific agents other than drugs of abuse".)

SUMMARY AND RECOMMENDATIONS

- The vast majority of patients who have ingested a poisonous substance or a toxic quantity of a drug can be managed with supportive measures and possibly the administration of a single dose of activated charcoal. However, the severity of the ingestion and pharmacologic properties of the toxin may prompt consideration of techniques to enhance elimination of the poison in a small percentage of cases.

- Few studies have assessed changes in clinical outcomes when enhanced elimination techniques are employed, and the efficacy of these techniques has been judged primarily on the basis of improvement in elimination kinetics. Each technique is associated with potential complications, and the decision to use a particular technique should be based upon the drug ingested, the actual and predicted severity of poisoning, the presence of contraindications to the technique, and the effectiveness of alternative methods of treatment. The decision to employ enhanced elimination techniques is reserved for patients with a high likelihood of severe poisoning based upon the ingested dose or serum concentration of toxicant or those manifesting severe poisoning who have failed to respond to aggressive supportive care.

- Despite these concerns, the following general recommendations can be offered:

- Multiple dose activated charcoal may be useful following specific ingestions. (See "Gastrointestinal decontamination of the poisoned patient", section on 'Multidose activated charcoal'.)

- Urinary alkalinization and isotonic saline solution diuresis may be useful after poisonings with agents that are weak acids and eliminated to a large extent in the urine (eg, salicylates and phenobarbital).

- Hemodialysis may be useful for patients with significant ingestion of alcohols, theophylline, lithium, or salicylates. (See "Methanol and ethylene glycol poisoning: Pharmacology, clinical manifestations, and diagnosis" and "Theophylline poisoning" and "Lithium poisoning" and "Salicylate (aspirin) poisoning in adults".)

- Hemoperfusion is an alternative to hemodialysis and may result in more rapid clearance of toxins such as theophylline, carbamazepine, valproic acid, or procainamide. (See "Theophylline poisoning" and "Carbamazepine poisoning" and "Valproic acid poisoning".)

- Peritoneal dialysis, hemofiltration, and exchange transfusion are rarely indicated in the management of poisoned patients.

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Topic 325 Version 15.0

GRAPHICS

Methods for enhanced elimination of poisons

Multiple-dose activated charcoal
Isotonic saline or lactated Ringer's solution diuresis
Urinary ion trapping
Alkalinization
Extracorporeal methods
Hemodialysis
Hemoperfusion
Hemofiltration
Plasmapheresis
Exchange transfusion
Cation exchanger binding in intestinal tract
Chelation therapy
Cerebrospinal fluid removal
Enterohepatic circulatory binding of toxins
Hyperbaric oxygen
Intravenous lipid emulsion therapy
Specific antibody-toxin binding
Whole-bowel irrigation

Graphic 57040 Version 3.0

Poisons for which diuresis with isotonic saline or lactated Ringer's solution may enhance elimination

Barium
Bromides
Calcium
Chromium
Cisplatin
Cyclophosphamide
Fluoride
5-Fluorouracil
Iodide
Isoniazid
Lithium
Meprobamate
Potassium
Thallium
Tritium

Graphic 56838 Version 3.0

Agents for which alkaline diuresis may enhance elimination

2,4-D chlorphenoxyacetic acid (herbicide)
Chlorpropamide
Salicylates
Diflunisal
Fluoride
Methotrexate
Barbiturates
Phenobarbital
Primidone
Barbital
Sulfonamides

Graphic 75710 Version 1.0

Poisons and drugs amenable to hemodialysis*

Acetaminophen (when serum concentration >1000 mcg/mL [or 6600 micromol/L])
Aminoglycoside antibiotics
Alcohols
Ethanol
Isopropanol
Acetone
Methanol
Ethylene glycol; diethylene glycol
Propylene glycol
Atenolol
Barbiturates
Biguanide (eg, metformin) when associated with lactic acidosis
Bromides
Caffeine
Chloral hydrate (and metabolite trichloroethanol)
Dabigatran
Disopyramide
Ethambutol
Gabapentin
Heavy metals (possible)
Lithium
Meprobamate
Methotrexate
Nadolol
Pregabalin
Procainamide
Salicylates
Sotalol
Theophylline
Valproate (when serum concentration >1300 mg/L [or 9100 micromol/L])

*While the medications listed can be removed using hemodialysis, it does not mean that hemodialysis is a preferred therapy for toxicity caused by these medications. Please refer to the respective UpToDate toxicology topic for guidance.

Graphic 82353 Version 5.0

Common toxins whose elimination may be enhanced by hemoperfusion

Barbiturates	Amanita mushroom amatoxins
Phenobarbital	Carbamazepine
Primidone	Valproate
Sedative-hypnotics	Procainamide + N-acetylprocainamide
Meprobamate	Caffeine
Methaqualone	Chloral hydrate
Glutethimide	Dapsone
Ethchlorvynol	Methotrexate
Phenytoin	Phenylbutazone
Theophylline	Carbon tetrachloride
Disopyramide	Paraquat
Chloramphenicol	

Graphic 71695 Version 3.0

Complications of central venous catheterization

Immediate
Bleeding
Arterial puncture
Arrhythmia
Air embolism
Thoracic duct injury (with left SC or left IJ approach)
Catheter malposition
Pneumothorax or hemothorax
Delayed
Infection
Venous thrombosis, pulmonary emboli
Venous stenosis
Catheter malfunction
Catheter migration
Catheter embolization
Myocardial perforation
Nerve injury

SC: subclavian; IJ: internal jugular.

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Contributor Disclosures

Michael J Burns, MD Nothing to disclose **Larissa I Velez, MD** Nothing to disclose **Stephen J Traub, MD** Nothing to disclose **Michele M Burns, MD, MPH** Nothing to disclose **Jonathan Grayzel, MD, FAAEM** Nothing to disclose

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