

Clinical Toxicology

Initial Evaluation & Management of the Poisoned Patient (III)

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University of Mustansiriyah/College of Pharmacy

Department of Pharmacology & Toxicology

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Objectives of lecture:

Objectives of this lecture are:

- to identify the methods used for enhancement of poison elimination, &
- to identify the antidotes & therapeutics used in poisoning.

Techniques applied to enhance elimination:

- Forced diuresis,
- Manipulation of urinary pH,
- Whole-bowel irrigation, &
- Extracorporeal techniques which include:
 - Peritoneal dialysis,
 - Hemodialysis,
 - Hemoperfusion, &
 - Plasmapheresis.

Forced diuresis:

- Forced diuresis by volume expansion with isotonic sodium-containing solutions, such as 0.9% NaCl & lactated Ringer solution, may increase renal clearance of some molecules.
- This therapy would theoretically be most useful for xenobiotics such as lithium for which the glomerular filtration rate (GFR), which is the volume of plasma filtered across the glomerular basement membrane per minute, is an important determinant of excretion.

- In people with normal extracellular fluid (ECF) volume who have not had loss of sodium via renal, GI, or other routes of excretion, the increase in GFR expected with plasma volume expansion is variable & unpredictable & may not lead to significant increases in xenobiotic elimination.
- The effect of diuresis is potentially more important in patients who have had contraction of the extracellular fluid (ECF) volume because of sodium loss.

- The significant risk of this therapy is ECF volume overload, manifested by pulmonary & cerebral edema.

This complication may be particularly likely in patients with long-standing lithium use in whom chronic tubulointerstitial disease may lead to renal insufficiency that does not improve with fluid therapy.

Manipulation of urinary pH:

- Many xenobiotics are weak acids or bases that are ionized in aqueous solution to an extent that depends on the pK_a of the compound & the pH of the solution.
- Cell membranes are relatively impermeable to ionized, or polar molecules, while nonionized, nonpolar forms may cross more easily.

- If the urinary pH is manipulated to favor the formation of the ionized form in the tubular lumen, the xenobiotic is trapped in the tubular fluid & is not passively reabsorbed into the bloodstream. This is referred to as ion trapping.

- Clinical use of this alkalization procedure requires adequate urine flow & close clinical monitoring including that of the pH of the urine.
- The procedure is accomplished by adding sterile sodium bicarbonate to sterile water with 5% dextrose for intravenous (IV) infusion and administering the mixture intravenously to titrate the urine pH to 7.5 to 8.5.
- The drugs for which this procedure has been shown clinically efficacious include salicylate compounds & phenobarbital.

- Theoretically, there are similar advantages to be gained from acidification of the urine regarding enhancement of clearance of drugs such as amphetamine & phencyclidine; however, there are significant adverse events associated with acidification such as acute renal failure & acid-base & electrolyte disturbances.

For this reason, acidification of the urine is not recommended as a therapeutic intervention in the treatment of poisoning.

Dialysis techniques:

- The dialysis techniques, either hemodialysis, or peritoneal dialysis, relies on passage of the toxic chemical through a semipermeable dialysis membrane (or the peritoneal membrane for peritoneal dialysis).
- Dialysis is governed by the laws of osmosis. A diffusible chemical dissolved in water partitions across a semipermeable membrane, & the solution moves from an area of higher concentration (i.e., the blood) to one of lower concentration (i.e., a dialyzing solution).

Peritoneal dialysis:

Peritoneal dialysis is the most easily performed method and is associated with the lowest risk for complications. However, it is also the least effective method for removing most poisons.

Procedure of peritoneal dialysis:

- A warmed sterile dialyzing solution (up to 2 L for adults and 1 L for children) is introduced into the peritoneal cavity over a period of 15 to 20 min.
- The fluid is left in place for 45 to 60 min for equilibration to occur and then removed.
- A fresh solution is reintroduced & the process repeated. Up to 30 L or more of dialysis fluid may be used.

Complications of peritoneal dialysis:

These include abdominal pain, intraperitoneal bleeding, intestinal, bladder, liver, or spleen perforation, & peritonitis.

Hemodialysis:

- In order for this method to be clinically beneficial, the chemical must have:
 - a relatively low volume of distribution (V_d) ($V_d < 1 \text{ L/kg}$),
 - low protein binding,
 - a relatively high degree of water solubility, &
 - low molecular weight (MW) (MW < 500 daltons).

- Vascular access is best attained via the femoral vein.
- Hemodialysis & hemoperfusion are usually performed using a double-lumen catheter manufactured for dialysis.

Blood is pumped through one lumen, passed through the machine, & returned to the venous circulation through the second lumen.

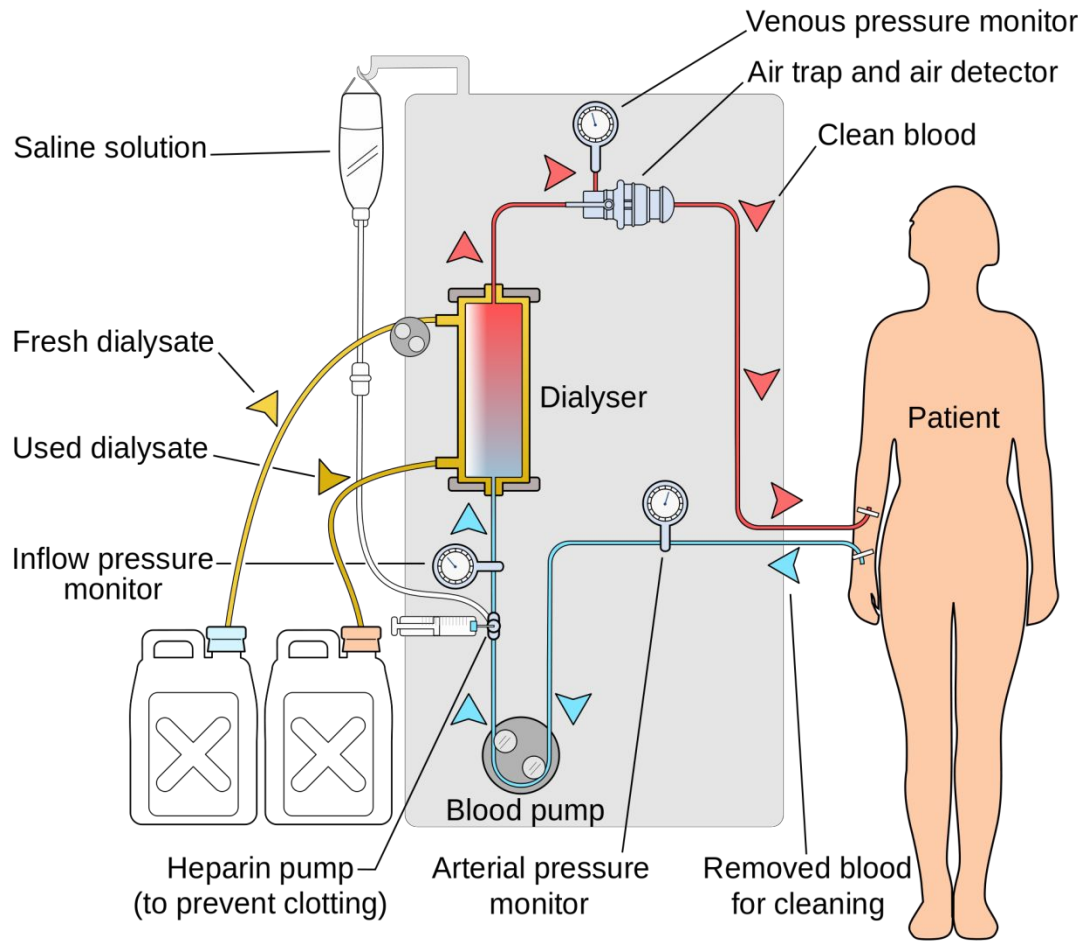


Diagram illustrating hemodialysis

- For anticoagulation, heparin is usually required, unless it is contraindicated.
- In poisoned patients, hemodialysis is usually performed for 4 to 8 hours.

- Drugs & chemicals for which hemodialysis has been shown to be clinically effective in the treatment of poisoning by these agents is shown in Table 1.

Table 1. Chemicals for which hemodialysis has been shown effective as a treatment modality for poisoning

Alcohols	Meprobamate
Antibiotics	Metformin
Boric acid	Paraldehyde
Bromide	Phenobarbital
Calcium	Potassium
Chloral hydrate	Salicylates
Fluorides	Strychnine
Iodides	Theophylline
Isoniazid	Thiocynates
Lithium	Valproic acid

- Complications of acute hemodialysis are relatively rare. These include:
 - Bleeding or thrombosis at the site used for vascular access, usually the femoral vein, is infrequent with normal hemostasis & adequate postprocedure.
 - Bleeding in the GI tract & elsewhere, caused by systemic anticoagulation with heparin, can be avoided if low doses of heparin are used.
 - Nosocomial bacteremia may occur if central lines are left in place for prolonged periods; central lines should be removed after 5 days at most.

Hemoperfusion:

- The technique of hemoperfusion is similar to hemodialysis except there is no dialysis membrane or dialysate involved in the procedure.
- The patient's blood is pumped through a perfusion cartridge containing an adsorptive material (usually activated charcoal) that has a coating of material such as cellulose or a heparin-containing gel to prevent the adsorptive material from being carried back to the patient's circulation.

- As with hemodialysis, patients must be anticoagulated with heparin.
- Hemoperfusion is usually performed for 4 to 6 hours at flow rates of 250 to 400 mL/min as tolerated.
- The principle characteristics for a drug or other chemical to be successfully removed by this technique are
 - low volume of distribution (V_d) ($V_d < 1$ L/kg) &
 - adsorption by activated charcoal.

- This method can be used successfully with lipid soluble compounds & with higher molecular weight compounds than for hemodialysis.
- Protein binding does not significantly interfere with removal by hemoperfusion.

- The medical risks of this procedure include thrombocytopenia, hypocalcemia, & leukopenia.
- This technique is primarily used for the treatment of serious theophylline overdose, & possibly amanita toxin exposure, as well as paraquat & meprobamate poisoning.
- A practical problem limiting the use of charcoal hemoperfusion is the availability of the cartridges.

- Chemicals removed by hemoperfusion (more efficiently than hemodialysis) are listed in Table 2.

Table 2. Chemicals removed by hemoperfusion (more efficiently than hemodialysis)

Amanitin	Paracetamol
Barbiturates (all categories)	Paraquat
Carbon tetrachloride	Phenols
Chloral hydrate	Phenylbutazone
Chlorpromazine	Promethazine
Dapsone	Propoxyphene
Diazepam	Quinidine, quinine
Digoxin	Salicylates
Diphenhydramine	Theophylline
Organophosphates	Tricyclic antidepressants

Plasmapheresis & exchange transfusion:

- Plasmapheresis & exchange transfusion are intended to eliminate xenobiotics with large molecular weights that are not dialyzable. This includes xenobiotics & endogenous molecules with molecular weights greater than 150,000 daltons, typified by immunoglobulins.
- The xenobiotic to be eliminated should also have limited endogenous metabolism to make pheresis or exchange worthwhile.

- By removing plasma proteins, both techniques offer the consequent potential benefit of removal of proteinbound molecules such as Amanita toxins, thyroxine, & vincristine.
- Pheresis is particularly expensive, & both pheresis & exchange transfusion expose the patient to the risks of infection with plasma- or blood-borne diseases.

- Replacement of the removed plasma during plasmapheresis can be accomplished with fresh-frozen plasma, albumin, or combinations of both. The former is associated with hypersensitivity reactions, such as fever, urticaria, wheezing, & hypotension.
- A different setting in which exchange transfusion may be an appropriate technique is in the management of small infants or neonates in whom dialysis or hemoperfusion may be technically difficult or impossible.

- In premature neonates, a single volume exchange appeared to alleviate manifestations of theophylline toxicity.

The therapy has been successfully used to treat other pediatric patients with poisonings, including severe salicylism.

Antidotes & therapeutics for the treatment of poisonings & overdose:

Therapeutics	Uses
Atropine	Bradycardias, cholinesterase inhibitors (organic phosphorus compounds, physostigmine)
Benzodiazepines	Seizures, agitation, stimulants, ethanol and sedative-hypnotic withdrawal, cocaine, chloroquine, organic phosphorus compounds
Dantrolene	Malignant hyperthermia
Deferoxamine mesylate	Iron
Dextrose in water (50% adults; 20% pediatrics; 10% neonates)	Hypoglycemia
Digoxin-specific antibody fragments (Digibind & Digifab)	Cardioactive steroids

Therapeutics	Uses
Dimercaprol (BAL, British anti-Lewisite)	Arsenic, mercury, gold, lead
Flumazenil	Benzodiazepines
Glucagon	β -Adrenergic antagonists, calcium channel blockers
N-acetylcysteine	Acetaminophen
Naloxone hydrochloride	Opioids, clonidine
D -Penicillamine	Copper
Pralidoxime chloride,	Acetylcholinesterase inhibitors (organic phosphorus agents & carbamates)
Protamine sulfate	Heparin anticoagulation
Succimer	Lead, mercury, arsenic
Vitamin K1	Warfarin or rodenticide anticoagulants

Thank
you

