CHAPTER 99

# Extracorporeal Therapies in Acute Intoxication and Poisoning

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**OBJECTIVES**

This chapter will:

1. Present the indications for extracorporeal therapies in the treatment of acute poisoning.
2. Describe principles of drug removal and how they apply to selection of modality.
3. Describe the utility and complications of combining chelating agents to improve clearance of heavy metals.
4. Discuss clinical presentation and treatment (including extracorporeal therapy) with regard to specific intoxicants.

Management of the poisoned patient begins with an assessment of organ function and dysfunction and consideration of known or suspected poisons. Evidence of electrolyte and acid-base derangements or studies suggesting or confirming a specific poison (including drug levels), are typically available in advance and can inform treatment.

Treatment of acute intoxication involves application of nonspecific measures, such as cardiopulmonary support and activated charcoal, as well as specific measures, such as antidotes and enhanced elimination by modulation of urinary pH. Extracorporeal therapies, including hemodialysis, hemofiltration, and hemoperfusion, are useful adjuncts in the treatment of poisoning.[1]

Criteria for initiating drug (or poison) removal by extracorporeal methods and for the selection of modality are discussed below along with the use of chelating agents to enhance removal of metals. Finally, detailed consideration is given to specific intoxicants.

## CRITERIA FOR CONSIDERATION OF EXTRACORPOREAL THERAPY

Discrete indications to recommend the use of dialysis exist for many specific intoxicants, including agents with delayed toxicity, such as mushrooms, paraquat, methanol, and ethylene glycol. Dialysis also should be considered when endogenous drug clearance is impaired or markedly slower (e.g., cardiac, renal, or hepatic failure) than with available extracorporeal therapy.

In most cases, the decision to use dialysis for drug clearance during intoxication is clinical. Symptoms to consider include abnormalities in vital signs suggesting hemodynamic instability; clinical deterioration despite adequate supportive treatment; and mental status deterioration (including confusion, lethargy, stupor, and coma). In addition to removing the offending agent, dialysis may improve electrolyte abnormalities and correct the metabolic acidosis that may accompany some types of poisoning. Dialytic therapies, involving dialysate and diffusion to lower potassium concentration or deliver alkali, should be considered when concomitant metabolic disorders are present. Hypotensive patients requiring hemodynamic support with an indication for dialysis should receive an infusion of adrenergic or vasopressin-agonist pressors distal to the dialysis or sorbent cartridge. Furthermore, careful monitoring

of circulatory status is essential because pressor clearance will be increased by the modalities and requirements may change.

## HEMODIALYSIS

Hemodialysis is the most commonly used method of extracorporeal drug removal in the treatment of poisoning.[2] Factors governing the efficiency of drug removal with hemodialysis are drug related and dialysis related. Drug factors that increase removal are small molecular size (molecular weight <500 Da), high water solubility, low degree of protein-binding, small volume of distribution (<1 L/kg), and rapid equilibration of plasma and tissue to maintain a concentration gradient.[3] Limited drug clearances should be expected with drugs that are highly lipid soluble, tightly tissue bound, with large volumes of distribution, and slow plasma equilibration. Dialysis factors include access type, blood and dialysate flow rates, and dialyzer properties (material, surface area, and pore size). The use of low blood flow rates may prevent hemodynamic instability but necessitate longer or continuous treatments for adequate clearance. Although higher dialysate flow rates will increase diffusive clearance to some degree, there is limited benefit beyond flow rates greater than 1.5 times that of blood.

With the use of membranes having larger pore size, larger molecular weight drugs can be cleared. For example, vancomycin is cleared readily with large pore (high-flux) membranes despite a molecular weight of 1400 Da.[4] As molecular weight increases, drug removal is less a function of diffusion than convection (the creation of an ultrafiltrate).[5]

Efficient clearance of a large molecular weight intoxicant may be accomplished best by combining filtration and dialysis. Although modern dialysis employs convection for volume removal and accurately can be termed convection dialysis, a discrete and emerging modality, hemodiafiltration, uses ultrafiltration across a high-flux dialysis membrane and countercurrent flow of dialysate for combined diffusive and convective clearance. The principle of hemofiltration, which relies upon convective clearance alone, is discussed subsequently.

A list of readily dialyzable drugs is provided in Box 99.1.

### Hemofiltration

Hemofiltration is employed in a continuous manner with several possible variations. In the simplest form, blood circulates under arterial pressure (continuous arteriovenous hemofiltration, or CAVH) or is pumped out of the venous circulation to return passively (CVVH). Blood in the circuit enters the filtration cartridge (hollow fibers with large pores), and an ultrafiltrate of plasma forms from pressure across the membrane. Solutes are cleared into the ultrafiltrate by solvent drag, while cells and solutes larger than the pore size remain in the blood and return to the circulation. Hemofiltration requires anticoagulation of the blood circuit and continuous replacement of fluid and electrolytes lost into the ultrafiltrate.

Depending upon pore size, hemofiltration can remove molecules with molecular weight up to 50,000 Da. In addition to molecular weight, the principal determinant of clearance is degree of protein binding. As plasma proteins are filtered (or not ultrafilterable), convective clearance across the pore is greatest with unbound molecules. The ability of a molecule to pass convectively across the membrane is quantifiable and is called the sieving coefficient (SC). Clearance is equal to the SC multiplied by the ultrafiltration rate; and for molecules that pass completely (an SC of 1) the plasma clearance is equal to the ultrafiltration rate. Increasing the ultrafiltration rate thus increases clearance of any intoxicant with an SC of more than 0. Drug and membrane interactions, such as binding of aminoglycosides (e.g., tobramycin and Biospal AN69 membranes) may impair sieving.[6] Furthermore, in vitro measurements of SC, obtained using saline rather than blood, may not closely reflect clinical drug sieving and actual clearance.

Continuous hemofiltration, with fluid and electrolyte replacement, is likely to be useful for the removal of drugs when diffusive modalities are inadequate (despite large dialyzer pores) and dialysate requirements are excessive, for example, drugs with large volume of distribution or slow equilibration (e.g., procainamide).

There are few data on drug removal from patients and treatment of poisoning by continuous hemofiltration. However, this modality has been used to remove large molecule antibiotics such as aminoglycosides and vancomycin, as well as complexes of metals and chelators. (For more on chelators, see later in this chapter.) Some investigators have reported clinical improvements (cardiac function, drug levels) in patients with digoxin overdose treated with hemofiltration. In animal studies, CAVH was ineffective in the removal digoxin-Fab complexes. These complexes are molecules with weights of 45,000 to 50,000 Da, the size limit for passage through hemofiltration pores.[7]

## HEMOPERFUSION

Although available for several decades, hemoperfusion is used infrequently to treat acute intoxications. In practice, the apparatus consists of a blood circuit identical to that of hemodialysis, including blood pumps and pressure monitors, but with a cartridge containing a large surface area column containing charcoal or resin. The column is first primed with saline, and then anticoagulated blood is pumped through the cartridge where drugs with molecular size between 100 and 40,000 Da are removed by adsorption. Activated charcoal has greater affinity for water-soluble molecules, whereas resins have greater affinity for lipid-soluble molecules.

The rate of removal of drugs adsorbed to charcoal may exceed that achieved with hemodialysis. For example, the extraction ratio of theophylline is 99% with hemoperfusion as compared with 50% with hemodialysis. However, the sorbent column may become saturated and extraction ratios may decline progressively throughout treatment.

High extraction ratios and clearance rates may not predict improved clinical outcomes. In fact, no controlled studies in poisoned patients have been performed to determine if hemoperfusion (or hemodialysis) reduces morbidity or mortality as compared with supportive measures. Evidence of effectiveness is based upon pharmacokinetic data, animal studies, case reports, and retrospective studies.

Adverse effects of hemoperfusion, including flushing, dyspnea, and thrombocytopenia, largely have been reduced with changes to preparatory methods and the coating of absorbents with polymers.

Clinical experience has shown that a "rebound" of drug concentration may occur after hemoperfusion, as the drug redistributes from tissues into the plasma compartment. The use of short, intermittent hemoperfusion treatments provides several advantages: less "rebound" effect with

## BOX 99.1

### Drugs Removed With Hemodialysis

**Antimicrobials**

***Cephalosporins***
cefadroxil
cefamandole
cefazolin
cefmenoxime
cefmetazole
(cefonicid)
(cefotaxime)
cefotetan
cefotiam
cefoxitin
cefpirome
cefroxadine
ceftazidime
(ceftriaxone)
cefuroxime
cephacetrile
cephradine
cephalexin
cephalothin
(cephapirin)
Penicillins
penicillin
amoxicillin
ampicillin
carbenicillin
(cloxacillin)
(methicillin)
(nafcillin)
ticarcillin
temocillin
piperaicillin
(mezlocillin)
mecillinam
floxacillin
(dicloxacillin)

***Macrolides***
(erythromycin)
(azithromycin)
(clarithromycin)

***Aminoglycosides***
amikacin
dibekacin
**fosfomycin**
gentamycin
kanamycin
neomycin
netilmicin
sisomicin
streptomycin
tobramycin
bacitracin
fleroxacin

**Other antimicrobials**
clavulanic acid
para-aminosalicylic acid (PAS)
moxalactam
metronidazole
nitrofurantoin
sulfonamides
tetracycline
(doxycycline)
(minocycline)
ethambutol
colistin
trimethoprim
aztreonam
cilastatin
imipenem
chloramphenicol
amphotericin
ciprofloxacin
(norfloxacin)
ofloxacin
(clindamycin)
(cycloserine)
isoniazid
vancomycin
pyrazinamide
pentamidine
(praziquantel)
rifampin
chloroquine
quinine
(itraconazole)
(fluconazole)
(ketoconazole)
(miconazole)
(ribavirin)
acyclovir
amantadine
didanosine
foscarnet
ganciclovir
***zidovudine***

**Antineoplastics/Cytotoxics**
5-flourocytosine
methotrexate
azathioprine
cyclophosphamide
vidarabine

**Barbiturates**
amobarbital
aprobarbital
barbital
butabarbital
phenobarbital
cyclobarbital
(secobarbital)
pentobarbital
quinalbital

**Nonbarbiturate Hypnotics, Sedatives, Tranquilizers**
carbromal
carbamazepine
chloral hydrate
chlordiazepoxide
(diazepam)
(diphenylhydantoin)
(diphenhydramine)
ethinamate
ethchlorvynol
ethosuximide
gallamine
glutethimide
(heroin)
meprobamate
(methaqualone)
methsuximide
methyprylon
paraldehyde
primidone
valproic acid

**Cardiovascular Agents**
acebutolol
(amiodarone)
atenolol
betaxolol
(bretylium)
(calcium channel blockers)
captopril
enalapril
fosinopril
lisinopril
quinapril
ramipril
(diazoxide)
(digoxin)
(encainide)
(flecainide)
(lidocaine)
metoprolol
methyldopa
(ouabain)
N-acetylprocainamide
nadolol
pindolol
practolol
(quinidine)
(timolol)
sotalol
tocainide

**Alcohols**
ethanol
ethylene glycol
isopropanol
methanol

**Analgesics/Antirheumatics**
acetaminophen
acetylsalicylic acid
colchicine
(d-propoxyphene)
acetophenetidin
methylsalicylate
salicylic acid

**Antidepressants**
(amitriptyline)
amphetamines
(imipramine)
isocarboxazid
MAO inhibitors
(pargyline)
(phenelzine)
tranylcypromine
tricyclics

**Solvents/Gases**
acetone
camphor
carbon monoxide
(carbon tetrachloride)
(eucalyptus oil)
thiols
toluene
trichloroethylene
sodium citrate

***Plants/Animals/Herbicides/Pesticides***
alkyl phosphates
amanitin
demeton sulfoxide
dimethoate
diquat
methylmercury complex
(organophosphates)
paraquat
snake bite
sodium chlorate
potassium chlorate

**Miscellaneous**
acipimox
allopurinol
aminophylline
aniline
borates
boric acid
(chlorpropamide)
chromic acid
(cimetidine)
dinitro-o-cresol
folic acid
mannitol
methylprednisolone
potassium dichromate
theophylline
thiocyanate
ranitidine

**Anticoagulants**
dabigatran

Modified from Winchester JF. Active methods for detoxification. In: Haddad LM, Shannon MW, Winchester JF, editors. *Clinical Management of Poisoning and Drug Overdose.* 3rd ed. Philadelphia: WB Saunders; 1998.
() Not well removed.

possible clinical improvements; reduction in the hematologic side effects; and as devices saturate with longer treatments, overall improved drug clearance.

If a poison is eliminated equally well with hemodialysis, hemodialysis is preferred because it is less expensive and can address any superimposed metabolic disorder. Trends in extracorporeal treatments used for poisoned patients show that hemodialysis has supplanted largely hemoperfusion and other modalities.[8] There are, however, some poisonings for which hemoperfusion is superior and is the

## BOX 99.2

**Drugs and Chemicals Removed With Hemoperfusion**

**Barbiturates**
amobarbital
butabarbital
hexobarbital
hentobarbital
pentobarbital
quinalbital
secobarbital
thiopental

**Nonbarbiturate Hypnotics, Sedatives, Tranquilizers**
carbromal
chloral hydrate
(diazepam)
diphenhydramine
ethchlorvynol
glutethimide
meprobamate
methaqualone
methsuximide
methyprylon
promazine
promethazine
(valproic acid)

**Solvents/Gases**
carbon tetrachloride
ethylene oxide
trichloroethane
xylene

**Analgesics/Antirheumatics**
acetaminophen
acetylsalicylic acid
colchicine
d-propoxyphene

**Antimicrobials/Anticancer**
(adriamycin)
ampicillin
carmustine
chloramphenicol
chloroquine
clindamycin
dapsone
doxorubicin
gentamicin
isoniazid
(methotrexate)
thiabendazole
(5-flourouracil)

**Antidepressants**
(amitriptyline)
(imipramine)
(tricyclics)

**Metals**
(aluminum)*
(iron)*

**Plants/Animals/Herbicides/ Pesticides**
amanitin
chlordane
demeton sulfoxide
dimethoate
diquat
methyl parathion
nitrostigmine
(organophosphates)
phalloidin
polychlorinated biphenyls
paraquat
parathion

**Cardiovascular**
digoxin
diltiazem
(disopyramide)
flecainide
metoprolol
n-acetylprocainamide
procainamide
quinidine

**Miscellaneous**
aminophylline
(fluoroacetamide)
(phencyclidine)
phenols
(podophyllin)
theophylline

Modified from Winchester JF. Active methods for detoxification. In: Haddad LM, Shannon MW, Winchester JF, editors. *Clinical Management of Poisoning and Drug Overdose.* 3rd ed. Philadelphia: WB Saunders; 1998.
() Not well removed; ()* removed with chelator.

preferred modality: lipid-soluble drugs, cardiac glycosides, barbiturates, and other types of hypnotics/sedatives/tranquilizers. Box 99.2 lists some chemicals and drugs removed by hemoperfusion.

## USE OF CHELATING AGENTS WITH EXTRACOPOREAL MODALITIES

Dialysis and hemoperfusion do not remove efficiently heavy metals, metalloids, or their salts. The addition of chelating agents, pre- (and possibly post-) treatment, can improve total clearance through dialysis, filtration, or adsorption of the metal-chelator complex.

In the past, when aluminum hydroxide was used as a phosphate binder, aluminum intoxication in dialysis patients was treated effectively with desferoxamine (DFO) and either hemodialysis or hemoperfusion, with clinical improvement in osteomalacia, anemia, and encephalopathy.[9] The use of dialysis with high-flux polysulfone membranes likely results in equivalent or superior clearance of aluminum DFO complexes than with charcoal hemoperfusion.[10] Furthermore, hemodialysis is less expensive and will not result in the thrombocytopenia and leukopenia evident with hemoperfusion. Although not a common acute intoxicant, iron also can be removed effectively from the body with DFO and hemodialysis or charcoal hemoperfusion.[9]

Little evidence supports the addition of extracorporeal therapies to standard chelation therapy. Dimercaptosuccinic acid (DMSA or succimer) and dimercaptopropane sulfonate

(DMPS) are the chelators most often used in the treatment of heavy metal toxicity (supplanting dimercaprol or BAL).[11] DMSA and DMPS are water soluble and can be given orally or intravenously to increase urinary excretion of arsenic, cadmium, lead, methylmercury, and inorganic mercury. Use of DMSA and DMPS is contraindicated in patients with renal failure, in whom hemodialysis may be useful to remove metal-chelator complexes.[12] The use of DMPS with CVVHDF appears to have provided clearance and clinical benefit in the treatment of inorganic mercury poisoning.[13] In addition, DMPS with conventional dialysis has been employed in patients with inorganic mercury, arsenic, and copper intoxications. Administration of these chelating agents also increases excretion of essential minerals such as copper, selenium, zinc, and magnesium, needing replenishment of them before and after treatment.[14] Side effects also can include mucocutaneous eruptions, which can be expected to resolve when discontinued.

In the future, chelating microspheres in specialized hemoperfusion column may improve clearance of many metallic poisons.[15]

## INTOXICATION WITH SPECIFIC AGENTS

Table 99.1 lists the optimal techniques for removing specific poisons.

### Lithium

Lithium, with an atomic number of 3 and an atomic weight of 6.94, is the lightest of all metals. Carbonate and citrate salts of lithium are used in the treatment of bipolar affective disorder, and despite known toxicity and a narrow therapeutic index, substantial clinical efficacy as a "mood stabilizer" explains the persistent widespread use.

The clinical effects of lithium intoxication are primarily neurologic and renal. Neurologic symptoms increase with blood concentrations and include progression from confusion and lethargy to stupor and coma as well as motor symptoms such as fine tremor, spasticity and hyperreflexia, dystonia or choreiform movements, cogwheel rigidity, and cerebellar signs. The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is a rare neurologic consequence and can occur after discontinuation, with variable clinical features including cerebellar and cognitive deficits.[16] The principal renal manifestation is nephrogenic diabetes insipidus, resulting in polyuria and polydipsia and possibly hypernatremia. Lithium impairs urinary concentrating ability through interruption of cyclic-AMP signaling and insertion of aquaporins into the luminal surface of collecting duct cells. Cardiovascular effects may be evident and include hypotension, myocarditis, ST depression, lateral T-wave inversions, heart block, and premature atrial beats. Finally, gastrointestinal symptoms include vomiting, diarrhea, and gastroenteritis. Acute toxicity may be characterized by marked gastrointestinal symptoms, which are absent in chronic toxicity. Chronic renal toxicity of lithium includes persistent nephrogenic diabetes insipidus, chronic cystic interstitial nephritis, and nephrotic glomerulopathies.[17]

With the exception of sustained-release preparations, lithium is rapidly (1 to 2 hours) and completely absorbed from the gastrointestinal tract. If administered shortly after ingestion, sodium polystyrene sulfonate resin modestly reduces the oral bioavailability of lithium.[18] However, the effective dose and schedule is uncertain, and potassium lowering may result. Once absorbed, lithium distributes freely in body water, where it competes with other cations (in order: sodium, potassium, magnesium, and calcium), displacing them from bones and cells. Lithium does not bind to serum proteins but distributes widely in total body water with an initial volume of distribution of 0.5 L/kg, which later increases to 0.7 to 0.9 L/kg. Uptake by and release of lithium from the central nervous system (CNS) may be delayed by as much as 24 hours, resulting from slow passage across the blood-brain barrier. Lithium is eliminated by the kidneys and clearance parallels creatinine clearance. In adults, the average half-life is 29 hours. Factors that decrease lithium clearance include any decrease in glomerular filtration rate and conditions that promote proximal tubular reabsorption of lithium via sodium pathways: hypovolemia, NSAID use, and thiazide diuretics. Conversely, clearance can be increased with volume expansion, loop diuretics, and interruption of distal sodium (and lithium) reabsorption with amiloride or triamterene. Acute overdosage is fatal in approximately 25% of cases, whereas intoxication during maintenance therapy has a mortality of 9%.[19] Approximately 10% of patients with acute intoxication will have permanent neurologic and/or renal damage.

The therapeutic steady-state lithium concentration is 0.6 to 1.2 mEq/L. No toxicity is generally apparent (except in very elderly patients) with blood levels below 1.3 mEq/L; mild toxicity with levels of 1.5 to 2.5 mEq/L; moderate toxicity with levels of 2.6 to 3.5 mEq/L; and severe (life-threatening) toxicity with levels greater than 3.6 mEq/L.

For acute lithium intoxication, with levels less than 2.5 mEq/L, general measures such as gastric lavage, volume expansion with fluids, and use of diuretics (loop, amiloride, or triamterene) are usually sufficient. Extracorporeal treatment is recommended if there is decreased consciousness, seizures, or significant dysrhythmia at any lithium level, or if endogenous kidney function is impaired and the level is greater than 4.0 mEq/L. Extracorporeal treatment is indicated if the level is greater than 5.0 mEq/L, or if multiple levels at different intervals plotted on a log-linear scale predict levels above 1 mEq/L at 36 hours. Hemodialysis and hemofiltration are effective modalities. Intermittent hemodialysis is the preferred modality; and lithium extraction is more than 90% (as expected because of low molecular weight, water solubility, and low degree of protein binding). Plasma levels may rebound after treatment because of redistribution or continued gastrointestinal reabsorption and should be monitored. Intermittent hemodialysis treatments are recommended until levels remain below 1 mEq/L. A single 6-hour hemodialysis treatment with a high efficiency membrane is likely sufficient to achieve a low serum lithium

**TABLE 99.1**

**Suggested Optimal Techniques for Removing Poisons**

| HEMODIALYSIS | HEMOPERFUSION |
|---|---|
| Lithium | Lipid-soluble drugs |
| Bromide | Barbiturates |
| Ethanol | Nonbarbiturate hypnotics, sedatives, tranquilizers |
| Methanol | (e.g., carbamazepine, valproic acid) |
| Ethylene glycol | Digitalis glycosides (anecdotal evidence only) |
| Salicylates | Procainamide |
| Theophylline | |

level and can be followed by use of slower modalities. Sustained low efficiency daily dialysis (SLEDD) and CVVH are likely acceptable, but less efficient, alternatives to intermittent HD. Peritoneal dialysis does not provide adequate clearance.[16]

## Methanol

Methanol is a widely available commercial and industrial solvent and a potentially fatal intoxicant. Although toxicity is possible after skin absorption or inhalation, ingestion is the major route of poisoning. Ingestion usually is isolated to cases involving alcoholic derelicts; however, outbreaks of "wood alcohol" poisoning traced to counterfeit liquor sources also have occurred. As little as 60 to 240 mL of methanol, or 15 to 30 mL of 40% solution, can be fatal.[20] Peak blood levels of methanol follow ingestion by 30 to 90 minutes, with a volume of distribution of 0.6 to 0.7 L/kg.[21] Elimination is via biotransformation in the liver and kidneys to formaldehyde and then formic acid, with only 5% of ingested methanol excreted unchanged into the urine. The metabolites of methanol are, in fact, principally responsible for toxicity.

Early signs of intoxication include inebriation and drowsiness. Delayed symptoms may be ocular, including blurred vision, dilated pupils, and retinal toxicity (optic disc hyperemia and possible blindness) secondary to local conversion to formaldehyde. Other delayed symptoms include vomiting, diarrhea, back pain, vertigo, cold and clammy extremities, bradycardia, delirium, agitation, and urine with the smell of formaldehyde. Severe intoxications may result in Kussmaul respiration, coma, inspiratory apnea, and death with opisthotonus and convulsions. A particular severe complication of methanol poisoning is necrosis of the putamen.[22] Pancreatitis also has been found at autopsy.

Laboratory findings include high serum osmolal gap (early in intoxication, from unmetabolized methanol), followed by high anion gap (resulting from formate retention) metabolic acidosis with low bicarbonate. Additional findings may include high hematocrit, high mean corpuscular volume, high glucose, and high serum amylase.

Patients with suspected methanol toxicity first should receive gastric lavage to remove residual gastric methanol. Because the symptoms often are delayed, treatment then involves prevention, and if necessary, removal of toxic metabolites. The enzymatic oxidation of methanol to formaldehyde requires alcohol dehydrogenase (ADH), an enzyme with greater affinity and efficiency for ethanol. Ethanol or another ADH inhibitor, 4-methylpyrazole (4-MP), should be administered to patients to prevent conversion to formaldehyde. Folic and folinic acid also help to convert formate to water and carbon dioxide.[23] Most authorities recommend 4-MP as soon as the diagnosis is considered, if 4-MP is available from hospital pharmacies.[24,25]

Hemodialysis is an effective modality to remove methanol and metabolites and correct the metabolic acidosis. It should be considered when patients have levels above 50 mg/dL, serious symptoms, or refractory acidosis. Dialysis should continue until levels are below 20 mg/dL, with monitoring for rebound of plasma concentrations. If ethanol is administered, it may be placed into the dialysate or replaced after dialytic removal.[20] Because the half-life of metabolism is slow, treatment with 4-MP alone is not recommended because prolonged intensive care stays may result. If this is the case, hemodialysis should be used to shorten the half-life of methanol.[26,27] Dialysis also removes 4-MP, and dose adjustment is necessary.

## Ethylene Glycol

Another intoxicant involved in ingestions among alcoholics, suicide attempts, and occasionally by accident is ethylene glycol. This irritant alcohol is found widely in cosmetics and antifreeze (car radiator) fluid. Ethylene glycol is sweet to the taste and may contain fluorescent dye added to aid in identification. As with methanol, ethylene glycol undergoes biotransformation into metabolites with fatal toxic potential.

Peak blood levels follow ingestion by 1 to 4 hours, and ethylene glycol is filtered and reabsorbed in the kidneys. The toxic metabolites of ethylene glycol are glycoaldehyde, glycolate, glyoxalate, lactate, and oxalate. Deposition of birefringent calcium oxalate crystals in the renal tubules causes renal failure with interstitial nephritis and hemorrhagic necrosis. Similar tissue destruction occurs in meningeal blood vessels, liver, and pericardium. A profound metabolic acidosis occurs from lactic acidosis and production of glyoxalate metabolites, which inhibit the citric acid cycle and produce further lactate. Furthermore, glycolate recondenses to form glycine and carbon dioxide with further consumption of bicarbonate.

Early signs of intoxication include inebriation with absent alcoholic breath. Focal seizures, nystagmus, paralysis of eye muscles, hyporeflexia, tetany, and coma may be evident. This initial CNS depression is due to glycol and aldehydes and occurs about 30 minutes to 12 hours postingestion. The second phase of intoxication begins 12 to 14 hours postingestion and results from calcium oxalate deposition and tissue destruction. Signs include tachycardia, hypotension, pulmonary edema, and congestive heart failure. The final phase occurs 24 to 72 hours postingestion and includes flank pain and tenderness with oliguric acute tubular necrosis. Kussmaul respiration may accompany acidosis.

Laboratory findings include high serum osmolal gap, azotemia, and high anion gap metabolic acidosis. Hypocalcemia and hyperkalemia also may be present. Urinary findings may include calcium oxalate crystalluria, hematuria, proteinuria, oliguria, and low specific gravity.

Patients also should receive gastric lavage to remove residual ethylene glycol. Ethanol or 4-MP should be administered to patients to prevent conversion to metabolites. Pyridoxine (50-100mg IV Q6), used to stimulate glyoxalate conversion to alpha- or beta-ketoadipate, and thiamine (100 mg IV Q6), used to convert glyoxalate to glycine, also are recommended.

Most authorities recommend 4-MP as soon as the diagnosis is considered, and if 4-MP is available from hospital pharmacies.[20,21] Hemodialysis removes ethylene glycol and metabolites and correct the metabolic acidosis. It should be considered when metabolites are present and acidosis complicates the clinical picture. If ethanol is administered, it can be mixed with dialysate or given intravenously. As opposed to methanol, the half-life of ethylene glycol elimination is sufficiently rapid to allow treatment of uncomplicated poisonings with 4-MP alone, without hemodialysis.[28,29] As noted, dialysis also will remove 4-MP and dose adjustment will be necessary.

## Salicylates

Salicylates are a subclass of nonsteroidal antiinflammatory drugs (NSAIDs) with well-described acute and chronic toxicity. This discussion is limited to acute intoxication only.

Salicylates are absorbed in the jejunum of the small intestine. Delayed gastric emptying (e.g., food in stomach)

and enteric coating of pills may prolong absorption time up to 12 hours. During first-pass metabolism, acetylsalicylic acid is hydrolyzed into salicylic acid, which then slowly is cleared from the blood (half-life of 20 to 30 hours). Excretion occurs by conjugation with glycine and glucuronic acid to form salicyluric acid, salicylphenolic acid, and acylglucuronides.

Clinical features of acute intoxication invariably include tinnitus, deafness in varying degrees, bounding pulse, profuse sweating, and flushing with warm extremities. Nausea and vomiting may be present because of gastrointestinal irritation. Acid-base disorders with salicylate toxicity are common but variable in presentation according to patient age. These include a respiratory alkalosis, from central hyperventilation with increased rate and depth of breathing, and high anion gap metabolic acidosis from accumulation of salicylates and bicarbonate consumption. In younger children, under age 4 years, acidosis predominates. In older children and adults, respiratory alkalosis is more common. CNS signs are more common in children and include agitation and uncommunicative behavior followed by coma. CNS symptoms correlate with the degree of acidemia, which facilitates entry of salicylates into the cerebrospinal fluid, and death may result from cerebral edema. Increased vascular permeability also may result in pulmonary edema. Petechiae of the eyelids, face, and neck may be present.

Laboratory findings include mixed acid-base disorders: with high anion gap metabolic acidosis, respiratory alkalosis, or respiratory acidosis if respiratory failure develops. Hypocalcemia or hypercalcemia and hypokalemia also may be present. Clotting profile also may show prolonged vitamin K–dependent coagulation.

Recommended gastrointestinal decontamination involves the use of single- and multiple-dose activated charcoal. Induced vomiting with ipecac is not recommended. Intravascular volume replacement should be given along with intravenous bicarbonate to address acidemia and reduce CNS entry of salicylate facilitated by acidemia, as well as enhance elimination through ion trapping by alkalinizing the urine. In patients with acidosis and organ dysfunction with levels greater than 60 mg/dL in adults or 35 mg/dL in children, enhanced elimination via urinary alkalinization is recommended. The urine should be alkalinized and maintained at target pH of 8. However, aggressive administration of bicarbonate to patients with alkalemia (as with predominate respiratory alkalosis) or pulmonary edema is not recommended.

Dialysis effectively removes salicylates, and intermittent hemodialysis is the preferred modality and widely available. Although slower modalities (e.g., SLEDD) may be effective, they are less efficient in clearance and base delivery. Hemodialysis is recommended for any patient with levels greater than 100 mg/dL, severe acidemia (pH < 7.2), CNS dysfunction, and risk of pulmonary edema; and for levels greater than 90 mg/dL in patients with impaired kidney function. Although hemoperfusion also removes salicylates effectively, hemodialysis is preferred to correct acid-base disturbances.[30]

## Key Points

1. Indications for use of extracorporeal therapies in drug intoxication are primarily clinical.
2. Extracorporeal therapy should be considered for agents with delayed toxicity, when endogenous clearance is impaired, or evidence exists for clinical benefit.
3. Dialysis may improve electrolyte abnormalities and correct the metabolic acidosis that may accompany some types of poisoning.
4. Dialysis efficiently removes drugs of small molecular size, high water solubility, low protein-binding, and small volume of distribution.
5. Hemofiltration removes drugs of large molecular size and volume of distribution.
6. Although infrequently used, hemoperfusion removes lipid-soluble drugs, cardiac glycosides, barbiturates, and other types of hypnotics/sedatives/tranquilizers, with evident complications such as thrombocytopenia.
7. Use of the chelator desferoxamine (DFO) with hemodialysis or hemoperfusion improves clearance of aluminum and iron.
8. Hemodialysis may be a useful addition to chelation with dimercaptopropane sulfonate in patients with renal failure and arsenic, mercury, and other metal intoxications.
9. Hemodialysis effectively removes lithium, methanol, ethylene glycol, and salicylates.
10. Hemoperfusion is effective in the removal of theophylline during intoxication.

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