Management of Poisoning and Drug Overdose

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Most poisonings with common intoxicants are effectively treated with only supportive measures [1 – 3]. This includes appropriate therapy for the complications that often accompany intoxications, namely hypotension, arrhythmias, and seizures. Antidotes are also available for many intoxications (Table 1). They work by directly binding the toxin (e.g. digoxin-specific F_{ab} fragents), by altering its metabolism (e.g. N-acetylcysteine in acetaminophen overdose), or by reversing its toxic effect (e.g. naloxone in opiate intoxication).

Initial Management

The foremost priorities in any intoxication are:

- establishing an airway,
- providing ventilation, and
- maintaining adequate circulation.

Subsequent management should include intravenous (IV) glucose for possible hypoglycemia in any patient with coma or seizures, naloxone to reverse narcotic-induced respiratory and central nervous system (CNS) depression, and oxygen (O_2). Thiamine also should be administered to any patient with altered mental status to prevent or treat possible Wernicke's encephalopathy [1].

The next step in the care of any patient with presumed drug toxicity is the administration of activated charcoal. Routine gastric emptying procedures should be discouraged given their serious morbidity, and only considered in conscious patients who have ingested non-caustic substances not adsorbed by charcoal (iron, lithium, methanol, ethylene glycol, boric acid, malathion) [1, 2].

Multiple doses of activated charcoal (MDAC) prevent poison absorption and increase poison clearance through intestinal dialysis [4, 5]. Recommended initial adult dose is 50 – 100 g in 250 mL water, then 30 g every 3 – 4 hours. It should be mixed with a cathartic (70% sorbitol is most effective). Shorter dosing intervals should be used for drugs with short half-lives $t_{1/2}$ (theophylline) and longer intervals for drugs with longer $t_{1/2}$ (phenobarbital). Whole bowel irrigation with a polyethylene glycol-electrolyte solution may also play a role in the future for treating acute overdose [6]. This technique has been useful in iron poisoning, lithium toxicity, and in cases of ingestion of cocaine packets or "crack" vials.

Forced diuresis and the manipulation urinary pH can abet the excretion of certain toxins [7]. An alkaline diuresis (urine pH 7.5 – 8.0), achieved by infusing 5% glucose in water (D_5W) with 2 ampules of sodium bicarbonate ($NaHCO_3$) at 250 mL/hour, can hasten the renal excretion of salicylates and long-acting barbiturates. Urinary acidification (urine

Table 1. Antidotes for Selected Poisonings

Poison	Antidote	Adult dose and comments
Methanol/ethylene glycol	Ethanol	Loading: 0.6 g/kg or 10 mL of 10% solution/kg PO, NG, or IV Maintenance: 154 mg/kg/hour (alcoholic) 66 mg/kg/hour (non-alcoholic) Double dose during hemodialysis Titrate to blood ethanol level + 100 mg/dL (22 mmol/L)
	4-Methyl pyrazole*	Limited experience Loading Dose = 15 mg/kg IV followed by 10 mg/kg IV every 12 hours for 48 hours then 15 mg/kg every 12 hours until ethylene glycol level is < 20 mg/dL
Digitalis glycosides	Digoxin-specific F_{ab} antibody fragents	mg digoxin ingested/0.6 = # of vials required 10 – 20 vials IV if unknown amount ingested or $\frac{\text{Serum digoxin level (ng/mL)} \times 5.6 \times \text{Wt (kg)}}{600}$ = # of vials IV
Acetaminophen	N-acetylcysteine	140 mg/kg PO, NG, or OG initially, then 70 mg/kg × 17doses
Opiates	Naloxone	usual dose 2 mg IV > 2 mg for pentazocine, butorphanol, or propoxyphene Addicts - 0.2 – 0.4 mg
Organophosphates	Atropine/ pralidoxime	2 mg atropine IV; repeat until drying of pulmonary secretions; pralidoxime 1 g IV
Tricyclic antidepressants	Bicarbonate	For cardiac arrhythmias 1 – 2 mEq/kg
Benzodiazepines	Flumazenil	0.2 → 0.3 → 0.5 mg every 30 seconds (1st three) then 0.5 mg IV every one min - total 3 mg. Not to give if coingestion of tricyclic antidepressants
Anticholinergic agents	Physostigmine	1 – 2 mg IV over 5 min only for severe delirium arrhythmias/seizures
Beta-blockers	Glucagon	5 – 10 mg IV starting dose. Titrate to response. Maintenance dose 2 – 10 mg/hour
Calcium-channel blockers	Calcium	1 g $CaCl_2$ over 5 min IV; may be repeated. Monitor serum Ca after 3rd dose
Cyanide	Lilly Cyanide Antidote Kit	Amyl nitrite vials for inhalation 3% sodium nitrite IV, 2.5 – 5 mL/min (up to total 15 mL) 25% sodium thiosulfate, 25 – 50 mL slow IV
Carbon monoxide	Oxygen	100% or hyperbaric
Iron	Deferoxamine	50 – 100 mg IV every 4 – 8 hours

PO = orally, IV = intravenous, NG = nasogastric tube, OG = orogastric tube, *Dilute in 100 mL of NS or D5W and infuse over 30 minutes.

pH 5.5) and large urine volumes are important for the treatment of amphetamine and phencyclidine (PCP) overdoses. This can be initiated by the rapid infusion of 5% glucose in normal saline (D_5NS) at the rate of 1 L every 1 – 2 hours) with arginine or lysine hydrochloride (10 g IV over 30 min). Thereafter, D_5NS is continued with either oral (PO) ammonium chloride (1 – 2 g every 4 hours) or ascorbic acid (1 g every 6 hours). Acidification of the urine is contraindicated if myoglobinuria is a concern with PCP.

Although no fatalities have been recorded, the use of forced diuresis may be complicated by the development of hyponatremia and water intoxication, pulmonary edema, cerebral edema, hypokalemia, and either alkalemia or acidemia secondary to the use of alkaline or acidic agents, respectively, in promoting the diuresis. Severe hypokalemia is particularly prone to complicate forced diuresis during alkalinization of the urine with $NaHCO_3$ and/or use of acetazolamide. The increased urine flow as well as the bicarbonate diuresis favor distal nephron potassium secretion. For these reasons, any commitment to the use of forced diuresis must be accompanied by close vigilance and measurement of urinary pH and serum electrolytes (particularly potassium (K^+)) every 1 – 2 hours initially and frequently thereafter. Hypokalemia should be corrected without delay.

Extracorporeal Techniques

Extracorporeal modalities are beneficial for many drug intoxications which are already severe at the time of presentation or refractory to the aforementioned measures [8]. The indications and benefits of these techniques are reviewed in the section dealing with specific intoxications. Toxins with a small volume of distribution (V_d), low molecular weight (MW), and little protein binding are ideally removed by hemodialysis (HD). These include methanol, ethylene glycol, isopropanol, lithium, and salicylates. Peritoneal dialysis (PD) can also remove many of the drugs eliminated by HD and hemoperfusion (HP); but, at most, it is only 25% as efficient as HD for this task. Drugs with larger MW and high protein binding and relatively low V_d, as well as lipid-soluble drugs, are best removed by HP (e.g. theophylline, phenobarbital). Drugs with large V_d and/or tight tissue binding usually are not removed well by either HD or HP. Continuous extracorporealed techniques such as arteriovenous hemofiltration (HF) or venovenous HF may be beneficial in intoxications with drugs having large V_d, extensive tissue binding, or slow intercompartmental transfer (e.g. procainamide) [9]. Unfortunately, only limited data are available for drug removal by these techniques. The pharmacokinetic properties of drugs commonly removed by extracorporeal techniques are summarized in Table 2.

Indications

HD or HP should be considered when the clinical conditions listed in Table 3 apply. These extracorporeal techniques can also be considered if the serum levels of a drug or poison are found to be increased to values known to be associated with death or serious tissue damage. Critical serum concentrations for several drugs are listed in Table 3. These are only guidelines, and the decision to institute HD or HP must be made on an individual basis.

Table 2. Pharmacologic Toxicity of Drugs that are Substantially Removed by Extracorporeal Techniques

Intoxicant	MW	Protein Binding (%)	V_d (L/kg)	Severe toxic Levels[a]
Isopropyl alcohol	60	–	0.6	400 mg/dL
Methyl alcohol	32	–	0.6	50 mg/dL
Ethylene glycol	46	–	0.6	21 mg/dL[b]
Salicylate	138	50 – 90[c]	0.2	800 µg/mL (80 mg/dL)
Lithium carbonate	74	–	0.8	2.5 mEq/L
Theophylline	180	53 – 65	0.5	60 µg/mL (60 mg/L)

[a]levels that are often lethal unless aggressively treated, [b]practically any positive level accompanied by symptoms and especially by metabolic acidosis is potentially lethal, [c]protein binding high at low (therapeutic) plasma levels and progressively lower at toxic levels

Table 3. Clinical Considerations and Drug Concentration Criteria for Hemoperfusion or Hemodialysis in Poisoning

(A) *Clinical Criteria:*
- Continued deterioration despite intensive care
- Severe poisoning with mid-brain dysfunction
- Appearance of complications of coma
- Impairment of normal drug excretion (e.g. ethchlorvynol overdose in a cirrhotic patient)
- Poisons with metabolic and/or delayed effects (e.g.paraquat and phalloidin)
- Poisoning with an extractable drug removed at a greater rate than endogenous elimination

(B) *Biochemical Criteria:*
A potentially lethal amount has been ingested: phenobarbital (10 mg/dL), other barbiturates (50 mg/dL) glutethimide (4 mg/dL), ethchlorvynol (10 mg/dL), meprobamate (10 mg/dL), paraquat (0.2 mg/mL).

Hemoperfusion (HP)

HP is a process whereby blood is passed through a cartridge packed with a sorbent (activated charcoal or carbon). Two other sorbents may be used: ion exchange resins and non-ionic macroporous resins. The commonly used HP devices (Table 4) contain 70 – 300 g of activated charcoal, coated with polymer membranes ranging in thickness from 0.05 – 0.5 µm. Maximal adsorptive capacity is achieved through high surface porosity and high surface area (SA; approximately 1000 m^2/g). Each manufacturer produces cartridges with different amount of sorbent and different coating material. The Clark (company, etc.) cartridges are unsterilized (longer shelf life) and must be steam autoclaved prior to use. Gambro cartridges are sterilized with ethylene oxide. Erika cartridges are sold gamma sterilized and require no further sterilization. Clark cartridges are claimed to have less incidence of clotting because of the heparin hydrogel coating.

Table 4. Characteristics of Some Available Hemoperfusion Devices

Manufacturer	Device	Sorbent	Coating	Coating thickness	Grams of charcoal-carbon	Adsorbent surface (m^2)	Sterilization by manufacturer
Erika	Hemocart Alukart	Carbon	Cellulose Nitrate	< 0.05 μ	65, 80, 155	65,000, 200,000 104,000	Gamma Irradiation
Gambro	Adsorba 300 C	Charcoal	Cellulose	3 – 5 μ	150, 300	300,000	Ethylene Oxide
Clark Research and Development	Biocompatible Hemoperfusion Systems	Petroleum-derived carbon	Heparin-hydrogel	–	50, 100, 250		None

HP circuitry (Figure 1) is similar to HD arrangement, except that no blood warming apparatus is necessary unless the patient is hypothermic. Heparin requirements are slightly higher than HD (approximately 6000 U/session) because the charcoal adsorbs some of the heparin. Heparin should be given in amounts sufficient to maintain the activated clotting time (ACT) or whole blood partial thromboplastin time at about twice the normal value. The most efficient removal of toxin is achieved with blood flow rates of approximately 300 mL/min, and the most appropriate temporary vascular access to enable efficient treatment of poisoning is percutaneous cannulation of the femoral, internal jugular, or subclavian veins.

Priming the HP Circuit

Setup and priming procedures differ somewhat depending on the brand of cartridge used, and the manufacturer's literature should be consulted in all instances. The HP cartridge must be primed in a vertical position with the arterial side facing down. One manufacturer (Gambro) recommends that its cartridges be rinsed initially with 500 mL of D_5W to load the charcoal with glucose. This maneuver is alleged to result in a lesser drop in the serum glucose level during the HP treatment. Other manufacturers do not recommend a glucose rinse.

After the glucose rinse (if one is used), the cartridge is rinsed with 2 L of heparinized (2500 U/L) 0.9% sodium chloride (normal saline, NS) solution at a flow rate of 50 – 150 mL/min. In rinsing Clark cartridges, the manufacturer recommends that the final liter of rinsing fluid be infused at a relatively rapid rate, i.e. about 150% of the anticipated blood flow rate through the device (e.g. 300 mL/min if the blood flow rate will be 200 mL/min).

Pharmacokinetic Principles of HP

By measuring the concentration of a given drug in the blood just before the blood enters

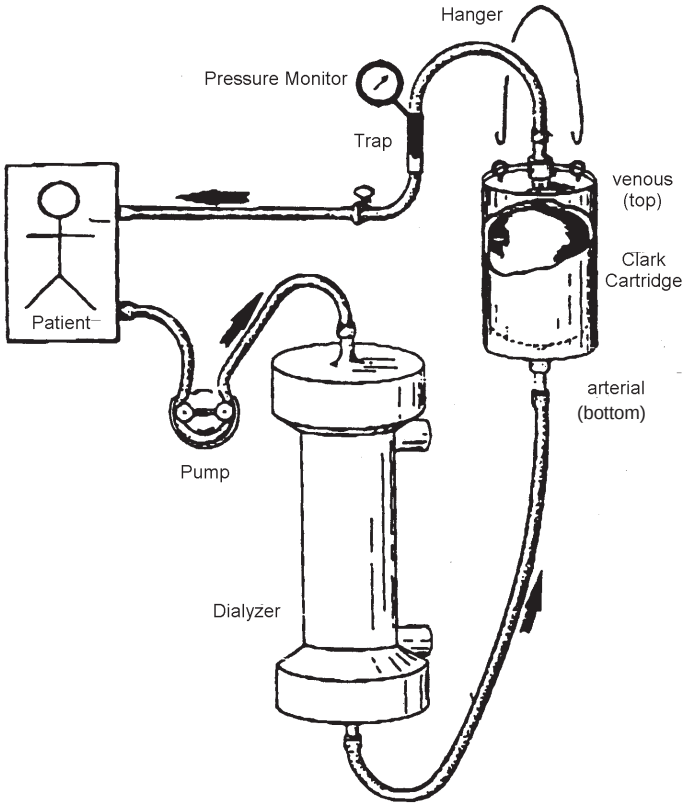

Figure 1. Schematic of a HP circuit. The Clark Biocompatible HP System may be used in conjunction with, or without, hemodialysis. Arrows indicate flow direction. (Clark Research and Development, Inc. Number 13 Park Lane, Folsom, Louisiana 70437)

and as it exits the HP cartridge, one can easily calculate the extraction ratio (ER) Of the drug with the formula: ER = (A-V)/A where, A = Concentration of toxin at inlet to HP cartridge, and V = Concentration of toxin at outlet; a ratio of 1.0 signifies complete extraction of the drug in one pass. By knowing the concurrent plasma flow rate through the cartridge, one can calculate the clearance rate (clearance = ER × Q_B, where Q_B = blood flow rate, in mL/min).

Data on drug ERs suggest that charcoal hemoperfusion is efficient in extracting a wide variety of poisons from the circulating blood, including theophylline (ER = 0.7), ethchlorvynol (ER = 0.7), methaqualone (ER = 0.5 – 1.0), phenobarbital (ER = 0.5) and glutethimide (ER = 0.65), as well as paraquat. However, despite the very high ERs and clearance rates that can be obtained with HP, other theoretical and clinical factors must be taken into consideration when assessing effectiveness of HP in the therapy of intoxications. These theoretical considerations focus on the fact that many common intoxicants have pharmacokinetic properties which predict that cleansing of the circulating blood, no matter how effectively done, may not result in a clinically detectable beneficial effect. These considerations also reveal that evidence derived only from ERs and clearance data can be misleading. After absorption, the distribution of each drug in the various body compartments is highly individualized and depends on several factors, which include the MW of the drug, its ionization at the prevailing pH of body fluids, its lipid solubility, the degree of protein binding, and the apparent volume of

distribution (V_d). The interplay of these factors determines not only the total amount of the drug that is present in various body tissues and in the extracellular fluid and plasma, but also dictates how easily the drug moves from one to another compartment, and how accessible it is to extracorporeal therapy.

Importance of Volume of Distribution (V_d)

The V_d of a substance is pharmacokinetically defined as:

$V_d = X/C_P$,

where X = dose administered in mg/kg, and C_P = Serum concentration in mg/L.The V_d of a substance is the space that represents the quantity of water in which a known amount of drug would have to be diluted to yield the serum concentration. By viewing the body as one compartment in which the substance is homogeneously distributed, V_d relates the dose of drug administered to its plasma concentration by the above equation. However, most substances are not homogeneously distributed but rather vary in their concentration throughout the body as a result of lipid solubility, protein binding, active transport and pH gradients. The apparent V_d corresponds to a physiologic space only for a substance, like methanol, that distributes in body water without significant binding to tissue or plasma proteins and without significant accumulation in adipose tissue. In this case V_d = 0.6 L/kg, the equivalent of body water. A V_d greater than the actual body water reflects a high degree of tissue concentration.

V_d is clinically important in 2 ways:

– Knowing the V_d and C_p of a particular drug allows calculation of the amount of drug ingested.

– V_d is one of the factors that determines accessibility of a drug to removal by extracorporeal therapy. Large V_d implies that the drug is concentrated in less accessible extravascular compartment, and hence not efficiently removed by HP (e.g. V_d of digoxin and tricyclic antidepressants, are 6 L/kg and 20 L/kg, respectively).

Conversely, a low V_d by no means ensures success with HP. For example, paraquat, glutethimide, and short-acting barbiturates are not readily removed by HP due to tight tissue binding.

Duration of HP

Assuming first-order kinetics and instantaneous equilibration of compartments, the removal of a substance during HP follows an exponential relationship:

$$C_{final} = C_{initial}\left(e\frac{-Kt}{V}\right)$$

Where
K = clearance which is equal to ($Q_B \times$ ER), in mL/min,
t = time elapsed (mins),
V_d = volume distribution (mL),
ER = extraction ratio, and
Q_B = blood flow rate, in mL/min.

Knowing the C_{initial} and desired C_{final}, one can estimate the duration of HP required to achieve the target concentrations of the toxin or drug being removed. In practice, however, a single 3 hour treatment will substantially lower the blood levels of most poisons for which HP is effective and prolonged HP (beyond 3 hours) is usually unnecessary. Indeed, more prolonged use of a HP cartridge is inefficient, because the charcoal tends to become saturated with the toxin or drug (especially

when cartridges containing < 150 g charcoal are used). Usually, replacement of saturated devices with fresh devices is not required, and any rebound in plasma drug concentrations consequent to tissue release can be treated with a second HP session.

Complications

The principal side effect of HP with charcoal or resin preparations is platelet depletion. Most studies of HP in humans show an average loss of 30% of platelets with coated or uncoated charcoal or resin preparations [10]. Occasionally, however, a higher drop in platelet count can occur, which may give rise to clinical bleeding problems. Other side effects noted are reductions in serum Ca and glucose and transient falls in white blood cell (WBC) counts, all of which are usually mild and can be managed clinically. In addition, with the recirculation of blood in the extracorporeal circuit, there is also a mild reduction of 1 – 2°C in body temperature, and frequent body temperatures should be taken in deeply comatose patients. Although hypotension as a consequence of circulation of blood in the extracorporeal circuit is an infrequent phenomenon in drug overdosage, pressor agents like dopamine for hypotensive comatose patients should be administered distal to the sorbent devices, since they are also adsorbed by the sorbent preparations. The observed falls in platelet concentrations usually return to normal limits within 24 – 48 hours following a single HP.

Intoxications Which Respond Readily to Extracorporeal Therapies

Intoxications with Methanol, Ethylene Glycol, and Isopropanol

An increased plasma osmolar gap characterizes intoxication with any of these 3 agents [11, 12]. Methanol and ethylene glycol also are associated with a high anion gap acidosis. Isopropyl alcohol, by contrast, affects acid-base status with far less frequency unless hypotension and tissue hypoxia ensue after ingestion.

Cardinal features which should alert physicians to suspect intoxication with these atypical alcohols are shown in Table 5. In addition to these characteristics, several other features are associated with atypical alcohol poisoning. Methanol and ethylene glycol may cause myoglobinuric acute renal failure (ARF). Methanol also can interfere with serum creatinine determinations while isopropanol can lead to spurious elevations in serum creatinine.

Despite the fact that intoxication with atypical alcohols results in an increased osmolar gap, the most common etiology for an elevated osmolar gap in clinical practice remains ethanol intoxication. Because ethanol ingestion may accompany intoxication with any of these agents, it is important to correct for the contribution of ethanol in determining the concentration of the toxin ingested. The equations for this calculation are shown in Table 6. These formulas serve to estimate the amount of toxin ingested.

Each of these alcohols manifests differences in toxicity and pharmacology [8]. The amount of methanol necessary to cause toxic-

Table 5. Cardinal Features of Intoxications with Atypical Alcohols

Clinical features

– METHANOL: Blurring of vision, “snowstorm” photophobia, blindness, sluggish or non-reactive dilated pupils, hyperemia of optic discs, retinal edema, and painful abdominal crisis due to pancreatitis.

– ETHYLENE GLYCOL: Alcohol-like intoxication without alcoholic fetor, “triphasic” clinical picture, urine sediment with abundant calcium oxalate crystals, and hypocalcemia.

– ISOPROPANOL: Acetonemia or acetonuria combined with fruity breath but no hyperglycemia or glycosuria.

Biochemical features

– Increased plasma osmolal gap.

– High anion-gap metabolic acidosis (methanol and ethylene glycol).

– Usually no change in acid-base status with isopropyl alcohol (unless hypotension and lactic acidosis prevail).

Table 6. Utility of the Osmolar Gap in Management of Intoxications

Substance	Structure	Molecular Weight	Lethal Level mg/dL	Corresponding Δ Osm
Ethanol	CH_3CH_2OH	46	350	76
Isopropanol	CH_3CHCH_3	60	340	56
Methanol	CH_3OH	32	80	25
Ethylene Glycol	CH_2-CH_2 OH OH	62	21	3.4
Acetone	CH_3-CO-CH_3	58	55	9.4

$$\text{Concentration of toxin (mg/dL)} = \frac{\Delta \text{ OsmX} \times \text{MW of X (mOsm/kg)}}{10}$$

where Δ OsmX = $\Delta \text{Osm}_{\text{total}} - \Delta \text{Osm}_{(\text{ethanol})}$

$$\Delta \text{Osm}_{\text{total}} = \text{“measured Osmolality”}^{*} - \text{“Calculated Osmolality”}^{+}$$

(*) by freezing point depression (LAB); (+) by formula $[2 \times \text{Na} + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8}]$

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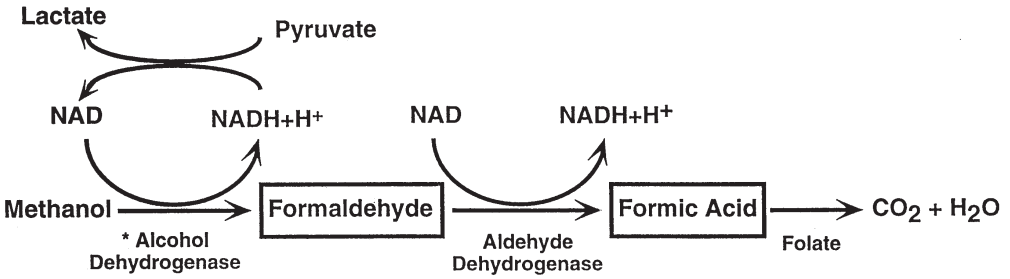

Figure 2. Methanol metabolism. Asterix indicates rate-limiting step. The affinity of methanol to alcohol dehydrogenase is only 1/10 the affinity of ethanol.

ity and death is variable, ranging from as little as 15 – 30 mL of a 40% solution to 60 – 240 mL. Death usually results at blood levels of 80 – 100 mg/dL (24 – 30 mmol/L). Serum methanol levels do not correlate well with prognosis; however, the degree of acidosis and serum formic acid levels are good predictors of mortality [19].

Peak blood levels of methanol occur 30 – 90 min after ingestion. Its V_d is 0.6 L/kg. Less than 5% of methanol is excreted unchanged by the kidney while the remaining 90 – 95% is excreted via hepatic metabolism (Figure 2). Alcohol dehydrogenase converts methanol to formaldehyde. This reaction, when it occurs in the retina, is responsible for the ocular toxicity associated with methanol poisoning [15]. Subsequently, formaldehyde is converted to formate by aldehyde dehydrogenase and other enzymes. Because ethanol has a 7 – to 10-fold fold greater affinity for alcohol dehydrogenase than methanol, it is used clinically to slow the metabolic transformation of methanol to its toxic product, formate.

The elimination $t^{1/2}$ for methanol in mild intoxications is 14 – 20 hours, but this increases to 24 – 30 hours in severe intoxications and 30 – 35 hours with the administration of ethanol. With ethanol and HD, this falls markedly to 2.5 hours [20].

Drowsiness is present early in methanol intoxication. A latent period follows (6 – 30 hours), but ends with the onset of the classical signs and symptoms of methanol poisoning: vomiting, vertigo, abdominal pain, change in vision, coma, and death [15].

Laboratory abnormalities associated with methanol ingestion include high osmolar and anion gaps as well as formic and lactic acidosis. The acidoses result from trapping of nicotinamide-adenine dinucleotide (NAD^+) as its reduced form (NADH) in the liver as a consequence of the oxidation of methanol to formic acid. This leads to an increase in formic acid concentration which reverses the normal oxidation of lactate to pyruvate; thereby, increasing blood lactate levels (Figure 2). Patients also may have hyperglycemia, an elevated hematocrit (HCT) and mean corpuscular volume (MCV), and an increase in serum amylase.

Treatment for methanol intoxication should be initiated as early as possible. Gastric lavage may be of benefit if the patient is seen early (< 2 hours) after ingestion. Ethyl alcohol should then be administered PO, IV, or via nasogastiric tube (NG) at a loading dose of 0.6 g/kg followed by a maintenance dose to achieve serum ethanol levels > 100 mg/dL (see Table 7). The metabolic acidosis also should be corrected readily [20, 21].

HD is indicated for methanol poisoning when the following are present:

Table 7. Guidelines for the Use of Ethanol in the Treatment of Atypical Alcohol Intoxications

- Maintain serum ethanol levels during treatment > 100 mg/dL
- Loading dose = 0.6 g/kg PO, NG, or IV
- Maintenance dose
  a. Alcoholic patient = 154 mg/kg/hour
  b. Non-alcoholic patient = 66 mg/kg/hour
  c. Double dose during hemodialysis
- PO or NG ethanol concentrations should not exceed 20%. IV ethanol is usually given as 10% ethanol in D_5W
- Continue ethanol until ethylene glycol or methanol are no longer detectable

- methanol blood levels > 50 mg/dL,
- visual, funduscopic, or mental status changes,
- severe metabolic acidosis,
- increased serum formic acid levels, or
- the patient consumed > 30 mL methanol [21].

Optimal dialysis can be achieved with a HCO_3^- dialysate bath, blood flows > 300 mL/min, and a large surface area dialyzer (1.5 m^2). HD should be continued until serum methanol levels are < 20 mg/dL. Folic acid may promote catalase-mediated formate metabolism to carbon dioxide (CO_2) and water and can be used at 2 mg PO daily. Finally, PD is an alternative if HD is not available.

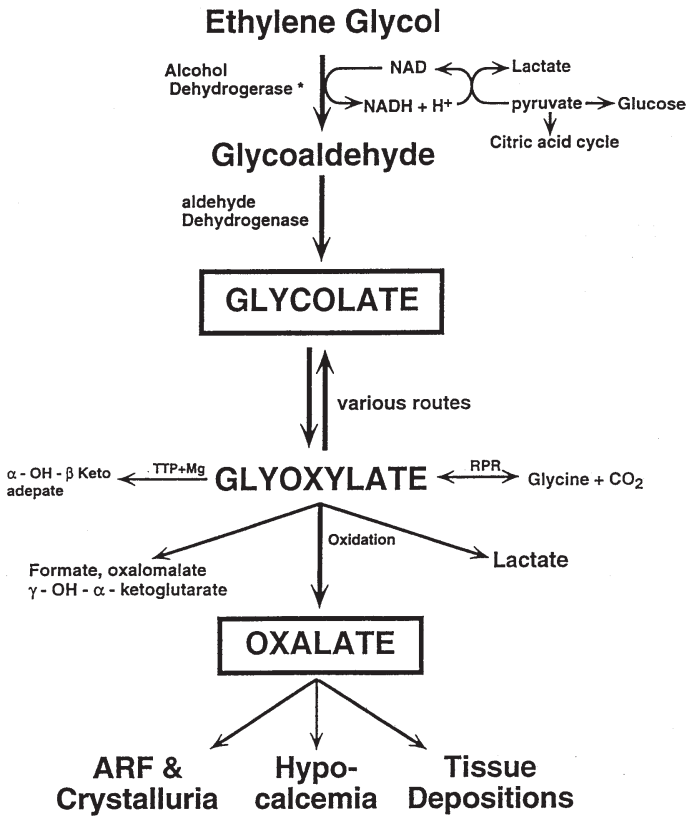

Figure 3. Ethylene glycol metabolism. Asterix indicates rate-limiting step. Ethanol has 100 × more affinity than ethylene glycol to alcohol dehydrogenase. TTP = thiamine as cofactor, PRP = pyridoxine as cofactor

Ethylene glycol has a V_d (0.6 L/kg) and lethal dose (100 mL) similar to methanol. Peak blood levels occur after 1 – 4 hours post-ingestion. Ethylene glycol is metabolized via alcohol dehydrogenase to several toxic compounds, including glycolic and oxalic acids (Figure 3). Alcohol dehydrogenase also has a far greater affinity for ethanol (100-fold) than ethylene glycol; hence, its administration is effective in delaying the breakdown of ethylene glycol to its toxic metabolites [13, 14].

The degree of toxicity and acidosis correlate best with the accumulation of glycolic acid; however, lactate production also may contribute to the metabolic acidosis. The $t^{1/2}$ for ethylene glycol without treatment is 3 – 8.5 hours; however, with ethanol treatment, it is 10 – 102 hours. Combined ethanol use and HD, as in the case of methanol ingestion, significantly shortens the elimination $t^{1/2}$ to 2.5 – 3 hours [22].

The clinical syndrome of ethylene glycol poisoning usually follows a triphasic course [14]. The earliest findings are neurologic abnormalities ranging from drunkenness to coma (Stage I). These are succeeded by pulmonary edema, cardiomegaly, and heart failure (Stage II). Acute tubular necrosis (ATN) occurs in the final stage (Stage III). This may be accompanied by calcium oxalate crystals in the urine and diverse laboratory abnormalities including: high osmolar and anion gaps, acidosis, leukocytosis, cerebrospinal fluid (CSF) xanthochromia, hypocalcemia, elevated creatine phosphokinase (CPK) and elevated liver function tests.

Therapy for ethylene glycol poisoning proceeds along many of the same guidelines outlined above for methanol intoxication. Initial treatment should entail gastric lavage and ethanol (see Table 7) as well as correction of the metabolic acidosis. An alternative to ethanol is fomepizole (4-methyl-pyrazole), a potent inhibitor of alcohol dehydrogenase [23, 24]. Treatment with fomepizole should be initiated as quickly as possible when there is a suspicion of ethylene glycol poisoning or a documented serum ethylene glycol concentration > 20 mg/dL. A loading dose of 15 mg/kg IV should be given, followed by doses of 10 mg/kg IV every 12 hours for 48 hours, then 15 mg/kg IV every 12 hours thereafter until ethylene glycol levels fall < 20 mg/dL. Fomepizole induces its own metabolism via the cytochrome P450 system, necessitating the increase in maintenance dose after 48 hours. The drug is dialyzable and its dosing must be intensified during HD. Preliminary data suggest that fomepizole is usually well tolerated but occasionally produces headache, nausea, dizziness, eosinophilia, or mild transient elevation of liver enzymes. Small studies or case series have documented prolongation of the $t^{1/2}$ of ethylene glycol from 3 – 16 hours and dramatic improvements in acidemia when the drug is administered. Fomepizole also prolongs the $t^{1/2}$ of ethanol, and the simultaneous use of both agents is not recommended.

Hypocalcemia also should be corrected if present. Hemodynamic monitoring may be necessary if the patient develops pulmonary edema or renal failure. IV fluids and mannitol should be given to patients without oligoanuria or pulmonary edema to maintain good urine output.

The 2 antidotes for ethylene glycol toxicity are pyridoxine which stimulates glyoxylate to glycine; and thiamine which hastens the metabolism of glyoxylate to α–OH ketoadipate. Pyridoxine should be given 500 mg intramuscularly (IM) 4 times daily and thiamine 100 mg IM 4 times daily. HD is indicated for a serum ethylene glycol level > 20 mg/dL or severe metabolic acidosis. Dialysis should be continued until the ethylene glycol level is < 20 mg/dL and the acidosis has resolved.

Isopropanol has a lethal dose between 150 – 240 mL. Life-threatening plasma levels approximate 400 mg/dL; nonetheless, clinical signs and symptoms are more reliable prognostic indicators than serum levels. Isopropyl alcohol is completely absorbed by 2 hours post-ingestion with an apparent V_d of 0.6L/kg. The elimination $t^{1/2}$ is 2.5 – 3.2 hours. Isopropanol undergoes oxidative metabolism by alcohol dehydrogenase to acetone which is excreted predominantly by the kidneys and, in part, by the lungs. Twenty to 50% of isopropanol does not undergo metabolism and is excreted directly by the kidneys. A proportion of absorbed isopropanol is re-secreted into saliva and stomach and hence the value of repeated MDAC even after its absorption.

Isopropanol, like the aforementioned atypical alcohols, is a CNS and myocardial depressant. Hemorrhagic gastritis, profound hypotension, hypothermia, and hypoglycemia also may complicate isopropanol ingestions. Hypotension also is important because this plays a critical factor in determining patient prognosis after isopropanol ingestion [18].

Therapy for most patients with isopropanol intoxication focuses upon supportive measures including IV fluids, pressor agents and mechanical ventilation, if necessary, as well as symptomatic treatment for GI distress. HD is of great benefit, effectively removing isopropanol and acetone from the plasma. The indications for HD are: 1) plasma levels > 400 mg/dL, 2) prolonged coma, 3) hypotension, 4) myocardial depression and tachyarrythmias, and 5) renal or hepatic failure [18].

Lithium Intoxication

Lithium carbonate is a valuable and widely-used drug in the treatment of bipolar affective disorders. However, this medication has a low therapeutic index and can induce a multitude of adverse and even, life-threatening complications. Acute overdose has a mortality rate approaching 25%. In contrast to many other drug poisonings, acute lithium intoxication usually results from chronic accumulation [8, 25, 26]. The clinical manifestations of toxicity such as neuromuscular irritability, mental status changes, and hypotension are often superimposed on the drug's chronic effects e.g. nephrogenic diabetes insipidus, renal acidification defects, interstitial nephritis, and goiter [25, 26].

Patients taking lithium who have polyuria are prone to lithium intoxication when they are unable to maintain an adequate fluid intake and, hence, suffer dehydration [27]. Old age also places patients at greater risk for lithium toxicity as a result of diminished renal clearance and V_d [28]

Lithium carbonate and lithium citrate are readily absorbed from the gastrointestinal tract with peak serum levels 2 – 4 hours after ingestion. Lithium is freely distributed in whole body water with a V_d of 0.8 L/kg. Steady-state plasma levels usually are reached within 5 days during conventional oral dosing (1200 – 1800 mg/day) [27].

Lithium is predominantly excreted by the kidney. Following filtration, 75 – 80% of filtered lithium is reabsorbed in the proximal tubule while the remainder is excreted in the urine. Any process which increases proximal tubule sodium reabsorption, e.g. extracellular volume depletion, decreases the renal clearance of lithium and thus, may necessitate a dosage change. The usual $t^{1/2}$ approximates 18 hours in young adults and increases to 36 hours in the elderly. Given these extended $t^{1/2}$, blood levels for monitoring serum lithium should be drawn no earlier than 12 hours after the last dose [27].

The clinical manifestations of lithium toxicity may be subtle especially during its prodromal phase. However, a good correlation

Table 8. Indications for Hemodialysis in Lithium Toxicity

- Serum lithium> 3.5 mEq/L regardless of patient presentation.
- Serum lithium > 2.5 mEq/L and,
  Markedly symptomatic patient
  Renal insufficiency
  Presence of condition(s) that increase renal sodium avidity (cardiac failure, cirrhosis).
- Serum lithium = 2.5 – 3.5 mEq/L, but asymptomatic
  Consider HD if serum lithium is not anticipated to be < 0.6 mEq/L by 36 hours.

exists between the symptomatology of lithium toxicity and serum lithium levels [29]. Mild (serum level = 1.5 – 2.5 mmol/L) and moderate (serum level = 2.5 – 3.5 mmol/L) lithium toxicity are characterized by neuromuscular irritability, weakness, delirium, nausea, emesis, and diarrhea. Sinus bradycardia and hypotension can also occur. Severe toxicity (serum level > 3.5 mmol/L) can result in seizures, stupor, coma, and a 10% risk of permanent neurologic sequelae, e.g. dementia or ataxia. Laboratory manifestations of lithium intoxication include a decreased serum anion gap (lithium is an unmeasured cation) and leukocytosis [25].

Recognizing and avoiding states predisposing to lithium intoxication are the best strategy for preventing this drug's significant toxicity. Nonetheless, some patients will develop acute lithium poisoning and require treatment commensurate with the adequacy of their renal function and the degree of intoxication. Initial therapeutic measures include the withdrawal of any concomitant diuretic therapy. These may be re-introduced, after correction of intravascular volume depletion, to control nephrogenic diabetes insipidus. Patients with cardiac disease, arrhythmias, or severe toxic reactions, e.g. obtundation, should be monitored in an intensive care unit (ICU). Maximizing lithium clearance by restoring sodium and water balance is essential. While administering IV fluids, it is important to avoid hypernatremia, therefore 0.45% NaCl solution (half-normal saline) or another hypotonic solution is advisable. Forced diuresis and large volume saline infusions have limited applications in the treatment of lithium toxicity unless the glomerular filtration rate (GFR) is reduced. Evidence suggests that the fractional excretion of lithium (FE_{Li})does not change consistently during saline administration unless hypovolemia and a depressed GFR are already present [27].

HD remains the therapy of choice for severe lithium toxicity. HD rapidly reduces serum drug levels and the $t^{1/2}$. The indications for HD are summarized in Table 8 [27, 30, 31]. HD effectively clears lithium at nearly 50 mL/min compared to 15 mL/min for PD. However, because intracellular lithium re-equilibrates slowly, serum levels may rebound after the cessation of dialysis. Continued or delayed gastrointestinal absorption related to sustained-release lithium formulations may also contribute to this rebound in serum levels. Extending the duration of dialysis can obviate this phenomenon. Generally, a 9-hour HD session removes 60% of the total lithium burden. One strategy is to perform dialysis for 8 – 12 hours initially and repeat dialytic treatments as necessary until the serum Li remains < 1.0 mmol/L, 6 – 8 hours post-dialysis. An alternative is simply a 6-hour HD with a large surface area dialyzer, reducing serum lithium to the desired level. Continuous arteriovenous hemodiafiltration (CAVHDF) may also prove to be a safe and efficacious therapy by significantly augenting lithium excretion [32, 33].

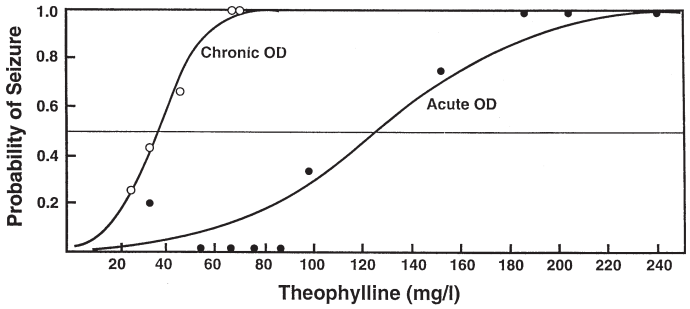

Figure 4. Probability of seizures as a function of peak measured theophylline concentration for acute single injection versus chronic overmedication. OD = overdose. Adapted from Olson, Am. J. Emerg. Medicine 1985; 3:386.

Theophylline Toxicity

Severe theophylline toxicity is associated with significant morbidity and mortality as a result of sustained or recurrent seizures, hypotension, and arrhythmias. With the extensive use of sustained-release theophylline products, prolonged toxicity is possible. Although the symptomatology of theophylline toxicity relates to the serum concentration, there is no predictable step-wise relationship between these factors. Nonetheless, 30% of patients with serum theophylline concentrations > 15 mg/mL will have mild toxicity, while toxic reactions will be present in 78% of patients with levels > 25 mg/mL (therapeutic, 10 – 20 mg/mL). The "acuteness" or "chronicity" of the intoxication also will affect the severity of symptoms (Figure 4). At any given serum level, chronic intoxication will have more pronounced manifestations than acute intoxication [34].

Many factors influence the development of theophylline toxicity by decreasing drug metabolism [35]. Significant cardiac or hepatic disease and concurrent drug use (erythromycin, cimetidine, ciprofloxacin, cephalexin, tetracycline, oral contraceptives, allopurinol, propranolol, and thiabendazole) can delay the metabolic clearance of theophylline, as can old age and early infancy (< 6 months).

Seizure activity may occur with serum theophylline concentrations as low as 25 mg/mL, but, more commonly at concentrations > 40 mg/mL. Seizures can occur many hours after the peak serum theophylline level in acute intoxications. The reason for this temporal discrepancy is unknown. Unexpected seizures may be the presenting clinical finding in chronic intoxication [34, 36]. Tachyarrythmias can occur with serum theophylline levels > 20 – 30 mg/mL. Cardiovascular collapse and respiratory arrest however, are rare unless the concentration is > 50 mg/mL in chronic overdose, or > 100 mg/mL in acute toxicity [36]. Metabolic abnormalities often accompany theophylline toxicity including hypokalemia, hypomagnesemia, hypophosphatemia, hypercalcemia, hyperglycemia, and respiratory alkalosis [37].

Theophylline is slightly more than 50% protein bound with a small V_d (0.4 – 0.6 L/kg). It is extensively metabolized by the hepatic cytochrome P-450 system with only 8 – 10% excreted unchanged in the urine. At therapeutic doses, blood levels follow first-order kinetics but at toxic levels, mixed first-order and zero-order kinetics prevail. The implications of a small V_d, rapid blood-tissue equilibration, and a prolonged $t^{1/2}$ due to low intrinsic clearance, are that a substantial amount of drug can be removed during a HD or HP session [35, 36].

Table 9. Indications for Extracorporeal Therapy in Theophylline Toxicity

- Seizures and/or arrhythmias with cardiovascular instability.
- Acute intoxication with plasma theophylline level ≥ 100 mg/L (550 μmol/L), or levels approaching 100 mg/L in 2 hours.
- Chronic intoxication in a patient over age 60 years with plasma theophylline level > 40 mg/L (220 μmol/L).
- Chronic intoxication in a younger patient with plasma theophylline level > 60 mg/L (300 μmol/L) and who cannot tolerate multiple doses of activated characoal or has other risk factors for major toxicity.
- Any intoxication with levels > 60 mg/dL in a patient who is at risk of seizure or has other medical complications:
  1. Impaired theophylline metabolism (chronic liver disease, CHF, hypoxemia (PO_2 < 40 mmHg), or neonate).
  2. History of epilepsy.
  3. Ischemic heart disease or severe chronic lung disease.

The mainstays for treating theophylline toxicity are supportive measures and oral activated charcoal [36, 38, 39]. The latter is indicated even for IV intoxications. Activated charcoal is administered 1 g/kg initially followed by 20 g every 2 hours for 6 – 12 hours. A cathartic such as sorbitol (50 – 75 mL of 70% solution) should also be considered. There are no firm indications for HD or HP. Table 9 lists well-accepted guidelines for the performing HP in theophylline toxicity. Most authors however, agree that either extracorporeal therapy is indicated for unstable patients with seizures, hypotension, or arrhythmias [36, 38, 40] (Table 9). Acute toxicity with serum theophylline levels > 100 mg/mL, chronic intoxication with a level > 60 mg/mL in a young person, or chronic intoxication with a level > 40 mg/mL in an individual older than 60 all warrant either HD or HP. Serial HD-HP (a dialysis membrane followed by a HP cartridge in the extracorporeal circuit) offers the advantage of each modality and delays saturation of the HP cartridge [41].

Other therapies also have demonstrated some efficacy in theophylline toxicity, albeit, in small studies or case reports. Plasmapheresis [42] has succeeded in lowering serum theophylline concentrations in children and exchange transfusion [43] has been beneficial in treating theophylline intoxication in infants and neonates. Further experience with these techniques will be necessary to assess their absolute effectiveness. Finally, when HD or HP are not available, it is reasonable to consider continuous arteriovenous or venovenous hemofiltration (CAVHF or CVVHF) to clear theophylline [9]. However, an extended treatment course is required to accomplish effective drug clearance due to the lower blood flow inherent in these techniques.

Salicylate Intoxication

Salicylate poisoning is a frequent and often overlooked cause of drug intoxication. Salicylate toxicity annually is responsible for 10% of intoxication-related deaths and 14% of severe intoxications in the United States. The most common form of salicylate is aspirin. Other sources include methyl salicylate (oil of wintergreen), sodium salicylate, salicylic acid, and many over-the-counter preparations.

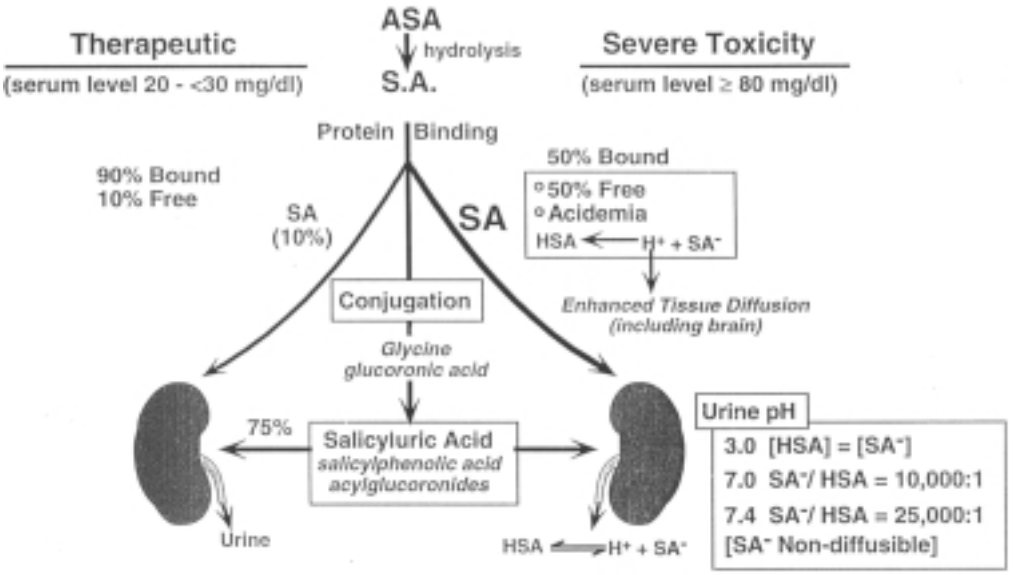

Figure 5. Biochemical basis of salicylate toxicity and its therapy. ASA = acetylsalicylic acid, SA = salicylic acid. ASA is rapidly converted to SA, and this metabolite exert the drug's toxic effects. At therapeutic levels 90% of salicylate is protein bound and thus, confined to the intravascular space. Subsequently, SA is 75% glycinated in the liver to salicyluric acid which is less toxic and excreted more rapidly by the kidney than SA. When salicylate toxicity occurs (serum levels > 40 mg/dL), the extent of protein binding declines and salicyluric acid formation becomes saturated. Salicylate concentrations increase and, with a fall in renal excretion, drug $t^{1/2}$ prolongs from 3 – 12 hours to 15 – 30 hours.

Several narcotic or sedative compounds also are prescribed in combination with salicylates. These include oxycodone (Percodan), propoxyphene (Darvon), and barbiturate (Fiorinal).

Acetylsalicylic acid is rapidly converted after ingestion to salicylic acid and this metabolite exerts the drug's toxic effects (Figure 5). At therapeutic levels (20 – 30 mg/dL), 90% of salicylate is protein bound and thus, confined to the intravascular space. Subsequently, salicylic acid is 75% glycinated in the liver to salicyluric acid which is less toxic and excreted more rapidly by the kidney than salicylic acid. When salicylate toxicity occurs (serum levels > 40 mg/dL), the extent of protein binding declines and salicyluric acid formation becomes saturated. Salicylate concentrations increase and, with a fall in renal excretion, drug $t^{1/2}$ prolongs from 3 – 12 hours to 15 – 30 hours [44].

A dose of 150 mg/kg is usually associated with toxicity. This roughly equates to 35 tablets or 10 g in an adult. Fatalities have occurred in adults after ingesting 10 – 30 g and, in children after doses of 3 g. Early symptoms of toxicity include tinnitus, vertigo, nausea, vomiting, and diarrhea. Severe intoxication can result in altered mental status, coma, noncardiogenic pulmonary edema and death.

A variety of acid-base disturbances accompany salicylate intoxication [45]. Salicylates directly stimulate the respiratory center resulting in a rapid fall in the pCO_2 and respiratory alkalosis. A high anion gap metabolic acidosis may ensue, primarily as a result of the accumulation of organic acids, including lactate and ketoacids. The respiratory alkalosis

normally promotes lactic acid production to counteract the pH increase, and this augents the development of the acidosis. Salicylic acid (MW 138) itself contributes only minimally to the acidosis since a plasma level of 50 mg/dL is equivalent to < 3 mEq/L.

The result of these metabolic changes is that most adults with salicylate intoxication have either a respiratory alkalosis or a mixed respiratory alkalosis-metabolic acidosis. A pure metabolic acidosis is highly unusual except in children. An acute respiratory acidosis also can occur, especially if the patient has ingested other medications or has progressed to severe toxicity.

An accurate diagnosis of salicylate intoxication is often suspected from the history and the presence of acid-base disturbances. Rapid diagnosis also can be culled from the urinalysis. A positive serum Phenistix (brown discoloration with phenothiazines or salicylates > 700 mg/mL) or a positive urine ferric chloride test (purple color when 4 drops ferric chloride are added to 1 mL urine) are strongly suggestive of salicylate intoxication. Confirmation of the diagnosis is made by measuring plasma drug levels [46].

The serious toxicity of salicyclates is related to their tissue concentrations. Therefore, initial therapeutic objectives are aimed at reducing drug absorption by administering activated charcoal (50 g every 3 hours) and decreasing drug accumulation by systemic alkalinization. $NaHCO_3$ (2 ampules in 1L D_5W) should be given to raise the arterial pH to 7.45 – 7.50. This promotes a marked reduction in tissue salicylate concentrations.

The next goal of therapy is rapid drug elimination. Urinary alkalinization is important to pursue as it increases salicylate removal. Salicylate primarily enters urine through the organic anion secretory pathway in the proximal tubule. The rate of salicylate excretion can be markedly enhanced by urine alkalinization. $NaHCO_3$, administered as above, should be targeted to raise the urinary pH to 7.5 – 8.0. This can increase salicylate excretion up to 5-fold. Acetazolamide, a carbonic anhydrase inhibitor, also induces a bicarbonate diuresis by inhibiting proximal bicarbonate reabsorption. However, urinary HCO_3^- loss will lead to an undesired fall in systemic pH, thereby increasing salicylate entry into the brain and aggravating the toxic state. Acetazolamide therefore is not advocated as sole therapy for aspirin intoxication and should rarely be considered, only in concert with $NaHCO_3$ therapy, once systemic acidemia has been corrected [44, 47].

HD also is highly efficacious for treating salicylate toxicity. Save for its extensive protein binding, salicylate satisfies the criteria for toxins readily removed by HD. This modality should be utilized when plasma salicylate concentrations are > 80 mg/dL, especially in the presence of impaired renal function. It should also be implemented in the setting of salicylate intoxication with volume overload (compromising $NaHCO_3$ administration), coma, or progressive clinical deterioration. Finally, HD also is indicated to correct the acid-base and fluid and electrolyte disturbances which may occur in salicylate poisoning, especially in patients with renal failure [8].

Valproic Acid Intoxication

Valproic acid is an effective anti-epileptic drug, often used for simple and complex absence (petit mal) seizures. In spite of its efficacy, accidental or intentional overdose with valproic acid can cause serious toxicity and even death.

Valproate sodium is readily converted to valproic acid after ingestion in the stomach. The drug is rapidly and almost completely

absorbed from the GI tract with peak serum levels 1 – 4 hours after ingestion for valproate sodium and 3 – 5 hours after a single oral dose of divalproex sodium. Valproic acid demonstrates significant protein binding (80 – 90%) and achieves a V_d of 0.1 – 0.5 L/kg. It manifests first-order kinetics with an elimination $t^{1/2}$ of 5 – 20 hours, although this may extend to > 30 hours in the setting of valproate intoxication. Valproic acid is primarily metabolized by the liver with glucuronide conjugates excreted by the kidney. Only small amounts of drug are excreted unchanged in the urine.

Therapeutic plasma concentrations for valproic acid have not been well established, but 50 – 100 mg/mL may be an appropriate target for patients taking 1.2 – 1.5 g of valproic acid daily. Drug toxicity with valproate is variable, ranging from nausea, vomiting, and indigestion to CNS changes encompassing lethargy, drowsiness, and coma. Patients may have elevated serum transaminase levels, hyperammonemia, and an apparent bleeding diathesis with petechiae, ecchymoses, and a prolonged bleeding time. Some individuals also may have a false positive urine test for ketones related to one of the valproate metabolites.

Treatment for valproic acid intoxication has classically centered around early gastric lavage and activated charcoal followed by forced diuresis. This however, has had limited utility given the small amount of valproic acid excreted unchanged in the urine. While no immediate antidotes are available for this drug, several studies have outlined successful combination HD / HP treatment in valproic acid poisoning. Though these are primarily case reports, they suggest that HD performed "in series" with HP can rapidly lower serum valproate levels and, possibly, stave off the ill effects of drug toxicity [48]. The efficacy of valproic acid removal by HD increase in the overdose setting. At blood levels > 90 – 100 mg/mL, protein binding sites become saturated, leading to a progressive increase in free valproic acid concentrations and, thus, enhanced clearance across dialysis membranes. Successful removal of valproic acid has been reported especially when HD has been initiated at plasma drug concentrations of 700 – 750 mg/mL [49]. A report from the University of Texas Southwestern Medical Center also has proposed that higher blood flows may contribute to the rapid and significant valproic acid extraction achieved during extracorporeal therapy [48]. With these limited data, it is difficult to standardize the indications for dialytic and/or HP therapy in valproic acid intoxication. It is reasonable however, to suggest that HD at blood flows of 300 – 350 mL/min with or without HP may benefit patients who are profoundly ill (CNS toxicity, bleeding diathesis, increased serum transaminases, increased serum ammonia level, and increased bleeding time).

Intoxications Less Responsive to Extracorporeal Therapies

Acetaminophen Toxicity

Acetaminophen is a remarkably safe drug when used at normal therapeutic doses. Massive acute overdose however, can result in fulminant hepatic failure and death [50]. Fortunately, the antidote for acetaminophen intoxication, N-acetylcysteine, can prevent fatalities, if administered in a timely fashion [51]. Thus, prompt recognition of acetaminophen overdose and rapid institution of therapy are of the utmost importance.

At therapeutic doses (10 – 15 mg/kg/dose in children; 325 – 1000 mg/kg/dose in adults) 90% of acetaminophen is metabolized in the liver to sulfated and glucuronide conjugates that are excreted in the urine. The remaining 10% is metabolized by the cytochrome CYP2E1 (P450 2E1) mixed function oxidase pathway to a toxic intermediary N-acetylimidoquinone NAPQI). Normally, this compound is then conjugated with hepatic glutathione to form a non-toxic mercapurate. With toxic doses, the sulfate and glucuronide pathways become saturated and an increased acetaminophen fraction is metabolized by cytochrome P-450 mercapturic acid utilizing glutathione. Once glutathione is depleted to < 70%, N-acetylimidoquinone begins to accumulate. This compound covalently binds hepatic macromolecules and, ultimately results in hepatocyte lysis [52].

In addition to the toxic effects of NAPQI, a rat model of hepatotoxicity suggests that nitric oxide also may contribute to the hepatic injury [53]. In this model, acetaminophen increased nitric oxide production via enhanced expression of inducible nitric oxide synthetase. Furthermore, the hepatic injury was substantially ameliorated by treatment with aminoguanidine which by inhibiting inducible nitric oxide synthase, reduced nitric oxide production. This benefit was achieved without change in CYP2E1 protein expression or NAPQI formation.

Within 2 – 12 hours after acetaminophen poisoning, patients may have nausea, emesis, diaphoresis, lethargy, and malaise. Temporary symptomatic improvement may then ensue for the next 1 – 2 days. At this stage, some individuals manifest minor elevations in serum transaminases, a prolonged prothrombin time, and hepatomegaly with right upper quadrant pain. The hepatic stage usually begins 72 – 96 hours after ingestion when patients develop mental status changes, hyperammonemia, marked increases in hepatic enzymes, and a bleeding diathesis. Greater than 2-fold prolongation of the prothrombin time and/or serum bilirubin > 4 mg/dL on the 3rd – 5th day post-ingestion are indicative of severe hepatotoxicity.

At this stage, ARF also may appear, usually as a result of ATN. However, papillary necrosis can also occur. The overall incidence of renal dysfunction in acetaminophen overdose ranges from 5% (in patients without hepatic failure) to 53% (in patients with fulminant hepatic failure). The mechanism of nephrotoxicity may be similar to that of hepatotoxicity. A toxic intermediate is formed in situ in renal tissue via the P-450 pathway and binds covalently to renal macromolecules. This results in renal cell necrosis. Oliguric ARF usually occurs. Proteinuria and hematuria may also be evident 2 – 4 days after overdose. Recovery of renal function transpires 2 – 4 weeks after ingestion although some patients do require dialysis.

The diagnosis of acetaminophen intoxication is made by history and determining the serum acetaminophen level. This laboratory value (when obtained 4 – 24 hours after ingestion) should be plotted against the Rumack-Matthew nomogram (Figure 6) to establish the risk of hepatotoxicity and the need for N-acetylcysteine therapy [54]. Serum levels obtained before 4 hours may not represent peak levels.

Therapy for acetaminophen toxicity should begin with gastric decontamination and activated charcoal. Activated charcoal avidly adsorbs acetaminophen and should be administered to any patient who presents within 4 hours after ingestion to minimize the 4 hour plasma acetaminophen level. Charcoal then should be removed from the gastrointestinal tract since it also adsorbs N-acetylcysteine, the antidote for acetaminophen intoxication.

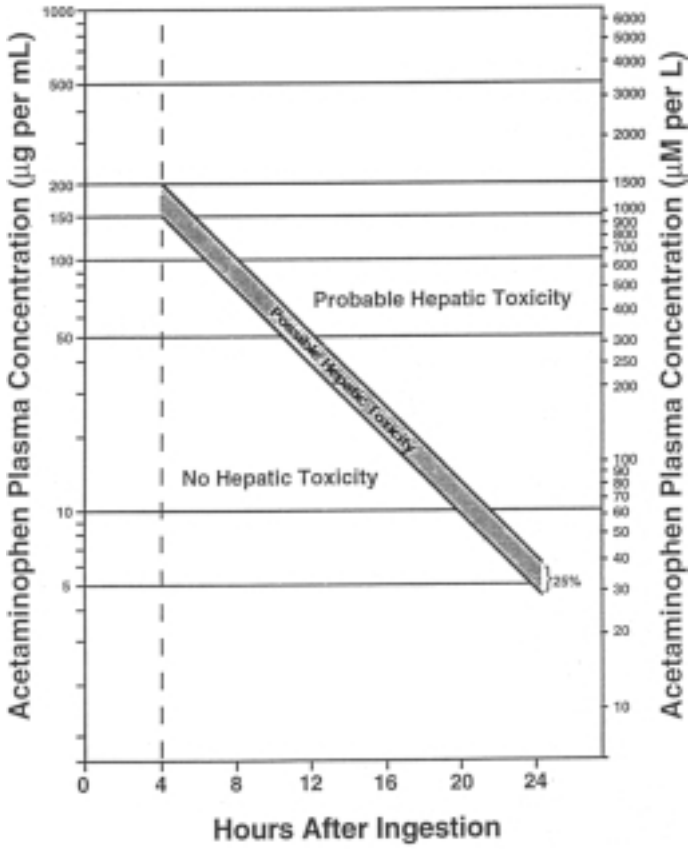

Figure 6. Rumack-Matthew nomogram for acetaminophen poisoning.

N-acetylcysteine is administered as a loading dose of 140 mg/kg of a 20% solution PO, NG or via orogastric tube (OG) followed by 70 mg/kg every 4 hours for 17 doses. Any doses vomited should be repeated. Treatment should be initiated within 8 – 10 hours after ingestion as the incidence of hepatotoxicity significantly increases when N-acetylcysteine therapy is delayed for > 10 hours post-ingestion. The efficacy of N-acetylcysteine therapy declines progressively if started 10 – 16 hours after ingestion, but some benefit is seen even if N-acetylcysteine cannot be initiated until 24 hours after ingestion.

To reduce nausea and vomiting that occur with N-acetylcysteine, given its "rotten egg" odor, the 20% solution can be diluted 1 : 3 with cola, orange juice, or grapefruit juice. Chilling the solution, slow NG administration or antiemetics also may decrease these side effects. IV N-acetylcysteine is available in the United States only for investigational studies. This mode of administration precludes the GIside effects and has been used successfully in Europe, Britain, and Canada [55].

N-acetylcysteine acts by enhancing glutathione stores, thus, providing a glutathione substitute. This, in turn, enhances non-toxic sulfate conjugation and prevents the accumulation of N-acetylimidoquinone. Aside from the aforementioned side effects, N-acetylcysteine administration has been associated with

bronchospasm, rhinorrhea, fever, chills, angioedema, hypotension, hemolysis, anaphylactoid reactions, and cardiovascular collapse.

HD and HP

The efficacy of acetaminophen removal by HD or HP in protecting against hepatic failure following acetaminophen has not been demonstrated [52, 56, 57]. As a result, these modalities are not recommended in the management of acetaminophen intoxication [44 – 46], with the possible exception of patients who present late in the course (> 24 hours) when N-acetylcysteine would be of limited value [58]. In this situation, HP may be associated with lesser elevation in plasma transaminases when compared to supportive therapy alone or to the administration of N-acetylcysteine. However, we do not use HP for an acetaminophen overdose, because the potential risks probably outweigh the slight benefit that might be achieved.

Digitalis Intoxication

Cardiac glycoside poisoning often results during chronic use. Indeed, one-half of life-threatening digitalis intoxications transpire during long-term digitalis therapy. The 2 preparations in clinical use today are digoxin and digitoxin. These drugs act at the cellular level to inhibit membrane-bound Na^+-K^+-ATPase. This results in the intracellular loss of K^+ ions and gain of Na^+ and Ca^{2+}. These compounds have excellent bioavailability ranging from 80% for digoxin to nearly 100% for digitoxin. Approximately 7% of digoxin and 26% of digitoxin is recycled through the enterohepatic circulation. The serum half-lives ($t^{1/2}$) for digoxin and digitoxin are 1.6 and 5 days, respectively [59].

Digoxin has a tremendous V_d (5.6 L/kg). Its major depot is skeletal muscle; dosage requirements and the likelihood of toxicity can be anticipated on the basis of muscle mass. A third of digoxin body stores are excreted daily (30% as digoxin in urine and 3% as metabolites in stool). By contrast, nearly 20% of digitoxin's total body stores are excreted daily, primarily as inactive metabolites [59].

Several factors predispose patients to digitalis toxicity. Cardiac medications such as quinidine, verapamil, and amiodarone increase serum digoxin levels. Erythromycin and tetracycline may increase digoxin levels by altering gut flora instrumental in digitalis metabolism. Another antibiotic, rifampin, reduces digoxin levels. Potassium-sparing diuretics increase drug levels by impairing tubular digoxin secretion. Old age, cardiac disease and metabolic disturbances, e.g. hypokalemia and hypomagnesemia, also alter patient sensitivity to digoxin and potentiate drug toxicity. Finally, renal dysfunction results in a decrease in renal digitalis excretion; thereby, increasing total body digoxin and prolonging the $t^{1/2}$ [59].

Digitalis toxicity has multiple and non-specific manifestations. They range from fatigue, blurred vision, and altered color perception to anorexia, nausea, emesis, and abdominal pain. CNS changes include headache, confusion, and delirium. The cardiac signs of digitalis toxicity encompass an array of arrhythmias, some life-threatening. The combination of supraventricular tachyrhythmia and atrioventricular block is highly suggestive of cardiac glycoside toxicity. Hypokalemia tends to aggravate digitalis toxicity especially in the setting of chronic intoxication whereas hyperkalemia usually results from acute overdosage [59].

Steady-state serum digoxin levels are reached 6 – 8 hours after administration; therefore, samples for drug monitoring should not be obtained until at least 6 hours after the last dose was administered. This interval may need to be extended to 12 – 24 hours in patients with renal failure given the prolonged $t^{1/2}$ for digoxin in this setting [59].

False positive elevations of serum digoxin levels can occur in patients with end-stage renal disease (ESRD), hepatobiliary disease, pregnancy, and in neonates [60]. These are believed secondary to elevations in endogenous digoxin-like substances The assay method can improve the specificity of serum digoxin measurements. Combined liquid chromatography/ radioimmunoassay significantly eliminates digoxin-like substance immunoreactivity as does centrifugal ultrafiltration prior to a fluorescence polarization immunoassay for digoxin [61].

Serum digoxin levels should only be used as an adjunct to clinical judgent for therapeutic dosing and recognition of toxicity. Patients can manifest clinical toxicity despite serum digoxin levels < 2 ng/mL whereas, some individuals may necessitate and tolerate digoxin therapy at serum levels between 2 – 3 ng/mL without overt signs of intoxication.

Successful treatment for digitalis intoxication depends upon early recognition. Once the physician recognizes digitalis toxicity, initial therapy should include the administration of activated charcoal to adsorb digitalis and its metabolites excreted via the biliary tract. Cholestyramine also can be used to decrease drug absorption especially if ingestion occurred within 6 – 8 hours. Measures to correct serum K^+ and other electrolyte imbalances are paramount. Acute digitalis poisonings often are complicated by severe hyperkalemia and may require treatment with sodium bicarbonate, insulin and glucose solutions, exchange resins, or even, dialysis.

Symptomatic bradyarrhythmias are appropriately treated with IV atropine (0.5 – 2 mg) and electrical pacing, if necessary. Other cardiovascular therapy, especially antiarrhythmic drugs and cardioversion, is reserved for more complex forms of cardiac ectopy.

Severe digitalis overdose may necessitate therapy with digoxin-specific antibody fragents (F_{ab} fragents) (Table 10) [62]. F_{ab} fragents, purified from sheep IgG, are indicated for massive digoxin ingestion, profound toxicity, or hyperkalemia in the presence of life-threatening arrhythmias associated with cardiac glycoside toxicity. These F_{ab} fragents rapidly bind intravascular digoxin and diffuse into the interstitial space to bind free digoxin. F_{ab}-bound digoxin cannot associate with the a-subunit of Na^+-K^+-ATPase and F_{ab} and drug molecule are thus, filtered at the glomerulus and rapidly excreted in the urine. F_{ab} fragents are also successful in patients with renal failure and dialysis. The theoretical possibility exists that digoxin could be released from the complex when excretion of F_{ab}-bound digoxin is delayed by renal failure. This could result in "rebound" digitalis toxicity. While this has been an infrequent occurrence in studies examining the utility of F_{ab} in patients with renal failure, at least one report has posited the benefit of plasmapheresis 24 – 40 hours after F_{ab} treatment in patients with renal failure to forestall this possibility [63].

F_{ab} treatment has been associated with untoward effects in approximately 10% of patients including exacerbations of congestive heart failure (CHF), tachyarrythmias, and hypokalemia. Allergic or anaphylactic reactions are rare, occurring in < 1% of treated patients, but skin testing is appropriate for individuals with known allergy to sheep proteins or those treated previously with F_{ab} [62].

HD or HP may help control hyperkalemia or volume overload; however, these approaches are generally inadequate for treating

Table 10. Determination of Equimolar Digoxin-specific F_{ab} Fragent Dose

– Steady-State serum concentration (SDC is known)
Total Body Load (TBL) = SDC × V_d × weight

$$\text{TBL (mg)} = \frac{\text{SDC(ng/mL)} \times 5.6\text{L/kg} \times \text{W (KG)}}{1000} [\text{Digoxin}]$$

$$\text{Eqimolar dose of Fab} = \text{TBL} \times \frac{\text{MW (50000)}}{\text{MW Digoxin (781)}}$$

$$= \text{TBL} \times 64$$

1 vial F_{ab} (40 mg) neutralizes 40/64 (or 0.6 mg digoxin)

$$\text{Therefore, \# Vials } F_{ab}\text{*} = \frac{\text{TBL (mg)}}{0.6}$$

$$\text{\# vials Fab} = \frac{\text{SDC (ng/ml)} \times \text{WT (kg)}}{100} [\text{Digoxin}]$$

$$\text{\# vials Fab} = \frac{\text{SDC (ng/ml)} \times \text{WT (kg)}}{1000} [\text{Digitoxin}]$$

– Amount ingested is known
Body load (mg) = Dose ingested (mg) [Digitoxin]; given a bioavailability of 100%
= Dose ingested (mg) × 0.8 [Digoxin]; given a bioavailability of 80%

– Amount ingested and SDC unknown
vials (F_{ab}) = 10, repeat 10 vials if clinically indicated (total 20 vials, adult, acute overdose)
chronic toxicity, SDC not known, give 6 vials (adult), 1 vial (children)

*Reconstitute each vial in 4 mL sterile water and administer total dose intravenously over 15 – 30 min. In cardiac arrest dose can be given as a bolus.

digitalis toxicity secondary to the drug's extensive tissue binding and large V_d.

Procainamide Toxicity

The pharmacokinetics of procainamide and its major metabolite, N-acetylprocainamide (NAPA), are significantly altered in patients with chronic renal failure. The usual therapeutic plasma concentrations of procainamide range from 4 – 8 mg/L and for NAPA, 9 – 20 mg/L. Cardiotoxicity can occur with concentrations of procainamide as low as 10 mg/L and is common at concentrations > 16 mg/L. Plasma concentrations of procainamide be-

tween 20 – 30 mg/L frequently cause serious hypotension and conduction disturbances and have been implicated in several deaths [64]. Combined levels of procainamide and NAPA > 60 mg/L can cause severe cardiac toxicity, profound hypotension and lethargy [65]. The main route of elimination of procainamide and NAPA is renal, with 60%and 80% excreted unchanged, respectively.

In addition to renal failure, several drugs, either by inhibiting the metabolism of procainamide or its renal excretion, or through pharmacodynamic interactions, especially class IA drugs, may increase the toxicity of procainamide. These include amiodarone, cimetidine, quinidine, trimethoprim, calcium channel blockers, and tricyclic antidepressants (TCA).

Treatment

Because procainamide and NAPA are substantially eliminated by the kidney, it is important to maintain adequate renal function in patients intoxicated with these drugs. Optimizing cardiac function and aggressive treatment of arrhythmias in the setting of procainamide toxicity is therefore crucial. Treatment consists of GI decontamination and supportive therapy [66, 67]. Because of potentially slow absorption, emesis or lavage and charcoal should be used even many hours after ingestion. Hypotension, bradyarrhythmias, and seizures are treated with standard measures. Bradyarrhythmias are managed with isoproterenol or pacing (may require higher than usual pacing voltage). Ventricular tachyarrhythmias that cause hemodynamic instability should be treated with lidocaine, phenytoin, bretylium, or overdrive pacing. $NaHCO_3$ or sodium lactate (1 mEq/kg by IV bolus, every 5 – 10 min to achieve an arterial of pH 7.4 – 7.45) may be effective for tachyarrhythmias due to class IA drugs [68]. If associated with hemodynamic stability, sinus tachycardia usually requires no specific therapy. If associated with hypotension or ischemia, but not depressed conduction, sinus tachycardia is treated with propranolol. Mild hypokalemia (3 – 3.5 mEq/L) may be protective, and potassium levels ≥ 3.0 mEq/L may be best treated by close monitoring. For torsades de pointes (polymorphous or atypical ventricular tachycardia), magnesium sulfate (4 g or 40 mL of 10% solution IV as an initial dose) and overdrive pacing with isoproterenol or electricity may be effective [69].

Seizures should be treated with IV administration of diazepam initially and then phenytoin (15 mg/kg IV), at a rate < 50 mg/min.

Patients with persistent hypotension and bradycardia require monitoring of pulmonary arterial pressure. Based on hemodynamic monitoring, unstable patients are treated as follows:

- if low cardiac output (CO) and low pulmonary arterial wedge pressure (PCWP) are present, give more crystalloid fluid;
- if low systemic vascular resistance (SVR) is found give norepinephrine or dopamine;
- if low CO with slow heart rate are present treat with isoproterenol or epinephrine; and
- if low CO and normal or high PCWP occur, use isoproterenol, dobutamine. For intractable cardiogenic shock, cardiac pacing, intra-aortic balloon pump counterpulsation, and cardiopulmonary bypass may be necessary.

Extracorporeal Therapy

Procainamide is extensively distributed to body tissues and is only slightly (15%) protein bound. A relatively small fraction of the total amount of procainamide (V_d = 2.4 L/kg) in the

body is in the vascular compartment, so that extracorporeal removal of the drug is not very effective. In normal persons, the endogenous clearance of the drug is 8.6 – 9.8 mL/kg/min, with a $t^{1/2}$ of about 2.6 – 3.5 hours; in ESRD the clearance is reduced to 4.3 mL/min/kg with a resultant $t^{1/2}$ of 10 – 14 hours. In healthy persons, the clearance of procainamide is not substantially greater than endogenous clearance [68 mL/min by HD 6.4 by PD, and 75 mL/min by HP] [68, 70 – 72]. In contrast, NAPA has a smaller V_d (1.4 L/kg) and minimal protein binding (10%) and a lower endogenous clearance of 3.1 mL/min/kg, so that accelerated drug removal techniques are more useful [65, 71, 72]. Clearance of NAPA by HD is 68 mL/min, with HP 73 mL/min, and with combined HD and HP it increases to 107 mL/min [67]. While the $t^{1/2}$ of procainamide is increased to about 10 hours in ESRD, the $t^{1/2}$ of NAPA (normal 6 hours) is increased to about 36 hours [65].

While the amount of NAPA removed by HP or HD might be a small percentage of the total body burden of the metabolite, potentially fatal dysrhythmias may disappear during these techniques [71, 73 – 76]. Thus a rapid decrease in plasma NAPA during extracorporeal techniques can stabilize cardiac rhythm independently of the total amount removed.

It is important during HD to avoid hypotension. Hypotension can decrease drug clearance due to decreased drug mobilization from tissues into the blood secondary to decreased tissue perfusion [74, 76].

The pharmacokinetics of procainamide and NAPA would suggest that continuous removal would be more efficient. While clearances of NAPA by continuous HD (20 mL/min) [77], continuous arteriovenous hemofiltration (CAVHF) (10 mL/min) [78] and continuous venovenous hemofiltration CVVHF (28 mL/min) [78] are lower than acute HD for 4 hours (54 mL/min) [79], or acute HD plus HP (107 – 117 mL/min) [79] or charcoal HP alone (75 mL/min) [79], the total daily clearances are equal (if not superior) with the continuous techniques (29 – 37 L/day) [77, 78, 80] compared to intermittent therapies (13 – 24 L/day) [79].

Therefore, in conclusion, when the usual routes of drug elimination of procainamide and NAPA are depressed or absent, such as when renal or hepatic failure complicates overdose with these drugs, or when extracorporeal circulation is used to support a failing circulation, HD, HP, or a combination of HD and HP or continuous therapies (CAVHF or CVVHF) should be strongly considered. More specifically, extracorporeal therapy in procainamide toxicity is indicated when:

- serum procainamide concentration are >20 mg/L and either serious cardiovascular or renal failure exist [2];
- combined procainamide and NAPA concentrations are > 60 mg/mL (60 mg/L). This combined level usually is predictive of serious toxicity [65, 67].

Tricyclic Antidepressant Intoxication (TCA)

TCA overdose is the leading cause of hospitalization and death due to excessive ingestion of prescription drugs. Although accidental and intentional exposures to TCAs represented only 1.8% of all poisoning cases reported to the national poison centers during the 1980s, they accounted for 43.8% of all hospital admissions for poisoning, 18% of all poisoning deaths, and for 24% of major morbidity attributed to all sources of drugs or chemicals [81]. Ironically, TCAs remain the most frequently prescribed drugs to treat depressed patients who may be (or may become) suicidal.

Pharmacology and Toxicology

The TCAs are 3-ringed structures resembling phenothiazines. They possess anticholinergic, α-adrenergic blocking, and adrenergic uptake inhibiting properties [82].

The TCAs are rapidly and completely absorbed from the GI tract, with peak plasma concentrations occurring 2 – 8 hours after a therapeutic dose. These agents are metabolized to more polar forms by the liver; the polar metabolites are primarily excreted in the urine. Drug half-life ranges from 24 – 76 hours at therapeutic levels, but may be much longer after an overdose. Other factors that can influence the severity of an overdose include:

– TCAs undergo enterohepatic recirculation, which prolongs the absorption and toxic effects seen in an overdose situation.
– Absorption of TCAs may be considerably delayed in overdose due to their anticholinergic effects.
– The TCAs have a large V_d (10 – 20 L/kg) because they are lipophilic. They are also highly bound to plasma proteins (up to 95% binding at physiologic pH). The combination of a large V_d and protein binding means that forced diuresis, dialysis, and HP have no role in the management of TCA overdose [82, 83].
– Concurrent ingestion of other drugs can affect TCA handling. The catabolism of ethanol, for example, generates an excess of reducing equivalents which diminish the oxidative metabolism of TCAs. Neuroleptics, fluoxetine (Prozac), and toxic hepatic metabolites of acetaminophen also impair TCA metabolism, potentially increasing plasma drug levels.
– Toxic hepatic metabolites of acetaminophen would delay TCA elimination.
– The elderly have slower rates of drug elimination and are particularly susceptible to a TCA overdose.

Clinical Presentation

The presenting signs of a TCA overdose include cardiac arrhythmias, hypotension, and anticholinergic signs (hyperthermia, flushing, dilated pupils, intestinal ileus, urinary retention, and sinus tachycardia) [82, 83, 84 – 86]. CNS involvement is also common. Early signs, such as confusion, delirium, and hallucinations, typically occur before the onset of seizures or coma. The physical examination may reveal clonus, choreoathetosis, hyperactive reflexes, myoclonic jerks, and a positive Babinski sign.

Cardiotoxic effects are responsible for the mortality of TCA overdose. This usually occurs after the ingestion of > 1 g (10 – 20 mg/kg), which can lead to plasma levels > 1000 ng/mL [83]. The most important electrophysiologic action of TCAs is inhibition of the fast sodium channel, leading to slowing of phase 0 depolarization in His-Purkinje tissue and the myocardium [82 – 84]. This toxic effect, which is inhibited by $NaHCO_3$ (see below), slows conduction with resultant QRS prolongation and the potential emergence of reentry arrhythmias (such as ventricular tachycardia, ventricular fibrillation, and torsades de pointes).

As noted above, sinus tachycardia occurs early in TCA overdose when anticholinergic symptoms predominate. In the presence of a wide QRS, however, sinus tachycardia may be difficult to distinguish from ventricular tachycardia.

Hypotension and pulmonary edema are other common findings in TCA overdose. The fall in blood pressure is due both to impaired myocardial contractility and to decreased pe-

ripheral vascular resistance (PVR) induced by α-adrenergic blockade [83, 84, 86, 87]. The decrease in contractility also contributes to pulmonary edema which can be exacerbated by fluid overload. For this reason TCA toxicity must be managed with only maintenance fluid replacement (unless the patient is hypotensive) and preferably with central hemodynamic monitoring in the ICU [82, 83].

Treatment

Treatment of TCA overdose must be aggressive from the outset. Initial therapy consists of establishing airway and breathing, continuous electrocardiographic (ECG) monitoring, gastric lavage, and the administration of activated charcoal [82, 83, 87]. In contrast, syrup of ipecac is contraindicated with any TCA ingestion due to the possibility of rapid neurological deterioration and high incidence of seizures.

Gastric decontamination can be considered for up to 12 hours after ingestion because the anticholinergic properties of these drugs delay gastric emptying. TCAs in the gastrointestinal tract are well absorbed by activated charcoal at a 10:1, charcoal-to-drug ratio. The initial recommended dose of charcoal, 1 – 2 mg/kg body weight, should be given with a cathartic, such as sorbitol or magnesium citrate [87]. This may be followed by an additional 2 – 3 doses at intervals of several hours. These doses can be given with water if catharsis is adequate or with a cathartic if bowel motility is minimal.

$NaHCO_3$

IV $NaHCO_3$ is the single most effective intervention of the management of TCA cardiovascular toxicity [88 – 90]. This agent can reverse QRS prolongation, ventricular arrhythmias, and hypotension. Because acidosis aggravates TCA toxicity, the beneficial action of $NaHCO_3$ may be partly due to correction of acidosis. It is clear, however, that $NaHCO_3$ administration is effective even when the arterial pH is normal. The beneficial effect appears to be mediated by increases in both pH and the plasma sodium concentration ($[Na^+]$) [91]. Alkalinization to an arterial pH of 7.5, for example, appears to reduce the incidence of cardiac arrhythmias, and IV $NaHCO_3$ (in a dose of 1 – 2 mEq/kg) is the treatment of choice for sudden-onset ventricular tachycardia, ventricular fibrillation, or cardiac arrest. To maintain an arterial pH of 7.5, an IV infusion of two 50 mL ampules of $NaHCO_3$ (containing approximately 90 mEq of $NaHCO_3$) in 1 L D_5W is started in all comatose patients, particularly those with a QRS duration > 0.10 sec (100 msec).

Arrhythmias

Lidocaine is the drug of choice for TCA-induced ventricular dysrhythmias. However, care must be taken to avoid precipitation of seizures. In comparison, many antiarrhythmic drugs should not be used with TCA overdoses. Propranolol, for example, depresses myocardial contractility and conduction, while procainamide, disopyramide, and quinidine, via membrane stabilizing effects, may enhance TCA toxicity.

Hypotension

IV fluids are the preferred therapy in hypotensive patients. Dopamine can be used if needed because it has both inotropic and vaso-

constrictor activity. On the other hand, sympathomimetic vasopressor agents carry the risk of precipitating tachyarrhythmias. Levarterenol is generally considered an adjunctive pressor agent [83, 87, 92].

Seizures

Diazepam is the drug of choice in the management of acute-onset seizures. Phenytoin or phenobarbital may be used as second-line drugs.

Physostigmine

Physostigmine, a short-acting cholinesterase inhibitor, has been referred to as the antidote for TCAs because of its ability to increase cholinergic tone and reverse anticholinergic effects. It can, however, cause severe bradycardia, seizures, and asystole by overcompensating for cholinergic tone and suppressing supraventricular and ventricular pacemakers [93, 94]. In the aggregate, physostigine-associated risks often outweigh the benefits. As a result, physostigine should only be used in patients with coma or those with convulsion or arrhythmias resistant to standard therapy.

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