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EXTRACORPOREAL REMOVAL OF DRUGS AND POISONS BY HEMODIALYSIS AND HEMOPERFUSION

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INTRODUCTION

Accidental or intentional overdose and poisoning cause much sickness and death. Agents involved in overdoses include illicit drugs such as opiates and cocaine, prescribed drugs such as antiepileptics and cardiovascular agents (digoxin, antiarrhythmics), and poisons (metals, herbicides). Overdose and poisoning also occur by deliberate ingestion of carbon monoxide, barbiturates, alcohol, psychotherapeutics, analgesics (acetaminophen, salicylates), and autonomic agents.

Treatment of overdoses or poisoning includes prevention of further drug absorption, antidotal therapy if available, support of vital organ function, and enhancement of drug elimination. This article reviews drug elimination, with an emphasis on extracorporeal methods.

Although approximately 40% of patients recognizably poisoned require hospitalization, few die. These impressive statistics are of recent origin and are based on the body's potential for detoxification and elimination of a wide spectrum of chemical agents. Clemmensen & Nilsson documented that intensive supportive care, without massive gastric lavage or analeptic agents, produced a mortality rate of 1.5% (1). Only about 10% of these patients need intensive medical assistance to maintain vital function; the rest recover with adequate nursing care. Methods to increase poison elimination are either feasible or appropriate in fewer than 5% of cases (2). Forced urinary diuresis

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Table 1 Poisons responsive to hemodialysis or hemoperfusion

Hemodialysis	Hemoperfusion
Salicylates	Salicylates
Phenobarbitol	Phenobarbitol
Methanol/ethanol	Other barbiturates
Ethylene glycol	Ethchlorvynol
Lithium	Glutethimide
Isopropanol	Meprobamate
Theophylline	Methaqualone
	Trichloroethanol derivatives
	Disopyramide
	Theophylline

and/or extracorporeal removal (Table 1) are directed toward this small group of patients. The safety and efficacy of these techniques in poisonings remain unproven, since most studies reported neither control nor randomized selection of therapy. Extracorporeal devices may be applied under the following conditions (2). (*a*) The drug or toxic substance should either diffuse easily through the dialysis membrane or be readily taken up by an absorbent. (*b*) A significant proportion of the poison should be present in plasma water or capable of rapid equilibration with it. (*c*) The pharmacological effect of the toxin should be directly related to the blood concentration. (*d*) Dialysis or hemoperfusion should add significantly to other body mechanisms of elimination.

PHARMACOKINETIC CONCEPTS

Pharmacokinetic principles indicate why dialysis or hemoperfusion is infrequently useful in treating drug overdose (3–5). The rate of removal of any substance from a single body compartment parallels its plasma clearance (Cl_p), which is the product of the apparent volume of distribution (V_d) of the agent and the elimination rate constant (K_{el}):

$$Cl_p = V_d \cdot K_{el}. \qquad 1.$$

Volume of Distribution

The V_d is the volume of water in which a specific amount of an agent would yield the concentration found in plasma. A large V_d implies that most of the agent is tissue bound and not readily accessible for removal from the blood by dialysis or hemoperfusion. The V_d corresponds to a physiological compart-

ment only for substances like lithium and methanol that distribute in body water without significant tissue binding. Agents with high lipid solubility usually have a large V_d, diffuse rapidly into the brain and fat depots, and are slowly removed from these sources because of poor partitioning into plasma water and relatively low blood flow.

Certain diseases may alter the V_d of some agents, e.g. renal failure increases the V_d for phenytoin but decreases it for digoxin. Impairment of major organs of chemical excretion, such as the liver and kidneys, causes significant reduction in the overall elimination rate of many agents. Digoxin, a drug commonly associated with toxicity, illustrates these concepts. In individuals with normal renal function, digoxin has a V_d of 7.1 liter (l)/kg body weight, a Cl_p of 165 ml/min with more than 90% of a loading dose excreted unchanged in the urine. In those with end-stage renal disease (ESRD), the V_d is decreased to 4.2 l/kg, and the Cl_p falls to 35 ml/min (6). This marked reduction of Cl_p of digoxin in ESRD is caused by both the decreased V_d and the reduced renal elimination.

Protein Binding

Only unbound substances participate in diffusion and are dialyzable. In contrast to hemodialysis, plasma protein binding and water solubility have little influence on the efficiency of hemoperfusion (3). Protein binding occurs in plasma, mostly to albumin, and in tissues to intracellular proteins. The affinity of most chemicals for proteins is low and readily reversible, but some interactions may be covalent and relatively irreversible. As noted by Gibaldi (7), the fraction of unbound agent in blood and tissues influences the V_d:

$$V_d = V_B + V_T\,(F_B/F_T), \qquad 2.$$

where V_B and V_T are the actual volumes of water in blood and tissues and F_B and F_T are the fractions of free drug in blood and tissues, respectively. Consequently, an increase in the free fraction of an agent in blood without a corresponding increase in the free fraction in tissue would produce an increase in V_d. This situation may occur in renal failure with drugs like phenytoin and clofibrate, but the opposite occurs with methotrexate and digoxin, where V_d falls by 30% to 50%, respectively.

Distributive Kinetics

Most substances introduced into the body are not confined to the vascular compartment but are distributed at varying rates to extravascular tissues. After the initial distribution phase (indicated by a rapid decline in plasma concentration following intravenous injection), the fall of concentration over time is usually linear when plotted semilogarithmically. This linearity indicates that a

pseudoequilibrium exists between movement from extravascular tissues into the blood and elimination from the vascular space. Rapid removal of an agent from the blood by an extracorporeal device may disrupt this pseudoequilibrium. If the rate of distribution of the agent from extravascular tissues is slower than the overall elimination rate, the agent will be removed from the blood more rapidly than it can be replaced from tissue stores. This occurrence results in a rebound in blood concentration of the agent on cessation of extracorporeal removal. Such rebounds are common when the V_d of an agent is large (>1 l/kg). Unfortunately, most reported studies have not considered these principles. Thus, reported declines of blood concentrations following the use of extracorporeal devices are useless for evaluating a significant reduction in total body stores of an agent unless the amount of drug removed in the effluent is measured.

Extracorporeal Elimination

The contribution of dialysis or hemoperfusion to the overall clearance of a drug ($Cl_p + Cl_d$) must be determined by first considering the intrinsic plasma clearance of the drug without extracorporeal removal. Amitriptyline, a tricyclic antidepressant, illustrates this requirement. The V_d of this agent is 20 l/kg; thus 1 gram of amitriptyline in a 70-kg subject yields a plasma concentration of 0.7 mg/l. Assuming complete extraction of amitriptyline by an extracorporeal device, with a 200 ml/min blood flow through the device, clearance would theoretically be 200 ml/min. However, the actual amount of drug removed would be a negligible 0.14 mg/min or 33.6 mg in 4 hours (hr) of treatment. Although extracorporeal removal is highly efficient in this example, the clinical results are ineffective.

Measurement of the total amount of drug removed in the dialysate effluent or absorbed to the hemoperfusion column is the best method of determining the efficiency of treatment. However, the tables in this review are a compromise; they contain the calculated fractional removal of the body stores of certain therapeutic agents and poisons during 4 hr of hemodialysis or hemoperfusion treatment based upon reported data obtained largely from changes in plasma concentrations. Fractional removal without and with hemodialysis or hemoperfusion is calculated to show the contribution of extracorporeal removal.

Concentration-Dependent Kinetics

With an overdose it is possible that first-order kinetics of an agent may become concentration dependent and approach zero-order kinetics (4). Saturation kinetics may be a consequence of decreased metabolic clearance at high plasma concentrations as occurs, for example, with capacity-limited hepatic metabolism of ethchlorvynol, or changes in protein binding similar to

alterations in V_d seen with phenytoin. Since many drugs may be subject to concentration-dependent kinetics, and only limited pharmacokinetic data are available for toxic doses of many drugs, it is perhaps incorrect to extrapolate kinetics during overdose from data derived during therapeutic dosage studies. Therefore, whenever possible, determination of the elimination half-life or Cl_p of a drug should be made in intoxicated patients to indicate the benefit derived from dialytic or hemoperfusion therapy.

EXTRACORPOREAL DEVICES

Dialysis

The dialyzability of a drug depends upon physicochemical properties of the agent and the dialysis system. The specific properties of a chemical that predict the efficacy of dialysis are molecular weight or size, lipid or water solubility, and protein binding.

Removal by dialysis of an agent from either peritoneal fluid or blood decreases as the molecular weight of the agent increases: a small solute such as lithium (74 daltons) is dialyzable, but a larger drug such a vancomycin (1800 daltons) is not, despite its low protein binding (10%). Further, solutes insoluble in water do not diffuse from the blood into aqueous dialysates. For example, despite a low molecular weight of 252 daltons, phenytoin is insoluble in water at a pH of 7.4, highly protein bound, and not dialyzed.

In conventional dialysis, unbound solute removal is principally accomplished by diffusion down a concentration gradient between plasma water and dialysate. Therefore, as the protein binding of a solute increases, the dialysis clearance decreases. With this ratio the possible benefit of dialysis can be predicted. However, customary protein binding of a drug may be altered in a patient with intoxication. If saturation of binding sites occurs, then an increased unbound fraction is available for diffusion. This situation happens with salicylic acid and disopyramide, where plasma protein-binding capacity may be exceeded even when the concentration of either drugs is within the therapeutic range (5). The presence of renal disease is also commonly associated with reduction of drug protein binding, which increases the amount of unbound drug available for diffusion (8).

Specific properties of the dialysis system that affect solute or drug removal are the permeability and surface area of the membrane and the flow rates of both blood and dialysate. Small molecules (<500 daltons) exhibit high membrane permeability with a rapid decline in blood to dialysate gradient; the limiting determinants of clearance are blood and dialysate flow rates. In contrast, large molecules exhibit low membrane permeability, maintain a gradient across the membrane, and their clearance is dependent on membrane

surface area rather than the rate of blood or dialysate flow. Therefore, a low cardiac output in the intoxicated patient may preclude the effectiveness of either peritoneal or hemodialysis by reducing blood flow rates and compromising the effective membrane surface area.

Whereas estimation of plasma clearance is fairly simple, the measurement of Cl_d is complicated. Over thirty years ago, Wolf et al (9) suggested using the Fick principle:

$$Cl_d = Q(A-V)/A \quad 3.$$

where Q is the dialyzer blood flow, A and V the concentration of any substance entering and leaving the dialyzer, respectively. Several derivatives from this general equation are possible, including

$$Cl_d = Q_p(A_p-V_p)/A_p, \quad 4.$$

$$Cl_d = Q_b(A_b-V_b)/A_b, \text{ and} \quad 5.$$

$$Cl_d = Q_b(A_p-V_p)/A_p, \quad 6.$$

where p is plasma, b is blood, Q_p is plasma flow $[(1-hct)Q_b]$, and hct is the hematocrit.

Because concentrations of drugs and other agents are usually measured in plasma, Equation 4 can be used to estimate Cl_d. However, this relationship only holds if the agent is confined to plasma alone and is neither within, on, nor removed from, blood cells. A possible solution to this complication would be to use whole-blood assays and Equation 5. However, since Cl_p is usually calculated from plasma concentration data, Equation 5 will not relate to Cl_p unless corrections are made for the fraction of red cells to plasma and the free fraction of the agent in plasma.

Unfortunately, both past studies and many recent reports use, inappropriately Equation 6. In this calculation whole blood-flow rate is combined with the plasma-extraction ratio. An overestimate of Cl_d occurs if the agent is only removed from plasma; an underestimate occurs if the agent is carried on or in blood cells, and is removed from them as well as from the plasma. Other important assumptions that are made when Equation 6 is used are often invalid under certain circumstances and are discussed elsewhere (10–12).

Equations 4–6 assume accurate measurement of dialyzer blood flow, a major potential weakness. Errors in this measurement can be as much as 30–40% if based on bubble transit time or if using pumps that are not calibrated before and after any study of dialyzer clearance. In addition, the ultrafiltration of plasma water during dialysis may proceed at a rate greater

than that of the agent of interest, producing a relative increase of concentration in the dialyzer outlet port. This change can be estimated:

$$V_{p'} = V_p[1-(V_{hct}-A_{hct})/V_{hct}], \quad 7.$$

where p' is the corrected venous plasma concentration and p is the observed plasma concentration. Changes in plasma protein concentration could also be used in place of changes in hematocrit.

Although somewhat more difficult, the benchmark for measurement of dialyzer clearance is

$$Cl_d = R/AUC_d, \quad 8.$$

where R is the total recovery of unchanged agent in the expended dialysate and AUC_d is the area under the curve of the plasma concentration vs time plot during hemodialysis. Plasma measurements are done on blood entering the dialyzer. This equation is independent of changes in dialyzer blood flow, alterations in plasma concentration produced by ultrafiltration, and the effects of any blood cell uptake of the agent. Not surprisingly, Cl_d measured by this technique can exceed actual blood or plasma flow rate if the agent is present in, and removed from, blood cells.

Peritoneal Dialysis

Peritoneal dialysis clearances are considerably less than those of hemodialysis and rarely exceed 10 ml/min. This technique is, therefore, rarely useful for treating poisonings unless conducted over prolonged intervals.

Hemoperfusion

Hemoperfusion removes substances from the blood by direct contact with an adsorbent material. Any material that has greater affinity than blood for a given substance removes both native and foreign substances. The concept, first applied by Muirhead & Reid in 1948 with mixed ion exchange resins, was used to remove "uremic toxins" from animals (13). Early column use was plagued with complications including febrile reactions, destruction of blood cells, embolization of charcoal particles, electrolyte disturbances, and thrombosis (14). The development in the early 1970s of coated charcoal, fixed-bed charcoal, and the discovery of newer polymer resins overcame these technical problems (15).

Properties intrinsic to the adsorbent and the substance being removed, as well as certain technical factors, influence the efficacy of hemoperfusion (Table 2). Of the two basic types, charcoal and polymer resin, only charcoal devices are commercially available in the United States. Charcoal

Table 2 Factors Influencing Substance Removal by Hemoperfusion

Factor	Adsorbent	Pharmacokinetics	Technical
Surface properties	Surface properties	Distributive kinetics	Blood flow
Affinity for sorbent	Pore size:	Distribution volune	pH
Configuration	macro 50 nm		Temperature
Lipophilicity	micro 2 nm		Viscosity
Plasma protein binding	Pore configuration		
Size/molecular weight	Saturation		
Water solubility	Surface area		
	Adsorbent capacity		
	Affinity for substance		
	Coating (membrane)		

hemoperfusers use either fixed, uncoated, or coated particulate columns. The coating, although decreasing embolization, forms a membrane barrier (.05–5 μm), the effect of which is negligible except with high-molecular-weight substances (16). Activated charcoal, a nonspecific adsorbent, removes both water and lipid soluble substances from 113 to 40,000 daltons in size (14).

The adsorptive capacity of most charcoal columns is large, but the nonspecificity allows many bloodborne substances to adhere to the charcoal, which quickly reduces its capacity to adsorb desired toxins. Consequently, removal rate declines progressively with prolonged use, necessitating column replacement.

Assessing Total Body Removal

Although the efficiency of extracorporeal agent removal is commonly measured in terms of dialysis or hemoperfusion clearance, such measurements do not directly correlate with the amount of agent removed from body stores. Gwilt recently reported an equation that allows calculation of changes in body stores produced by extracorporeal removal (17). If the mass balance of a substance is considered, then

$$X_s = X_d + X_{el} + X_f, \qquad 9.$$

where X_s and X_f are the amounts of drug in the body at the beginning and the end of extracorporeal removal, respectively, and X_d and X_{el} are the amounts of an agent eliminated by extracorporeal removal and by the body during usual elimination routes during extracorporeal procedures. Equation 9 may be expressed as:

$$X_s = (Cl_d \cdot AUC_1) + (Cl_p \cdot AUC_1) + (Cl_p \cdot AUC_2), \qquad 10.$$

where AUC_1 is the area under the plasma concentration versus time curve during extracorporeal removal and AUC_2 is the area under the plasma concentration versus time curve from the termination of extracorporeal removal to infinity. The fraction of drug in the body at the start of extracorporeal removal that is removed by the device is given by:

$$f = X_d/X_s \qquad 11.$$

which, from Equation 9 may be expressed as:

$$f = (Cl_d \cdot AUC_1)/|(Cl_p + Cl_d)AUC_1 + (Cl_p \cdot AUC_2)|. \qquad 12.$$

SPECIFIC DRUG OR AGENT REMOVAL

Central Nervous System Agents

ALCOHOLS Ethanol, methanol, isopropanol, and ethylene glycol are readily dialyzable because of their diffusibility, water solubility, nonprotein binding, and small V_d. Consequently, hemodialysis is the treatment of choice in intoxication states rather than hemoperfusion. As noted in Table 3, the fractional removal of all these agents by dialysis is substantial and clinically useful.

Ethanol Levels in excess of 350 mg/dl are potentially dangerous, but concentrations greater than 500 mg/dl may be fatal. Ethanol is eliminated primarily by hepatic metabolism and demonstrates concentration-dependent kinetics. Its metabolism increases by 25% following intravenous administration of fructose (18). Body clearance increases 50% with hemodialysis to 300–400 ml/min; removal rate of ethanol is increased to 280 mg/min (19).

Isopropanol Since the acute effects of simple alcohols on the central nervous system increase in correlation to their molecular weight, isopropanol may be twice as potent as ethanol. About 80% of an absorbed dose is metabolized, predominantly to acetone. Acetone is excreted along with the unchanged form by the kidneys and lungs. Whereas the ingestion of 20 ml may cause mild symptoms, 150–240 ml can be lethal. Hemodialysis is indicated in cases with hypotension and hypothermia (coma) or serum alcohol concentration exceeding 400–500 mg/dl (20).

Methanol Intoxication with methanol is characterized by central nervous system depression or coma and formate production, which mediates retinal

Table 3 Pharmacokinetic properties of selected drugs and poisons

Drug name	Apparent volume of distribution (l/kg)	Plasma clearance (ml/min)	Plasma protein binding (%)	Hemodialyzer clearance (ml/min)	Hemoperfusion clearance (ml/min)	Fractional removal in 4 hr (%)		
						Normal patient	With hemodialysis	With hemoperfusion
Central nervous system agents								
Alcohols								
Ethanol	0.6	170–320	0	120–160	—	76	87	—
Isopropanol	0.6		0	—	—	—	79	—
Methanol	0.6	44	0	98–176	—	22	56	—
Ethylene glycol	0.8	64	—	—	—	—	—	—
Sedative hypnotics								
Chloral hydrate	6	600	35–41	120	157–238	29	34	37
Ethchlorvynol	2.8	90	30–50	64	125–300	10	17	23
Glutethimide	2.7	180	45	50	60–250	20	25	32
Meprobamate	0.75	60	0–20	60	85–150	24	42	56
Methyprylon	—	—	20–80	5–171	25–171	50	—	—
Methaqualone	6	140	80	23	216	8	9	18
Pentobarbital	1	36	66	22	50–300	12	18	27
Phenobarbital	0.75	9	25–60	80	80–290	4	33	39
Secobarbital	1.42	5	70	NS[a]	20–119	1	1	16
Analgesics								
Acetaminophen	1	400	10–21[b]	120	125	75	83	83
Aspirin	0.21	45	73–94	20	90	52	65	89

Anticonvulsant drugs								
Carbamazepine	1	59	70-80	NS	80-129	17	17	36
Ethosuximide	0.7	10	0	140	—	5	52	—
Phenytoin	0.57[c]	25	87-93	NS	76-189	14	14	61
Primidone	0.6	40	0	98	98	20	55	55
Sodium Valproate	0.15-0.4	10	90-95	23	—	12	33	
Psychotherapeutic drugs								
Amitriptyline	20	—	96	NS	14-210	—	—	—
Chlordiazepoxide	0.3	25	86-93	NS	—	—	—	—
Chlorpromazine	—	—	90	NS	—			
Desipramine	—	—	69-76	NS		—		—
Diazepam	0.74[d]	35	90	NS		15	15	—
Haloperidol	23	1330	90	NS	—	—	—	
Imipramine	11	1000	86-96	18		27	27	—
Lithium carbonate	0.79	20	0	150	—	8	52	—
Nortriptyline	21	740	94	NS	14-210	11	11	12
Cardiovascular agents								
Antiarrhythmic drugs								
Bretylium	7	725	1-6	NS	—	—		—
Disopyramide	0.83	93	5-65[e]	123		32	40	—
Flecainide	8.7	567	40	NS	—	—	—	
Lidocaine	1.2	606	66	NS	75-90	82	82	86
Mexiletine	7-10	846	70	NS		29	29	—
Procainamide	2	810	15	65	—	75	78	
NAPA[f]	1.5	200	10	41-97	125	37	49	—
Quinidine	2	270	80-85	11-18	24	37	39	40
Tocainide	3.2	182	10-15	25		18	20	—
Antihypertensive drugs								
Acebutolol	1.4	665	11-19	43		80	82	
Atenolol	1.2	176	<5	29-39		40	45	—
Diazoxide	0.12	7	94	25	—	18	60	—
Nadolol	2	135	20-30	46-102	—	21	30	

Table 3 (*continued*)

Drug name	Apparent volume of distribution (l/kg)	Plasma clearance (ml/min)	Plasma protein binding (%)	Hemodialyzer clearance (ml/min)	Hemoperfusion clearance (ml/min)	Fractional removal in 4 hr (%)		
						Normal patient	With hemodialysis	With hemoperfusion
Cardiotonic agents								
Digitoxin	0.5	3	90	NS	19	2	2	14
Digoxin	7.1	160	20–30	20	80	7	8	11
Spasmolytic agents								
Theophylline	0.45	46	60	70	100–225	30	59	74
Antineoplastic agent								
Methotrexate	0.64[g]	52	50–70	—	54–137	24	—	64
Metals and minerals								
Fluoride	0.5	100	—	100–188	—	—	—	—
Mercury	—	—	99	NS	—	—	—	—
Methylmercury	—	—	99	50–150[h]	—	—	—	—
Herbicides and insecticides								
Paraquat	2.8	28	—	NS	57–156	—	—	—
Demeton-s-methyl-sulfoxide	—	—	—	53	84	—	—	—

[a]NS = not significant.
[b]Data are for the metabolite trichlorethanol.
[c]Concentration dependent.
[d]V_d in uremia is 1.4 l/kg body weight.
[e]V_d in uremia is 2.2 l/kg body weight.
[f]Binding is concentration dependent.
[g]*N*-acetylprocainamide.
[h]Volume of distribution reduced to 0.42 l/kg in ESRD.
[i]With concurrent L-cysteine infusion.

cell injury and severe metabolic acidosis. Formate concentrations, rather than methanol, correlate clinically with, and are a more direct indicator of, toxicity and the need for intervention therapy (21). Ethanol and folate provide the preliminary therapy and may be fully effective in mild intoxication. Folate enhances formate oxidation, and ethanol competitively inhibits alcohol dehydrogenase and reduces the formation of formate from methanol. Early hemodialysis treatment is indicated particularly as the clearances of both methanol and formate are enhanced tenfold by this method. Hemodialysis clearance of methanol is 98–176 ml/min (22). During ethanol therapy hemodialysis achieves about 90% of total body clearance (23). Sorbent systems for dialysate regeneration are not effective, as is presumably also true of hemoperfusion devices (24). Postethanol rebound in serum formate concentrations has been recorded. The ethanol dose should be increased during dialysis to 7 g/hr above the predialysis infusion rate to maintain adequate blood ethanol concentrations.

Ethylene glycol Alcohol dehydrogenase is involved in the metabolism of ethylene glycol to aldehyde, oxalate, and organic acids. Oxalate formation produces renal and cerebral dysfunction with hypocalcemia secondary to calcium oxalate deposition, whereas citric acid–cycle inhibition results in lactic acidosis. Initial therapy consists of an ethanol infusion of 10–20 g/hr, increasing by 7 g/hr during dialysis to maintain a blood concentration of 100–200 mg/dl, which competitively inhibits ethylene glycol metabolism. Hemodialysis shortens the plasma half-life from 9 to 2.5 hours (25, 26). Hemodialysis is critical in removing the toxic alcohol, aldehyde metabolites, and organic acids (27). Postdialysis rebound in plasma ethylene glycol concentration is attributed to either a continuation of gastrointestinal absorption or redistribution from the peripheral to central compartment.

SEDATIVES AND HYPNOTICS

Barbiturates Most barbiturates are rapidly absorbed from the gastrointestinal tract, and therefore induction of emesis, gastric lavage, or administration of activated charcoal should be done immediately. Indications for extracorporeal intervention are high drug concentrations, prolonged coma, or cardiorespiratory complications that are unresponsive to intensive care.

Barbiturates can be divided into short- and long-acting varieties by their differing physiochemical properties that also correspond to contrary detoxification procedures. Long-acting compounds like phenobarbital have a low pK_a value, increased water solubility, decreased protein binding, and effective removal by hemodialysis. The short-acting barbiturates are lipid soluble, highly protein bound, and more effectively removed by charcoal and

resin hemoperfusion (28). Resin hemoperfusion is more efficient, since the clearance is limited by blood flow rather than adsorbent capacity of the column or the affinity of the drug to the adsorbent (29). However, rebound distribution from the peripheral compartment to the blood and to highly perfused organs such as the brain results in deterioration after discontinuing perfusion. Therefore, dialytic or perfusion treatments should be prolonged or repeated.

Ethchlorvynol The lethal dose of ethchlorvynol is from 10–25 g but may be as little as 2.5 g if alcohol is also ingested. Because of a large V_d, hemodialysis removes a small amount despite clearances of 20–82 ml/min (30). Of the two, resin is more effective than charcoal hemoperfusion, with 100% extraction of the drug by a single pass using Amberlite XAD-4 resin perfusion (29, 31, 32). Hemoperfusion clearance is about 3-fold that of the plasma clearance. Despite this removal rate, reduction of body stores is slow, and prolonged extracorporeal treatment is needed to achieve any benefit.

Chloral hydrate The lethal dose of chloral hydrate ranges between 4 and 30 g. It is rapidly absorbed and metabolized by alcohol dehydrogenase to trichloroacetic acid and trichloroethanol, the latter of which is the pharmacologically active metabolite. In therapeutic doses the half-life of trichloroethanol is 8 (4–12) hr, but in toxic levels the half-life increases to 35 hr, possibly due to saturation kinetics. Hemodialysis removes trichloroethanol effectively with an average clearance of 162 ml/min, removing 34% of body stores over 4 hr (33). Charcoal hemoperfusion is also effective with comparable clearances (34).

Glutethimide This substance, structurally similar to, but more lipid soluble than, phenobarbital, is almost entirely metabolized. Its erratic gastric absorption, enterohepatic circulation, and large V_d make the use of extracorporeal devices controversial (35). Hemoperfusion is preferred since hemodialysis is limited by protein binding and lipid solubility (29, 36). Patient deterioration may result from rebound in drug concentration after extracorporeal removal secondary to drug redistribution or enterohepatic recirculation.

Methyprylon Although therapeutic and toxic plasma concentrations have not been definitely established for methyprylon, plasma concentrations of 10 mg/l reportedly produce therapeutic effect; concentrations of 30 mg/l or greater may produce coma; and those in excess of 100 mg/l are potentially lethal. Overdose prolongs the usual half-life of 4 hr to 7–50 hours, probably because of saturation kinetics. Hemodialysis, and especially hemoperfusion, is effec-

tive in removing the drugs from the blood (37, 38), but body elimination is low because of the presumed large V_d.

Meprobamate Deep coma occurs at a serum concentration of 12 mg/dl of meprobamate, and death occurs at about 24 mg/dl. Protein binding is low, and clearances using hemodialysis average 60 ml/min (39). With charcoal hemoperfusion, clearances average 153 ml/min (40). Extraction of the drug is almost complete (82–100%), with resin (XAD-4) hemoperfusion and clearance ranges between 162–222 ml/min (41). Despite high rates of removal by hemoperfusion, only about 50% of body stores are removed by 4–6 hr treatments.

Methaqualone This drug, related to both glutethimide and methyprylon, is rapidly absorbed, highly protein bound, and metabolized by the liver. Hemodialysis clearance is 23 ml/min, and charcoal hemoperfusion clearances averaged 137 ml/min (42, 43). Hemoperfusion is suggested when the plasma concentration exceeds 40 mg/l (2), but its effectiveness is unproven.

ANALGESICS Although useful for salicylates, extracorporeal removal of acetaminophen, propoxyphene, or any of the nonsteroidal antiinflammatory drugs is ineffective.

Salicylates Unlike barbiturates, most deaths from salicylates occur after hospital admission and are, therefore, potentially avoidable with appropriate treatment.

The V_d of salicylates is small (0.21 l/kg), and removal of substantial quantities by extracorporeal devices or renal excretion is excellent. Animal toxicity studies with salicylates show a marked reduction in mortality when hemoperfusion is used (44, 45). Thus, hemoperfusion or hemodialysis (which also may correct any underlying acid-base defects), are appropriate when forced diuresis is contraindicated or inadequate.

Acetaminophen Increasing acute poisoning with high mortality rate is associated with this salicylate substitute. Although hemodialysis and hemoperfusion plasma clearance rates are high (100–125 ml/min), the large V_d, and frequent associated circulatory insufficiency, severely limits drug removal. The maximum amount removed has never exceeded 13% of the known quantity of acetaminophen ingested (46, 47). However, anecdotal experience suggests that drug removal may be of value in some cases (48).

Early intervention with the antioxidant *N*-acetylcysteine is effective. Although unproven, combined treatment of *N*-acetylcysteine with hemoperfusion or hemodialysis may be more beneficial than antioxidant treatment alone.

Currently, extracorporeal removal should be considered only adjunctive treatment.

ANTICONVULSANTS Because plasma protein binding exceeds 70% for carbamazepine, phenytoin, and valproic acid, hemodialytic removal is negligible. However, the fractional 4-hr removal is about 50% for ethosuximide and 55% for primidone during hemodialysis. These percentages represent an increase of 10-fold and 2.5-fold, respectively, above nondialysis removal rates (49, 50). With hemoperfusion clearances about 100 ml/min, the 4-hr fraction removal is increased 2-fold for carbamazepine and 4-fold for phenytoin (51, 52). Such enhancements may be of clinical benefit for overdose.

PSYCHOTHERAPEUTIC AGENTS

Antidepressants Tricyclic agents such as amitriptyline, imipramine, and nortriptyline are extremely lipid soluble, are highly tissue and protein bound, and have very large V_d. As anticipated, active elimination techniques including hemodialysis and hemoperfusion are ineffective even if instituted within hours of drug ingestion.

Benzodiazepines These drugs, including diazepam, flurazepam, lorazepam, and chlordiazepoxide are generally benign when taken in excess. However, their depressor effect may persist despite insignificant concentrations of the parent drug because much of the drug is converted in the liver to several active metabolites. Both the parent drug and its metabolites are widely distributed into body tissues and are highly bound to plasma proteins. A 57% decrement in plasma benzodiazepine concentration occurs with in vitro hemoperfusion (53). Clinical reports regarding the value of hemoperfusion, however, are lacking.

Lithium Hemodialysis is a very effective means of lithium removal but is limited by the large V_d and slow equilibration between central and peripheral compartments, necessitating prolonged treatment (54, 55). Extended hemodialysis (8–12 hr) is indicated in the treatment of patients with severe clinical symptoms or serum lithium levels greater than 4 mEq/l.

Cardiovascular Agents

CARDIAC GLYCOSIDES In a recent study of iatrogenic hospitalizations, digitalis products were surpassed only by aspirin as a cause. The large V_d of digoxin and the extensive plasma protein binding of digitoxin preclude exten-

sive removal of these agents by hemodialysis. The current treatment of choice for digoxin toxicity is administration of a specific antibody to bind and inactivate the drug (56). Data suggest that significant amounts of digitoxin can be removed by hemoperfusion. Although clearance of digitoxin by a charcoal (about 30 ml/min) or resin (about 20 ml/min) column is low, its small V_d makes removal of significant quantities of drug possible. Hemoperfusion increases total body clearance 8–20 times, producing a significant fall in total body store of the drug (57).

ANTIARRHYTHMIC DRUGS The large V_d, extensive plasma protein binding, and/or rapid biotransformation of amiodarone, bretylium, flecainide, lidocaine, mexiletine, procainamide, propranolol, and tocainide confirm the inadequacy of extracorporeal removal for toxicity. The low plasma clearance, particularly in renal failure, and small V_d of disopyramide, *N*-acetylprocainamide, and possibly quinidine suggest that extracorporeal removal may be feasible.

Disopyramide Plasma protein binding falls as the concentration of disopyramide rises. Hemodialysis removal during overdose is effective, with a rate about 30 ml/min (58). Hemoperfusion removal rates may be three times greater and produce a substantial reduction in plasma concentrations and body stores (59).

Procainamide and N-*acetylprocainamide (NAPA)* The hemodialysis clearance of procainamide (65 ml/min) and its active metabolite NAPA (45 ml/min) is substantial (60). However, as the metabolic clearance of procainamide is much greater, hemodialysis or hemoperfusion does not contribute significantly to total body removal. However, hemodialysis and particularly hemoperfusion substantially increase the removal of NAPA, especially in renal sufficiency, since NAPA is normally excreted at a rate comparable to the glomerular filtration rate (GFR) (61).

ANTIHYPERTENSIVES: ATENOLOL AND NADOLOL Overdoses with atenolol and nadolol have yet to be reported. As with other beta-blockers, adverse hemodynamic effects are best treated with glucagon. Although protein binding is not high, V_d is >1 l/kg, making fractional removal by extracorporeal devices not very effective. However, with diminished renal function, the major route of elimination of these drugs is impaired, and extracorporeal removal could be a significant form of overdose treatment. Hemodialysis clearance is 29–39 ml/min for atenolol and 46–102 ml/min for nadolol (6). No hemoperfusion data are available.

Antimicrobial Agents

Extracorporeal removal has little effect on the plasma clearance of most antibiotics when hepatic and renal function are normal because 80–90% of the dose is eliminated by these normal routes. However, charcoal hemoperfusion improves removal of chloramphenicol when intoxication occurs in newborns (62). This problem is unlikely to occur in adults because of greater intrinsic metabolism of chloramphenicol.

Spasmolytic Drugs: Theophylline

Although hemodialysis removes theophylline, hemoperfusion is more efficient. With charcoal, the extraction was 75–100%, depending on blood flow. A single 3-hr hemoperfusion removes approximately 60% of the total body load of theophylline without serum concentration rebound (39, 63, 64).

Antineoplastic Agents: Methotrexate

About 80% of a dose of methotrexate appears unchanged in the urine; therefore, toxicity may occur when renal function is compromised unless appropriate adjustments are made. Hemoperfusion is more efficient than hemodialysis in drug removal because of 50–70% plasma protein binding. Extracorporeal removal may enhance the rate of elimination 2- or 3-fold when renal function is normal, with fractional elimination of about 60% of body stores over 4 hr (65).

Metals and Minerals

GENERAL No pertinent data concerning extracorporeal removal in humans are available for antimony, barium, cadmium, chromium, magnesium, manganese, selenium, or zinc. Where applicable, urinary and/or intestinal elimination of most metals is enhanced by the use of chelation. Only with iron and aluminum overload in ESRD has extracorporeal removal been found useful in addition to chelation.

ALUMINUM Kinetics of aluminum have not been extensively studied. At plasma concentrations found in healthy subjects, aluminum is primarily excreted through bile. Urine elimination increases when plasma concentrations become elevated (66). Toxic aluminum loads are associated with ESRD when the dialysate is contaminated, or when patients are given chronic, high doses of aluminum salts for the chelation of oral phosphates. Intravenous deferoxamine can chelate aluminum, increase plasma concentrations, and allow increased elimination by either hemodialysis or hemoperfusion, although hemoperfusion is more effective (66).

ARSENIC Poisoning is treated with supportive measures and chelation therapy using dimercaprol or penicillamine. Acute intoxication may be associated with renal failure. Hemodialysis has been used to remove arsenic; clearances of 76–87 ml/min have been recorded (67). Although kinetic data are not available, substantial tissue binding would probably prevent significant fractional removal of this toxin. The use of chelation in addition to dialysis or hemoperfusion has not been described.

COPPER Chelation and excretion by customary elimination routes are the main treatment for copper poisoning. Addition of albumin to the dialysate enhances peritoneal dialysis removal (68). Because of extensive plasma protein binding, hemodialysis is ineffective; no data are available for hemoperfusion or the combination of chelation plus extracorporeal devices.

FLUORIDE The V_d of flouride is 0.5 l/kg, plasma protein binding is negligible, and the molecular weight is low. Thus, hemodialysis is effective in removing over 80% of body stores of this agent within 4 hr (29, 69). No data are currently available for the effectiveness of hemoperfusion, but it is expected to be less effective than hemodialysis.

IRON Acute or chronic iron overload is best treated by phlebotomy or chelation using deferoxamine (70). Chelation therapy increases iron elimination through the kidney and gut. Deferoxamine and extracorporeal devices replace phlebotomy, which cannot be used in renal failure. Elimination kinetics of iron following deferoxamine chelation and maintenance hemodialysis in ESRD have not been reported but must be low, as it takes months, in our experience, to substantially reduce serum ferritin concentrations with an iron overload.

LEAD Hemodialysis without concurrent chelation is of no value in removal of body stores of lead (71). When hemodialysis is used with EDTA chelation the plasma half-life decreased from 96 to 9 hr, as compared to elimination with EDTA alone in one study (72).

MERCURY Poisoning with elemental and inorganic mercury is treated with dimercaprol chelation for symptomatic patients and penicillamine for less severe exposures (73). Concurrent chelation with hemodialysis does enhance removal when compared with coincident excretion through the urine and gut (74). However, the extensive distribution of the agent suggests that fractional removal of body stores will be small.

METHYLMERCURY Hemodialysis has been combined with regional (infusion into the dialyzer inflow port) chelation therapy using L-cystine and

N-acetylcysteine for treating methylmercury poisoning (75, 76). Both chelators enhance removal by dialysis, but clearances are low and fractional removal of body stores is trivial. Hemoperfusion using polymercaptal microspheres shows promise (77).

Herbicides and Insecticides

PARAQUAT AND DIQUAT Paraquat poisoning is associated with a mortality rate of approximately 70%. Although extracorporeal removal has often been attempted along with gastric lavage and forced diuresis, the extensive tissue distribution of these agents and evidence of rebound in plasma concentrations after stopping hemoperfusion suggests that fractional removal of these toxins is clinically insignificant (78, 79).

ORGANOPHOSPHATES Organophosphates have cholinesterase-inhibiting activity. Parathione is a nondialyzable, lipophilic drug. It is metabolized to paraxon, which is probably the actual toxic agent in parathione poisoning. Unlike parathione, paraxon is removable by hemodialysis, and both agents are removable by charcoal hemoperfusion (80, 81). Two other organophosphates, demeton-*S*-methyl sulfoxide and dimethoate, have been reported to be removed by hemodialysis, charcoal, and resin hemoperfusion in laboratory studies (81, 82). In a clinical case report, 70% of the total body load of the poison was removed during 5 hr of hemoperfusion (82).

Mushroom Poisoning

The death cap *(Amanita phalloides)* and the destroying angel *(Amanita verna)* are appropriately named, for death follows in about 30% of those who ingest these toxins. The toxins are dialyzable and have a high affinity for charcoal (83, 84). Case reports provide strong circumstantial evidence that charcoal hemoperfusion is effective in removing toxins from the blood even 24 hr after ingestion (84). Seven patients who had ingested more than 3 death caps each received hemoperfusion within 16–24 hr following ingestion; all recovered.

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