Extracorporeal treatment of intoxications

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Purpose of review

The purpose of this article is to provide the critical care clinician with a comprehensive review of the indications for extracorporeal elimination of toxic substances, to summarize the different techniques and the intoxications for which these techniques are suitable.

Recent findings

In the last year, several excellent reviews about toxicological topics have been published. These reviews focused on intoxications in children, the approach of the patient with an unknown overdose, management of intoxications with salicylates, β-blockers and calcium antagonists and liver support systems. Important developments include the use of high-flux, high-efficiency membranes and albumin dialysis using the molecular adsorbent recirculating system (MARS). This system offers possibilities for the removal of protein-bound substances such as diltiazem, phenytoin and theophylline.

Summary

Although large randomized controlled trials are scarce in the field of toxicology, the treatment of intoxications is becoming more and more evidence based. This review summarizes the current knowledge and recommendations concerning the extracorporeal treatment of intoxications and discusses new developments in the field, such as the use of high-flux, high-efficiency membranes and albumin dialysis.

Keywords

hemodialysis, hemofiltration, hemoperfusion, intoxication, poisoning

Curr Opin Crit Care 13:668–673.

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Current Opinion in Critical Care 2007, 13:668–673

Abbreviation

MARS molecular adsorbent recirculating system

1070-5295

Introduction

Although intoxication is a common problem in adult and pediatric medicine, serious morbidity is unusual. In 2004, only 3% of all toxic exposures reported to the Toxic Exposure Surveillance System of the American Association of Poison Centers were treated in an ICU and in only 0.05% extracorporeal treatment was needed [1]. Extracorporeal treatment, however, may be lifesaving in victims of poisoning, especially when natural elimination mechanisms are impaired. This article reviews the characteristics of different extracorporeal techniques and summarizes the intoxications for which they are suitable.

Indication

The use of extracorporeal techniques to remove toxins is justified if there is an indication of severe toxicity (Table 1) and if the total body elimination of the toxin can be increased by 30% or more by using an extracorporeal technique [2]. Whether extracorporeal removal is possible depends on characteristics of the toxin itself and of the elimination technique used (Table 2). As the majority of reported toxic exposures occur in children of less than 6 years old [3•], it is important to know which substances are lethal for children, even in low doses [4,5]. These substances are summarized in Table 3.

Techniques available for extracorporeal removal of toxins

The extracorporeal techniques most frequently employed for the removal of toxins are hemodialysis, continuous hemofiltration techniques, hemoperfusion and the molecular adsorbent recirculating system (MARS).

Hemodialysis

During hemodialysis, toxins and other substances are cleared from the blood by diffusion across a semipermeable membrane down a concentration gradient from blood into dialysate. In order to be removed by hemodialysis, the toxic substance must be water soluble and must have a low molecular weight, low protein binding and a low volume of distribution (Table 2). During hemodialysis, the clearance of a toxic substance depends on membrane surface area and type, as well as on blood and dialysate flow rates. The larger the membrane surface, the greater the amount of toxin removed. Newer high-flux membranes can also remove high-molecular weight substances. Increasing blood and dialysate flow rates can increase the concentration gradient between blood and dialysate, thus optimizing the rates of diffusion and elimination. The major drawback of hemodialysis is the risk of rebound toxicity

Table 1 Indications of severe toxicity

(1) Ingested quantity associated with severe toxicity
(2) Ingestion of a toxin with serious delayed effects
(3) Natural removal mechanism impaired
(4) Clinical condition deteriorating
(5) Clinical evidence of severe toxicity: hypotension, coma, metabolic acidosis, respiratory depression, dysrhythmias or cardiac decompensation

Adapted from Orlowski *et al.* [2].

Table 2 Necessary properties for extracorporeal removal by three different techniques

	Hemodialysis	Hemofiltration	Hemoperfusion
Solubility	water	water	water or lipid
Molecular weight	<500 Da	<40 000 Da	<40 000 Da
Protein binding	low (<80%)	low	low or high
Volume of distribution	<1 l/kg	<1 l/kg	<1 l/kg
Endogenous clearance	<4 ml/min/kg	<4 ml/min/kg	<4 ml/min/kg
Distribution time	short	longer	short

Adapted from Orlowski *et al.* [2].

after cessation of the treatment, due to redistribution of the toxin.

Continuous techniques

In continuous hemofiltration techniques such as continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHD), the blood passes through large pore hollow fibres, allowing the convective removal of molecules up to 40 kDa. The advantages of continuous techniques are their applicability in hemodynamically unstable patients and the prolonged duration of therapy, minimizing the risk of a rebound effect [6]. The disadvantage of continuous techniques is their lower clearance compared with hemodialysis. In postdilutional hemofiltration, the clearance is equal to the ultrafiltrate flow rate, which is usually no more than 4 l/h or 67 ml/min, whereas with hemodialysis a clearance up to 500 ml/min can be achieved [2].

Table 3 Substances able to kill children at low doses

Calcium antagonists
Camphor
Clonidine and other imidazolines
Lomotil (diphenoxylate/atropine)
Opiates
Salicylates
Sulfonylureas
Toxic alcohols
Tricyclic antidepressants

Adapted from Michael and Sztajnkrycer [5].

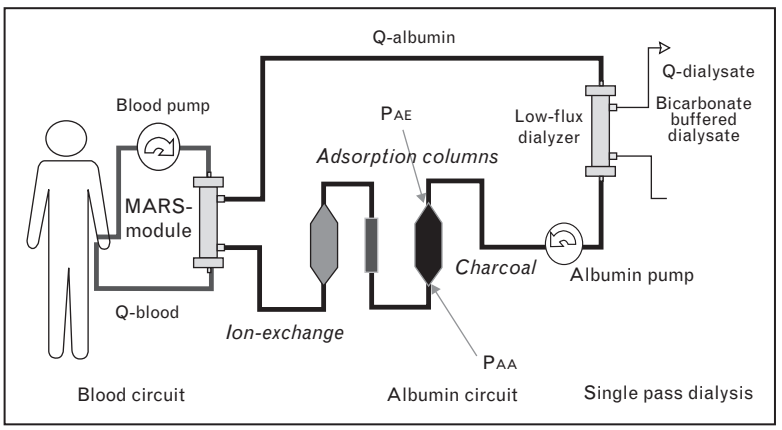
Hemoperfusion

During hemoperfusion, the blood passes through a cartridge containing a sorbent material able to adsorb the toxin. There are three types of sorbents: charcoal-based sorbents, synthetic resins and anion exchange resins. In order to be removed by hemoperfusion, the toxic substance must have binding affinity to the sorbent in the cartridge and a low volume of distribution (Table 2). Charcoal efficiently removes molecules in the 1000–1500 kDa range, but does not remove protein-bound molecules [7]. Resins are more effective in the removal of protein-bound and lipid-soluble molecules. Despite their efficacy, the use of hemoperfusion cartridges has declined over the last 20 years, due to limitations of their indications and shelf life. Moreover, hemoperfusion is technically more difficult to perform than hemodialysis, and lacks the possibility of correcting acid–base, fluid and electrolyte abnormalities [8].

Molecular adsorbent recirculating system

MARS is a blood purification system, aimed at removing albumin-bound toxic molecules [9•,10•]. It consists of three serial extracorporeal circuits: a blood circuit, an albumin detoxification circuit and a hemodialysis circuit (Fig. 1) [11]. The patient's blood passes the blood compartment of a high-flux dialyzer, where albumin flows

Figure 1 Molecular Adsorbent Recirculating System (MARS) circuit



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through the dialysate compartment in a countercurrent fashion. Protein-bound and water soluble substances can enter the albumin circuit by means of diffusion. The albumin circuit contains two filters, an activated charcoal filter which absorbs the toxins and an anion-exchange resin filter to cleanse the albumin. Finally, the albumin passes through the blood compartment of a second dialyzer, where small molecules are filtered down a concentration gradient to bicarbonate dialysate [12]. Although the efficacy of MARS in the removal of protein-bound drugs such as diltiazem, phenytoin and theophylline has been demonstrated in case reports, the use of MARS is limited by its availability, technical applicability and high costs.

Intoxications for which extracorporeal removal may be indicated

Due to the characteristics required for extracorporeal removal, the number of substances suitable for this technique is limited. Drugs and toxins for which extracorporeal removal is indicated are summarized in Table 4 and will be discussed in alphabetical order. When one of these agents is suspected, consultation of a nephrologist is warranted [13••].

Barbiturates

Phenobarbital is a long-acting barbiturate, commonly used as an anticonvulsant since 1912 [14]. It has a low volume of distribution, a slow intrinsic elimination and it binds readily to charcoal. Most patients with phenobarbital overdose can be managed by means of oral administration of activated charcoal and urine alkalization [15]. Whether extracorporeal treatment for barbiturate overdose is indicated depends on the severity of the toxicity and the response to therapy, rather than on the serum level. Extracorporeal removal should be considered in cases of severe hypotension, respiratory depression or deep and prolonged coma. Until recently, hemoperfusion was the treatment of choice [15]. With the use of high-flux, high-efficiency membranes, however, similar or even better elimination can be obtained with hemodialysis [15,16].

Lithium

Lithium is widely used in the treatment of bipolar affective disorders. It has a molecular weight of 74 Da, a distribution volume of 0.6–0.9 l/kg body weight and it is not protein bound, which makes it an ideal substance to be removed by hemodialysis. With hemodialysis, an extraction ratio of 90% and a clearance ranging from 63 to 114 ml/min is achieved, making it the treatment of choice for extracorporeal lithium removal [17]. Hemodialysis is even more effective in removing lithium than the kidney itself, as 70–80% of lithium filtered by the kidney is reabsorbed in the proximal tubule. Hemodialysis should be started in cases of central nervous system abnormalities such as confusion, stupor, coma or seizures. A negative anion gap and an elevated osmolar gap may be diagnostic clues [18•]. Although the serum lithium level is effectively lowered by hemodialysis, a rebound rise in serum levels occurs 6–8 h after cessation of the treatment, as lithium redistributes to the circulation from the interstitial space [19]. Therefore, hemodialysis should be continued until the serum lithium level remains below 1 mEq/l. In this respect, continuous techniques such as CVVH and CVVHD may be advantageous, as they couple a longer running time to an acceptable clearance [6]. Depending on the ultrafiltrate flow rate, clearances up to 67 ml/min can be reached by postdilutional hemofiltration [20].

Table 4 Substances for which extracorporeal treatment may be indicated

Substances	Preferred method
Barbiturates	Hemoperfusion
Lithium	Hemodialysis
Metformin	Hemodialysis
Salicylates	Hemodialysis
Theophylline	Hemoperfusion
Toxic alcohols	Hemodialysis
Valproic acid	Hemodialysis

Original table.

Metformin

The biguanide metformin is the most widely used oral antidiabetic agent in the world, however it carries the risk of metformin associated lactic acidosis (MALA), which usually occurs in cases of overdose or renal failure. Although rare, MALA carries a mortality risk of 50% [21•]. Metformin has a molecular weight of 166 Da, is not protein bound and is excreted by the kidney by means of glomerular filtration and tubular secretion. Its renal clearance therefore exceeds the creatinine clearance and ranges from 552 to 642 ml/min, reaching a plasma elimination half life of 1.5–4.7 h [22]. Metformin intoxication itself, however, can induce acute renal failure, which aggravates toxicity [21•]. By means of hemodialysis or hemofiltration, metformin can be removed with clearances up to 170 ml/min [23]. Extracorporeal treatment should be performed in cases of refractory lactic acidosis or impaired renal function [24–26].

Salicylates

At therapeutic levels, salicylates have over 90% protein binding, which decreases to 50–75% at toxic levels, due to saturation. Salicylates are metabolized in the liver and eliminated by the kidney. The elimination half life is dose dependent, ranging from 2 h at a low dose to 30 h at a high dose. Treatment with hemodialysis should be started when the serum level exceeds 700 mg/l or when the clinical situation deteriorates (altered mental status, respiratory failure, pulmonary edema, severe acid–base disturbances, renal failure) [27••]. Although hemoperfusion is more effective in removing salicylates, hemodialysis is

recommended, since it more rapidly corrects metabolic acidosis and electrolyte disturbances [28].

Theophylline

Theophylline is more than 50% protein bound and under normal conditions metabolized by the p450 enzyme in the liver. At therapeutic levels its elimination obeys first-order kinetics, while limitation of the enzyme capacity results in zero order kinetics at higher concentrations [29]. Since theophylline binds readily to charcoal, hemoperfusion is the treatment of choice [8]. In acute toxicity, it should be started at serum levels greater than 90 μg/ml, and in chronic intoxication at levels greater than 40 μg/ml in the presence of signs of severe toxicity. When hemoperfusion is not available, hemofiltration is also effective. By means of hemofiltration, the half life of theophylline could be reduced from 5 days to 6 h in a case of severe theophylline poisoning [29]. By means of MARS, even a half life of 2 h was achieved [30•].

Toxic alcohols

The toxic alcohols include ethylene glycol, methanol and isopropanol.

Ethylene glycol

Ethylene glycol is a compound used in antifreeze and windshield washer solutions. It is converted by alcohol dehydrogenase to glycolate, which causes renal failure and pulmonary and cerebral edema. Therefore, the mainstay of the treatment of ethylene glycol poisoning is the inhibition of alcohol dehydrogenase by means of ethanol or fomepizole [31,32]. Hemodialysis should be started when signs and symptoms of severe toxicity are present (deteriorating vital signs, severe metabolic acidosis, acute kidney injury, pulmonary or cerebral edema) or when the serum level exceeds 0.5 g/l [32]. Refractory serum hyperosmolality and a glycolic acid level greater than 10 mmol/l have also been described as indications [33,34]. Hemodialysis effectively clears glycolate with an elimination half life of 155 ± 474 min compared with a spontaneous elimination half life of 625 ± 474 min [32,35].

Methanol

Under physiological circumstances, methanol is metabolized by alcohol dehydrogenase to formaldehyde, and by aldehyde dehydrogenase to formic acid, which is responsible for the acidosis and toxic manifestations. Therefore, the primary step in the treatment of methanol intoxication is inhibition of alcohol dehydrogenase with ethanol or fomepizole [31,32]. The usual criteria for hemodialysis include severe acidosis, visual impairment, renal failure, electrolyte disturbances or a plasma methanol concentration greater than 0.5 g/l [36]. Hemodialysis, however, does not substantially enhance the endogenous clearance of formate: in a prospective multicenter trial the endogenous half life of formic acid was 205 ± 25 min, whereas the hemodialysis half life was 185 ± 63 min [37].

Isopropanol

Isopropanol is a colorless liquid with a bitter taste, used in the manufacturing of acetone and glycerin. The minimal lethal dose for adults is approximately 100 ml. Unlike ethylene glycol and methanol, most of the toxic effects of isopropanol are due to the parent compound itself. Isopropanol is metabolized to acetone by alcohol dehydrogenase. The clinical signs of intoxication occur within 1 h of ingestion and include gastrointestinal symptoms, confusion, stupor and coma. Severe intoxications may present with hypotension due to cardiac depression and vasodilatation [38]. Hypotension is the strongest predictor of mortality. Inhibition of alcohol dehydrogenase is not indicated, as acetone is less toxic than isopropanol. Hemodialysis is indicated for patients with an isopropanol level greater than 4 g/l and significant central nervous system depression, renal failure or hypotension [38], although this indication has been debated [39].

Valproic acid

Valproic acid is a 144 Da branched chain carboxylic acid primarily metabolized in the liver. At therapeutic levels it is 90% protein bound, but protein binding decreases at toxic serum levels due to saturation. Valproic acid has a small volume of distribution (0.1–0.5 l/kg) and a plasma half life of 6–16 h [40]. Clinical manifestations of toxicity vary from mild confusion and lethargy to coma and death. In addition to neurological symptoms, valproate can cause hypothermia, hypotension, tachycardia, gastrointestinal disturbances and hepatotoxicity as well as hypernatremia, hyperosmolarity, hypocalcemia and metabolic acidosis. Valproic acid was demonstrated to be eliminated by hemodialysis alone and in combination with hemoperfusion. With these techniques half lives of 2–4 h could be reached [40–43]. Extracorporeal treatment is justified in cases of refractory hemodynamic instability or metabolic acidosis [44].

Substances for which extracorporeal removal may be possible

For some drugs and toxins extracorporeal removal is possible, but the effect on outcome is uncertain.

Carbamazepine

Carbamazepine is an iminostilbene derivative anticonvulsant. It has a molecular weight of 236 Da, is 80–85% protein bound and has a target serum level of 4–12 μg/l. Under normal circumstances, it is metabolized in the liver and eliminated by the kidney, with an elimination half life of 2–6 days. Acute overdose can result in cardiovascular and neurologic impairment with possible fatal outcome [45•]. Although supportive care is usually sufficient [46], extracorporeal removal by either hemoperfusion or

hemodialysis may be indicated in patients with unstable cardiac status, status epilepticus or refractory bowel hypomotility [45•,46,47]. A recent article demonstrated that both techniques are equally effective, reaching a half life of approximately 6 h [45•].

Diltiazem

Calcium blocker overdose can result in marked and sustained hypotension with a mortality rate as high as 10% [48]. Diltiazem is a calcium channel blocker which is 80% protein bound at therapeutic levels and has a distribution volume of 5 l/kg. Therefore, it is not suitable for hemodialysis or hemofiltration [49•]. Recently, however, the effective removal of diltiazem from the circulation by means of albumin dialysis (MARS) was described, reaching a half life of approximately 16 h [48].

Phenytoin

Phenytoin is one of the most commonly used antiepileptic drugs. It is 90% albumin bound, metabolized in the liver and excreted by the kidney. Its median elimination half life is 24 h, ranging from 7 to 42 h. It has a narrow therapeutic range and a serum level exceeding 80 μM is associated with clinically relevant toxicity. Although there is no evidence that enhanced elimination is beneficial [50], phenytoin was described to be effectively removed by albumin dialysis (MARS), reaching a half life of approximately 6 h [51].

Mushrooms

Although the reports of severe and fatal mushroom poisonings have increased during the past 50 years, fatalities due to mushroom poisoning are rare (0.0006%) [1]. Most fatalities are caused by cyclopeptide-containing species from the genera *Amanita*, *Galerina* and *Lepiota* and are the result of late-onset hepatorenal failure [52]. The cyclopeptides are divided into three classes of peptides: amatoxins, phallotoxins and virotoxins. The amatoxins may be enterohepatically recirculated and interact with RNA polymerase II, leading to liver cell necrosis by inhibition of protein synthesis. Amatoxins exhibit limited protein binding and are eliminated in urine, vomitus and feces. Theoretically, it should be possible to eliminate them by hemoperfusion, as they have a low molecular weight (900 Da) and a high affinity for charcoal and polymers. The utility of extracorporeal removal, however, is questionable, given the low serum concentration of amatoxins and the fact that the intracellular amatoxin concentration reached within 1 h of ingestion is crucial to the magnitude of liver cell necrosis, as it determines the extent of mRNA blockage [53,54]. In this respect, the success of MARS in the treatment of mushroom poisoning may be attributed to its liver support function as a bridge to liver cell regeneration or liver transplantation [11,54].

Conclusion

The treatment of intoxication with an extracorporeal technique is justified if there are signs of severe toxicity and if elimination of the toxin can be increased by 30% or more using an extracorporeal technique. Hemodialysis is most frequently indicated and the use of high-flux, high-efficiency membranes is recommended for the removal of substances with a higher molecular weight. Continuous techniques are preferable in hemodynamically unstable patients and in cases of toxins with rapid redistribution. Hemoperfusion is infrequently used because of its limited indications and technical difficulties. For some highly protein bound substances such as diltiazem, phenytoin and theophylline, albumin dialysis may play a role.

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