Hemoperfusion is an extracorporeal treatment based on adsorption, historically reserved for the treatment of acute poisonings. Its use was popularized in the 1970s after several in vitro and animal experiments had demonstrated its efficacy, and was even preferred over hemodialysis in the management of overdosed patients.

The principle of hemoperfusion (HP) is based on the adsorption of a poison to a column that is perfused by blood of a poisoned patient. If effective, HP will decrease the concentration of the poison in the blood, thereby decreasing the severity of toxicity and/or duration of poisoning.

The clinical use of HP has fluctuated over the last 50 years and remains a treatment of choice for poisoned patients in some parts of the world. In this review, we will discuss (i) the technique of HP, (ii) the components of the circuit, (iii) the factors influencing HP clearance of poisons, (iv) the adverse reactions related to its use, (v) its current application, as well as (vi) the future research directions in the use of HP in the treatment of poisoned patients.

History of the Use of Hemoperfusion

The use of adsorptive treatments, in particular using charcoal, was reported in ancient Greece. The first published application of HP was performed by Muirhead and Reid in 1948 using an ionic resin to remove uremic toxins in dogs (1). In 1960, HP using an anion-exchange resin was shown to remove salicylate and phenobarbital from intoxicated dogs (2). Schreiner later successfully used an ion-exchange resin in a patient with barbiturate poisoning (3). Results of these studies were sufficiently favorable to lead to further research and clinical use.

Early clinical experience with HP suggested that it was more effective than alternative treatments for enhanced elimination, including hemodialysis (HD), peritoneal dialysis and urinary alkalinization, especially for poisons for which antidotes were not available, such as barbiturates, theophylline, and paraquat (4–6). The superior clearances achieved by HP compared to HD, which are less limited by protein binding, led to its enthusiastic following in some centers in the 1970s and 1980s. During this time, there were improvements in HP technology including modifications to adsorbants (such as the coating of charcoal to reduce complications) and newer resin columns. HP was later employed sporadically for other uses such as hepatic failure, vasculitis, and autoimmune diseases with inconsistent results (7–10).

As suggested by the declining number of HP reports during the 1990s (11), there was waning interest for HP for several reasons; the rate of complications is greater during HP than during HD...
(12) and the cost of cartridges is significantly higher than that of dialyzers, even more so if they are replaced regularly because of column saturation (13).

Furthermore, although the advantage of HP over HD for poison clearance appeared to be initially convincing for theophylline and carbamazepine (14), data later showed comparable results with newer high-flux, high-efficiency dialysis filters (12,13). There were also several examples of misapplication of HP in several settings (for example, use in poisons with large volumes of distribution) (15). This may explain why the use of HP consistently decreased in many countries, including the United States (16) (Fig. 1). Coupled with the decreasing use of HP in most countries, it is now increasingly difficult to obtain a HP cartridge in a timely manner, although data regarding the utilization and availability of HP in countries other than the United States are extremely limited (17). This has resulted in a decrease in expertise in the clinical application and monitoring required to perform HP in many parts of the world. The trends in ECTR reports published in this issue did confirm, however, a solid following of HP in Asia today so a working understanding of adsorption based techniques remains pertinent.

**Influence of Physicochemical and Pharmacokinetic Properties on the Effect of Hemoperfusion**

The potential for an extracorporeal technique to enhance the elimination of a poison is largely determined by its physicochemical and pharmacokinetic properties; these are well established. These principles hold for each type of extracorporeal blood purification technique and allow us to estimate the effect of an enhanced elimination technique.

From the pharmacokinetic perspective, poisons with a large volume of distribution (generally considered to exceed approximately 1 l/kg) and exhibiting multicompartmental kinetics with slow intercompartmental transfer constants are not likely to be extensively removed by HP (18). This is particularly the case when HP is initiated in the post-distribution phase because much of the poison is outside of the vascular compartment at this stage. In this setting, even when the extraction ratio of poison from the blood is high, the actual amount of poison removed from the body during a single standard treatment will be small, so a prolonged treatment may be required.

For poisons with a high endogenous or systemic clearance, usually due to extensive metabolism, it is unlikely that additional clearance by HP will lead to a clinically significant increase in total clearance. Conversely, in the setting of low systemic clearance (e.g., impaired kidney function) extracorporeal clearance by HP may increase the clearance to a significant extent (10,12), although HD may be preferred in this setting because it is also useful in azotemia (18,19).

However, there are some notable differences in the extent to which HP or hemodialysis/hemofiltration can increase clearance (see examples in Table 1) and this largely reflects the physicochemical properties of the poison and its affinity for the adsorbent column.

Water soluble poisons are cleared by most extracorporeal treatments, in particular HD, hemofiltration, and HP. In contrast, lipophilic poisons are cleared to a lesser extent by HD or hemofiltration, partly because they often display a high degree of protein binding. Clearance is reduced because only

**Fig. 1.** Temporal changes in the number of cases where HP and HD were utilized in the treatment of poisoned patients in the United States. Data obtained from the annual reports of the American Association of Poison Control Centers’ National Poison Data System (NPDS).
the free poison (unbound to protein) is readily available to be cleared by these modalities. With HP, especially with resin columns, clearance of lipophilic compounds is favored. Although the extraction of highly protein-bound poisons is less than that for unbound poisons (20), studies using an adsorbent cartridge showed extraction ratios consistently exceeding 80% when the proportion of protein-bound poison is less than 90% (21,22). Furthermore, some poisons exhibit saturable protein binding at higher concentration, such as valproic acid (23), salicylates (24) and 4-chloro-2-methylphenoxyacetic acid (MCPA) (25). Unfortunately, simple measurements of the lipophilicity of a poison, such as the log-transformed octanol-water coefficient (log \( P \)), are insufficient to predict whether the clearance of a poison will be highest with HD or HP (Fig. 2A).

Molecular size does not appear to have a major influence on clearance by HP, except when the molecular weight exceeds 5000 Da (26-29). In that case, clearance appears significantly reduced, although in vivo adsorption of very large proteins to the HP column suggests that there is no absolute cut-off (as opposed to HD).

Although extracorporeal clearance of a poison is expected to be independent of its plasma concentration, an increase in clearance has been noted at higher concentrations, for example in isolated studies for theophylline and cisplatin (30,31). The reason for this observation is unclear, but could relate to concentration-dependent changes in protein binding, whereby there is an increase in the proportion of free (unbound) poison at higher concentrations.

Components of the Hemoperfusion Circuit, Including Technical Considerations

Circuit

There are many similarities between the extracorporeal circuit used for HP and that used for HD or hemofiltration. A large bore dual lumen catheter is inserted into a central vein and blood passes through a disposable column and purified blood returns to the patient. In contrast to HD or hemofiltration, there is no effluent production. HP columns can be used in a number of brands of

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**TABLE 1. Relative effect of hemoperfusion and hemodialysis on the clearance of selected compounds and poisons**

<table>
<thead>
<tr>
<th>Compound</th>
<th>HP &gt; HD</th>
<th>HD &gt; HP</th>
<th>HD ( \cong ) HP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide (115)</td>
<td>Creatinine (119,154)</td>
<td>Carbamazepine (57,105,166-168)</td>
<td></td>
</tr>
<tr>
<td>Bromine (73)</td>
<td>Glufosinate (162)</td>
<td>Procaainamide (170–172)</td>
<td></td>
</tr>
<tr>
<td>Barbiturates (47,64,119–123)</td>
<td>Methaqualone (20,41,123,130,163)</td>
<td>Theophylline (12,30,77,173,174)</td>
<td></td>
</tr>
<tr>
<td>Bromide (inorganic) (124)</td>
<td>Nifedipine (164)</td>
<td>Phosphorus (154)</td>
<td></td>
</tr>
<tr>
<td>Camphor (125,126)</td>
<td>Urea (154,165)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbromal (73,123,124,127)</td>
<td>CCl(_4) (130,137)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine (128)</td>
<td>Methotrexate (44,141–143)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone (129)</td>
<td>Paraoxon (130,137)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitoxin (20,130–132)</td>
<td>Parathion (20,130,137)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dicog disin (67,131–134)</td>
<td>Paraquat (5,20,61,65,66,130,144–150)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethoate (130,135–137)</td>
<td>Pentamidine (151)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gluthetimide (138)</td>
<td>Pine oil (152)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid (139,140)</td>
<td>Thallium (123)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metasystox (130,137)</td>
<td>Thiabendazole (153)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate (44,141–143)</td>
<td>Tricyclic antidepressants (58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraanoxon (130,137)</td>
<td>Uric acid (154)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parathion (20,130,137)</td>
<td>Valproic acid (155,156)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraquat (5,20,61,65,66,130,144–150)</td>
<td>Verapamil (157)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The purpose of this table is to demonstrate the variability in clearance between different extracorporeal techniques. Compounds and poisons listed here are only those for which head-to-head studies are available. This table is not a list of indications for certain extracorporeal treatments. Indeed, many studies were performed with technology that is now out of date, so different results may be observed if they are repeated using modern equipment.

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**Fig. 2.** The log \( P \) of a poison is a poor predictor of the differences in clearance between (A) hemodialysis and hemoperfusion, and (B) charcoal and resin-based hemoperfusion (based on compounds listed in Tables 2 and 3; log \( P \) obtained from www.chemspider.com).
machines that are routinely used for other extracorporeal treatment modalities and a similar anticoagulation regimen is used (Fig. 3).

Types of Adsorbent, and Relative Adsorptive Capacity

The structure of the column is a key determinant of the effect of HP to enhance the elimination of a poison. The column is most commonly made from activated charcoal but resins are also available. Examples of commercialized products are listed in Table 2. Other adsorbent columns have been trialled experimentally, including poison-specific antibodies (e.g., paraquat, digoxin), non-specific adsorbents such as Fuller’s earth, and specific adsorbents (e.g., β2-microglobulin), but very few have been used commercially (32).

Compared to activated charcoal, resins such as XAD exhibit enhanced adsorption and clearance of lipophilic compounds, but less adsorption of hydrophilic compounds. Unfortunately, log P is also an inadequate parameter for predicting whether clearance will be enhanced by resin or charcoal (Fig. 2B). Endogenous substances such as urate, creatinine, and guanidines can be removed by charcoal, but urea, alcohols, or most metals are not adsorbed significantly by either charcoal or resin HP (33–36).

Charcoal

Activated charcoal reversibly adsorbs compounds by Van der Waal forces (attractive forces between molecules not due to covalent or electrostatic interaction of charged molecules or hydrogen bonds). Activated charcoal is an effective and popular oral agent for preventing gastrointestinal absorption of certain poisons.

Charcoal columns were first employed in the 1960s, using in vitro and in vivo experiments for the purpose of enhanced elimination (36).

<table>
<thead>
<tr>
<th>Name of the column</th>
<th>Company</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAC</td>
<td>Chang</td>
<td>Albumin-colloidal or colloid coated charcoal</td>
</tr>
<tr>
<td>Adsorba 150 or 300c</td>
<td>Gambro</td>
<td>150 or 300 g of extruded charcoal coated with cellulose acetate</td>
</tr>
<tr>
<td>Alu-kart</td>
<td>National Medical Care</td>
<td>100 g or 155 g of encapsulated colloid charcoal</td>
</tr>
<tr>
<td>Ambersorb XE-34</td>
<td>Westlake Plastics</td>
<td>200 g of carbonaceous spherical bead pyrolyzed resin</td>
</tr>
<tr>
<td>Amberlite</td>
<td>Sigma-Aldrich</td>
<td>XAD-4 (surface area = 725 m²/g) is derived from polystyrene-divinyl benzene, XAD-7 is derived from polyacrylic ester-divinylbenzene</td>
</tr>
<tr>
<td>XAD-4, XAD-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biocompatible system</td>
<td>Clark</td>
<td>100 or 250 g heparinized polymer coated charcoal</td>
</tr>
<tr>
<td>Detoxifier Type 1</td>
<td>Shanghai</td>
<td>Cross-linked gelatin coated charcoal</td>
</tr>
<tr>
<td>Detoxyl I</td>
<td>Mitsubishi/Sorin</td>
<td>Uncoated petroleum-based spherical charcoal</td>
</tr>
<tr>
<td>DHP-1</td>
<td>Kuraray, Osaka</td>
<td>100 g or 160 g poly-HEMA coated petroleum-based activated carbon beads</td>
</tr>
<tr>
<td>Dow 1X-2</td>
<td>Dow Chemicals</td>
<td>Anionic resin</td>
</tr>
<tr>
<td>Dowex 50 WX8</td>
<td>BDH Chemicals</td>
<td>Strongly acidic cation-exchange resin</td>
</tr>
<tr>
<td>Hemodetoxyfiber</td>
<td>Becton-Dickinson</td>
<td>87 g of uncoated coconut-shell fixed-bed charcoal on a polyester film</td>
</tr>
<tr>
<td>(hemoadsorber)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemosorba</td>
<td>Asahi</td>
<td>170 g bead charcoal, either uncoated or coated with colloid petroleum-based charcoal poly-HEMA</td>
</tr>
<tr>
<td>Hemocarbo</td>
<td>Nissho</td>
<td>Colloid coated spherical charcoal</td>
</tr>
<tr>
<td>Hemocel</td>
<td>Teijin</td>
<td>50 g cellulose coated activated charcoal</td>
</tr>
<tr>
<td>Hemocel 100, Hemocel</td>
<td>Smith &amp; Nephew</td>
<td>100 g or 300 g. coconut-shell acrylic-hydrogel coated charcoal packed in a polystyrene casing</td>
</tr>
<tr>
<td>Hemopur 260</td>
<td>Organon-Teknika</td>
<td>250 g Norit extruded charcoal cellulose acetate coated</td>
</tr>
<tr>
<td>Haemoresin</td>
<td>Braun</td>
<td>350 g uncoated XAD-4 resin</td>
</tr>
<tr>
<td>Lixelle</td>
<td>Kaneka Corporation</td>
<td>Porous cellulose beads bound to a hydrophobic organic compound (hexadecyl alkyl chain), β2-microglobulin adsorption column</td>
</tr>
<tr>
<td>Norit RBX1</td>
<td>Norit-Clydesdale, UK</td>
<td>Extruded peat based charcoal either coated with cellulose or uncoated</td>
</tr>
<tr>
<td>XR-004</td>
<td>Extracorporeal Medical Specialties</td>
<td>312 g uncoated XAD-4</td>
</tr>
</tbody>
</table>
these and other experiments demonstrated enhanced elimination of a number of medications, they were associated with serious complications including severe thrombocytopenia, leukocytopenia, charcoal embolism or pyrogenic reactions. Later refinements to the columns minimized embolization and enhanced its efficiency by:

(i) “Activating” the charcoal, a process of subjecting charcoal to either physical (steam, \( \text{CO}_2 \)) or chemical activation (zinc chloride), causing an increase in the surface area and adsorptive capacity.

(ii) Various charcoal structures were tested, including varying the thickness (0.05–5.0 \( \mu \text{M} \)) and components (granules, cloths, fibers, beads, or a spherical matrix) (37). Charcoal can also be fixed to a membrane or to a polyethylene backing and wound into a spiral. Animal studies showed comparable efficacy of fixed-bed when compared to loose-bed charcoal HP (38).

(iii) Coating or encapsulating the charcoal columns by a thin porous membrane, which may be composed of colloidon, albumin-colloidon, cellulose acetate, nylon, methacrylate, polymer, or agarose (39). Coating reduces embolization of the particles and improves the biocompatibility of charcoal columns (28). However, coating can also reduce the in vitro clearance of several poisons, especially larger molecular weight compounds (>5000 Da) (27,40–42), although this has not been consistently observed in animal and human reports (35,43–46). In some publications, poison clearance using coated columns has even surpassed uncoated cartridges (47), although this could reflect other factors such as the structure of column. The coating of charcoal columns was not universally adopted, as other improvements in the column design permitted the manufacturing of new uncoated cartridges (48). Although coating has been mostly applied to charcoal HP, it can also be used with resin HP, even if they carry a lower risk of embolization (49,50).

(iv) Pretreatment of charcoal and resins with endogenous substances such as human plasma, albumin, or heparin can enhance biocompatibility and minimize the removal of these and other biological components during clinical use (51,52). For example, the adsorption of creatinine to charcoal is greater when the column has been pretreated with albumin compared to heparin (53). However, the influence of this pretreatment on poison clearance is incompletely described. Pretreatment with large molecules (e.g., albumin) reduces the adsorption capacity for larger but not for smaller molecules, which may be acceptable considering that most encountered poisons are small (<1000 Da) (51,54).

Resins

Most commercially available resins are made from heat-stable polymeric material in the form of cross-linked insoluble beads which can either be charged (e.g., Amberlite IRA-900) or uncharged, (e.g., Amberlite XAD-2 [now discontinued] or Amberlite XAD-4). Rosenbaum et al. developed and tested these lipophilic resins in the 1970s in animals and human subjects (55). Amberlite XAD-2 and XAD-4 are both derived from polystyrene-divinyl benzene, while Amberlite XAD-7 is derived from polyacrylic ester-divinyl benzene and has an affinity for moderately polar compounds. Uncharged resins have a macroreticular aromatic structure with a special surface affinity for nonpolar substances and are therefore better adapted to liposoluble poisons than either ionic resins or charcoal. Ion exchangers are usually composed of a porous matrix containing diffusible ions throughout its surface, which can be exchanged with those from the blood compartment. They may be constructed using an organic (e.g., cellulose, dextran) or inorganic (e.g., zeolite, oxides) matrix (56). Resin particles have less of a tendency to fragment and cause embolisms, but both decrease platelet counts.

Other Column Properties

In addition to the type of adsorbent used, other characteristics of the column influence its adsorptive capacity and, therefore, clearance of the poison. These characteristics are multiple and determining their net effect on poison clearance can be complicated. For example, factors anticipated to influence the adsorptive capacity irrespective of the type of poison include the column’s mass, surface area, size and configuration of the pores. For example, Amberlite XAD-4 has more than twice the surface area of XAD-2 (i.e., 750 m\(^2\)/g vs. 350 m\(^2\)/g) so it is predicted that clearance by XAD-4 will exceed that of XAD-2. However, based on extraction ratios and the calculated in vitro clearances, this was not demonstrated for carbamazepine, tricyclic antidepressants, or amanita toxin (57–59).

Apparent advancements in technology do not necessarily reach clinical practice. For example, while in vitro and in vivo experimental results were encouraging from both an efficacy and safety perspective, when activated charcoal was arranged into small beads, a commercial application did not follow this experiment (60–63).

Some poisons are preferentially bound to resin or charcoal columns on the basis of in vitro and in vivo data, as shown in Table 3. Data included in this table are limited to publications, where both types of columns were tested in the same experiment. However, caution is required when interpreting these results because factors related to composition and structure also influence the net amount adsorbed so differences in clearance can be observed between individual
reasonable. A possible explanation is that the surface area of even the smaller-sized cartridges is sufficient to remove most poisons relative to the rate of saturation from biological debris on the column rather than saturation of poison binding sites.

Data suggest that the capacity of a column depends on the amount of adsorbent employed, whereas the rate of drug adsorption depends on the size of the adsorbent particles. In an in vitro study the devices having the smallest particles (20–50 mesh particles) provided high initial clearances, while the devices having the largest particles (5–10 mesh particles) provided low initial clearances (48).

### Influence of the Hemoperfusion Prescription on Poison Clearance

#### Site of Insertion and Type of Catheter

In HP, as in HD, clearance may be influenced by the site and size of the catheters. This is due to uncleansed blood being mixed with blood returning from the extracorporeal circuit, a phenomenon termed recirculation (70). However, there are no data to confirm the influence of these variables for HP.

#### Type of Pump

Since the widespread use of veno-venous techniques, compared to arterio-venous techniques, blood pumps have become necessary for effective delivery of an extracorporeal therapy. An animal study comparing a pulsatile blood pump to a peristaltic roller pump for paraquat removal reported that the type of pump used does not influence clearance (71,72).

#### Blood Flow

The velocity of the blood flow ($Q_B$) through the HP column influences drug and poison clearances. This principle is similar to the one observed with HD which is why $Q_B$ is maximized in end-stage renal disease (ESRD) patients to favor removal of phosphate, potassium, and uremic toxins. This is readily predicted based on first-principles and as such it is always included in pharmacokinetic equations that are used to calculate the clearance of a poison by an extracorporeal treatment.

This effect of $Q_B$ on poison clearance has been confirmed in numerous in vivo and in vitro experiments for multiple poisons, as well as human reports, for both resin and charcoal columns (4,20,22,30,67,68,73–78). The relationship is particularly pronounced for poisons that are less bound to plasma proteins. However, in contrast to HD where $Q_B$ usually exceeds 300 ml/minute in clinical practice, the manufacturers of HP columns often recommend limiting $Q_B$ to 300–350 ml/minute to minimize the degree of hemolysis (79).

### TABLE 3. Relative adsorptive characteristics of charcoal and resin hemoperfusion columns for selected compounds and poisons*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Charcoal (88)</th>
<th>Resin (119)</th>
<th>Equal/Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Amanita A and B</td>
<td>Bromine (73)</td>
<td>Adriamycin (44)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>(59,116–118)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Carbamazepine</td>
<td>Aminophenazone</td>
<td></td>
</tr>
<tr>
<td>(41)</td>
<td>(57,105,166–168)</td>
<td>(22,41)</td>
<td></td>
</tr>
<tr>
<td>Cisplatin (31)</td>
<td>Barbiturates</td>
<td>Disopyramide</td>
<td></td>
</tr>
<tr>
<td>Didropyridine (41)</td>
<td>Carbohydrate</td>
<td>Imipramine (41,42)</td>
<td></td>
</tr>
<tr>
<td>Digitoxin (20,130–132)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diquat (175)</td>
<td>Daunorubicin</td>
<td></td>
<td>Theophylline (12,30,77,173,174)</td>
</tr>
<tr>
<td>Etoxolamine (41)</td>
<td>Diazepam (88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate (44,141–143)</td>
<td>Digoxin (67,131–134)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orellanine (176)</td>
<td>Dimethoate (130,135–137)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talinolol (41)</td>
<td>Meprobamate (87,123)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (154)</td>
<td>Metamizole (22)</td>
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<td></td>
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<tr>
<td></td>
<td>Metasystox (130,137)</td>
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<tr>
<td></td>
<td>Methaqualone (20,41,123,130,163)</td>
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</tr>
<tr>
<td></td>
<td>Oxyphebutazone (22)</td>
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<td></td>
<td>Paraoxon (130,137)</td>
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<td></td>
<td>Parathion (20,130,137)</td>
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<tr>
<td></td>
<td>Phenylbutazone (22,178)</td>
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<td></td>
<td>Pine oil (152)</td>
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<td></td>
<td>Procainamide (170–172)</td>
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<td>Propyphenazone (22)</td>
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<td>Selenium (179)</td>
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<td></td>
<td>Tricyclic antidepressants (58,138)</td>
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<td>Valproic acid (155,156)</td>
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</tr>
<tr>
<td></td>
<td>Vasopressors (180)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The purpose of this table is to show relative differences in adsorptive capacity of different HP cartridges. This is a separate issue from whether the clearance achieved by HP is clinically significant in the context of an overdose. As such, this table should not be considered a guide for which poisons should receive HP (in many cases, there are insufficient human data confirming that HP is clinically useful).
Number of Columns

A single HP column is usually sufficient in the treatment of most poisonings, but it is possible to use two or more columns in series on some circuits to enhance poison removal. This leads to improved clearance in humans and animals poisoned with digitalis and tetramine poisoning, although the benefit is not additive (68,80,81). Furthermore, there is a risk of diminishing returns given the increasing cost and incidence of complications from HP.

The Influence of Order, When HP and HD Columns Are Used Concurrently

Several reports have shown that the simultaneous use of both HP and HD in series is superior to HD or HP alone (82,83). An in vitro study noted that paraquat and creatinine clearances were enhanced when using HD-HP (dialysis followed by coated charcoal perfusion) compared to HP-HD and HP alone. These results may apply to other middle and larger molecules, but more studies are required to confirm this, and to test whether other arrangements (e.g., HP alone or HP-HD) offer advantages for the clearance of poisons with other characteristics (84).

Duration of HP

Saturation of a HP column occurs after 2–6 hours of continuous use and results in a progressive decrease in clearance of the poison. Saturation results from the deposition of cellular debris and plasma proteins on the HP column; accumulation of adsorbed poison has a smaller contribution given the relatively massive surface area of most resin and charcoal cartridges (69). In some studies, saturation of charcoal cartridges occurred more quickly compared to resins (85–87), although this is not a consistent finding (88).

To minimize the effect of progressive column saturation, it is necessary to replace the cartridge approximately every 3–4 hours, if ongoing HP is necessary. However, in the majority of poisonings, a 4–6 hour treatment is usually sufficient to reverse toxic symptoms and reduce serum concentrations to a safe range. Longer treatment durations may be required in some cases, although at some point the effect of HP will become clinically insignificant.

Adverse Reactions to Hemoperfusion

To make an objective and balanced assessment of the value of HP, the incidence and severity of complications during HP should be known. HP requires the insertion of a temporary catheter for perfusion purposes, which is identical to those used for HD, hemofiltration and plasma exchange. Catheter insertion carries a risk of arterial puncture, pneumothorax, hemothorax, and bleeding, depending on the vascular site chosen (89,90). Ultrasonographic guidance has reduced the incidence of catheter-related mechanical complications (91). Because HP is rarely required for longer than 48 hours, the catheter can usually be removed within this time frame, so the incidence of catheter-related infections and septicaemia in this context is negligible (92).

Most of HP-related complications occur because of non-specific adsorption of biological components to the HP column. The more commonly reported adverse reactions are thrombocytopenia, leucopenia, hypocalcemia, hypophosphatemia, hypoglycemia, and a decrease in fibrinogen. On average, the platelet count will decrease 20–50% from its baseline value with any adsorption column (41,93–95). Fortunately, this decrease in platelet count is usually temporary and rarely contributes to bleeding complications, although these have been reported in large cohorts (96). The decrease in white cell count is variable: it has been reported as high as 50% in some studies, and altogether absent in others (41,95,97). Electrolyte and glucose concentrations vary unpredictably during HP (97), but clinically significant hypoglycemia and life-threatening arrhythmias are extremely rare. HP also lowers other biological components such as prealbumin, amino acids, hormones, \( \beta \)-lipoprotein, haptoglobin, fibronectin, immunoglobulins, coagulation factors, and complement (95,98–103). Early HP devices produced more significant side effects, including charcoal embolization, pyrogenic reactions and hemolysis but these have been overcome to a large extent with modern preparatory methods such as the coating of charcoal columns (96,104).

Current Role of Hemoperfusion and Future Research Priorities in the Treatment of Poisoned Patients

Both HD and HP have been used historically for the treatment of poisonings. As previously mentioned, the earlier enthusiasm for HP has tailed off and HD is currently the favored treatment of poisoned patients for various reasons, including:

(i) The cost of a HD filter is much lower than that of a HP cartridge (105),

(ii) Complications can occur with HP that do not occur with HD as detailed above. These are rarely life-threatening or can be readily corrected (e.g., hypoglycemia or hypocalcemia) (12),

(iii) Higher doses of anticoagulation are usually required during HP. Although heparin can theoretically be avoided with both techniques when treating patients at a higher risk of bleeding, this is more practical with HD when heparin can be replaced (e.g., by saline flushes) without significantly compromising clearance,

(iv) Saturation of the cartridge limits the effect of HP, which is not an issue with HD filters. As
such, HP cartridges need to be replaced every 3–4 hours to maintain the effect of the treatment.

(v) HD is also a renal replacement therapy, correcting electrolyte and acid-base abnormalities and permitting fluid removal in patients with impaired kidney function. In contrast, HP is inefficient for some of these functions. Early experiments with HP showed inadequate removal of urea due to saturation of the HP cartridge (106). Although certain ion-exchange resins can remove potassium and other ions (107), this process is indiscriminate and can cause other serious electrolyte disturbances. HD does not pose this risk because of the use of a dialysate, which can be tailored to various conditions and electrolyte requirements.

(vi) HD is more widely available than HP. Expertise for HD is less restricted geographically, in contrast to HP for which cartridges are often unavailable and to which staffs have infrequent exposure.

Despite this, HP appears to be a popular treatment in parts of the world, in particular East Asian countries for the treatment of pesticide poisonings. Authors of meta-analyses and uncontrolled observational studies have reported benefits with HP (108,109), however, there is a lack of consensus and agreement by nephrologists and clinical toxicologists regarding its place in treatment. Many studies were conducted in single centers and reporting of the methods and outcomes were incomplete. Further studies are required, including multicentre international randomized controlled trials with clear methodology. In their absence, or at least as an initial step, it is reasonable to conduct observational studies in which clinical and kinetic outcomes should be carefully determined.

The importance of comparing the effect of HP to HD for enhanced elimination cannot be overemphasized. Given the added costs, complications and logistical issues associated with treating a patient with HP, it is necessary to confirm that HP offers benefits that exceed those of HD. The advent of new high-flux, high-efficiency dialysis filters, larger catheters, higher dialysate and blood flows during HD and intermittent online hemodiafiltration have greatly improved small and middle molecular weight solute clearances. HD filters now permit clearance of much larger molecular weight poisons, including up to 10,000 Da, compared to the cut-off of 500 Da that was historically reported for older filters. Poisons that are highly protein-bound, such as phenytoin and carbamazepine, also appear to be removed by modern techniques if there is a constant substrate of unbound (free) poison in plasma (see previous discussion regarding protein binding) (110–112). Clearance by this method may not be as high as that from HP, but it may be sufficient for clinical use when offset against the disadvantages of HD discussed above. Thus, head-to-head studies are required to confirm that HP clearance exceeds that of HD to a clinically significant extent prior to embarking on more definitive studies with HP.

In the event that HP is administered for the treatment of a patient poisoned by a substance for which there are no data confirming that HP is useful, it is necessary to measure the clearance of the compound. This should be compared to the endogenous clearance which, if renally cleared, can be readily calculated.

**Quantifying the Effect of Hemoperfusion on Poison Removal**

The necessity of quantifying the effect of HP on poison removal has been highlighted above. The most common method used to measure the clearance of the poison is:

\[ CL = Q_B (1 - \text{Hematocrit}) \times \frac{[(C_A - C_V)/C_A]}{C} \]

where \(Q_B\) is the blood flow through the column, \(C_A\) is the precolumn plasma concentration, and \(C_V\) is the postcolumn plasma concentration. \([(C_A - C_V)/C_A]\) is known as the extraction ratio. Here, a high ratio suggests that a large proportion of the poison passing through the cartridge is eliminated (but, depending on the poison’s volume of distribution, this is not necessarily a large portion of the body burden of the poison). Alternatively, the apparent half-life of a poison during HP can also be compared to its half-life before or after HP. However, this approach can be complicated by the unknown effect of ongoing absorption, distribution, or rebound in plasma concentrations after completion of the treatment (18).

A potentially more accurate, but infrequently utilized, alternative method of quantifying the effect of HP is to extrude the poison from the column after it has been used, quantify its content, and compare this to the amount ingested so that the proportion of the dose removed can be calculated (113,114).

**Summary**

The use of HP adsorbents in extracorporeal treatments can enable the removal of a variety of poisons and toxins. The use of HP has been declining in recent years due to the development of high-flux HD technology, which demonstrates an enhanced capacity for clearing poisons at lower costs and complication rates. This manuscript reviewed factors influencing poison clearance during HP but it is apparent that the actual effect is not readily predicted and that confirmatory studies are required. HP remains an interesting and valid alternative, particularly for poisons with a low volume of distribution and higher degree of protein binding. However, there is a need to confirm that clearance by HP exceeds HD clearance to a clinically significant
extent. The type of adsorbent material used needs to be carefully considered from physicochemical and/or in vitro data but in vivo studies supporting this approach are limited. Until more high quality research is performed and reported, on the basis of the current data we believe that the role of HP in the treatment of the poisoned patient is limited.

References

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