CHAPTER 100

Plasmapheresis in Acute Intoxication and Poisoning

François Madore and Josée Bouchard

OBJECTIVES

This chapter will:

1. Review the possible mechanisms of action of plasmapheresis in poisoning and drug overdose.
2. Describe the pharmacokinetic factors that affect the elimination of poisons and drugs by plasmapheresis.
3. Explain the limitations of published studies on the efficacy of plasmapheresis in poisoning and drug overdose.
4. Review published data on the efficacy of plasmapheresis for specific poisons/drugs.

Plasmapheresis is widely accepted as a therapeutic modality for a number of immunologic, metabolic, and inherited diseases.[1] Plasmapheresis is also useful as an extracorporeal blood purification technique in the treatment of various intoxications and poisonings. The basic premise of plasmapheresis use in poisoning and drug overdose is that removal of the circulating toxin/drug will reduce toxic-induced damage and minimize related complications. Plasmapheresis can clear albumin-poison complexes, which is not feasible with other extracorporeal therapies other than liver support devices. Although the clearance attainable by plasma exchange is relatively low, it may be the only practical option for some poisons that are highly (>90%) bound to proteins.

MECHANISMS OF ACTION

The therapeutic benefit of plasmapheresis in acute poisoning and drug overdose is based on the rapid removal of drugs or toxins that cannot be eliminated adequately by usual therapeutic interventions. Plasmapheresis can remove rapidly toxins of all sizes, including protein- and lipid-bound toxins with a low volume of distribution.[2] As for any extracorporeal technique, plasmapheresis only removes substances located in the vascular compartment. As the volume of distribution increases, the usefulness of any extracorporeal treatments (ECTR) decreases substantially.[3] The tissue stores of a poison will remain unaffected except for reequilibration with decreasing plasma concentrations. Other possible benefits of plasmapheresis in the treatment of poisoning and drug overdose are the effects on toxins-induced complications such as hemolysis or thrombotic thrombocytopenic purpura.[2] For instance, in cases of drug-induced hemolysis, plasmapheresis has the potential for removing red blood cell destruction products and hemoglobin.[4,5] In addition, infusion of normal plasma may have beneficial effects, independent of removal of toxic circulating compounds. For example, plasmapheresis with autologous plasma as replacement fluid provides an opportunity to administer active cholinesterase in organophosphate poisonings.[6]

TECHNICAL OVERVIEW

Plasmapheresis involves withdrawal of venous blood, separation of plasma from blood cells, and reinfusion of cells with autologous plasma or another replacement solution. Plasma and blood cells are separated by centrifugation or membrane filtration. Usually, the equivalent of 1 to 1.5 plasma volumes (or 2.5 to 4.0 L) is removed during a session. To maintain plasma volume, the removed plasma is replenished with an equal amount of replacement fluids. The typical replacement fluids are fresh-frozen plasma, 5% albumin or other plasma derivatives (e.g., cryosupernatant), and crystalloids (e.g., 0.9% saline, Ringer's lactate). The choice of fluid affects oncotic pressure, coagulation, efficacy of the procedure, and potential side effects. Albumin usually is preferred to plasma because of the risk of hypersensitivity reactions and transmission of viral infections with the latter. For some indications for which infusion of normal plasma may be beneficial (e.g., organophosphate poisoning), fresh frozen plasma is the preferred replacement solution. With poisons tightly bound to albumin, removal by plasmapheresis without replacement of albumin theoretically could increase its free fraction and may cause a transient resurgence of clinical toxicity. Similarly, in drugs that are highly bound to alpha-1-acid glycoprotein, such as quinidine, the combination of 5% albumin and fresh frozen plasma could be considered, although alpha-1-acid glycoprotein has a low binding capacity[7] and there are no studies to confirm the clinical efficacy of this approach.

COMPARISONS WITH OTHER EXTRACORPOREAL DETOXIFICATION METHODS

There are some advantages of plasmapheresis over other extracorporeal detoxification methods, such as hemodialysis and hemoperfusion. The removal of toxins by plasmapheresis is not dependent on the size of the molecule as is the case for hemodialysis.[2] Plasmapheresis can remove a number of substances that are not removed effectively by either hemodialysis or hemoperfusion (e.g., protein-bound compounds),[2] because it can clear albumin-poison complexes. Plasmapheresis also can remove active metabolites as well as unchanged drugs.[4] Liver support devices have similar clearance properties as plasmapheresis[8]; however, it is not as frequently available and more expensive than plasmapheresis. Intoxications with substances with lower percentages of protein binding are best treated with hemodialysis (e.g.,

BOX 100.1

Poison/Drug Characteristics Favoring the Use of Plasmapheresis

Pharmacologic
Endogenous clearance < 4 L/kg/min (for any extracorporeal therapy)
Low volume of distribution < 2 L/kg
Molecular weight ≥ 50,000 up to 1,300,000 Da[a]
High protein binding, e.g., ≥95%[a]

Clinical
Expected toxicity of unchanged poison/drug
Expected toxicity of metabolites
Severity of symptoms and complications
Availability of specific antidote or standard therapy (e.g., forced diuresis)
Time interval from exposure
Related complications (e.g., hemolysis)
Potential to shorten length of stay

[a]In comparison, hemodialysis and hemoperfusion are more efficient for smaller substances with lower percentages of protein binding.
Modified from Ghannoum M, Roberts DM, Hoffman RS, Ouellet G, Roy L, Decker BS, et al. A stepwise approach for the management of poisoning with extracorporeal treatments. *Semin Dialysis.* 2014;27(4):362–370.

methanol, ethylene glycol) because the clearance attainable by hemodialysis is clearly superior.[8] In addition, certain drugs that induce metabolic complications in poisoned patients are treated more appropriately with hemodialysis, which also corrects acid-base and electrolyte abnormalities associated with these poisons (e.g., aspirin).[4] Therefore the choice of the extracorporeal detoxification modality clearly depends on the characteristics of the drugs or toxins implicated. Box 100.1 shows the characteristics of poisons/drugs that must be considered in the choice of the detoxification method, with specific indications for plasmapheresis.

PHARMACOKINETIC CONSIDERATIONS

As for any extracorporeal therapy used in poisoning, plasmapheresis should be considered only for drugs or toxins that have a prolonged half-life. For substances that are metabolized rapidly (i.e., have a high endogenous clearance), plasmapheresis is unlikely to accelerate the removal rate significantly (see Box 100.1).[9,10] Furthermore, the additional clearance provided by plasmapheresis may be insufficient to induce clinical benefit.

The elimination of drugs or toxins by plasmapheresis is governed by several factors. The extracorporeal elimination efficiency of plasmapheresis for a given substance depends on the volume of distribution, protein binding, intercompartment equilibration, and exchange plasma volume.[8,11] In addition, the time interval between ingestion and plasmapheresis initiation seems to be a crucial factor affecting its elimination.[12] The ideal drug for removal by plasmapheresis is one that is highly protein bound, without restriction to molecular weight (MW), and a small volume of distribution. A large proportion of poisons have a MW in the 100 to 1000 Da range and are removable by other extracorporeal therapies.[8] Some advocate that plasmapheresis is useful only when the plasma protein binding is greater than 80% to 95%[8] and the volume of distribution is lower than 0.2 L/kg body weight.[11] Examples include rituximab (MW = 145,000)[13] and immunoglobulins such as IgM (MW = 925,000).[14] Other examples include cisplatin,[15,16] vincristine,[17] and L-thyroxine.[18] Liver support devices are available in some centers around the world and share similar clearance capacities (e.g., high level of protein binding) compared with plasmapheresis.[8] The molecular adsorbent recirculating system (MARS) and single-pass albumin dialysis (SPAD) can clear molecules up to 60,000 Da,[19,20] whereas the Prometheus system has a cutoff of approximately 200,000 Da.[21–23] However, evidence supporting the efficacy of albumin dialysis in removing highly protein-bound poisons is even more limited.[24,25]

LIMITATIONS OF PUBLISHED REPORTS

Several limitations complicate the interpretation of published reports that evaluated the efficacy of plasmapheresis in acute intoxication and poisoning. First, no randomized controlled trial has been carried out to determine the range of indications, potential benefits, and cost effectiveness of plasmapheresis in acute intoxication and poisoning. Most reports evaluating plasmapheresis efficacy are case reports or case series. Second, in most studies, patients were treated concurrently with hemodialysis and/or specific antidotes, rendering it difficult to evaluate the effect of plasmapheresis. Third, the majority of published studies failed to report important pharmacokinetic data to evaluate the efficacy of plasmapheresis to eliminate the drugs or toxins. For instance, most reports failed to report the total amount of the drug or toxin in the discarded plasma and the procedure's contribution to total drug clearance. The amount of drug removed in the discarded plasma is the best parameter evaluating drug removal, because plasma concentrations can be misleading.[12] Therefore treatment recommendations on the use of plasmapheresis in acute poisoning and drug overdose are limited.

EFFICACY OF PLASMAPHERESIS IN SPECIFIC INTOXICATIONS

The treatment of poisoning with plasmapheresis has been reported for a number of agents (Table 100.1).

Amanita phalloides

Amanita phalloides (the death cap mushroom) contains the most deadly toxin (the amanita toxin) of all poisonous mushrooms. Reported mortality after ingestion of *Amanita phalloides* ranges from 25% to 50%.[26] The lethal dose of amanita toxin is 0.1 mg/kg body weight and therefore severe poisoning can occur with as little as 5 to 7 mg of amanita toxin, an amount that can be present in a single mushroom.[26] The amanita toxin is eliminated by the kidneys and usually is undetectable in the plasma 48 hours after ingestion. Therefore rapid therapeutic intervention is required to avoid serious complications. Some case series reported improved survival when compared with historical survival rate.[27] In contrast, other studies have raised doubts on the efficacy of plasmapheresis in the treatment of *Amanita phalloides* poisoning. Piqueras et al. found that forced diuresis eliminated between 20,000 and 350,000 ng of toxin, whereas plasmapheresis never eliminated more than 10,000 ng.[28] In addition, some studies using supportive

TABLE 100.1

Plasmapheresis and Poisoning

SPECIFIC POISONS	POSSIBLE BENEFIT[a]	NO OR LITTLE BENEFIT	REFERENCES
Amanita	X		31–33
2,4-dichlorophenoxyacetic acid		X	39
Ethylene dibromide	X		56
Heavy Metals			
Aluminum		X	40
Arsenic		X	41
Chromium		X	41,42
Gold		X	43
Mercury		X	44,45
Silver		X	46,47
Thallium		X	48
Vanadium		X	49
Organophosphates	X		6,53,54
Paraquat		X	55
Sodium chlorate		X	37,38

[a]Possible benefit in selected cases.

measures without plasmapheresis found survival rates identical to those reported by using plasmapheresis.[29,30] In conclusion, plasmapheresis has not been shown to improve survival nor to provide pharmacokinetic evidence of benefit. Therefore there is no clear evidence to support its use[31–33] despite a category II indication for plasmapheresis by the American Society for Apheresis (ASFA) guidelines.[34]

2,4-Dichlorophenoxyacetic Acid and Sodium Chlorate

The use of plasmapheresis has been reported in poisoning with 2,4-dichlorophenoxyacetic acid[35] and sodium chlorate,[36] toxic components included in herbicides. However, these substances are dialyzable because neither is highly protein bound. The beneficial effect of plasmapheresis is thought to be due to removal of red blood cell destruction products and hemoglobin, because these agents cause severe hemolysis.[4] Therefore plasmapheresis is not intended to clear the toxic compound, but it may be useful in removing free hemoglobin and blood cell debris from the circulation.[4] Most recent reports or recommendations mention the use of hemodialysis for 2,4-dichlorophenoxyacetic acid or sodium chlorate poisoning but do not include any recommendation on plasmapheresis.[37–39]

Heavy Metals

Plasmapheresis has been attempted in cases of heavy metal intoxications. Removal of aluminum by plasmapheresis has been reported to be disappointing with approximately 1% of total body aluminum removed.[40] Removal of other heavy metals by plasmapheresis has been attempted for arsenic,[41] chromium,[41,42] gold,[43] mercury,[44,45] silver,[46,47] thallium,[48] and vanadium.[49] Although some heavy metal removal is possible with plasmapheresis, the evidence is anecdotal for the most part.

Organophosphates

Organophosphates are among the most commonly used insecticides in the world. Organophosphates cause a specific and irreversible inhibition of acetylcholinesterase. Treatment of organophosphate poisoning consists of atropine and pralidoxime.[50] Plasmapheresis has been attempted in cases of organophosphate poisonings such as parathion[51] and dimethoate.[52] Plasmapheresis with fresh frozen plasma as replacement fluid has been reported successful in a case unresponsive to atropine and pralidoxime, whose cholinesterase levels were declining despite antidotal therapy.[6] Fresh frozen plasma contains active cholinesterase and may be used to augment plasma cholinesterase levels.[6] Therefore plasmapheresis with autologous plasma as replacement fluid may be beneficial by rapidly increasing cholinesterase levels. Plasmapheresis may allow the rapid administration of fresh frozen plasma without the risk of volume overload. In a recent Chinese meta-analysis including 433 patients, mortality rate was lower with plasmapheresis than without (RR = 0.30, 95% CI [0.19–0.49], $p < .01$).[53] In addition to plasma administration, atropine and pralidoxime may be beneficial in organophosphate poisoning.[54]

Paraquat

Paraquat is a toxic herbicide that impairs renal function. This compound is not significantly protein bound and has a short half-life. Its persistence in the circulation may be prolonged because elimination depends on renal function.[4] The total removal by plasmapheresis has been reported as nonsignificant in the context of endogenous metabolic clearance.[55]

Ethylene Dibromide

Ethylene dibromide (EDB) is a highly protein bound pesticide widely used in India. Plasmapheresis has been used to treat 47 patients as early as possible after exposure to remove the pesticide before it metabolizes into toxic products causing liver and kidney damage.[56] In this study, those who underwent plasmapheresis within 24 hours of ingestion had a significantly higher survival rate compared with those who were treated after 24 hours of ingestion.[56] However, there were no clearance nor toxin reduction ratios reported in this study.

TABLE 100.2

Plasmapheresis and Drug Overdose

SPECIFIC DRUGS[a]	POSSIBLE BENEFIT[b]	NO OR LITTLE BENEFIT	REFERENCES
Acetaminophen (5%)		X	57–59
Anticonvulsants			
Carbamazepine (6%)		X	69,108
Phenobarbital (38%)		X	2,65,66
Phenytoin (11%)		X	60–62
Valproic acid (7%)		X	67,68
Benzodiazepines		X	5
Biologic Agents			
Natalizumab (to facilitate immune reconstitution)	X		70,71,74
Rituximab (severe infusion reaction)	X		
Calcium Channel Blockers			
Diltiazem		X	109,110
Verapamil		X	96–98
Chemotherapeutic Agents			
Cisplatin	X		15,16,76–78
Vincristine	X		17,75
Colchicine		X	100
Cyclosporine (1%)		X	104
Dabigatran		X	105
Digoxin (0.5%)		X	79
L-thyroxine (33%)	X		18,83–85,88
Memantine		X	99
Prednisone (1%)		X	103
Propranolol (30%)		X	94,95
Quinine (1%)		X	101
Salicylates (10%)		X	89
Theophylline		X	92
Tobramycin (8.8%)		X	102
Tricyclic antidepressants		X	93

[a]Estimated percentage of total body toxin removed by one plasmapheresis in parentheses (when available).
[b]Possible benefit in selected cases.

EFFICACY OF PLASMAPHERESIS IN SPECIFIC DRUG OVERDOSE

The treatment of drug overdose with plasmapheresis has been reported for a number of substances (Table 100.2).

Acetaminophen

Plasmapheresis has been attempted in cases of severe acetaminophen intoxication with acute liver failure.[57,58] Although clinical benefits have been reported in some patients, the total amount of acetaminophen removed during a typical plasmapheresis session is less than 5%,[59] and the efficacy of N-acetylcysteine (NAC) precludes the use of plasmapheresis in acetaminophen intoxication.

Anticonvulsants

Phenytoin often is considered an ideal drug for removal by plasmapheresis because of its protein binding (approximately 90%) and its small volume of distribution. During a typical plasmapheresis session, it is estimated that the total phenytoin clearance increases from 20.8 mL/min to 42.5 mL/min.[60] However, plasma concentrations of the drug are not significantly altered by plasmapheresis after redistribution because only a small percentage (less than 11%) of total body stores are removed during pheresis.[60–62] A recent review and systematic review showed that in severe poisonings, hemodialysis is useful.[63,64] Phenobarbital intoxications respond favorably to urinary alkalinization, forced diuresis, and dialysis.[2,65,66] Plasmapheresis makes only a minor contribution to valproic acid elimination.[67] The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup recommended intermittent hemodialysis as the preferred extracorporeal therapy in valproic acid poisoning after a systematic review of the literature.[68] Similar findings were reported by the workgroup for carbamazepine as well.[69]

Benzodiazepines

Plasmapheresis may appear useful in benzodiazepines intoxication because of high protein binding (up to 95%). However, plasmapheresis has no significant role to play because the extravascular compartment cannot be cleared effectively by extracorporeal detoxification methods.[5] In addition, an effective antidote is available, flumazenil.

Biologic Drugs

Over the last decade, biologic agents have been used increasingly to treat autoimmune conditions and cancer. Plasmapheresis has been used to treat side effects associated with drug exposure. Biologic agents include monoclonal antibodies with prolonged half-life. Natalizumab is a monoclonal antibody that has been associated with the occurrence of progressive multifocal leukoencephalopathy caused by the polyoma JC virus. Case reports have shown that plasmapheresis can reduce the levels of natalizumab[70] and facilitate immune reconstitution to eradicate the JC virus.[71–73] Recently,

plasmapheresis was used successfully to treat a near-fatal infusion reaction to rituximab.[74]

Chemotherapeutic Agents

Plasmapheresis has been attempted in cases of vincristine[17,75] and cisplatin overdose.[15,16,76–78] Treatment with plasmapheresis was associated with a significant reduction in the plasma concentrations of cisplatin, with concomitant improvement in clinical symptoms. However, rebound occurs, which has led some authors to recommend at least 10 plasmapheresis treatments over 10 to 14 days after cisplatin overdose to manage its toxicity. Data are more limited with vincristine. The use of plasmapheresis may be justified because of high protein binding and the absence of recognized therapy.

Digitalis

Plasmapheresis is not effective for digitalis because of extensive tissue binding and large volume of distribution.[79] In patients treated with digoxin-immune antigen-binding fragments (Fab), plasmapheresis has been reported to increase the clearance of the digoxin-antidigoxin complexes.[80] Because these complexes are excreted renally, plasmapheresis is useful for removing digoxin-Fab complexes, thus preventing rebound digoxin toxicity.[81,82] Some authors therefore have suggested to initiate plasmapheresis within 3 hours after Fab administration in patients with digitalis intoxication and renal failure.[82]

L-Thyroxine

Most but not all reports of plasmapheresis for the removal of thyroid hormones have been encouraging.[18,83–85] Two reports mentioned that plasmapheresis removed approximately 10% of the ingested dose.[86,87] A single exchange procedure may not decrease serum thyroxine levels significantly because of the rapid rebound of thyroid hormone from the tissues into the plasma.[4] Plasmapheresis and charcoal hemoperfusion may be effective in decreasing the duration of thyroxine intoxication. Some authors have reported that plasmapheresis is more effective than hemoperfusion in the extraction in the drug.[83,88]

Salicylates

The effects of plasmapheresis on the removal of salicylate have been studied in a group of volunteers who were administered 3900 mg/day.[89] The total amount of salicylate removed by plasmapheresis was very limited. In addition, because aspirin intoxications respond favorably to urinary alkalinization, forced diuresis, and dialysis, there is no indication for plasmapheresis in salicylate intoxication.

Theophylline

The usual recommendations for the treatment of theophylline intoxication are that hemodialysis and hemoperfusion are the preferred detoxification methods given their high efficacy.[52] The use of plasmapheresis has been reported in several instances.[52,90,91] After a systematic review of the literature, the EXTRIP workgroup recommended intermittent hemodialysis as the modality of choice in severe poisonings, and continuous renal replacement therapy or hemoperfusion if intermittent hemodialysis is unavailable.[92]

Tricyclic Antidepressants

Successful use of plasmapheresis has been reported in cases with severe cardiac and central nervous system toxicity.[52] In one case, a 64% reduction in amitriptyline plasma levels has been reported with plasmapheresis associated with significant improvement in clinical condition.[52] However, although tricyclic antidepressants are highly bound to plasma proteins, plasmapheresis is relatively ineffective to remove significant amounts of tricyclics total body stores because of their large volume of distribution. Indeed, the EXTRIP workgroup considered that poisoned patients with tricyclic agents are not likely to benefit from any extracorporeal therapy and recommends not to use these in tricyclic poisoning.[93]

Other Agents

The effects of plasmapheresis on propranolol elimination were reported in a nonoverdose situation.[94] The half-life of propranolol was reduced to one third of normal during plasmapheresis.[94] There are very limited data on the role of plasmapheresis in propranolol overdose[95] and its large volume of distribution (4 L/kg) do not support its use in poisonings. Plasmapheresis also has been reported in cases of verapamil and diltiazem intoxications with possible clinical benefits.[96–98] However, their large volume of distribution (>3–4 L/kg) clearly limits the efficacy of plasmapheresis in this setting.[99,100] More robust data are needed with these agents. The same comment applies to memantine and colchicine, which have very large volume of distribution (9–11 L/kg and 5–8 L/kg, respectively).[99,100] Plasmapheresis has been compared to forced diuresis in cases of quinine intoxication.[101] Forced diuresis removed 1625 mg of quinine over 75 hours, and plasmapheresis, 8.5 mg over 3 hours,[101] reinforcing the absence of benefit of extracorporeal therapies with drugs with a large volume of distribution. Similarly low percentages of total body drug removal by plasmapheresis have been reported with tobramycin (8%),[102] prednisone (1%),[103] and cyclosporine (1%).[104] Because of these minimal reductions, the use of plasmapheresis is not warranted for these agents given the cost and risks associated with the procedure. Finally, plasmapheresis has been reported for dabigatran removal; however, dialysis is a better option given its properties.[105]

Complications

The prevailing belief that "plasmapheresis is a benign procedure" undoubtedly contributed to its use in poisoning and drug overdose despite the lack of evidence in favor of a clear benefit for many toxins/drugs. Although plasmapheresis is relatively safe when performed by skilled clinicians, complications related to either vascular access or the composition of replacement fluids are frequent. The reported overall incidence of adverse reactions ranges from 1.6% to 25%,[106] with severe reactions occurring in 0.025% to 0.3%.[107] Hematomas, pneumothorax, and catheter infections are the most frequent complications of vascular access. Complications related to the replacement fluids include anaphylactoid reactions to fresh frozen plasma, coagulopathies induced by

inadequate replacement of clotting factors, or transmission of viral infections. Other complications include hypocalcemia resulting from citrate infusion and hypotension triggered by delayed or inadequate volume replacement, hypo-oncotic fluid replacement, or anaphylaxis. Plasmapheresis also may predispose patients to an increased incidence of infection. However, this effect is observed primarily with repeated plasmapheresis treatments. Other complications are related to the removal of drugs prescribed therapeutically during plasmapheresis and the requirement of supplementary doses of these drugs after plasmapheresis. Finally, the incidence of death is reported to be 0.05%, but many of these deaths are due to preexisting conditions and not the plasmapheresis procedure.[107]

SUMMARY

Although plasmapheresis has been applied for the treatment of various intoxications and drug overdoses, a clear evidence of benefit is lacking. Most reports evaluating treatment with plasmapheresis are case reports or case series in which most of patients were concomitantly treated with dialysis and/or specific antidotes. No randomized controlled trial has compared plasmapheresis with other treatment modalities. Thus, because of the uncontrolled nature of studies reported, it is impossible to determine whether the improvement in patient survival reported in many studies is attributable to plasmapheresis or to other factors, such as patient selection, earlier diagnosis, variability in presentation, progress in supportive measures, or other adjunctive in the treatment of poisonings and overdose. Close communication with a poison center or a clinical toxicologist always is recommended to help assess the benefits and risks of the technique for a given patient. The use of plasmapheresis may be limited to research protocols or to exceptional cases presenting with life-threatening complications unresponsive to conventional therapy. If plasmapheresis is attempted, the total amount of drug/toxin removed should be documented to assess the contribution of plasmapheresis to total clearance and improve the quality of the supporting literature.

Key Points

1. Treatment recommendations for the use of plasmapheresis in acute poisoning and drug overdose are limited because of the lack of randomized controlled trials.
2. The ideal drug for removal by plasmapheresis is highly protein bound, has a small volume of distribution, and has a prolonged half-life.
3. The use of plasmapheresis should be limited to research protocols or to exceptional cases presenting with life-threatening complications unresponsive to conventional therapy, considering the toxin characteristics.
4. Close communication with a poison center or a clinical toxicologist always is recommended to help assess the benefits and risks for a given patient.
5. Dosing adjustment of all concomitant medications may be needed, depending on their removal.

Key References

4. Jones JS, Dougherty J. Current status of plasmapheresis in toxicology. *Ann Emerg Med*. 1986;15(4):474-482.
34. Szczepiorkowski ZM, Winters JL, Bandarenko N, et al. Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. *J Clin Apher*. 2010;25(3):83-177.
52. Nenov VD, Marinov P, Sabeva J, et al. Current applications of plasmapheresis in clinical toxicology. *Nephrol Dial Transplant*. 2003;18(suppl 5):v56-v58.

A complete reference list can be found online at ExpertConsult.com.

References

1. Winters JL, Pineda AA, McLeod BC, et al. Therapeutic apheresis in renal and metabolic diseases. *J Clin Apher*. 2000;15(1-2):53-73.
2. Kale-Pradhan PB, Woo MH. A review of the effects of plasmapheresis on drug clearance. *Pharmacotherapy*. 1997;17(4): 684-695.
3. Pond SM. Extracorporeal techniques in the treatment of poisoned patients. *Med J Aust*. 1991;154(9):617-622.
4. Jones JS, Dougherty J. Current status of plasmapheresis in toxicology. *Ann Emerg Med*. 1986;15(4):474-482.
5. Seyffart G. Plasmapheresis in treatment of acute intoxications. *Trans Am Soc Artif Organs*. 1982;28:673-676.
6. Guven M, Sungur M, Eser B. The effect of plasmapheresis on plasma cholinesterase levels in a patient with organophosphate poisoning. *Hum Exp Toxicol*. 2004;23(7):365-368.
7. Roberts DM, Buckley NA. Pharmacokinetic considerations in clinical toxicology: clinical applications. *Clin Pharmacokinet*. 2007;46(11):897-939.
8. Ghannoum M, Roberts DM, Hoffman RS, et al. A stepwise approach for the management of poisoning with extracorporeal treatments. *Semin Dial*. 2014;27(4):362-370.
9. de Pont AC. Extracorporeal treatment of intoxications. *Curr Opin Crit Care*. 2007;13(6):668-673.
10. Fertel BS, Nelson LS, Goldfarb DS. Extracorporeal removal techniques for the poisoned patient: a review for the intensivist. *J Intensive Care Med*. 2010;25(3):139-148.
11. Samtleben W, Mistry-Burchardi N, Hartmann B, et al. Therapeutic plasma exchange in the intensive care setting. *Ther Apher*. 2001;5(5):351-357.
12. Ibrahim RB, Balogun RA. Medications in patients treated with therapeutic plasma exchange: prescription dosage, timing, and drug overdose. *Semin Dial*. 2012;25(2):176-189.
13. Puisset F, White-Koning M, Kamar N, et al. Population pharmacokinetics of rituximab with or without plasmapheresis in kidney patients with antibody-mediated disease. *Br J Clin Pharmacol*. 2013;76(5):734-740.
14. Solomon A, Fahey JL. Plasmapheresis therapy in macroglobulinemia. *Ann Intern Med*. 1963;58:789-800.
15. Chu G, Mantin R, Shen YM, et al. Massive cisplatin overdose by accidental substitution for carboplatin. Toxicity and management. *Cancer*. 1993;72(12):3707-3714.
16. Choi JH, Oh JC, Kim KH, et al. Successful treatment of cisplatin overdose with plasma exchange. *Yonsei Med J*. 2002;43(1): 128-132.
17. Pierga JY, Beuzeboc P, Dorval T, et al. Favourable outcome after plasmapheresis for vincristine overdose. *Lancet*. 1992; 340(8812):185.
18. Jha S, Waghdhare S, Reddi R, et al. Thyroid storm due to inappropriate administration of a compounded thyroid hormone preparation successfully treated with plasmapheresis. *Thyroid*. 2012;22(12):1283-1286.
19. Rubik J, Pietraszek-Jezierska E, Kaminski A, et al. Successful treatment of a child with fulminant liver failure and coma caused by Amanita phalloides intoxication with albumin dialysis without liver transplantation. *Pediatr Transplant*. 2004;8(3):295-300.
20. Stadlbauer V, Krisper P, Aigner R, et al. Effect of extracorporeal liver support by MARS and Prometheus on serum cytokines in acute-on-chronic liver failure. *Crit Care*. 2006;10(6): R169.
21. Vienken J, Christmann H. How can liver toxins be removed? Filtration and adsorption with the Prometheus system. *Ther Apher Dial*. 2006;10(2):125-131.
22. Krisper P, Stauber RE. Technology insight: artificial extracorporeal liver support–how does Prometheus compare with MARS? *Nat Clin Pract Nephrol*. 2007;3(5):267-276.
23. Mitzner S, Klammt S, Stange J, et al. Albumin regeneration in liver support-comparison of different methods. *Ther Apher Dial*. 2006;10(2):108-117.
24. Churchwell MD, Pasko DA, Smoyer WE, et al. Enhanced clearance of highly protein-bound drugs by albumin-supplemented dialysate during modeled continuous hemodialysis. *Nephrol Dial Transplant*. 2009;24(1):231-238.
25. Sen S, Ratnaraj N, Davies NA, et al. Treatment of phenytoin toxicity by the molecular adsorbents recirculating system (MARS). *Epilepsia*. 2003;44(2):265-267.
26. Jander S, Bischoff J, Woodcock BG. Plasmapheresis in the treatment of Amanita phalloides poisoning: II. A review and recommendations. *Ther Apher*. 2000;4(4):308-312.
27. Jander S, Bischoff J. Treatment of Amanita phalloides poisoning: I. Retrospective evaluation of plasmapheresis in 21 patients. *Ther Apher*. 2000;4(4):303-307.
28. Piqueras J, Duran-Suarez JR, Massuet L, et al. Mushroom poisoning: therapeutic apheresis or forced diuresis. *Transfusion*. 1987;27(1):116-117.
29. Finestone AJ, Berman R, Widmer B, et al. Thioctic acid treatment of acute mushroom poisoning. *Pa Med*. 1972;75(7):49-51.
30. Zulik R, Bako F, Budavari J. Death-cap poisoning. *Lancet*. 1972;2(7770):228.
31. Karvellas CJ, Tillman H, Leung AA, et al. Acute liver injury and acute liver failure from mushroom poisoning in North America. *Liver Int*. 2016.
32. Garcia J, Costa VM, Carvalho A, et al. Amanita phalloides poisoning: Mechanisms of toxicity and treatment. *Food Chem Toxicol*. 2015;86:41-55.
33. Giordano C, Rivas J, Zervos X. An Update on Treatment of Drug-Induced Liver Injury. *J Clin Transl Hepatol*. 2014;2(2):74-79.
34. Szczepiorkowski ZM, Winters JL, Bandarenko N, et al. Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. *J Clin Apher*. 2010;25(3):83-177.
35. Bradberry SM, Proudfoot AT, Vale JA. Poisoning due to chlorophenoxy herbicides. *Toxicol Rev*. 2004;23(2):65-73.
36. Davison A, Mascie-Taylor BH, Robinson A, et al. The use of plasma exchange, transfusion and hemodialysis in the management of sodium chlorate intoxication. In: Sieberth HG, ed. *Proceedings of the International Symposium on Plasma Exchange*. Stuttgart: Schattauer.; 1980:373-374.
37. Ranghino A, Costantini L, Deprado A, et al. A case of acute sodium chlorate self-poisoning successfully treated without conventional therapy. *Nephrol Dial Transplant*. 2006;21(10): 2971-2974.
38. Helliwell M, Nunn J. Mortality in sodium chlorate poisoning. *Br Med J*. 1979;1(6171):1119.
39. Bradberry SM, Watt BE, Proudfoot AT, et al. Mechanisms of toxicity, clinical features, and management of acute chlorophenoxy herbicide poisoning: a review. *J Toxicol Clin Toxicol*. 2000;38(2):111-122.
40. Elliott HL, Macdougall AI, Haase G, et al. Plasmapheresis in the treatment of dialysis encephalopathy. *Lancet*. 1978;2(8096):940-941.
41. Breuer C, Oh J, Nolkemper D, et al. Successful detoxification and liver transplantation in a severe poisoning with a chemical wood preservative containing chromium, copper, and arsenic. *Transplantation*. 2015;99(4):e29-e30.
42. Meert KL, Ellis J, Aronow R, et al. Acute ammonium dichromate poisoning. *Ann Emerg Med*. 1994;24(4):748-750.
43. Hansen RM, Csuka ME, McCarty DJ, et al. Gold induced aplastic anemia. Complete response to corticosteroids, plasmapheresis, and N-acetylcysteine infusion. *J Rheumatol*. 1985;12(4): 794-797.
44. Sauder P, Livardjani F, Jaeger A, et al. Acute mercury chloride intoxication. Effects of hemodialysis and plasma exchange on mercury kinetic. *J Toxicol Clin Toxicol*. 1988;26(3-4): 189-197.
45. Suzuki T, Hongo T, Matsuo N, et al. An acute mercuric mercury poisoning: chemical speciation of hair mercury shows a peak of inorganic mercury value. *Hum Exp Toxicol*. 1992;11(1):53-57.
46. Iwasaki S, Yoshimura A, Ideura T, et al. Elimination study of silver in a hemodialyzed burn patient treated with silver sulfadiazine cream. *Am J Kidney Dis*. 1997;30(2):287-290.
47. Mirsattari SM, Hammond RR, Sharpe MD, et al. Myoclonic status epilepticus following repeated oral ingestion of colloidal silver. *Neurology*. 2004;62(8):1408-1410.
48. Tian YR, Sun LL, Wang W, et al. A case of acute thallotoxicosis successfully treated with double-filtration plasmapheresis. *Clin Neuropharmacol*. 2005;28(6):292-294.

49. Schlake HP, Bertram HP, Husstedt IW, et al. Acute systemic vanadate poisoning presenting as cerebrovascular ischemia with prolonged reversible neurological deficits (PRIND). *Clin Neurol Neurosurg*. 1994;96(1):92-95.
50. Sivagnanam S. Potential therapeutic agents in the management of organophosphorus poisoning. *Crit Care*. 2002;6(3):260-261.
51. Bambauer R, Jutzler G, Stolz D, et al. Die Tooxikation mittels eines technisch vereinfacten plasma filtrations systems. *Intensivmedizin*. 1982;19:79-82.
52. Nenov VD, Marinov P, Sabeva J, et al. Current applications of plasmapheresis in clinical toxicology. *Nephrol Dial Transplant*. 2003;18(suppl 5):v56-v58.
53. Qiu HM, Zheng SC, Wan WG, et al. [Meta-analysis of the effectiveness of plasma exchange in treatment of severe and acute organophosphate poisoning]. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. 2011;29(10):779-781.
54. Peter JV, Moran JL, Pichamuthu K, et al. Adjuncts and alternatives to oxime therapy in organophosphate poisoning–is there evidence of benefit in human poisoning? A review. *Anaesth Intensive Care*. 2008;36(3):339-350.
55. Miller J, Sanders E, Webb D. Plasmapheresis for paraquat poisoning. *Lancet*. 1978;1(8069):875-876.
56. Pahwa N, Bharani R, Jain M, et al. Therapeutic plasma exchange: an effective treatment in ethylene dibromide poisoning cases. *J Clin Apher*. 2013;28(5):374-377.
57. Kondrup J, Almdal T, Vilstrup H, et al. High volume plasma exchange in fulminant hepatic failure. *Int J Artif Organs*. 1992;15(11):669-676.
58. Inoue S, Yamamoto I, Akieda K, et al. [Alcohol abuse case of severe liver dysfunction induced by acetaminophen poisoning which was diagnosed as non-hepatic toxicity on admission]. *Chudoku Kenkyu*. 2006;19(3):265-271.
59. Fauvelle F, Leon A, Niakate MT, et al. Pharmacokinetics of paracetamol, diclofenac and vidarabine during plasma exchange. *Int J Artif Organs*. 1988;11(3):195-200.
60. Liu E, Rubenstein M. Phenytoin removal by plasmapheresis in thrombotic thrombocytopenic purpura. *Clin Pharmacol Ther*. 1982;31(6):762-765.
61. Nasca TJ, Huff N, Livengood BH. Phenytoin pharmacokinetics in therapeutic plasmapheresis. *J Clin Pharmacol*. 1985;25(4):302-304.
62. Larsen LS, Sterrett JR, Whitehead B, et al. Adjunctive therapy of phenytoin overdose–a case report using plasmaphoresis. *J Toxicol Clin Toxicol*. 1986;24(1):37-49.
63. Ghannoum M, Troyanov S, Ayoub P, et al. Successful hemodialysis in a phenytoin overdose: case report and review of the literature. *Clin Nephrol*. 2010;74(1):59-64.
64. Anseeuw K, Mowry JB, Burdmann EA, et al. Extracorporeal Treatment in Phenytoin Poisoning: Systematic Review and Recommendations from the EXTRIP (Extracorporeal Treatments in Poisoning) Workgroup. *Am J Kidney Dis*. 2016;67(2):187-197.
65. Jacobs F, Brivet FG. Conventional haemodialysis significantly lowers toxic levels of phenobarbital. *Nephrol Dial Transplant*. 2004;19(6):1663-1664.
66. Palmer BF. Effectiveness of hemodialysis in the extracorporeal therapy of phenobarbital overdose. *Am J Kidney Dis*. 2000; 36(3):640-643.
67. Lai CW, Leppik IE, Jenkins DC, et al. Epilepsy, myasthenia gravis, and effect of plasmapheresis on antiepileptic drug concentrations. *Arch Neurol*. 1990;47(1):66-68.
68. Ghannoum M, Laliberte M, Nolin TD, et al. Extracorporeal treatment for valproic acid poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)*. 2015;53(5):454-465.
69. Ghannoum M, Yates C, Galvao TF, et al. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)*. 2014;52(10):993-1004.
70. Khatri BO, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. *Neurology*. 2009;72(5):402-409.
71. Clifford DB, De Luca A, Simpson DM, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol*. 2010;9(4):438-446.
72. Linda H, von Heijne A, Major EO, et al. Progressive multifocal leukoencephalopathy after natalizumab monotherapy. *N Engl J Med*. 2009;361(11):1081-1087.
73. Wenning W, Haghikia A, Laubenberger J, et al. Treatment of progressive multifocal leukoencephalopathy associated with natalizumab. *N Engl J Med*. 2009;361(11):1075-1080.
74. Hastings D, Patel B, Torloni AS, et al. Plasmapheresis therapy for rare but potentially fatal reaction to rituximab. *J Clin Apher*. 2009;24(1):28-31.
75. Kosmidis HV, Bouhoutsou DO, Varvoutsi MC, et al. Vincristine overdose: experience with 3 patients. *Pediatr Hematol Oncol*. 1991;8(2):171-178.
76. Jung HK, Lee J, Lee SN. A case of massive cisplatin overdose managed by plasmapheresis. *Korean J Intern Med*. 1995; 10(2):150-154.
77. Yamada Y, Ikuta Y, Nosaka K, et al. Successful treatment of Cisplatin overdose with plasma exchange. *Case Rep Med*. 2010;2010:802312.
78. Hofmann G, Bauernhofer T, Krippl P, et al. Plasmapheresis reverses all side-effects of a cisplatin overdose–a case report and treatment recommendation. *BMC Cancer*. 2006;6:1.
79. Keller F, Hauff A, Schultze G, et al. Effect of repeated plasma exchange on steady state kinetics of digoxin and digitoxin. *Arzneimittelforschung*. 1984;34(1):83-86.
80. Rabetoy GM, Price CA, Findlay JW, et al. Treatment of digoxin intoxication in a renal failure patient with digoxin-specific antibody fragments and plasmapheresis. *Am J Nephrol*. 1990; 10(6):518-521.
81. Santos-Araujo C, Campos M, Gavina C, et al. Combined use of plasmapheresis and antidigoxin antibodies in a patient with severe digoxin intoxication and acute renal failure. *Nephrol Dial Transplant*. 2007;22(1):257-258.
82. Zdunek M, Mitra A, Mokrzycki MH. Plasma exchange for the removal of digoxin-specific antibody fragments in renal failure: timing is important for maximizing clearance. *Am J Kidney Dis*. 2000;36(1):177-183.
83. Binimelis J, Bassas L, Marruecos L, et al. Massive thyroxine intoxication: evaluation of plasma extraction. *Intensive Care Med*. 1987;13(1):33-38.
84. van Huekelom S, Kinderen LH, der Vingerhoeds PJ. Plasmapheresis in L-thyroxine intoxication. *Vet Hum Toxicol*. 1979;21(suppl):7.
85. Liel Y, Weksler N. Plasmapheresis rapidly eliminates thyroid hormones from the circulation, but does not affect the speed of TSH recovery following prolonged suppression. *Horm Res*. 2003;60(5):252-254.
86. Henderson A, Hickman P, Ward G, et al. Lack of efficacy of plasmapheresis in a patient overdosed with thyroxine. *Anaesth Intensive Care*. 1994;22(4):463-464.
87. May ME, Mintz PD, Lowry P, et al. Plasmapheresis in thyroxine overdose: a case report. *J Toxicol Clin Toxicol*. 1983;20(5):517-520.
88. Preuschof L, Keller F, Bogner U, et al. Plasma exchange and hemoperfusion in iodine-induced thyrotoxicosis. *Blood Purif*. 1991;9(3):164-168.
89. White RL, Garnett WR, Poynor WJ, et al. Salicylate removal during plasma exchange in normal volunteers. *Clin Pharm*. 1984;3(4):396-402.
90. Laussen P, Shann F, Butt W, et al. Use of plasmapheresis in acute theophylline toxicity. *Crit Care Med*. 1991;19(2):288-290.
91. Jacobi J, Mowry JB. Use of plasmapheresis in acute theophylline toxicity. *Crit Care Med*. 1992;20(1):151.
92. Ghannoum M, Wiegand TJ, Liu KD, et al. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)*. 2015;53(4):215-229.
93. Yates C, Galvao T, Sowinski KM, et al. Extracorporeal treatment for tricyclic antidepressant poisoning: recommendations from the EXTRIP Workgroup. *Semin Dial*. 2014;27(4):381-389.
94. Talbert RL, Wong YY, Duncan DB. Propranolol plasma concentrations and plasmapheresis. *Drug Intell Clin Pharm*. 1981;15(12):993-996.
95. Kolcz J, Pietrzyk J, Januszewska K, et al. Extracorporeal life support in severe propranolol and verapamil intoxication. *J Intensive Care Med*. 2007;22(6):381-385.

96. Kuhlmann U, Schoenemann H, Muller T, et al. Plasmapheresis in life-threatening verapamil intoxication. *Artif Cells Blood Substit Immobil Biotechnol*. 2000;28(5):429-440.
97. Kuhlmann U, Schoenemann H, Muller TF, et al. Plasmapheresis in fatal overdose with verapamil. *Intensive Care Med*. 1999;25(12):1473.
98. Maclaren G, Butt W, Cameron P, et al. Treatment of polypharmacy overdose with multimodality extracorporeal life support. *Anaesth Intensive Care*. 2005;33(1):120-123.
99. Cekmen N, Bedel P, Erdemli O. A memantin HCL intoxication responsive to plasmapheresis therapy. *Bratisl Lek Listy*. 2011;112(9):527-529.
100. Demirkol D, Karacabey BN, Aygun F. Plasma exchange treatment in a case of colchicine intoxication. *Ther Apher Dial*. 2015;19(1):95-97.
101. Sabto JK, Pierce RM, West RH, et al. Hemodialysis, peritoneal dialysis, plasmapheresis and forced diuresis for the treatment of quinine overdose. *Clin Nephrol*. 1981;16(5):264-268.
102. Appelgate R, Schwartz D, Bennett WM. Removal of tobramycin during plasma exchange therapy. *Ann Intern Med*. 1981;94(6):820-821.
103. Stigelman WH Jr, Henry DH, Talbert RL, et al. Removal of prednisone and prednisolone by plasma exchange. *Clin Pharm*. 1984;3(4):402-407.
104. Chan GL, Hodge EE. Effect of plasmapheresis on cyclosporine pharmacokinetics. *DICP*. 1991;25(2):211.
105. Kamboj J, Kottalgi M, Cirra VR, et al. Direct thrombin inhibitors: a case indicating benefit from 'plasmapheresis' in toxicity: a call for establishing "guidelines" in overdose and to find an "antidote". *Am J Ther*. 2012;19(6):e182-e185.
106. Mokrzycki MH, Kaplan AA. Therapeutic plasma exchange: complications and management. *Am J Kidney Dis*. 1994;23(6):817-827.
107. Kaplan A. Complications of apheresis. *Semin Dial*. 2012;25(2):152-158.
108. Kale PB, Thomson PA, Provenzano R, et al. Evaluation of plasmapheresis in the treatment of an acute overdose of carbamazepine. *Ann Pharmacother*. 1993;27(7-8):866-870.
109. Samtleben W. [Successful plasmapheresis in severe diltiazem poisoning]. *Dtsch Med Wochenschr*. 1995;120(28-29):1023, author reply 5.
110. Gadow KA, Sprenger KB. [Successful plasmapheresis in severe diltiazem poisoning]. *Dtsch Med Wochenschr*. 1995;120(28-29):1023-1024, author reply 5.