

Current applications of plasmapheresis in clinical toxicology

Vesselin D. Nenov¹, Petko Marinov², Julia Sabeva² and Dimitar S. Nenov¹

¹Renal Division, Medical University of Varna and ²Clinic of Toxicology, Military Hospital of Varna, Bulgaria

Abstract

The clinical applications of plasmapheresis are rapidly increasing in number and scope. This trend is also observed in the application of plasmapheresis as a method of detoxification in clinical toxicology. Because of a lack of large controlled series, the rationale for using plasmapheresis must be confirmed in each type of intoxication by evidence of effective clearance, as well as by high plasma protein binding and a low volume of distribution of the toxic substance. Plasmapheresis is used mostly to treat phalloid mushroom intoxications. In this potentially fatal intoxication, for which there is no antidote, plasmapheresis is at least as effective as haemoperfusion in reducing mortality from as high as 30–50% with conventional therapy to <20%. In our series of 28 patients treated with plasmapheresis, mortality was 17.8%. In our experience, plasmapheresis is also very effective in the treatment of life-threatening intoxications with tricyclic (amitriptyline) and 4-cyclic (maprotyline) antidepressants. We confirmed a 63% reduction in the plasma level of amitriptyline in one patient after single plasmapheresis. Other drugs such as L-thyroxine, verapamil, diltiazem and carbamazepime are also removed effectively by plasmapheresis, as are theophylline and heavy metals (mercury and vanadate). Phosphoroorganic substances are not removed effectively. We measured the plasma concentrations of dimethoate in two patients with this intoxication and did not find clinically significant clearance with plasmapheresis.

Keywords: amitriptyline; maprotyline; phalloid intoxication; plasmapheresis; theophylline

methods are usually applied in selected cases of diagnosed severe forms of intoxications as the only option of fast elimination of the intoxicating agent. They are, however, also applied whenever certain potentially lethal intoxications are diagnosed and/or suspected, even without evidence of life impediment at the time of institution of therapy. Finally, these methods are applied even in severe cases, when the toxic substance is unknown, because of the high risk of death and the probability of success. Even in such cases, combined extracorporeal detoxification is justified, given that there is sufficient technical expertise to minimize the risk of complications of the technique.

According to the volume of distribution, protein binding and solubility in water, different methods should be chosen in different intoxications. While haemodialysis is the best method for water-soluble and dialysable substances such as ethylene glycol or methanol, other intoxications, such as phenobarbital poisoning, are best treated by charcoal haemoperfusion. There is a third group of substances, which remain highly bound to plasma proteins and are not removed effectively by either haemodialysis or haemoperfusion. In such cases, plasmapheresis is reasonably the best option available. There are, however, no controlled studies on the usefulness of plasmapheresis in any particular intoxication because of the lack of large reported series. Case reports are published instead and, depending on the severity of the reported intoxication and on the plasmapheresis protocol used, either dramatic improvement or no effect is reported. Documentation of removal of the toxic substance from the blood therefore remains the major objective judgement of the effectiveness of plasmapheresis in any particular type of intoxication.

Introduction

Extracorporeal blood purification has an established role in the treatment of various intoxications. These

Plasmapheresis in phalloid intoxication

The highest number of plasmaphereses has been performed in the treatment of phalloid mushroom intoxications. *Amanita phalloides* contains the most deadly toxin (the amanita toxin) of all poisonous mushrooms. Because mortality ranges between 25 and

Correspondence and offprint requests to: Dimitar S. Nenov, Renal Division, Medical University of Varna, 55 M. Drinov St., 9002 Varna, Bulgaria. E-mail: dnenov@abv.bg

50% [1], prompt institution of gastrointestinal lavage and decontamination with activated charcoal must be followed by prompt extracorporeal blood purification by either haemoperfusion or plasmapheresis in all cases of diagnosed and/or highly suspected phalloid intoxication, irrespective of the patient's current clinical condition. Detection by radioimmunoassay of amatoxins in the serum and urine of patients treated with plasmapheresis has shown that this therapeutic treatment can be effective within ~36 h from the time of ingestion [2]. In different series, plasmapheresis has been shown to decrease mortality from >20% to as little as 4.8% in a series of 21 patients [3]; to 12.7% in another series of 50 patients [2]; or to 19% in another series of 31 patients [4]. In our series of 28 patients with phalloid mushroom intoxication treated with plasmapheresis, mortality was 17.8%. Plasmapheresis is at least as potent as haemoperfusion in reducing mortality associated with phalloid mushroom intoxication, but whether it is superior or not requires larger series to compare, and the current literature lacks such comparisons.

Plasmapheresis to eliminate drugs

In cases of severe intoxication, a number of drugs, which are poorly removed by haemodialysis because of high protein binding and which are not cleared well by haemoperfusion, may be eliminated using plasmapheresis. Some advocate that plasmapheresis is useful only when the plasma protein binding of the substance is high (>80%) and the volume of distribution is low (<0.2 l/kg bw)[5]. Tricyclic (amitriptyline) and 4-cyclic (maprotyline) antidepressants, though highly bound to plasma proteins, are well eliminated by forced diuresis but, in the face of severe cardiac and central nervous system toxicity, extracorporeal elimination is necessary. These drugs are, however, not dialysable and are poorly removed by haemoperfusion. Plasmapheresis can be life saving in the most severe cases, where a dramatic improvement in the clinical condition may be observed [6]. Using gas chromatography with mass spectrometry, we measured the plasma levels of amitriptyline before and after a single plasmapheresis (Table 1) in one patient with acute amitriptyline intoxication. A 63% reduction in the plasma level was observed.

Plasmapheresis is also effective in removing L-thyroxine, which is highly protein bound [7,8], verapamil [9,10], diltiazem [11] and carbamazepine

Table 1. Amitriptyline levels before and after a single plasmapheresis in a patient with acute amitriptyline intoxication

	Before	After
Amitriptyline ($\mu\text{g/ml}$)	4.03	1.49

Plasma levels were measured by gas chromatography/mass spectrometry.

Table 2. Theophylline and coffeine levels before and after a single plasmapheresis in a patient with mixed intoxication

	Before	After
Theophylline ($\mu\text{g/ml}$)	23.42	3.25
Coffeine ($\mu\text{g/ml}$)	13.08	9.94

Plasma levels were measured by HPLC.

[12,13]. Plasmapheresis has been used as adjunctive therapy in addition to anti-digoxin antibodies in digitalis intoxication in patients with renal failure to prevent the rebound caused by dissociation of the digoxin-antidigoxin complexes [14]. Plasmapheresis may also be effective in eliminating theophylline. Approximately 50–65% of the circulating theophylline is protein bound, its clearance is low (0.7–1.0 ml/min/kg bw), its metabolism is predominantly hepatic and the volume of distribution is low (<50% of the body weight). The usual recommendations are that haemodialysis and haemoperfusion are highly effective in decreasing the plasma levels of theophylline. Occasional reports support the use of plasmapheresis [15]. Table 2 represents the chromatographically documented clearance of theophylline (86% reduction) and of coffeine (24% reduction) after a single procedure of plasmapheresis in one case, that was observed by us with mixed coffeine and theophylline intoxication.

Other substances

In addition to drug elimination, plasmapheresis is probably able to remove protein-bound heavy metals in plasma, such as mercury [16,17], in one report as a long-term therapy in conjunction with chelation therapy [18]; or vanadate [19].

Plasmapheresis has also been attempted in acute phosphoroorganic intoxications, such as paraquat [20]. We treated two patients with acute dimethoate intoxication with plasmapheresis. The plasma levels of this phosphoroorganic pesticide decreased from 213 to 180 $\mu\text{g/ml}$ (15.5%) in the first patient and from 90 to 79 $\mu\text{g/ml}$ (12.3%) in the second patient after a single plasmapheresis. Our results showed insignificant removal of dimethoate, and therefore plasmapheresis has no role in this intoxication.

Conclusion

At present, plasmapheresis is used successfully in the treatment of phalloid mushroom intoxications, some drug intoxications (tricyclic and 4-cyclic antidepressants, L-thyroxine, verapamil, diltiazem, carbamazepine) and some heavy metal intoxications (mercury, vanadate). In all other applications, the role of plasmapheresis is provisional. Its rationale must be confirmed

by measuring the substance elimination, and must be supported by high plasma protein binding (> 80%) and a low volume of distribution (< 0.21/kg bw).

References

- Nenov D, Nenov K. Therapeutic apheresis in exogenous poisoning and in myeloma. *Nephrol Dial Transplant* 2001; 16 [Suppl 6]: 101–102
- Langer M, Vesconi S, Iapichino G, Costantino D, Radrizzani D. The early removal of amatoxins in the treatment of *Amanita phalloides* poisoning. *Klin Wochenschr* 1980; 58: 117–123
- Jander S, Bischoff J. Treatment of *Amanita phalloides* poisoning: I. Retrospective evaluation of plasmapheresis in 21 patients. *Ther Apher* 2000; 4: 303–307
- Lapinski TW, Prokopowicz D. Epidemiological factors of mushroom poisoning in the north-east of Poland. *Przegl Epidemiol* 1998; 52: 463–467
- Samtleben W, Mistry-Burchardi N, Hartmann B, Lennertz A, Bosch T. Therapeutic plasma exchange in the intensive care setting. *Ther Apher* 2001; 5: 351–357
- Asparuchova M, Nenov V, Katelieva S, Georgiev V. Severe intoxication with maprotylin—dramatic improvement after plasmapheresis [abstract]. *Nephrol Dial Transplant* 1996; 11: 743
- van Huekelom S, Kinderen LH, der Vingerhoeds PJ. Plasmapheresis in L-thyroxine intoxication. *Vet Hum Toxicol* 1979; 21 [Suppl]: 7
- Binimelis J, Bassas L, Marruecos L *et al.* Massive thyroxine intoxication: evaluation of plasma extraction. *Intens Care Med* 1987; 13: 33–38
- Siebenlist D. Plasma separation in verapamil poisoning. *Dtsch Med Wochenschr* 1990; 115: 797
- Kuhlmann U, Schoenemann H, Muller T, Keuchel M, Lange H. Plasmapheresis in life-threatening verapamil intoxication. *Artif Cells Blood SubImmobil Biotechnol* 2000; 28: 429–440.
- Gutschmidt HJ. Successful plasmapheresis in severe diltiazem poisoning. *Dtsch Med Wochenschr* 1995; 120: 81–82
- Gambi D, Oggioni R, Mangani V, Librenti M, Manescalchi F, Tulli G. Acute carbamazepine poisoning treated with plasmapheresis. Description of a clinical case. *Minerva Anesthesiol* 1993; 59: 547–552
- Duzova A, Baskin E, Usta Y, Ozen S. Carbamazepine poisoning: treatment with plasma exchange. *Hum Exp Toxicol* 2001; 20: 175–177
- Rabetoy GM, Price CA, Findlay JW, Sailstad JM. Treatment of digoxin intoxication in a renal failure patient with digoxin-specific antibody fragments and plasmapheresis. *Am J Nephrol* 1990; 10: 518–521
- Laussen P, Shann F, Butt W, Tibballs J. Use of plasmapheresis in acute theophylline toxicity. *Crit Care Med* 1991; 19: 288–290
- 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: 189–197
- 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: 53–57
- Yoshida M, Satoh H, Igarashi M, Akashi K, Yamamura Y, Yoshida K. Acute mercury poisoning by intentional ingestion of mercuric chloride. *Tohoku J Exp Med* 1997; 182: 347–352
- Schlake HP, Bertram HP, Husstedt IW, Schuierer G. Acute systemic vanadate poisoning presenting as cerebrovascular ischemia with prolonged reversible neurological deficits (PRIND). *Clin Neurol Neurosurg* 1994; 96: 92–95
- Tsatsakis AM, Perakis K, Koumantakis E. Experience with acute paraquat poisoning in Crete. *Vet Hum Toxicol* 1996; 38: 113–117