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Intoxication with Calcium Channel Blockers and Other Highly Protein-Bound Drugs: Why Use MARS? Two Clinical Case Reports

Juan José García Martínez[1,2*], **Frédéric Mollard**[1], **Frédéric J. Baud**[3,4,5] **and Karim Bendjelid**[1,2,6]

[1]*Intensive Care Unit, Geneva University Hospitals, 4 Rue Gabrielle-Perret-Gentil, 1205 Geneva, Switzerland*

[2]*Faculty of Medicine, University of Geneva, Geneva, Switzerland*

[3]*Adult Intensive Care Unit, Department of anesthesiology and intensive care and SAMU 75, CHU Necker-Enfants Malades; Assistance Publique - Hôpitaux de Paris, Paris, France*

[4]*EA 7323, Pharmacologie pédiatrique, 75015 Paris, France*

[5]*University Paris Sorbonne Cité, Paris Diderot, Paris, France*

[6]*Geneva Hemodynamic Research Group, Geneva, Switzerland*

[*]**Corresponding author:** Juan José García Martínez, Hôpitaux Universitaires de Genève, Service des soins intensifs, 4 Rue Gabrielle-Perret-Gentil, 1205 Genève, Switzerland, Tel: 0041767356684; Fax: 41223729105; E-Mail: juanfeira@outlook.com

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Abstract

Overdose with calcium channel blockers is often a life-threating condition that is frequently exacerbated by the availability of extended-release preparations with slow drug clearances. In the annual report of the American Association of Poison Control Centers, calcium channel inhibitor overdose is one of the most deadly poisonings. In addition, calcium channel blockers are highly bound to proteins, making them difficult to remove using standard dialysis techniques. We describe two cases of amlodipine overdose that presented with profound circulatory shock and were treated with the Molecular Adsorbent Recirculating System™ (MARS™). In this regard, the authors reviewed other cases reported in the literature to discuss the rationale for using albumin dialysis techniques in the setting of highly protein-bound drug intoxication.

Keywords: MARS; Albumin dialysis; Highly protein-bound drugs; Intoxication; Overdose

Introduction

Intentional or unintentional poisoning with legal drugs is a worldwide problem. In the USA, cardiovascular drugs are one of the substance categories most frequently involved in poisoning and the second most common cause of death among pharmaceutical drugs, just behind analgesics. In 2016, amlodipine, a calcium channel blocker (CCB), ranked third among the pharmaceutical drugs most frequently implicated in fatal poisonings in the USA according to the National Poison Data System [1].

CCB overdoses can lead to severe depression of the cardiovascular system, impeding cardiac contraction and heart electrical conduction and producing arterial vasodilatation and deep hypotension. The resulting cardiogenic and vasoplegic shock state is poorly responsive to inotropic and vasopressive drugs or other supportive therapies. Other therapeutic options, such as calcium salts and glucagon administration and the so-called hyperinsulinemia-euglycemia therapy, and lipid emulsion, have been proposed.

In this context, the rationale of enhancing drug clearance may become the cornerstone of treatment, especially for amlodipine, which has a much longer elimination half-life. However, the fact that the drugs are highly protein-bound makes it difficult to remove them from blood with standard dialysis. The use of the Molecular Adsorbent Recirculating System™ (MARS™) or another type of albumin dialysis technique is rationally interesting for this field, and there are some cases that have been published in recent years that showed a faster removal of the drug and marked improvement in patient clinical status [2].

In the present paper, the authors present two cases of amlodipine intoxication treated with MARS. We reviewed the literature and discussed the rational for its use. Written informed consent for data analysis and publication of these two clinical reports was not required by our local IRB, as the reports are observational without any impact on existing diagnostic or therapeutic strategies.

Case Report No. 1

A male patient in his twenties, without significant prior disease, was admitted to the intensive care unit (ICU) 8 hours after ingestion of a large number of multiple pharmaceutical drugs. The patient ingested 840 mg of amlodipine (as amlodipine besilate) and 3360 mg of olmesartan medoxomil in a combined standard formulation. He also self-reported 14 g of acetylsalicylic acid (but salicylate plasma concentration was <1.1 mmol/L), 14 g of paracetamol (but the acetaminophen plasma concentration at admission was outside of the toxic range), 82 mg of acenocoumarol and less significant amounts of other drugs. The patient was conscious, hemodynamically stable and able to confirm the ingestion at the time of admission to the emergency department (ED), approximately 6 hours post-ingestion. His clinical condition deteriorated rapidly over the next two hours with deep hypotension about 7 hours after ingestion that was poorly responsive to high doses of vasopressor drugs, and progressive deterioration in consciousness led to orotracheal intubation and mechanical ventilation 8 hours post-ingestion. Vasodilatory shock was confirmed by transpulmonary thermodilution with a high cardiac

output (>10 L/min) and low systemic vascular resistances (<500 dyn·s·cm^{-5}). The patient presented with acute renal injury (AKIN 2) on admission and developed respiratory failure in the first hours following intubation. The patient received intravenous calcium (gluconate and chloride), continuous infusion of hyperinsulinemia-euglycemia therapy and a single dose of intravenous lipid emulsion (500 mL of Lipofundin MCT LCT, 20%™, ~6.5 mL/kg) 15 hours post-ingestion. He remained deeply in shock, despite adequate volume resuscitation and high doses of norepinephrine (up to 1.5 µg/kg/min) associated with terlipressin (1 mg every 6 hours). Low-dose corticosteroids (50 mg of hydrocortisone every 6 hours) and a single dose of 100 mg of methylene blue (~1.5 mg/kg) were administered in the context of refractory vasoplegia without improvement.

The first MARS session was conducted 8 hours after admission to the ICU (16 hours post-ingestion), with a rapid improvement in hemodynamic condition (Figure 1), which allowed for a drastic reduction in vasopressor drugs in the following hours. The MARS device consisted of a standard dialysis machine (PrismaFlex™ system; Baxter International Inc.) and an additional device for running and monitoring a closed-loop albumin circuit (MARS™ Monitor 1TC and X-MARS™ Treatment Kit; Baxter International Inc.). The MARS circuit was primed with 600 ml of 20% human serum albumin and was driven at the same rate as blood flow, between 80 ml/min and 150 ml/min (depending on hemodynamics). Continuous renal replacement therapy (CRRT) was used with standard prescriptions with a dialysate flow rate of 1500 mL/h and Prismasol 4™ (K^+ 4 mmol/L) was used as hemodialysis solution. Anticoagulation was carried out with unfractionated heparin. The MARS session lasted 5 hours. Two more MARS sessions were performed on day 2 and day 3 with similar parameters and duration. Table 1 shows total serum protein and albumin values during MARS therapy.

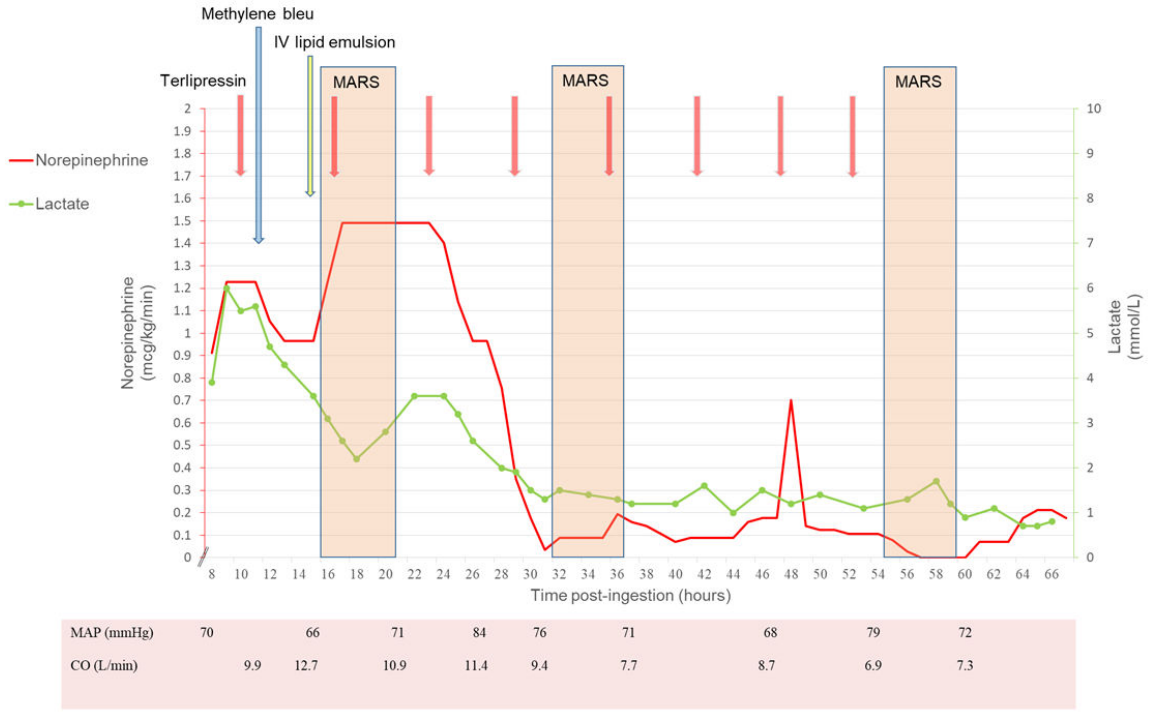

Figure 1: Graphic showing the time course of vasopressor drugs and lactate during MARS sessions in case report no. 1 (MAP: Mean arterial pressure; CO: Cardiac output).

The ICU stay was complicated on day 4 by a primary ARDS (with *Haemophilus influenzae* and *Streptococcus pneumoniae* found in a pulmonary specimen), which required prone position ventilation. The course was favorable with adequate antibiotic treatment. Norepinephrine was stopped definitively on day 9, and the patient was weaned from the ventilator on day 10. He was discharged from the ICU on day 11 without any sequelae.

Case Report No. 2

A man in his fifties with a medical history of hypertension and type 2 diabetes was admitted to the ED approximately 24 hours after ingesting nearly 1000 mg of amlodipine. In the ED, the patient complained of nonspecific chest and abdominal pain, vomiting and oliguria. He had a slight bradycardia (junctional rhythm) and severe hypotension associated with a lactic acidosis. He presented with renal insufficiency, AKIN III, and a slight cytolysis without hepatic failure. In the ED, the patient was given fluids, vasopressor drugs and intravenous calcium gluconate without improvement and was admitted to the ICU 26 hours post-ingestion. A Swan-Ganz catheter was inserted, which showed a vasoplegic shock with a normal cardiac index, low pulmonary artery occlusion pressure and systemic vascular resistance estimated at 500 dyn·s·cm^{-5}. Hemodynamic status worsened in the first hours following ICU admission with the need for very high doses of vasopressive drugs, up to 2.1 µg/kg/min of norepinephrine at

35 hours post-ingestion. Anuria and severe lactic acidosis persisted (maximum lactate 9.6 mmol/L).

Time post ICU admission (hours)	Albumin (g/L)	Total protein (g/L)
H0	38	58
H5	36	55
H19	34	54
H43	31	52
H67	26	50

Table 1: Total serum protein and albumin values during MARS therapy in case report no. 1.

The decision to start MARS therapy within 8 hours of ICU admission (34 hours post-ingestion), was based on our successful experience in the first case report. The MARS technique used was the same as previously described. The MARS circuit was driven at 130 ml/minute. Dialysate flow was kept at 1100 mL/h. The first session lasted 7 hours and allowed a drastic reduction in arterial lactate and even a temporary stop of vasopressor drugs at 40 hours post-ingestion (Figure 2). Two more MARS sessions were subsequently performed on day 3 and day 4 (with the same parameters, and durations of 7 and 5 hours, respectively) without any significant changes in hemodynamic status; however, the doses of vasopressor drugs were already lower. Of note, standard dialysis was continued between the MARS sessions. For the MARS sessions, anticoagulation was carried out with unfractionated heparin, while regional citrate anticoagulation was used when CRRT was performed alone. Total serum protein and albumin values during MARS therapy are shown in Table 2.

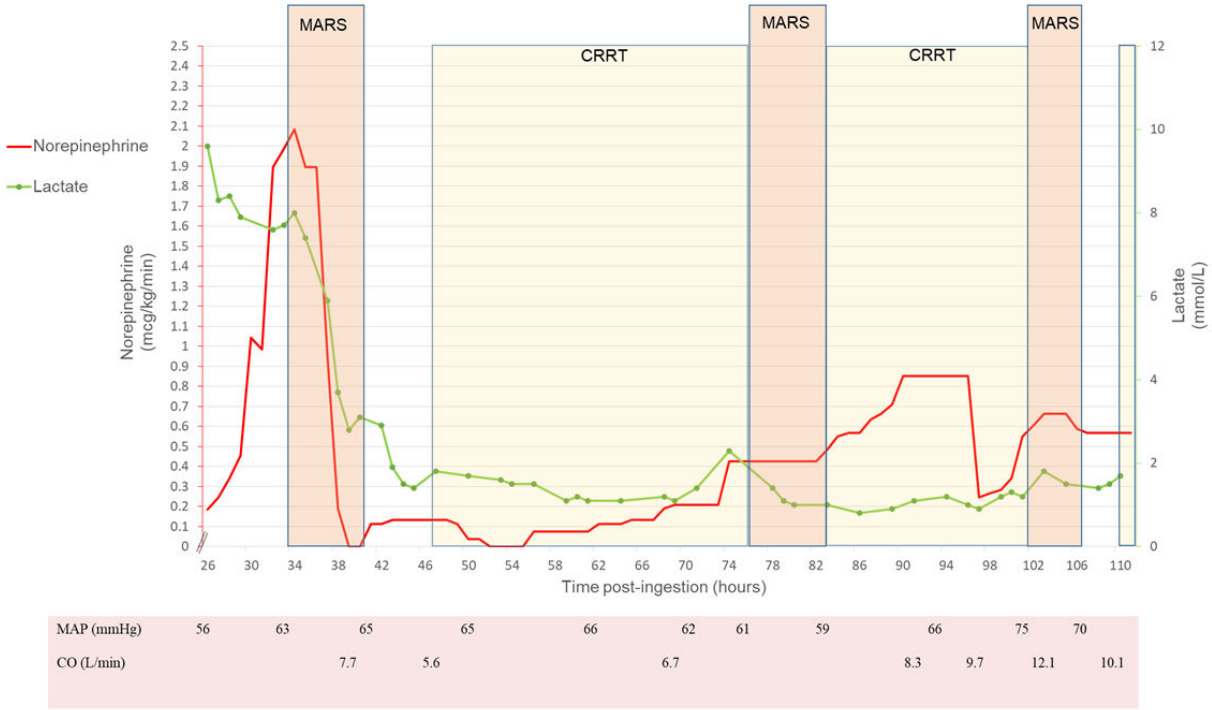

Figure 2: Graphic showing the time course of vasopressor drugs and lactate during MARS sessions in case report no. 2 (MAP: Mean arterial pressure; CO: Cardiac output).

On day 3, the patient developed respiratory failure that required invasive mechanical ventilation. He was diagnosed with aspiration pneumonia, which progressed favorably with the proper antibiotic treatment. The final evolution was satisfactory, and the patient was weaned from mechanical ventilation and vasopressor drugs on day 6. He was discharged to the ward on day 7 without sequelae.

Discussion

The present paper displays two clinical cases of severe intoxication with CCB drugs treated in a multidisciplinary intensive care unit. Most precisely, two intoxications with high doses of amlodipine, a low-clearance, long-acting 1,4-dihydropyridine calcium channel blocker. Like other CCB drugs, amlodipine directly inhibits voltage-gated, L-type calcium channel opening and calcium influx into myocardial and vascular smooth muscle cells, preventing calcium-dependent myocyte contraction and sinoatrial node depolarization. In myocardial tissue, CCBs' actions result in negative inotropy, chronotropy and dromotropy. By acting on vascular smooth muscle, anticalcic drugs prevent arterial contraction and reduce systemic afterload and arterial blood pressure. The CCBs also inhibit calcium L-type channels in pancreatic islet cells, reducing insulin secretion leading to a secondary hyperglycemia and decreasing myocardial glucose use.

Dihydropyridines, such as amlodipine, act preferentially on the peripheral vasculature, inducing systemic hypotension.

Time post ICU admission (hours)	Albumin (g/L)	Total protein (g/L)
H0	41	74
H4	42	72
H16		60
H19	35	63
H45		67
H69	35	67
H93		63

Table 2: Total serum protein and albumin values during MARS therapy in case report no. 2.

Amlodipine has some distinctive pharmacokinetic characteristics that are not seen with other CCB drugs, probably due to its high degree of ionization. A high volume of distribution and low clearance give amlodipine a slow rate of elimination (elimination half-life of 30-50 hours) compared to other CCB. It has high oral bioavailability (60%-80%) with a linear disposition relationship. Amlodipine is a highly bound drug with protein-binding in the range of 98% [3], mostly to albumin. In cases of overdose, the main toxic effect is refractory hypotension due to vasodilation, which presents similarly to distributive shock. This hypotension responds slightly to fluids and vasopressor drugs and results in hypoperfusion, tissue ischemia, lactic acidosis and multi-organ failure. Impaired cardiac glycolytic metabolism and contractility also contribute to the shock state but less frequently than with other CCB. The action in the pancreatic beta cells also has adverse consequences by reducing insulin release. The initial management of amlodipine overdose (like CCB intoxication in general) involves standard care with respiratory and hemodynamic assessment and stabilization. Intravenous calcium and glucagon administration are classically considered as the first-line therapy; however, there is insufficient, and sometimes conflicting, evidence to formally recommend their use. Hyperinsulinemia-euglycemia therapy has also been described in numerous CCB toxicity case reports and is used to counteract the hypoinsulinemic state and its detrimental effects on cardiac metabolism and function. The use of intravenous lipid emulsion can also be found anecdotally in the literature. Extracorporeal life support has been used to treat refractory cardiogenic shock and cardiac arrest induced by drug overdose, particularly by cardiovascular drugs, with poor results in CCB intoxications [4].

In view of the poor response to standard therapies and the long duration of action of amlodipine, the attempt to accelerate the elimination of amlodipine and other CCBs (often proposed in delayed-release formulations) becomes particularly important in a toxic situation. Classically, invasive techniques, such as intermittent hemodialysis (IHD) and hemofiltration (IHF), have been used to eliminate specific life-threatening toxins. These techniques are useful for drugs or metabolites that are water soluble, have a low volume of distribution, low plasma protein binding and ideally low molecular weight. However, improvements in dialyzers over the past three decades have allowed larger molecules and protein-bound substances to be removed (especially if there is a constant substrate of free drug in the plasma). The continuous renal replacement therapies (CRRT) performed in the intensive care unit have the same principles as intermittent techniques, but blood and effluent flows are normally lower, conditioning a lower clearance over time. Continuous techniques could prevent post-treatment rebound, but conventional dialysis should be preferred if rapid toxin removal is required.

For many years, there was enthusiasm for using hemoperfusion (HP) in the field of intoxication. Consisting of the passage of blood through an absorptive-containing cartridge (typically charcoal or resins), hemoperfusion allows the elimination of larger molecules than IHD or IHF, as molecular size does not appear to have a major influence on clearance by HP, except when the molecular weight exceeds 5000 Da. Furthermore, HP seemed to be more effective in removing highly protein-bound drugs, especially with resin columns; some studies using an adsorbent cartridge showed extraction ratios that consistently exceeded 80% when the proportion of protein-bound poison was less than 90% [5]. However, as stated above, the advent of new high-flux, high-efficiency dialysis filters and the use of larger catheters and higher dialysate and blood flows have drastically reduced these advantages compared to IHD or IHF. If we add up the complications related to the nonspecific adsorption of biological components, and the fact that hemodialysis is also renal replacement therapy, correcting the electrolyte and acid-base abnormalities that may be present during any intoxication, we can explain why the use of HP consistently decreased in many countries in this setting. Nonetheless, HP is still widely used for poisoned patients in some parts of the word. The use of other techniques, such as sustained low-efficiency dialysis, therapeutic plasma exchange or exchange transfusion, is anecdotal [6].

In the case of intoxication with highly protein-bound drugs, such as amlodipine, the use of some form of albumin dialysis technique seems strongly rational. The simplest system is called single-pass albumin dialysis (SPAD), which uses a standard CRRT where blood is dialyzed against an albumin-containing dialysate. This technique is based on two basic thermodynamic principles: protein-binding affinity and solute movement along a concentration gradient [7]. The elimination of toxins thus takes place through the diffusion process and depends on the free toxin concentration (mainly affected by the molar ratio of toxin to albumin). The albumin added to the dialysate binds the free toxin that crosses the dialyzer membrane due to the concentration gradient from the blood to the dialysate side. As soon as the toxin binds to albumin on the dialysate side, the concentration gradient is restored, and more blood-side toxin disassociates from albumin, crosses the membrane into the dialysate and then binds to the albumin on the dialysate-side. The dialysate is then discharged, and the toxins are removed from the system. In an *in vitro*, continuous hemodialysis model, Churchwell et al. [8] showed that drug clearance was mainly influenced by the concentration of albumin in the dialysate and the type of hemodialyzer used. They compared the effects of various blood flows, dialysate flows, dialysate albumin concentrations (0%, 2.5%, and 5% albumin concentrations) and dialyzers on the clearance of several highly protein-bound drugs. They demonstrated that the highest extraction ratios were achieved using the combination of 5% albumin dialysate and the larger polysulfone dialyzer (surface area 1.5 m^2). The importance of albumin concentration in the dialysate has also been confirmed by other researchers [9].

In the last two decades, new techniques have been developed in the field of extracorporeal liver assistance, mainly based on the principle of

albumin dialysis and the combination of filtration and adsorption. The most widely published system is the Molecular Adsorbent Recirculating System (MARS), developed by Stange et al. [10], which is composed of a blood circuit, an albumin circuit, and a classic 'renal' circuit. Following the same principles described above, blood is dialyzed through an albumin impregnated high-flux dialysis membrane (surface area of 2.1 m^2, membrane thickness of 100 nm and molecular cut-off of approximately 50 kDa) in such a way that albumin-bound toxins are released through the membrane and subsequently collected by albumin in the dialysate. Subsequently, the toxins are cleared when passing the absorber columns that contain activated charcoal and anion exchange resin, and albumin is regenerated and able to accept new toxins when it passes the membrane again. Additionally, the albumin circuit itself is dialyzed in the CRRT method, diminishing the load of water-soluble toxins.

Sen et al. [11] published a paper showing the ability of MARS to efficiently eliminate albumin-bound and other protein-bound drugs. The authors conducted an animal study using pigs in which acute liver failure was induced. The researchers used midazolam (mainly albumin-bound) and fentanyl (essentially alpha-1-acid glycoprotein bound) to keep the animals sedated during MARS therapy and measured the clearance of these drugs through MARS dialysis (note that the hemodiafiltration part of the system was disabled for the experiment). They demonstrated that this technique of albumin dialysis not only effectively extracted midazolam (mostly removed from the dialysate at the charcoal column site), but, surprisingly, also extracted fentanyl (which was found in the dialysate, mainly linked to albumin). Therefore, MARS could efficiently remove not only albumin-bound drugs but also those bound to other proteins. However, few attempts to use these techniques in the context of protein-bound drug intoxication have been described in the literature, despite the fact that MARS was approved by the U.S. Food and Drug Administration (FDA) for the treatment of drug overdoses and poisonings.

In this regard, we performed a search for relevant articles in PubMed and Web of Science with the search terms of Intoxication OR poisoning OR overdose AND MARS OR Prometheus OR liver dialysis OR hepatic dialysis OR extracorporeal hepatic assistance OR extracorporeal hepatic support OR albumin dialysis. The filter settings used were "English language" and "French language" and the "humans" filter. We set the range of "January 1, 2000" custom dates. Bibliographies of recovered articles were reviewed to identify any other relevant articles. We found only 11 papers reporting the use of MARS or some form of albumin dialysis to treat drug intoxication with the aim of accelerating drug elimination. The drugs reported were predominantly antiepileptic drugs: carbamazepine [12,13], lamotrigine [14], phenytoin [15], phenobarbital [16] and valproic acid [17]. There were 4 papers reporting the use of albumin dialysis or MARS to treat intoxication by different antihypertensive drugs: diltiazem [18,19], verapamil and bisoprolol [20] and amlodipine/valsartan [21]. One case report described the use of MARS for theophylline poisoning [22]. In these different studies, the authors showed a quicker elimination of these highly protein-bound drugs with MARS and a faster than expected improvement in the patient's clinical condition, which presented these techniques as promising tools.

In the specific field of CCB intoxications, Pichon et al. [20] described three cases of diltiazem and verapamil (in combination with bisoprolol) overdose that presented in circulatory failure with deep hypotension and cardiac dysfunction (inotropic and chronotropic) that was unresponsive to high doses of catecholamines and all other standard care, including the recommended antidotes. The patients had renal failure and severe lactic acidosis. In this paper, a single 4 to 6 hours session with MARS for each patient enhanced elimination of the drug and, most notably, allowed a drastic decrease in adrenergic support and reversed shock state, demonstrated by the expeditious normalization of lactate.

Gérard et al. [21] published a case report describing an overdose with amlodipine and valsartan, pretty similar to our first case but with half the dose of amlodipine and a much less comparable dose of an angiotensin II receptor blocker. Both patients presented in refractory shock with extremely low systemic vascular resistances (with a preserved cardiac index) and evolved into multiple organ failure. The authors applied two 16 hours MARS sessions and observed a rapid improvement in hemodynamic conditions, which enabled the weaning of catecholamine support. Astonishingly, the amount of amlodipine effectively removed by dialysis appeared not to be relevant. The authors pointed out the ability of MARS to remove nitric oxide (NO) as an alternative explanation for the hemodynamic stability achieved.

In the two clinical cases presented in this paper, the doses of amlodipine that patients confessed to taking were among the highest in the literature. In a recently published case report on poisoning with a similar dose of amlodipine, the patient developed refractory hypotension and, finally, cardiac arrest that was recuperated by ECMO. However, the patient was ultimately pronounced brain dead. Any depuration technique was attempted [23]. In both of the current cases, the patients presented in deep circulatory failure, requiring extremely high catecholamine support, associated with severe lactic acidosis. Both patients benefited from invasive hemodynamic monitoring that confirmed vasodilatory shock and received adjuvant treatment for vasoplegia. The culprit drug was amlodipine for both patients with an association with the angiotensin II receptor blocker, olmesartan medoxomil, in our first case. Different therapeutic options for CCB intoxications were tried without significant improvement in hemodynamic status. Nevertheless, the first MARS therapy session allowed a drastic reduction in vasopressor support in both patients and improved the organ failure.

The first hypothesis to explain the spectacular results achieved with the use of MARS is the acceleration in drug clearance, which has already been demonstrated by other authors. As stated above, the ability of MARS to efficiently remove protein-bound drugs has been proven in *in vitro* and *in vivo* studies. In our two clinical cases, MARS probably enhanced amlodipine clearance, which fundamentally contributed to the observed hemodynamic improvement. It should be noted that our first case required high doses of sedation, up to 60 mg per hour of midazolam combined with 300 μg per hour of fentanyl, both highly protein-bound drugs. They were also probably effectively eliminated by MARS, as demonstrated by Sen et al. [11]. The second hypothesis is the role of MARS in NO removal. Experimental studies have shown an increase in NO bioavailability with dihydropyridines. In particular, amlodipine may increase the release of NO, which is responsible for specific anti-inflammatory and antioxidative effects, and decrease its degradation [24-26]. The vasodilatory effect of NO is well known, and some studies have shown the ability of MARS to remove it [27-29], probably in its main circulating complex form, S-nitroso-serum albumin [30]. MARS could have also participated in the rapid stabilization achieved in our patients in this way.

Regarding limitations, the plasma concentrations of amlodipine were not measured in either patient of the presented reports, as the

specific test is not routinely available in our hospital. This also prevented the monitoring of plasma concentrations during MARS therapy. Plasma drug concentration as a predictor of outcome has been shown for some drugs, such as verapamil [31]. However, both patients confessed at the time of admission to taking the described amounts of drugs and reconfirmed their intake before being discharged from the ICU [32]. We should also note that there is no specific protocol in our hospital for MARS use in the field of drug intoxication. We used the standard protocol that applies when using MARS in the context of liver failure. The number and duration of MARS sessions were defined by the patient's clinical evolution, other cases described in the scientific literature and some technical limitations (availability of trained personnel to perform the procedure).

Conclusion

The usefulness of MARS in the case of highly protein-bound drug intoxication is clinically demonstrated in these two life-threatening CCB poisoning situations. MARS certainly enhanced the elimination of the drugs, as already described in the literature. In the case of amlodipine poisoning, the elimination of the potent vasodilator, NO, may also play a role. Further research is needed to correctly determine the advantages of MARS, or other albumin-based dialysis devices, over standard techniques in this setting. The most appropriate parameters for the use of the technique should also be established.

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