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Treatment of Severe Amlodipine Toxicity With Molecular Adsorbent Recirculating System

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INTRODUCTION

Amlodipine is a long-acting calcium channel blocker of the dihydropyridine class and is more than 90% protein-bound. Toxicity results in bradycardia, hypotension, atrioventricular and bundle branch block, decreased cardiac inotropy, and profound vasodilation.[1] We report a severe intentional ingestion in a pediatric patient requiring extracorporeal life support (ECLS) who was treated with molecular adsorbent recirculating system (MARS) while on extracorporeal membrane oxygenation (ECMO). The recommendations in "Guidelines for Reporting Case Studies on Extracorporeal Treatments in Poisonings: Methodology" were followed, as feasible.[2]

CASE PRESENTATION

Our patient is a 14-year-old girl with a history of autosomal recessive polycystic kidney disease, chronic kidney disease stage 3, hypertension, and depression. She presented to the emergency center of our community hospital with lethargy and hypotension, 4 hours after ingestion of a month's supply of her home dose of 15 mg amlodipine per day (approximately 450 mg). She weighed 42 kg and was 157 cm tall. Her baseline creatinine was 1.62 mg/dl (estimated glomerular filtration rate of 46 ml/min per 1.73 m^2).

She was intubated in the emergency center and suffered a hypotensive, bradycardic cardiac arrest with return of spontaneous circulation after 15 minutes of cardiopulmonary resuscitation. She was initially admitted to the pediatric intensive care unit at the community hospital on epinephrine, norepinephrine, and vasopressin infusions. Electrocardiogram showed complete heart block with accelerated junctional rhythm and prolonged QTc of 595 ms. Due to ongoing clinical deterioration, she was then transferred to the main campus pediatric intensive care unit where extracorporeal therapies were available, arriving approximately 9 hours after initial presentation. Veno-arterial ECMO was initiated for refractory hypotension via femoral-femoral approach, 15 hours after ingestion. Lactate on admission was 5 mmol/l, which peaked to 10.4 mmol/l 6 hours after ingestion. On admission, her pH was 7.15, bicarbonate was 14 mmol/l, and creatinine was 2.4 mg/dl.

Toxicology was consulted and she was started on both high-dose insulin drip at 1 unit/kg per hour and calcium chloride infusion. Amlodipine is highly protein-bound and not dialyzable through conventional hemodialysis. Given her severity, we elected to optimize toxin removal by extracorporeal treatments in addition to conventional medical management. Nephrology initiated albumin-augmented dialysis with MARS immediately after starting ECMO, approximately 20 hours after ingestion.

MARS was performed in series with the veno-arterial ECMO circuit. MARS monitor was used in conjunction with a continuous renal replacement therapy machine in continuous venovenous hemodiafiltration mode with 2000 ml/1.73 m^2 per hour of clearance. Blood and albumin flow rates were 150 ml/min each. Twenty percent albumin solution was used in the MARS circuit. Commercial MARS kits contain high-flux membranes of a 2.1 m^2 MARS albumin filter across which albumin-augmented dialysis occurs, in series with a 1.2 m^2 water-soluble regular dialyzer. Commercial bicarbonate-based dialysate and replacement solutions were used with appropriate electrolyte replacement.

We performed 3 MARS procedures in our patient with reductions in serum amlodipine levels over time

with each procedure. However, clearance was not linear, and levels rose between procedures, likely due to the high initial tissue penetration of the drug and the subsequent liberation of drug from tissues back into the bloodstream after procedures were completed. Improvements in hemodynamic stability were observed during and after each procedure, as measured by the Vasoactive Inotropic Score. The Vasoactive Inotropic Score, first described in postoperative pediatric cardiac patients, is a marker of illness severity, and calculated using the highest dosing of epinephrine, dopamine, dobutamine, vasopressin, milrinone, and norepinephrine infusions. First MARS treatment started on hospital day 1 and lasted for 11 hours before circuit clotting. It was restarted on day 2 for 8 hours when the circuit clotted again. Third MARS treatment, started on the third day, lasted for 26 hours. Serum amlodipine levels were analyzed by high-performance liquid chromatography/tandem mass spectrometry. Reported therapeutic serum levels range from 2 to 25 ng/ml and our patient had a peak amlodipine level of 340 ng/ml before MARS initiation (Figure 1).

On hospital day 2, the heart block resolved, lactate decreased to 2 mmol/l, and pH normalized. She was weaned off epinephrine and continued on norepinephrine and vasopressin infusions, which were gradually weaned. MARS was discontinued after clinical improvement on day 4. There were no unanticipated adverse events noted specifically related to MARS. She was decannulated from ECMO on day 5 and was off all vasopressors on day 7. She maintained urine output ranging from 0.5 to 2.5 ml/kg per hour while on ECMO with additional fluid removal through ultrafiltration on ECMO. She required continuous renal replacement therapy for uremia from days 9 to 15, after which she did not require further renal replacement therapy.

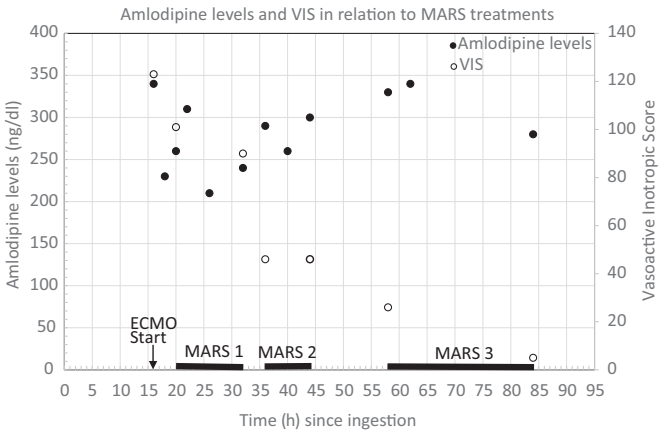

Figure 1. Graphical depiction of serum amlodipine levels and Vasoactive Inotropic Scores (VIS) as temporally related to MARS treatments. ECMO, extracorporeal membrane oxygenation; MARS, molecular adsorbent recirculating system.

DISCUSSION

Treatment Modalities for Amlodipine Ingestion

Initial treatment of calcium channel blocker poisoning is aimed at gastrointestinal decontamination. In more severe cases, administration of vasopressors, atropine, i.v. calcium, and extracorporeal life support is required. Drug levels can be lowered with hyperinsulinemia/euglycemia therapy and/or i.v. infusions of lipid emulsion.[3] Amlodipine is highly protein-bound and conventional modes of dialysis would not effectively improve drug clearance.

MARS and Its Use in Toxicology

MARS has been proposed for the management of acute poisoning with or without liver failure.[4] Using the MARS circuit, protein-bound toxins diffuse across the membrane of a high-flux dialyzer (with a molecular cutoff of approximately 50 kDa) from the blood and into an albumin solution. This albumin solution is then cleaned of its bound toxins by passage through an activated carbon adsorber and an anion exchanger placed in series in the albumin circuit. In addition, albumin is used to prime both sides of the MARS dialyzer, which allows albumin to coat the deep crypts of the membrane surface and aids in clearance of protein-bound substances in the blood.

There are case reports of using extracorporeal liver support to treat calcium channel blocker overdose.[5–8] Three individuals in cardiogenic shock from diltiazem and verapamil poisoning were treated with albumin dialysis. Another case involved a 70-year-old with diltiazem overdose,[5] and a third described a patient with overdose of amlodipine/valsartan therapy.[6] All reported individuals showed approximately 50% decreases in their serum drug levels: amlodipine 200 to 90 ng/ml after 12 hours,[6] diltiazem 2.66 to 1.40 mg/l and 8.58 to 5.67 mg/l after 4 to 6 hours, and verapamil 2.20 to 1.03 mg/l after 4 hours of therapy.[7] Four cases have been published in which plasmapheresis was performed on adults with calcium channel blocker overdose to decrease drug concentrations and improve hemodynamics.[9–11] Case reports exist for hemoperfusion,[12] charcoal hemoperfusion,[13] and continuous venovenous hemodiafiltration .[14,15]

ECMO for Hemodynamic Support in Calcium Channel Blocker Overdose

Durward *et al.*[16] first described a case of an adolescent who ingested toxic amounts of diltiazem. She developed cardiac standstill and was supported on ECMO for 48 hours with good recovery. A systematic review on

treatment for calcium channel blocker poisoning found that among all treatment modalities, high-dose insulin and ECLS were the interventions associated with improved survival.[8]

MARS and ECMO Combined

ECLS was initiated in our patient primarily for hemodynamic support but also for toxin removal. Sparks and colleagues[17] published their experience looking at survival in adults with multiorgan failure on ECMO, with and without MARS. They found that MARS therapy in patients on ECMO ($n = 14$ patients) safely accelerated recovery of liver function and improved survival to wean from ECMO, without increasing complications. For our patient already on ECLS, the addition of MARS did not add a significant burden or risk to the patient above the inherent risks of ECLS (e.g., catheter placement, blood product exposure, anticoagulation). To our knowledge, this is the first description on the use of MARS in tandem with ECMO for a pediatric patient, and for the use of calcium channel blocker toxicity in pediatrics.

Limitations

Our patient presented to a facility without ECLS support and the delay in transfer and initiating therapy could have adversely affected her outcome. The extent to which her preexisting renal disease might have influenced her drug metabolism and clinical course cannot be determined. The effect of the ECMO circuit on volume of distribution of amlodipine is unknown, as is the degree to which the ECMO circuit affects clearance by MARS. We do not know when the cartridges and albumin solution became saturated in order to guide replacement. Amlodipine levels were not available to use in real time so could not guide therapy by allowing purification dose to be titrated. Extremely high levels of >300 ng/ml possibly could be outside the limits for the assay.

Table 1. Teaching points

1. Amlodipine is a long-acting calcium channel blocker of the di-hydropyridine class
2. Amlodipine is highly protein-bound and not dialyzable through conventional hemodialysis
3. Treatment of toxicity includes vasopressor support, i.v. calcium, intralipids, and high-dose insulin-dextrose therapies
4. In very severe cases, extracorporeal membrane oxygenation (ECMO) maybe needed for hemodynamic support
5. Albumin-augmented dialysis can be used for clearance of protein-bound drugs
6. The molecular adsorbent recirculation system can be run in tandem with the ECMO circuit
7. Drug levels are often not available in real time and hence treatment needs to be based on clinical examination
8. Extremely high drug levels may be outside the limits for an assay and may not be accurately measured

CONCLUSION

Amlodipine is not dialyzable via conventional dialysis, but can be removed using albumin-augmented high cutoff circuits. MARS can be safely used in pediatric patients for extracorporeal treatments in tandem with ECMO. It would be a reasonable therapeutic option for amlodipine toxicity, in conjunction with medical therapies (Table 1).

DISCLOSURE

All the authors declared no competing interests.

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