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Hemoadsorption Therapy for Calcium Channel Blocker Overdose: A Case Report

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□ **Abstract—Background: Modern resin hemoadsorption/hemoperfusion for calcium channel blocker overdose is yet to be reported. The characteristics of calcium channel blockers make them unamenable to removal by hemodiafiltration or charcoal hemoperfusion; however, elimination, using styrene bead adsorption in an ex vivo model, has been demonstrated. Its clinical use is described. Case Report: A man in his 20s was admitted with shock into the Intensive Care Unit (ICU) after an overdose of amlodipine and risperidone. Resuscitation and supportive care were administered, but hypotension did not resolve despite the administration of intravenous fluids, infusions of calcium, adrenaline, and hyperinsulinemic-euglycemic therapy. Methylene blue was then administered to maintain the mean arterial pressures. However, the hemodynamic effect did not allow the weaning of the adrenaline. Drug clearance using hemoadsorption/hemoperfusion was attempted using a styrene resin filter (Jafron HA230; Jafron Biomedical Co., Ltd., Guangdong, China). During the two hemoperfusion sessions (6 h duration each, and 18 h apart) the patient had successfully weaned off all supportive measures, with lactate levels returning to normal and was later discharged home. At the end of each session, significant amlodipine concentrations were detected in blood aspirated from both filters, suggesting enhanced clearance. Why Should an Emergency Physician Be Aware of This?: Our case illustrates a temporal relationship between resin hemoperfusion therapy, resolution of hemodynamic instability, and shock without proving causation. Significant amlodipine elimination was suggested by high concentrations found in blood from the filter. At the same time, shock resolution after initiation of hemoperfusion occurred in less than one elimination half-life of amlodipine. © 2023 The Authors. Published by Elsevier Inc.**

□ **Keywords—Shock; Hemoadsorption; Hemoperfusion; Calcium channel blocker overdose; Critically ill**

Introduction

Calcium channel blockers (CCB) account for 35% of cardiovascular drug overdoses in the United States and are lethal in large amounts (1). Dihydropyridine CCBs have a greater affinity for smooth muscle L-type calcium channels, whereas non-dihydropyridine CCBs have an affinity for both cardiac and smooth muscle channels. Specific affinity is lost at high doses (1).

CCB overdose results in peripheral vasodilatation, reduced cardiac contractility, and possibly bradycardia, leading to circulatory compromise and shock (1). These drugs are lipid soluble, protein-bound with a large volume of distribution, and not amenable to removal by hemodiafiltration or charcoal hemoperfusion; however, removal using styrene bead adsorption (hemoadsorption/hemoperfusion [HP]) in an ex vivo model has been demonstrated (2,3).

Current management of CCB overdose is focused on supportive measures including vasoactive agents, calcium administration, and hyperinsulinemic-euglycemic therapy (4). Atropine is indicated for bradycardia. The use of methylene blue has been suggested for refractory

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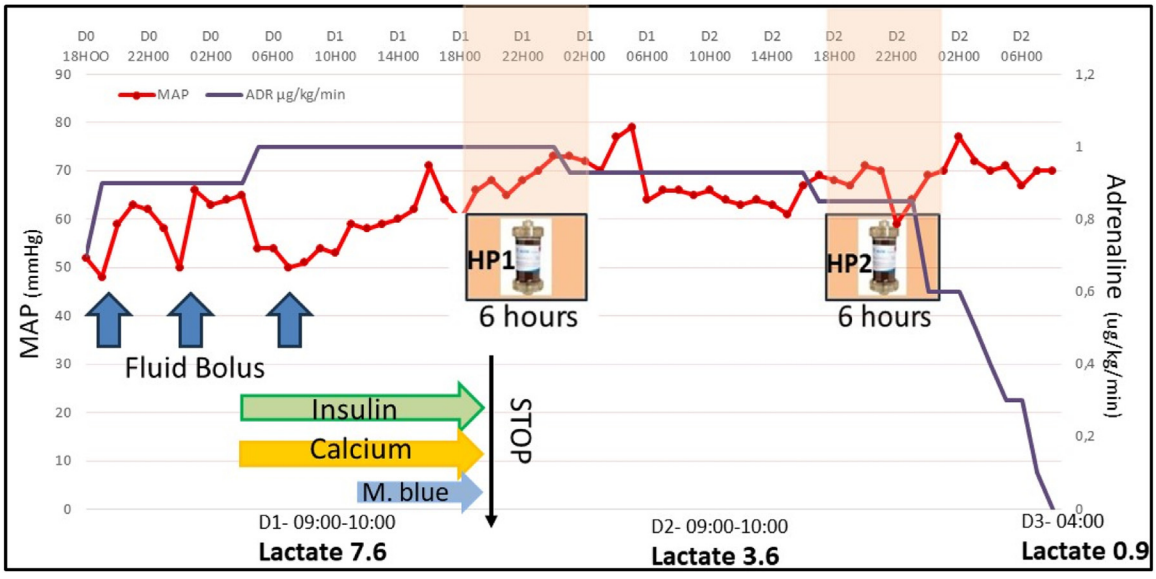

Figure 1. Timeline of the interventions and clinical course of shock. During the first cycle of hemoperfusion (HP1), mean arterial pressure (MAP) increased from 60 mm Hg to 73 mm Hg. Hyperinsulinemic-euglycemic therapy, calcium, and methylene blue (M-blue) infusions were stopped. Adrenaline (ADR) was weaned to 0.9 ug/kg/h and blood lactate decreased to 3.6 mmol/L. During the 2nd cycle of hemoperfusion (HP2), adrenaline was weaned to 0.6 ug/kg/min, with MAP remaining between 68 and 71 mm Hg. Four hours later lactate decreased to 0.9 mmol/L. Adrenaline was stopped a further 4 h later.

hypotension due to its inhibitory effect on guanylate cyclase (5).

Rescue therapy includes lipid emulsion, pacing, and venoarterial extracorporeal membrane oxygenation (4).

Case Report

Admission Day

A male patient in his 20s was admitted into the Intensive Care Unit (ICU) with hemodynamic instability and shock after an overdose of an unknown quantity of a dihydropyridine calcium channel blocker (amlodipine) and risperidone (atypical antipsychotic). On arrival in the ICU, the patient tested negative for paracetamol, salicylates, and tricyclic antidepressants. The history revealed the consumption of an unknown quantity of amlodipine (dihydropyridine CCB) in addition to risperidone. His full blood count, platelets, and renal function were within reference limits. An electrocardiogram did not show any acute changes, and the chest X-ray study was unremarkable.

Treatment

In the ICU, the patient required further increases in adrenaline infusion (1 ug/kg/min) and fluid challenges. Figure 1 provides the timeline of interventions related to hourly mean arterial pressure (MAP) changes, and lactate levels prior to and after each HP cycle until they normalized. High-dose insulin euglycemic therapy was initiated and titrated to 2 U/kg/h, maintaining euglycemia with 50% dextrose water. A 10% calcium chloride bolus over 10 min and subsequent infusion (0.2 mL/kg/h) was also initiated. Despite these interventions, his MAP was persistently inadequate, and lactate levels peaked at 7.6 mmol/L.

Methylene blue 2 mg/kg, followed by an intravenous infusion of 1 mg/kg/h, was initiated. Next, HP therapy was instituted using a continuous renal replacement therapy (CRRT) circuit with the adsorbent filter (Jafron HA230; Jafron Biomedical Co., Ltd., Guangdong, China) connected in series to the CRRT filter on the Prismaflex renal replacement system (Baxter International Inc., Deerfield, IL). Using a bicarbonate solution, we set the predilution to 500 mL/h and the blood flow rate to 180 mL/min. Heparin was administered into the circuit according to our CRRT protocol. We performed two 6-h cycles of HP therapy separated by an 18-h redistribution period.

Outcome and Follow-Up

During the first 6-h cycle of hemoperfusion therapy, the MAP increased from 60 mm Hg to 73 mm Hg, and the methylene blue, insulin, and calcium infusions were stopped. Adrenaline was weaned to 0.9 ug/kg/min and blood lactate decreased to 3.6 mmol/L (from a peak of 7.6 mmol/L).

During the second 6-h cycle of hemoperfusion, adrenaline was weaned to 0.6 ug/kg/min and stopped a

further 8 h later. The lactate decreased to 0.9 mmol/L, and a MAP of 70 mm Hg was maintained. There was no bleeding, blood product transfusion, or other adverse events associated with the procedure (extracorporeal circuit and anticoagulation). The patient was extubated 48 h later and then discharged home after a psychiatric referral. One year later the patient was clinically well, fully independent, and having weekly follow-up visits with a social worker based at the hospital.

Amlodipine measurement estimates using liquid chromatography-mass spectrometry on blood from the first and second hemoperfusion filters yielded concentrations of 80 mg/L and 40 mg/L, respectively. After the initiation of HP therapy, shock resolution (normal lactate and no vasopressor therapy) occurred within 38 h.

Discussion

We describe a temporal relationship between the application of hemoperfusion therapy and hemodynamic recovery due to amlodipine overdose. We found one case in the literature that utilized charcoal hemoperfusion for a CCB overdose (2). Roberts et al. found no clinical improvement during or immediately after hemoperfusion (2). In contrast, our findings showed both hemodynamic and shock improvement during and immediately after therapy.

Two important differences worth noting included both the type of CCB and filter. Amlodipine with a longer half-life ($T_{1/2} = 50$ h) was the CCB in this case vs. diltiazem in the case by Roberts et al. (2). Diltiazem is a non-dihydropyridine CCB with a $T_{1/2}$ 6–9 h and may cause bradycardia, as opposed to a reflex tachycardia caused by amlodipine (1). Roberts et al. used a single application of a charcoal filter for 3 h (2).

Charcoal adsorption filters can be used in an extracorporeal circuit to adsorb particles and enhance their elimination. They are useful for endogenous substances like urate and creatinine. Activated charcoal is a nonspecific adsorbent that creates weak Van de Waals forces with particles. Its elimination effect may therefore be quite limited. In addition, charcoal adsorption is associated with significant adverse effects like thrombocytopenia, leukocytopenia, charcoal embolism, and fever. Special charcoal coating has been attempted to reduce embolism, but this may also limit particle clearance (6).

Hemodiafiltration therapies are different from hemoadsorption treatments (charcoal and resin filtration); the former is useful in removing water-soluble substances. Hemofiltration removes larger particles using the process of convection, whereas hemodialysis uses diffusion to remove smaller particles. However, the prerequisite is water solubility for both (7). Given the lipid solubility and protein binding of amlodipine, both these therapies are unlikely to enhance the elimination of this drug.

We applied a multicycle approach using a resin filter composed of styrene beads and interrupted the two 6-h cycles with an 18-h interval. Charcoal binding is weak, whereas resins (styrene) are useful for protein-bound, lipid-soluble substances and have superior adsorbent properties (8).

The volume of distribution of both amlodipine and diltiazem is greater than the ideal of < 1 L/kg for effective hemoperfusion (6). It is possible that the use of an 18-h interval between the two HP cycles was important to allow the redistribution of amlodipine into the vascular compartment after initial clearance with the first cycle of HP therapy, compared with the single cycle of charcoal adsorption by Roberts et al. (2). This intercompartmental transfer, together with the superior adsorbent properties of the newer styrene material, may have been responsible for the effectiveness of hemoperfusion in our case. This is supported by an ex vivo model using an adsorbent filter composed of divinylbenzene co-polymer beads (similar to the adsorbent filter used in our case) (3). This model showed that amlodipine exhibited first-order kinetics in keeping with a two-compartment model. They demonstrated that 89% of amlodipine was removed after 2 h of adsorption (3).

In the case by Roberts et al., the combined adrenaline and noradrenaline dose was 40 ug/min (2). Our case required much higher doses of catecholamines (69 ug/min of adrenaline) and we used methylene blue, as vasopressin was not registered in South Africa at the time.

Although our case illustrates a temporal relationship between the HP therapy and clinical improvement, beyond determining that there was a significant concentration of amlodipine retained in the filter, we did not have sufficient information to calculate amlodipine clearance. It is worth noting that the shock resolution after initiation of hemoperfusion in our case occurred in less than one elimination $T_{1/2}$ of amlodipine (38 h vs. amlodipine $T_{1/2} = 50$ h).

Why Should an Emergency Physician Be Aware of This?

This case demonstrates a temporal relationship between resin hemoperfusion therapy, hemodynamic improvement, and shock resolution (normalization of lactate) without proving causation. Significant amlodipine concentrations were measured in blood from the hemoperfusion filter, whereas shock resolution after initiation of hemoperfusion occurred in less than one elimination $T_{1/2}$ of amlodipine. Early application of hemoperfusion using styrene resins can be considered to enhance amlodipine

elimination and may prove useful in addition to traditional rescue therapies like intralipid and venoarterial extracorporeal membrane oxygenation when hemodynamic stability is refractory to standard therapies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Stephen VS, Pluymers NA, Gauton SJ. Emergency management of calcium channel blocker overdose. S Afr Med J 2019;109:635–8.
2. Roberts DM, Roberts JA, Boots RJ, Mason R, Lipman J. Lessons learnt in the pharmacokinetic analysis of the effect of haemoperfusion for acute overdose with sustained-release diltiazem. Anaesthesia 2008;63:714–18.
3. Capponi V, Young W, Chan P, Lavonas E. A novel adsorbent system rapidly clears amlodipine from human blood. Updates in ICU Medicine: Controversies, Challenges and Solutions; 2017. Available at: https://www.crrtonline.com/conference/posters_2017/52%20Vincent%20Capponi.pdf. Accessed April 25, 2023.
4. St-Onge M, Anseeuw K, Cantrell FL, et al. Experts consensus recommendations for the management of calcium channel blocker poisoning in adults. Crit Care Med 2017;45:e306–15.
5. Fisher J, Taori G, Braitberg G, Graudins A. Methylene blue used in the treatment of refractory shock resulting from drug poisoning. Clin Toxicol (Phila) 2014;52:63–5.
6. Mirrakhimov AE, Barbaryan A, Gray A, Ayach T. The role of renal replacement therapy in the management of pharmacologic poisonings. Int J Nephrol 2016;2016. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5155094/. Accessed February 09,2024.
7. Jha VK, Padmaprakash KV. Extracorporeal treatment in the management of acute poisoning: what an intensivist should know? Indian J Crit Care Med 2018;22:862–9.
8. Ghannoum M, Bouchard J, Nolin TD, Ouellet G, Roberts DM. Hemoperfusion for the treatment of poisoning: technology, determinants of poison clearance, and application in clinical practice. Semin Dial 2014;27:350–61.