

# Calcium Channel Blocker Toxicity Causing Acute Respiratory Distress Syndrome: A Commonly Used Drug Triggering a Life-Threatening Condition

Fahad Aftab Khan Lodhi, MD; Sophie L. Shogren; Jayanth G. Vedre, MD; Najiya Haque, MD; Martin Reriani, MD; Rashid Ali, MD

## ABSTRACT

**Introduction:** Calcium channel blockers (CCBs) are commonly used but have the potential to cause substantial toxicity. One such underreported toxicity of CCB use is the development of acute respiratory distress syndrome (ARDS).

**Case Presentation:** A 44-year-old previously healthy woman presented to the emergency department (ED) having taken 60 tablets of 125 mg extended-release verapamil and 90 tablets of 0.25 mg clonazepam with the intent to commit suicide. On presentation to the ED, she was sedated and intubated for airway protection. She received aggressive medical resuscitation and was ventilated using low tidal volume mechanical ventilation. The hospital course was complicated by worsening hypoxia and a chest x-ray demonstrating bilateral patchy geographic areas of airspace opacities consistent with ARDS. On day 5 of hospitalization, the patient's clinical status improved significantly, and she was subsequently weaned off vasopressors and extubated.

**Discussion:** CCB toxicity can result in profound hypotension, shock, bradycardia, and conduction blocks, as well as hyperglycemia, acidosis and acute kidney injury, and ARDS. It is important for clinicians to understand the signs and symptoms of CCB toxicity, as well as how to treat it.

## INTRODUCTION

Calcium channel blockers (CCBs) are classified into 2 categories: dihydropyridine (amlodipine, nifedipine, felodipine) and nondihydropyridine (verapamil, diltiazem). Dihydropyridine CCBs act on L-type channels on the vasculature, whereas nondihydropyridine CCBs act on those on the myocardium. These drugs are commonly used and have the potential to cause substantial toxicity,

• • •

**Author Affiliations:** Marshfield Medical Center, Marshfield, Wis (Lodhi, Vedre, Reriani, Ali); University of Wisconsin School of Medicine and Public Health, Madison, Wis (Shogren); Fatima Memorial Hospital for Medicine and Dentistry, Lahore, Pakistan (Haque).

**Corresponding Author:** Fahad Aftab Khan Lodhi, MD, 1000 N Oak Ave, Marshfield Medical Center, Marshfield, WI 54449; phone 337.884.7866; email lodhi.fahad@marshfieldclinic.org.

a fact that is often underappreciated. In 2002, 9,500 cases of CCB poisoning were reported to poison centers in the United States.<sup>1</sup> CCBs constitute the leading form of cardiovascular drug overdose and have been implicated in up to 48% of deaths caused by such overdose.<sup>2</sup>

Dihydropyridine CCB toxicity is caused by arterial vasodilation with reflex tachycardia, and nondihydropyridine CCB toxicity is caused by peripheral vasodilation, bradycardia, and decreased cardiac inotropy.<sup>3</sup> The profound hypotension and end-organ ischemia resulting from severe overdose can cause complications such as stroke, seizure, myocardial infarction, renal failure, bowel ischemia, and acute respiratory distress syndrome (ARDS).<sup>4</sup>

## CASE REPORT

A 44-year-old previously healthy, ambulatory woman presented to the emergency department having taken 60 tablets of 125 mg extended-release verapamil and 90 tablets of 0.25 mg clonazepam with the intent to commit suicide. Her past medical history included major depressive disorder with previous suicide attempts via intentional ingestion, migraine headaches with aura, and restless leg syndrome. She was taking verapamil for migraine prevention and clonazepam for symptomatic relief from restless leg syndrome; the number of pills she took in attempt to overdose was provided via self-report.

At presentation, the patient was hypotensive and bradycardic with slurred speech and an altered mental state. Physical examination revealed a sedated female with a blood pressure of 80/40, heart rate of 46, respiratory rate of 16 and initial Glasgow Coma

Score of 12/15 (E3, V4, M5). Her pulse was slow and regular without S3 or S4 gallop. Systemic examination of the cardiorespiratory system was unremarkable; she had no new or changed murmurs, and her lungs were clear to auscultation.

The patient was emergently sedated and intubated for airway protection. Poison control was urgently consulted, and their recommendations were followed. Aggressive fluid resuscitation was followed by multiple doses of calcium chloride, calcium gluconate, and atropine. Additionally, insulin and dextrose, glucagon, and lipid emulsion therapy were used to combat CCB overdose. Vasopressor support comprised of epinephrine, norepinephrine, and dopamine was used to overcome resistant hypotension, and a temporary transvenous pacemaker was placed due to unstable bradycardia. The patient was mechanically ventilated with low tidal volume ventilation and permissive hypercapnia; arterial blood gases upon ventilation with 100% fraction of inspired oxygen (FiO<sub>2</sub>) were pH 7.37, PCO<sub>2</sub> 32, PO<sub>2</sub> 169.

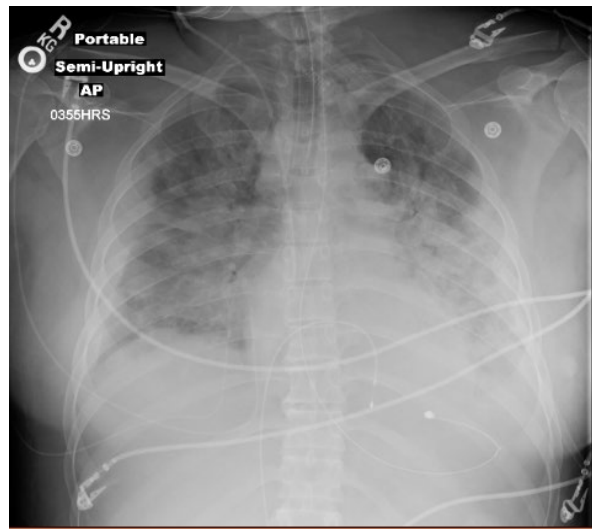
Initial labs revealed a blood glucose of 156 mg/dl, creatinine of 1.05, and an estimated glomerular filtration rate of 57 mL/min. The patient's urine drug screen was positive for benzodiazepines and negative for other drugs, and liver function tests showed mildly elevated aspartate aminotransferase levels. A urine pregnancy test was negative. The complete blood count and inflammatory markers were normal, and blood cultures displayed no growth. The chest x-ray initially showed left basilar atelectasis and on day 3 of her hospitalization revealed the findings depicted in Figure 1. Electrocardiogram (Figure 2) revealed a junctional rhythm with rates of 42, a prolonged QRS of 122 ms, and a corrected QT of 434 ms. Transthoracic 2D echocardiography revealed an ejection fraction of 62%, normal systolic function of both the left and right ventricle, and normal morphology. Mild thickening of the mitral valve with trivial to mild mitral valve regurgitation was detected; however, cardiac output of 3.7 L/min, stroke volume of 58.3 mL, E/e' < 15, and E/A ratio < 0.8 was consistent with normal cardiac function and left atrial filling pressure.<sup>5</sup>

Significant clinical improvement led to weaning of vasopressors and the pacemaker being turned off on day 5 of hospitalization. Ventilator weaning trials were initiated, and the patient was extubated on day 10 of hospitalization. She participated in daily physical therapy sessions and was discharged on day 13 of hospitalization, after she was able to breathe on room air while maintaining her heart rate, blood pressure, and oxygen saturation.

## DISCUSSION

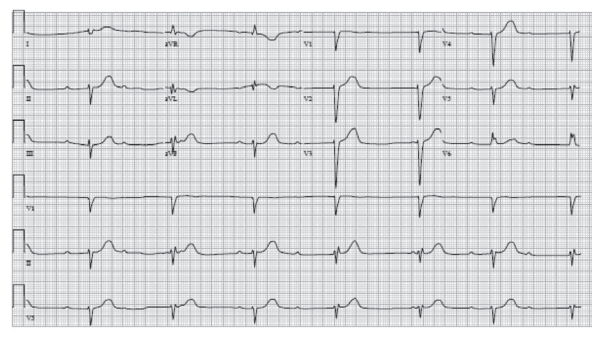
Acting through L-type calcium channels, CCBs cause vasodilation of peripheral vasculature and myocardial depression, which can result in profound hypotension, shock, bradycardia, and conduction blocks.<sup>6</sup> CCB toxicity also has been associated with hyperglycemia,<sup>7</sup> acidosis and acute kidney injury,<sup>8</sup> noncardiogenic pulmonary edema,<sup>9,10</sup> and ARDS.<sup>8,10-12</sup> The mechanism behind CCB toxicity causing ARDS is unknown, but 2 mechanisms have been

Figure 1. Patient Chest X-ray



Extensive, patchy geographic areas of airspace opacities throughout majority of the lungs with sparing of apices. Endotracheal tube tip lies 1.7 cm above the carina. Nasogastric tube lies with tip into the gastric body. Right internal jugular central line ends with tip in the high right atrium.

Figure 2. Patient Electrocardiogram



Sinus rhythm with atrioventricular dissociation and wide QRS rhythm.

proposed: one suggests that CCBs inhibit endothelin-1-stimulated surfactant secretion by type II epithelial cells, leading to alveolar collapse,<sup>11</sup> while another suggests that selective precapillary vasodilation causes excessive transudation of fluid from pulmonary capillaries into the alveoli.<sup>13</sup>

Although CCB-induced ARDS is a fairly rare occurrence, literature supports the notion that CCB intoxication can increase patient risk of developing ARDS. Siddique et al reported a 40-year-old male who developed ARDS following noncardiogenic pulmonary edema and aspiration pneumonitis from CCB intoxication.<sup>9</sup> Additionally, ingestion of high-dose verapamil and subsequent development of ARDS has been documented by Izdes et al,<sup>12</sup> and Magdylan et al reported a 22-year-old female developing ARDS after CCB intoxication.<sup>11</sup>

Though patients ingesting more than the maximum daily dose are at higher risk of developing serious intoxication, toxicity can occur even with therapeutic doses of CCBs in patients with underlying cardiac disease or metabolic derangements.<sup>14</sup> This can be further complicated by the fact that extended-release CCBs—like those the patient in this case took—decrease the rate of clearance via the liver, which ultimately increases duration of toxicity. For this reason, it is important for clinicians to understand the signs and symptoms of CCB toxicity, as well as how to treat it.

First-line therapy for CCB toxicity generally consists of intravenous (IV) calcium to promote calcium influx via unblocked L-type calcium channels, norepinephrine and/or epinephrine when the patient is in shock, and high-dose insulin therapy in the setting of cardiac dysfunction.<sup>15</sup> Both subtypes of CCBs affect the pancreas by reducing insulin secretion, causing insulin resistance in body tissues and inducing a carbohydrate-deficient intracellular state.<sup>9</sup> As such, lactic acidemia and metabolic acidosis can result. High-dose insulin therapy actively transports glucose into the energy-depleted cells, reverses metabolic derangements, and has a positive inotropic effect on the cardiac myocytes. Additionally, glucagon has been shown to improve heart rate and cardiac output and reverse atrioventricular blocks in animal studies.<sup>16</sup>

In patients refractory to first-line therapies, transcutaneous or transvenous pacemaker placement and IV lipid emulsion therapy is recommended.<sup>15</sup> CCBs are lipophilic, highly protein-bound, undergo extensive hepatic first-pass metabolism, and have a large volume of distribution (>2L/kg).<sup>4</sup> These characteristics make CCB decontamination difficult because at higher doses, clearance via the liver slows; additionally, methods of clearance like hemodialysis are ineffective due to the lipophilic and protein-bound nature of CCBs. Intravenous lipid emulsion therapy is useful in CCB toxicity because the lipid emulsion surrounds the lipophilic CCB, rendering it ineffective. The CCB gets trapped in an expanded plasma lipid compartment, which reduces the volume of distribution.<sup>17</sup> It has also been proposed that intralipids improve overall cardiac function by providing an energy source for the cardiac myocytes, since CCB toxicity shuts down fatty acid transportation to the cardiac myocytes.

## CONCLUSION

CCBs are commonly used in clinical practice and have the potential to cause serious side effects if over-ingested (unintentionally or with suicidal intent), used in combination with drugs that have interactions, or even when taken in therapeutic doses by patients with underlying cardiac disease or metabolic derangements. Cautious use of CCBs by clinicians, as well as maintaining awareness that these drugs increase risk of developing ARDS, can help prevent such adverse events from occurring. Additionally, since CCBs have unique metabolic properties that make toxicity challenging to treat, first and second-line treatments must be kept in mind when caring for acutely ill patients.

**Funding/Support:** None declared.

**Financial Disclosures:** None declared.

## REFERENCES

1. Hofer CA, Smith JK, Tenholder MF. Verapamil intoxication: a literature review of overdoses and discussion of therapeutic options. *Am J Med.* 1993;95(4):431-438. doi:10.1016/0002-9343(93)90314-f
2. Ghosh S, Sircar M. Calcium channel blocker overdose: experience with amlodipine. *Indian J Crit Care Med.* 2008;12(4):190-193. doi:10.4103/0972-5229.45080
3. Watson WA, Litovitz TL, Rodgers GC Jr, et al. 2002 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med.* 2003;21(5):353-421. doi:10.1016/s0735-6757(03)00088-3
4. Chakraborty RK, Hamilton RJ. Calcium channel blocker toxicity. StatPearls. Updated November 21, 2019. Accessed March 5, 2020. <https://www.ncbi.nlm.nih.gov/books/NBK537147>
5. Andersen OS, Smiseth OA, Dokainish H, et al. Estimating left ventricular filling pressure by echocardiography. *J Am Coll Cardiol.* 2017;69(15):1937-1948. doi:10.1016/j.jacc.2017.01.058
6. Rizvi I, Ahmad A, Gupta A, Zaman S. Life-threatening calcium channel blocker overdose and its management. *BMJ Case Rep.* 2012;2012:bcr0120125643. doi:10.1136/bcr.01.2012.5643
7. Salhanick SD, Shannon MW. Management of calcium channel antagonist overdose. *Drug Saf.* 2003;26(2):65-79. doi:10.2165/00002018-200326020-00001
8. Naha K, Suryanarayana J, Aziz RA, Shastri BA. Amlodipine poisoning revisited: acidosis, acute kidney injury and acute respiratory distress syndrome. *Indian J Crit Care Med.* 2014;18(7):467-469. doi:10.4103/0972-5229.136078
9. Siddiqi TA, Hill J, Huckleberry Y, Parthasarathy S. Non-cardiogenic pulmonary edema and life-threatening shock due to calcium channel blocker overdose: a case report and clinical review. *Respir Care.* 2014;59(2):e15-e21. doi:10.4187/respcare.02244
10. Sami Karti S, Ulusoy H, Yandi M, et al. Non-cardiogenic pulmonary oedema in the course of verapamil intoxication. *Emerg Med J.* 2002;19(5):458-459. doi:10.1136/emj.19.5.458
11. Magdalan J, Antończyk A, Kowalski K, Przewłocki M, Kochman K, Wasylko-Smolarek M. Severe pulmonary complications of massive intoxication with calcium channel blockers and isosorbide mononitrate—a case report. *Przegl Lek.* 2004;61(4):405-407.
12. Izdes S, Altintas ND, Soykut C. Acute respiratory distress syndrome after verapamil intoxication: case report and literature review. *Acta Clin Belg.* 2014;69(2):116-119. doi:10.1179/2295333714Y.0000000007
13. Humbert VH Jr, Munn NJ, Hawkins RF. Noncardiogenic pulmonary edema complicating massive diltiazem overdose. *Chest.* 1991;99(1):258-259. doi:10.1378/chest.99.1.258
14. Proano L, Chiang WK, Wang RY. Calcium channel blocker overdose. *Am J Emerg Med.* 1995;13(4):444-450. doi:10.1016/0735-6757(95)90137-X
15. 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(3):e306-e315. doi:10.1097/CCM.0000000000002087
16. St-Onge M, Dubé PA, Gosselin S, et al. Treatment for calcium channel blocker poisoning: a systematic review. *Clin Toxicol (Phila).* 2014;52(9):926-944. doi:10.3109/15563650.2014.965827
17. French D, Armenian P, Ruan W, et al. Serum verapamil concentrations before and after Intralipid® therapy during treatment of an overdose. *Clin Toxicol (Phila).* 2011;49(4):340-344. doi:10.3109/15563650.2011.572556

advancing the art & science of medicine in the midwest

**WMJ**

*WMJ* (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

© 2020 Board of Regents of the University of Wisconsin System and The Medical College of Wisconsin, Inc.

**Visit [www.wmjonline.org](http://www.wmjonline.org) to learn more.**