Case Report

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A Rare Cause of Refractory Vasodilatory Shock Due to Calcium Channel Blocker Toxicity from Drug–Drug Interaction Between Ritonavir–Boosted Nirmatrelvir (Paxlovid) and Manidipine

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Abstract

Herein, is a reported case of an 86–year–old woman, admitted due to complete atrioventricular block. During admission, she was diagnosed and treated with ritonavir–boosted nirmatrelvir (Paxlovid) for the coronavirus disease 2019 (COVID–19). Four days after initiating the treatment for COVID–19, an oral dose of 20 mg manidipine was administrated. Five hours later, the patient developed hypotension that eventually progressed to refractory shock requiring a maximum dose of 1.82 μg/kg/min of norepinephrine equivalent. Shock reversal dramatically improved within 17 hours after the cause of shock was diagnosed, and her having receiving specific treatment via intravenous calcium administration and high–dose insulin euglycemia therapy (HIE).

Keywords: COVID–19, critically ill patient, drug interaction, drug toxicity, intensive care unit, refractory shock

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Introduction

Circulatory shock is a common, life-threatening problem that requires immediate evaluation and management. Distributive shock is the most frequent cause of shock in the intensive care unit, and septic shock; accounting accounts for around half to two-thirds of all cases, is the most prevalent subtype of distributive shock[1, 2]. Therefore, the challenge is identifying the unusual cause of distributive shock that requires a high index of suspicion to provide both early diagnosis and specific treatment. Calcium channel blocker toxicity is one of the uncommon causes of distributive shock.

Case report

An 86-year-old woman, with underlying diseases of essential hypertension, hyperlipidemia, and asthma presented with pre-syncope 3 days prior to admission. She was diagnosed with complete atrioventricular (AV) block and showed pulmonary congestion on her chest radiograph. Her vital signs at the time of admission were as following: a body temperature of 38.6 ºC (101.5 ºF), pulse rate of 43 beats per min, respiratory rate of 24 per min, and blood pressure of 186/43 mmHg: her body weight was 50 kilograms.

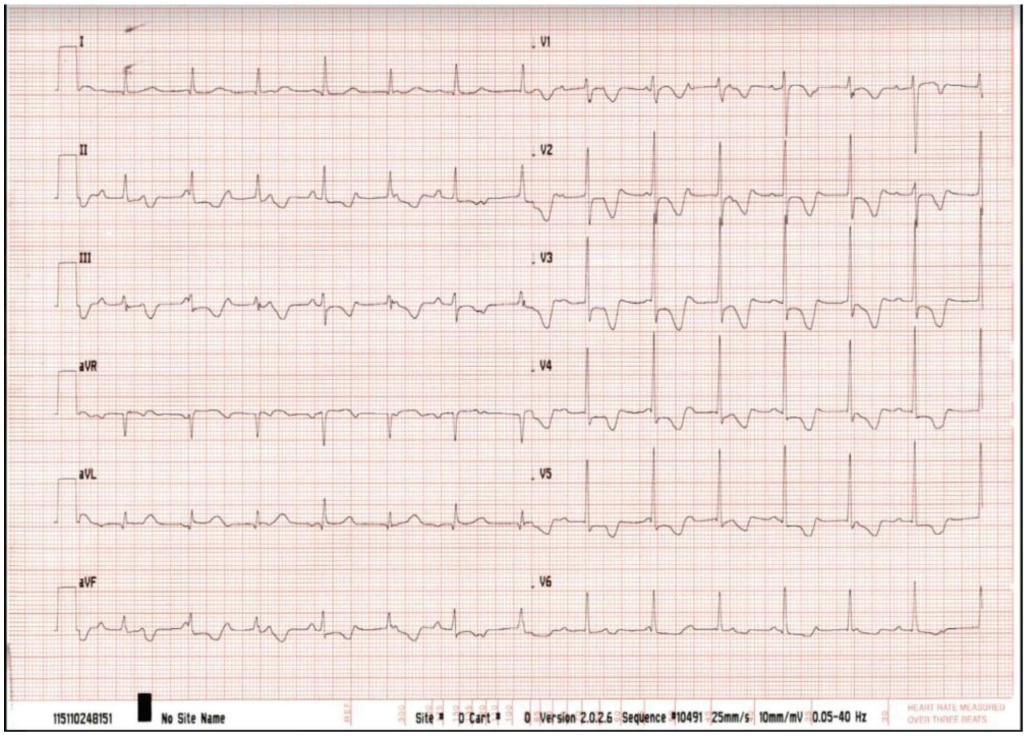
Echocardiography demonstrated a left ventricular ejection fraction (LVEF) of 60.0% and peak aortic valve velocity max of 4.5 m/sec. Therefore, severe aortic valve stenosis was suspected even in spite of this high output status. A transvenous, temporary pacemaker was implanted, and intravenous furosemide was administrated. Additionally, she had a low-grade fever with a runny nose. Due to ongoing pandemic, reverse transcription-polymerase chain reaction for coronavirus disease 2019 (COVID-19) was undertaken and returned as positive. Although, the patient had mild symptoms, she was at high risk of developing severe COVID-19; hence, ritonavir-boosted nirmatrelvir (Paxlovid) was given. The the dosage was modified, based on her glomerular filtration rate (GFR), and she was prescribed one tab of nirmatrelvir and one tab of ritonavir every 12 hours.

Four days after beginning treatment for her COVID-19 infection, oral manidipine 20 mg was administrated for blood pressure control. Five hours later, hypotension occurred, and her blood pressure decreased from 186/83 mmHg to 88/41 mmHg (mean arterial pressure; MAP 57 mmHg). On initial examination, the patient was conscious, afebrile, and had adequate urine output. Three hours later, anuria occurred, and her arterial lactate level increased from 1.0 to 2.9 mmol/L, with a maximum of 7.0 mmol/L. She rapidly developed refractory shock, which required a high dose of vasopressors and an inotropic drug. During the refractory shock phase, the patient experienced drowsiness, exhaustion, shivering, nausea and vomiting. The maximal doses of norepinephrine, adrenaline and dopamine administered were: 0.8 µg/kg/min, 0.8 µg/kg/min, and 33.3 µg/kg/min, respectively. These doses were determined to be equivalent to 1.82 µg/kg/min of norepinephrine. Advanced hemodynamic monitoring, using FloTrac/EV 1000, demonstrated a systemic vascular resistance (SVR), in the range of 810-1100 dynes-sec/cm^5, and a cardiac output (CO) ranging from 2.2-3.5 L/min.

Initial electrocardiogram (ECG) examination at the onset of hypotension revealed a ventricular pacing rate at 70 bpm. During the refractory shock phase, her ECG appeared as a complete AV block, with a ventricular escape rate at 80 bpm (Figure 1). Bedside echocardiography demonstrated good LVEF as well as an absence of regional wall motion abnormalities. Furthermore, hyperglycemia (serial capillary blood sugar at the event: 220-390 mg/dL), thrombocytopenia (platelet count: 80x10^3/L), hypokalemia (serum potassium: 3.17 mmol/L), metabolic acidosis (serum bicarbonate: 16.3 mmol/L) and rising of serum creatinine, from 0.54 to 1.18 mg/dL, were newly identified. The level of other electrolytes remained normal: serum sodium 138.2 mmol/L, chloride 104.4 mmol/L, correct calcium 8.7 mg/dL, and phosphorus 2.9 mg/dL. The patient had a hemoglobin level of 11.7 g/dL, a white blood cell count of 5.9x10^3/µL, and no pulmonary infiltration on

chest radiograph. The initial, provisional diagnosis was septic shock. Therefore, meropenem and vancomycin were administered intravenously as empirical antibiotic treatment.

Six hours later, owing to the rapid deterioration of refractory shock, the cause and management of shock were intensively reviewed and discussed by both the intensivist and cardiologist. The potential diagnosis was calcium channel blocker poisoning caused by drug-drug interactions between ritonavir-boosted nirmatrelvir and manidipine. Hence, ritonavir-boosted nirmatrelvir was discontinued and was switched to remdesivir. Moreover, 10% calcium gluconate intravenous and high-dose insulin were administered; starting with a dose of 10% calcium gluconate of 0.6 mL/kg (30 mL) intravenously for 5 minutes. This was followed by an intravenous drip of 0.4 mL/kg/h (20 mL/h) for 10 hours, and a regular insulin dose of 0.5 unit/kg/h plus 50%dextrose of 1 mL/kg/h titrated to maintain capillary a blood glucose level of 140-200 mg/dL. The patient's shock was dramatically reversed within 17 hours after the cause was diagnosed, and specific treatments were provided; additionally, the patient was successfully extubated within a day. A review of the course of treatment and its favorable outcome is demonstrated in Table 1. All of the septic workups had negative findings, and platelet counts returned to normal within 10 days after discontinuing the administration of ritonavir-boosted nirmatrelvir. The adverse effect of intravenous calcium treatment was hypercalcemia (maximum serum calcium 16.9 mg/dL), which could be corrected with aggressive intravenous crystalloid and furosemide therapy. The patient demonstrated satisfactory performance status upon hospital discharge, had marked improvement in appearance after a follow-up of 2 weeks, and she was able to effectively and dependently perform the activities of daily living; including cooking.



AV=atrioventricular, bpm=beats per minute

Figure 1 Electrocardiogram appeared as a complete AV block with a ventricular escape rate at 80 bpm

Table 1 Review the course of treatment and favorable outcome

Time (hours from start IV calcium and high dose insulin)	Accumulative dose of 10% calcium gluconate (gm)	Regular insulin IV drip (U/kg/h)	Ionized calcium (mmol/L)	Norepinephrine equivalent dose (μg/kg/min)	MAP (mmHg)	CO (L/min)	SVR dynes-sec/cm^5	Arterial lactate (mmol/L)
0	30 mL of 10% calcium gluconate (0.6 mL/kg) IV drip over 5 min, then IV drip 20 mL/h	0.4	1.15	1.6	84	3.7	1,500	4.8
1	5	0.4	1.5	1.54	89	2.9	1,900	4.4
2	7	0.5	1.62	1.32	83	2.9	2,100	–
3	9	0.6	1.70	1.20	88	2.9	2,100	4.5
4	11	0.5	1.77	0.92	88	2.6	2,100	4.3
				Off adrenaline				
5	13	0.6		0.80	97	2.6	2,300	–
6	15	0.1	1.9	0.72	88	2.6	2,200	
7	17	Off insulin		0.6	96	3.0	2,100	–
8	19		2.06	0.48	96	3.1	2,100	3.7
9	21			0.4	91	3.0	2,000	–
10	Off IV calcium		2.09	0.2	102	2.8	2,200	3.4
11				0.12	81	2.5	1,900	–
12			1.81	0.08	72	2.6	2,000	3.0
13				0.08	71	2.6	2,000	–
14				0.08	70	2.6	2,000	–
15				0.08	75	2.8	1,700	–
16				0.08	77	2.8	1,600	–
17				Off norepinephrine	69	3.0	1,600	–
18				–	75	3.4	1,500	–
19			1.81	–	72	3.2	1,300	–
20				–	76	3.1	1,800	–
21			1.61	–	77	3.1	1,800	–
22			1.47	–	81	3.0	1,700	2.6
23				–	77	3.1	1,600	–
24			1.45	–	84	3.1	1,600	2.6
26			1.34	–	85	3.2	1,600	2.1
34			1.29	–	86	3.9	1,600	1.9

IV=intravenous, MAP=mean arterial pressure, CO=cardiac output, SVR=systemic vascular resistance

Discussion

Shock is an acute, life-threatening circulatory failure that impairs tissue perfusion, and can deteriorate to irreversible end-organ failure. The definition of refractory vasodilatory shock varies, depending on vasopressor doses, which range from above 0.2 μg/kg/min to 0.5 μg/kg/min of a norepinephrine equivalent[3-5]. Patients with vasodilatory refractory shock have a poor prognosis, with mortality exceeding 50.0%[2,6]. Early recognition, rapid identification, and treatment of reversible etiology of shock are crucial to prevent clinical deterioration, and the progress to multisystem failure. The incidence of refractory shock is around 6.0-7.0% of critically ill patients by definition of administration of ≥0.5 μg/kg/min of a norepinephrine equivalent[3]. Although, septic shock is the most common cause of distributive shock, some unusual causes; such as intoxication-related causes, remain a concern. A thorough history and prescribed drug timeline are important for diagnostic intoxication and early specific treatment, or an antidote should be immediately recommended for administration. The evaluation of negative inotropy and low systemic vascular resistance is helpful for the selection of appropriate inotropes as well as vasopressors.

Calcium channel blockers (CCBs) are frequently prescribed to control blood pressure, and based on their physiological effects, CCBs are divided into two primary clinical categories: dihydropyridines (such as: amlodipine, nifedipine, felodipine, and nicardipine) and non-dihydropyridines (such as: verapamil, and diltiazem)[7]. CCBs are well absorbed orally, and undergo extensive hepatic first-pass metabolism by Cytochrome P450 enzymes (CYPs). However, the use of CYP inhibitors causes drug-drug interactions with CCBs that are clinically significant[8].

Manidipine is categorized in the dihydropyridine CCB group that directly blocks voltage-gate L-type calcium channel opening, calcium flux into the myocardium, and vascular smooth muscle cells. Therefore, dihydropyridine CCBs are potent vasodilators; however, at high doses they can negatively affect cardiac contractility or AV conduction; thus, suppressing the myocardium[9]. The clinical presentation of shock from CCB intoxication may initially manifest as hypotension ajoined with bradycardia, and can progress to cardiogenic shock. Moreover, CCBs also inhibit L-type calcium channels in pancreatic islet cells, reducing insulin secretion; resulting in hyperglycemia and reduced cardiac glucose utilization. Therefore, CCB toxicity should be evaluated in patients with hypotension with bradycardia, and new-onset of hyperglycemia. The serum levels of CCB agents are not frequently reported[7]. Additionally, hyperglycemia is a typical side effect of all CCB subclasses, and might serve as a helpful clinical indicator for the severity of intoxication[10]. Metabolic acidosis is a direct result of both of these side effects[11]; additionally, mild hypokalemia and mild-to-severe hypocalcemia are other frequent side effects[12]. Hemodynamic monitoring must guide vasopressor and inotropic agent selection for all patients with suspected CCB toxicity. Arterial blood gas, serum lactate, electrolytes, blood glucose in addition to renal function are required to be performed, and monitored to assess the level of toxicity and treatment response[13].

Although, CCB toxicity can be reversed using various therapy strategies, there is no agreement on a gold standard treatment strategy. However, some common suggestions consider providing patients with CCB toxicity treatment options to improve hemodynamic status. Vasopressors are indicated to restore hemodynamic stability. The 2017, Critical Care Medicine Experts Consensus recommended intravenous calcium as a first-line treatment, based on improved contractility and blood pressure; whereas, high-dose insulin therapy in combination with other first-line treatments is indicated if evidence of myocardial dysfunction is noted. By contrast, Critical Care Medicine Experts

Consensus discourages the use of glucagon, owing to its associated, unpredictable effects; such as significant vomiting, and hyperglycemia that have been reported in multiple case reports[13]. In cases of refractory shock, incremental doses of high-dose insulin (up to 10 U/kg/h) and lipid-emulsion therapy are recommended. A pacemaker should be considered in patients with unstable bradycardia or high-grade AV block. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) should be considered in those with cardiogenic shock or cardiac arrest admitted in centers where treatment is available[13].

According to The Evaluation of Protease Inhibitor for COVID-19 in High-Risk Patients (EPIC-HR) study[14], ritonavir-boosted nirmatrelvir reduced the probability of developing the severe disease without obvious safety issues. Therefore, the treatment guidelines advise non-hospitalized adults with mild to moderate COVID-19 whom are at high risk of disease progression to take ritonavir-boosted nirmatrelvir. However, this medication has considerable interactions, mainly because it contains ritonavir; a potent CYP3A inhibitor. As a result, there is a higher risk of significant drug toxicities. Moreover, it may also increase the concentrations of several concurrent drugs. The potential of drug-drug interaction between ritonavir-boosted nirmatrelvir coupled with concomitant medications should be reviewed before ritonavir-boosted nirmatrelvir is prescribed. The strategies for proper management of drug interaction include: increased monitoring, adjusting the dose, temporarily withholding concomitant medication, or using an alternative to any concomitant medication. According to the Food and Drug Administration (FDA), ritonavir-boosted nirmatrelvir should not be used with medications that are highly dependent on CYP3A for clearance, and for those that are known to cause serious or fatal side effects. FDA warnings along with precautions indicate that only a few clinical studies have examined the effects of ritonavir-boosted nirmatrelvir, and its serious, unanticipated side effects that have not been previously recorded with this new antiviral medication use that can occur. Therefore, the provision of FDA warnings is necessary; additionally, clinical monitoring of patients receiving CCBs is advised, and a dose reduction for CCB when co-administered with ritonavir-boosted nirmatrelvir may be required[15].

In this instance, the patient's hypotension progressed to refractory shock within 5 hours after administering 20 mg of manidipine along with ritonavir-boosted nirmatrelvir. The patient also had metabolic acidosis, hyperglycemia, and mild hypokalemia. Despite the high dose of vasopressors and inotropic agents, a target MAP of 65 mmHg was not achieved, and developed anuria including rising arterial lactate levels. Shock reversal dramatically improved with intravenous calcium, and high-dose insulin treatment. The definite diagnosis of vasodilatory refractory shock in this case was CCB intoxication, resulting in the interaction between ritonavir-boosted nirmatrelvir and manidipine. Ritonavir-boosted nirmatrelvir CYP3A inhibitor that increases the plasma concentration of CCB, which is extensively metabolized by CYP.

Conclusion

The diagnosis of life-threatening refractory vasodilatory shock due to CCB overdose from drug-drug interaction remains challenging. The cornerstone of treatment is timely identification in addition to prompt treatment prior to organ failure and cardiac arrest. In cases of CCB poisoning; wherein cardiotoxicity is evident, first-line therapy, a combination of intravenous calcium; vasopressors, and high-dose insulin combined with supplemental dextrose is required for refractory cases. Furthermore, a high alert system for the cautious use of ritonavir-boosted nirmatrelvir, and a list of drug-drug interactions between ritonavir-boosted nirmatrelvir and concomitant medications should be provided for patient safety, so as to avoid serious or life-threatening drug toxicities.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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