Severe Toxicity Following Combined Overdose of Verapamil, Atenolol, Propafenone, and Simvastatin in a Suicidal Attempt: A case study

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Abstract

\textbf{Background:} Overdoses with cardiovascular-active drugs are associated with significant morbidity and mortality. Intoxications involving multiple antiarrhythmic agents have been documented in several case reports, yet an instance of intentional overdose with three varieties of antiarrhythmics concomitant with simvastatin has not been previously reported. We report a rare case of severe toxicity from combined overdose of verapamil, atenolol, propafenone, and simvastatin, leading to resistant hypotension and total AV block.

\textbf{Case report:} A 25-year-old male patient was brought to the Emergency Department (ED) with decreased consciousness and vomiting following a suicide attempt. He had a documented medical history of depression but had not previously attempted suicide. Laboratory findings indicated metabolic acidosis, severe hypoxemia, acute kidney injury (AKI) and elevated liver enzymes. Prompt resuscitation measures, including high-dose inotropic infusions and intensive care unit (ICU) admission, were initiated. Hemodialysis led to significant improvement, and successful extubation was achieved on the second day of ICU care. Through aggressive medical intervention, the patient's hemodynamic status normalized, negating the need for a pacemaker. He was extubated on ICU day two and discharged on day eight.

\textbf{Conclusion:} This case underscores the clinical challenges associated with polypharmacy overdoses, their potential cardiac complications, and the crucial importance of aggressive and early intervention strategies.

\textbf{Keywords:} Atenolol; Propafenone; Overdose; Simvastatin; Suicide Attempt; Total AV block; Verapamil.

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Background
Overdoses with cardiovascular-active drugs are associated with significant morbidity and mortality (Gummin et al., 2022). Intoxications involving multiple antiarrhythmic agents have been documented in several case reports, yet an instance of intentional overdose with three varieties of antiarrhythmics concomitant with simvastatin has not been previously reported (Atemnkeng et al., 2021; Sandroni, 2004; Farooq et al., 2020).

Case presentation
A 25-year-old male patient was brought to the Emergency Department (ED) with decreased consciousness and vomiting following a suicide attempt. He had a documented medical history of depression but had not previously attempted suicide. However, he had demonstrated noncompliance with his prescribed regimen prior to this admission. Given the patient's unconscious state and the absence of eyewitnesses, the quantity of medication ingested was estimated based on the remnants of medication packaging, as reported by the patient's parents during anamnesis. All medications had been purchased online and matched the types of medications the patient's parents had been taking as part of their ongoing therapy. The patient was presumed to have ingested forty tablets of verapamil (40 x 150 mg, totaling 6 grams), eight tablets of atenolol (8 x 50 mg, totaling 400 mg), ten tablets of propafenone (10 x 150 mg, totaling 1.5 grams), and fifteen tablets of simvastatin (15 x 20 mg, totaling 3 grams) during his suicide attempt.

The patient arrived at the emergency department in the early morning, presenting with impaired consciousness and convulsions which had started half an hour before admission. Upon arrival at the ED, the patient reported experiencing frequent episodes of yellowish vomiting, up to 15 times, with no presence of blood. Accompanying symptoms included four instances of watery stools without any mucus or blood. Peripheral pulse was weak, and oxygen saturation was only 78%. High-flow oxygenation was administered using an oxygen mask. A nasogastric tube was also inserted, and gastric lavage was performed, revealing yellowish gastric contents. The patient also presented with bradycardia, and an attempt to administer atropine injection did not resolve the heart block.

Investigations
Upon admission, laboratory investigation showed Hemoglobin levels at 16.5 g/dL, Hematocrit at 49.6%, a Leukocyte count of 24,080 per microliter, Platelet count of 40,000 per microliter, Urea levels at 33 mg/dL, Creatinine at 1.5 mg/dL, Sodium at 139 mmol/L, Potassium at 3.7 mmol/L, Ionized Calcium at 1.23 mmol/L, and Magnesium at 2.10 mg/dL. The patient's arterial blood gas analysis revealed severe metabolic acidosis and severe hypoxemia. The values were as follows: pH: 7.227, pCO₂: 40.8 mmHg, pO₂: 39.5 mmHg on 50% FiO₂, bicarbonate (HCO₃⁻): 17 mEq/L, Standard Base Excess (BE-b): -10.7, and Lactate 7.40 mmol/L. While there was a suspicion of rhabdomyolysis due to simvastatin poisoning, it was unfortunate that creatine kinase testing could not be conducted at either the referring hospital or our own facility. Nevertheless, the routine urine examination yielded significant findings. Macroscopically, the urine was not dark but displayed a turbid, yellow hue. Chemical analysis of the urine revealed a specific gravity of 1.025, a pH of 5, protein at 2+, and erythrocytes at 3+, with negative results for glucose and ketones. Microscopic analysis further showed more than 50 erythrocytes per high power field, 12 granular casts per low power field, and the presence of calcium oxalate crystals. These findings are suggestive of potential renal damage, aligning with the patient's clinical presentation and history. The
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initial electrocardiogram (ECG) is presented below (Fig.1).

![ECG Image]

**Fig.1.** Upon presentation at the Emergency Department, the initial ECG showed: atrioventricular (AV) dissociation, a P wave rate of 60 beats per minute, a QRS rate of 52 beats per minute, a normal QRS axis (98°), a P wave duration of 0.04 ms with an amplitude of 0.1mV, a non-discernible PR interval, and a QRS duration of 0.10s. No pathological Q waves were identified, the ST segment was isoelectric, and no T wave inversions were observed. The R/S ratio in V1 was less than 1, the sum of S in V1 or V2 and R in V5 or V6 was less than 35 mm, the sum of R in aVL and S in V3 was less than 28 mm, the sum of S in V4 and the deepest S wave was less than 28 mm, and the corrected QT interval (QTc) was 372 ms. The ECG diagnosis was total AV block with a junctional escape rhythm.

**Treatment**

Due to signs of shock, crystalloid fluids were infused up to 3500 mL, and dopamine was initiated at a rate of 5 micrograms/kg body weight/minute to address the low pulse rate of 36 bpm. Additionally, a random blood glucose test revealed a glucose level of 236 mg/dL. The patient's non-responsiveness to conventional therapy necessitated the initiation of a high-dose inotropic infusion. This was followed by a rapid decline in the patient's hemodynamic status, leading to a sustained cardiopulmonary arrest. To secure the airway, endotracheal intubation was promptly performed. A multidisciplinary team within the emergency department managed to restore spontaneous circulation after carrying out three cycles of cardiopulmonary resuscitation, supplemented by the intravenous administration of epinephrine.

In the aftermath of resuscitation, the patient exhibited a heart rate of thirty beats per minute, indicative of a total heart block. A plan was formulated for the implantation of a temporary pacemaker, but the absence of the requisite facilities necessitated the patient's transfer to a higher-level referral center. During this transfer, the patient was given an intravenous drip of epinephrine at 10 mg/hour, dopamine at 20 mcg/kg body weight/minute, and esomeprazole at 8 mg/hour.

Upon arrival at the referral center, the patient was immediately prepared for admission to the Intensive Care Unit (ICU) to receive critical care. The management plan included mechanical ventilation, hemodialysis for acute kidney injury, and the implantation of a temporary pacemaker. Despite receiving dopamine, epinephrine, and norepinephrine, the
patient's blood pressure was still low at 80/37 mmHg, and the heart rate remained high at 160 beats per minute. The second admission blood gas analysis revealed a mixed respiratory and metabolic acidosis with severe hypoxemia. The pH level was 7.325, pCO2 was 33.5 mmHg, pO2 was 56.8 mmHg on a FiO2 of 50%, HCO3 was 17.6 mEq/L, and BE-b was -6.8. Further laboratory examinations indicated acute kidney injury with elevated levels of urea (56.2 mg/dL) and creatinine (2.65 mg/dL). Additionally, liver function tests showed an increase in Serum Glutamic-Oxaloacetic Transaminase (SGOT) levels to 129 U/L and Serum Glutamic Pyruvic Transaminase (SGPT) levels to 157 U/L, indicative of elevated liver enzymes. The patient was diagnosed with Total AV Block due to Drug Intoxication + Suicide Attempt + Post Return Of Spontaneous Circulation + Acute Kidney Injury (AKI) Stage III, along with stress gastric ulcer and reactive leukocytosis.

In the ICU, the patient's oxygen saturation was maintained between 95% and 100% on SIMV mode ventilation, with specific settings including a respiratory rate of 6 breaths per minute, tidal volume of 500 mL per breath, FiO2 of 50%, and PEEP of 5 cm H2O. Due to the presence of dark residual contents in the nasogastric tube, the patient was kept on fasting status during the first day of ICU admission. The maintenance fluid regimen for the patient consisted of Lactated Ringer's solution, administered at a rate of 1500 mL/24 hours. Sedation and analgesic measures to ensure ventilator compliance included midazolam infusion at a rate of 3 mg/hour, and fentanyl infusion at a rate of 25 mcg/hour. Blood pressure reading of 137/79 mmHg was supported with a combination of inotropic infusions, including epinephrine at a rate of 0.1 mcg/kg of body weight/minute, dopamine at 20 mcg/kg of body weight/minute and norepinephrine at 0.1 mcg/kg of body weight/minute. Gastroprotection was ensured through the administration of an esomeprazole infusion at a rate of 8 mg/hour. A urinary catheter had been inserted to facilitate accurate monitoring of the patient's urine output, a vital parameter in managing a patient with acute kidney injury. The patient's urine production was achieved at a rate of 1.2 mL/kg/hour, with a turbid yellow color.

By the second day, the patient's hemodynamics had stabilized significantly. Epinephrine and norepinephrine were no longer required, and dopamine was the only inotropic agent being administered. Despite a consistent urine output above 1 mL/kg of body weight/hour, there were concerns about declining renal function. As a result, the decision was made to proceed with intermittent hemodialysis in the ICU. This decision was influenced by the decreased renal function and the fact that atenolol, one of the ingested drugs, is dialyzable. (Huang et al., 2013)

The hemodialysis procedure was conducted over a span of 3 hours, using a polysulfone high-flux dialyzer (Elisio™ 15H, Synthetic Polynephron™ Hollow-Fiber Dialyser, Nipro Medical, Japan). The blood flow rate (Qb) was set at 150, the dialysate flow rate (Qd) at 300, and ultrafiltration (UF) at 500. The patient's systolic and diastolic blood pressure values during the hemodialysis treatment ranged between 136 to 141 mmHg and 70 to 74 mmHg, respectively. The patient tolerated
the conventional hemodialysis treatment well, with the dopamine infusion reduced to 5-8 mcg/kg of body weight/minute.

Pre-hemodialysis levels of urea and creatinine were 56.2 mg/dL and 2.65 mg/dL, respectively. Following the hemodialysis, these levels decreased to 25 mg/dL for urea and 1 mg/dL for creatinine. The Urea Reduction Ratio (URR), a measure of the effectiveness of the dialysis, was calculated to be approximately 55.36%, indicating a satisfactory response to the treatment.

Outcome and follow up

During the patient's ICU stay, the doses of inotropes and vasopressors were gradually reduced as the patient's hemodynamics improved. With reduced support, including the discontinuation of epinephrine and a dopamine dose of 8 micrograms/kg/minute, the patient achieved a blood pressure of 134/86 mmHg and a heart rate of 82 beats per minute with a sinus rhythm on the ECG monitor. Follow-up investigations revealed the following results: Hemoglobin (Hb) level of 13.5 g/dL, Hematocrit (Ht) of 41.9%, Leukocyte count of 12,650 per microliter, Platelet count of 173,000 per microliter. Renal function tests showed a urine (Ur) level of 28.8 mg/dL, creatinine (Cr) level of 0.87 mg/dL, and electrolyte levels of sodium (Na) 132 mmol/L, potassium (K) 4.0 mmol/L, calcium (Ca) 4.93 mmol/L. Arterial blood gas analysis results were as follows: pH 7.456, pCO2 45.1 mmHg, pO2 159.8 mmHg, bicarbonate (HCO₃⁻) 32.2 mM, total carbon dioxide (tCO₂) 33.6 mmHg and standard base excess (BE-b) 7.9. The results indicated a normal range of hemoglobin, hematocrit, leukocyte count, and platelet count. Renal function tests demonstrated improved kidney function with normal urine and creatinine levels, as well as stable electrolyte levels. Arterial blood gas analysis showed the absence of metabolic acidosis and severe hypoxemia that the patient had experienced two days prior. Subsequently, the patient was successfully extubated on the second day of ICU management. On the fourth day, the repeat ECG findings were obtained (Fig.2).

![Fig.2. Subsequent ECGs revealed the following: sinus rhythm, QRS rate of 88 beats per minute, no pathological Q waves were identified, the ST segment was isoelectric, and no T wave inversions were seen. The ECG diagnosis was normal sinus rhythm.](image-url)
Remarkably, on the eighth day of hospital admission, the patient was discharged, exhibiting a sinus rhythm and stable hemodynamics. He was discharged after a psychiatric consultation.

**Discussion**

According to the AHA Scientific Statements, a variety of antiarrhythmic drugs have the potential to induce different types of arrhythmias, including bradyarrhythmias. Bradyarrhythmias are typically classified into two main categories: sinus node dysfunction and atrioventricular (AV) block. Sinus node dysfunction can occur when medications inhibit the normal function of the sinus node, leading to sinus bradycardia, sinus pauses, or sinus arrest. On the other hand, AV block occurs when the conduction of electrical impulses through the AV node and the His-Purkinje system is hindered, or when the refractory period is prolonged. (Tisdale et al., 2020).

Among the various antiarrhythmic medications available, Calcium Channel Blockers (CCBs) stand out for their wide use in treating a range of cardiovascular diseases. Their effectiveness in managing hypertension, cardiac arrhythmias, and angina has been widely demonstrated. Verapamil, acting as a voltage-sensitive L-type calcium channel blocker, impedes the influx of calcium into cell membranes (Rizvi et al., 2012; Hofmann et al., 2014). This process, in turn, blocks myocardial and smooth muscle L-type calcium channels, resulting in myocardial depression and the suppression of electrical activity (Shah et al., 2012). Overdose of such calcium channel blockers carries a significant fatality risk, approximated at 38%, which often persists despite maximal therapeutic interventions (Atennkeng et al., 2021). As reported by the American Association of Poison Control Centers in its 2021 National Poison Data System (NPDS) Annual Report, CCBs, either in isolation or concomitantly used with other substances, rank sixth in causing drug toxicity-related deaths, superseded by beta-blockers (Gummin et al., 2022). Typically, patients initially present asymptomatic, but they may rapidly deteriorate thereafter (Atennkeng et al., 2021). The standard treatment for CCBs overdose entails intravenous fluid resuscitation, gut decontamination, calcium administration, glucagon, and atropine, alongside supportive care. In serious situations, bradycardia and hypotension could necessitate the insertion of a temporary pacemaker and the administration of vasopressors and inotropes. However, in numerous instances, the resulting shock may be unresponsive to vasopressors and inotropes, precipitating cardiovascular failure and mortality (Shah et al., 2012).

Atenolol, is a selective β1-adrenergic receptor antagonist and is one of the most widely used beta-blockers for the treatment of cardiovascular diseases and to treat hypertension, coronary heart disease, arrhythmias, sinus tachycardia and myocardial infarction. It acts preferentially upon the β1-adrenergic receptors in the heart (Batra and Bushan, 2018). Atenolol, as a beta-blocker, competitively bind to beta-adrenergic receptors, resulting in bradycardia and hypotension. Depending on lipid solubility, some beta-blockers also cause serious central nervous system manifestations, such as seizures, respiratory depression, and coma (Doepker et al., 2014). Beta-blockers overdose is potentially harmful due to the strong blood pressure-lowering and heart rate-lowering effects (Lauterbach, 2019).

Propafenone hydrochloride, a Vaughan Williams class IC antiarrhythmic drug, primarily acts as a potent sodium channel blocker but also shows beta-blocking and calcium channel blocking activities (Funk-Brentano et al., 1990; Gil et al., 2018). Thus, it is utilized as an antiarrhythmic agent in managing conditions such as ventricular and...
supraventricular tachycardia along with atrial fibrillation (Keramari et al., 2021). Propafenone overdose has been reported to be associated with features of severe cardiovascular and central nervous system toxicity (Ovaska et al., 2010). Following intoxication, the most life-threatening ECG abnormalities are expected to occur within three to six hours after oral administration (Keramari et al., 2021). A fatal overdose on propafenone is usually attributed to conduction abnormalities, leading to asystole or electromechanical dissociation (Gil et al., 2018). Propafenone toxicity shares a similar mechanism of action to beta-blockers, both affecting rapid-acting sodium channels in heart cells, leading to decreased heart rate and contractility. Overdoses of these drugs may result in bradycardia, hypotension, unresponsiveness, seizures, or cardiac arrest (Farooq et al., 2020). Lipid therapy, through the use of intravenous lipid emulsion, has shown success in sequestering lipophilic drugs and reducing their toxic effects (Deopker et al., 2014; Thakrar et al., 2014; Lashari et al., 2018; Cao et al., 2015; Gosselin et al., 2016). In cases of propafenone intoxication, lipid emulsion therapy has been used successfully (Bayram et al., 2015; Clarot et al., 2003).

Statins, specifically known as 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA-reductase) inhibitors, constitute the premier line of therapeutic management for hypercholesterolemia (Sadowitz et al., 2010). Simvastatin, a classical statins, used to regulate cholesterol synthesis via inhibiting HMG-CoA reductase. Nonetheless, the administration of simvastatin at elevated doses has been associated with hepatotoxicity (Thakrar et al., 2014). Mortality ensuing from hepatic damage has been reported in a limited number of patients who developed liver injury due to statin usage. It's noteworthy, however, that the vast majority of such patients have demonstrated recovery post-discontinuation of the therapy (Björnsson, 2017).

In the case of an overdose of sinus or atrioventricular node-blocking agents, certain emergency medical treatments can be implemented, depending on the timing of the overdose. Patients admitted with the presumed coinfection of beta-blockers and calcium channel blockers (CCBs) should be initially managed in accordance with standardized resuscitation protocols (the airway, breathing, and circulation (ABC) approach) (Lashari et al., 2018). Despite the decreased frequency of gastric lavage recommendations in recent literature, clinicians may still opt for gut decontamination by administering activated charcoal through a nasogastric tube. The rationale behind this approach lies in the capability of activated charcoal to absorb drugs ingested, aiding in their removal from the body, particularly when administered within 1-2 hours of ingestion by the patient. (Shah et al., 2012). Other treatment options often utilized include mechanical ventilation, fluid resuscitation, vasopressors, glucagon, lipid emulsion therapy, and early administration of sodium bicarbonate, although there is no universally accepted approach (Farooq et al., 2020). Additionally, for severely poisoned patients, extracorporeal membrane oxygenation (ECMO) can be a life-saving option if available in the hospital (Bouchard et al., 2021; Vignesh et al., 2018).

Glucagon is the first-line therapy for severe hypotension, heart failure, and cardiogenic shock caused by beta-blocker and/or calcium channel blocker poisoning. This typically involves an initial intravenous bolus of 3 to 10 mg of glucagon, followed by a continuous infusion at a rate of 3 to 5 mg per hour (Kusumoto et al., 2019). Glucagon works by activating adenylate cyclase in cardiac tissue through stimulation of a G protein at the beta receptor, leading to increased intracellular cAMP (Janah et al., 2019).
In cardiac myocytes, cAMP generated modulates excitation contraction coupling by activating protein kinase A (PKA) and the subsequent phosphorylation of the L-type Ca2+ channel (LTCC), thus increasing the amount of Ca2+ available for contraction (positive inotropic effect) \((Zaccolo, 2009)\). This increased heart rate helps to improve cardiac output and mitigate the negative effects of bradycardia caused by the drug overdose. In our case, glucagon was unfortunately unavailable both at the initial hospital where the patient was first treated and at the referral hospital.

Both beta-blockers and CCBs also disrupt the secretion of insulin by the beta cells of pancreatic islets \((Lashari et al., 2018)\). In various case reports of beta-blocker and calcium channel blocker poisoning, insulin with glucose and potassium supplementation has been used to support hemodynamics. The mechanism may involve increasing carbohydrate metabolism in cardiac cells and direct inotropic effects \((Sherwin and MacDonald, 2019)\).

Given the unavailability of our facilities to measure drug levels in the blood, the amount of medication consumed was approximated by examining the leftover drug packaging, as described by the parents of the patient during the medical history taking. All intensive therapy management in this case was directed solely based on the clinical presentation. In this case report, the patient initially received dopamine to address bradycardia that did not respond to standard management in the emergency department. Subsequently, following the occurrence of cardiac arrest, epinephrine, known for its potent catecholamine effects, was administered as part of the cardiopulmonary resuscitation management. Stimulation of \(\beta_1\) receptors by dopamine and epinephrine has various cardiovascular effects, including an increase in heart rate to counteract bradycardia. During resuscitation, the administration of epinephrine serves the primary goal of achieving Return of Spontaneous Circulation (ROSC). Additionally, epinephrine has the potential to stimulate glucagon secretion, which can further improve the patient's cardiac output \((Hamilton et al., 2018)\). High doses of inotropic agents have demonstrated effectiveness in reversing heart block and restoring sinus rhythm, eliminating the initial requirement for a planned pacemaker. This finding aligns with the recommendations outlined in the European Society of Cardiology (ESC) 2021 Guidelines On Cardiac Pacing And Cardiac Resynchronization Therapy (CRT). According to these guidelines, pacing is generally not recommended for patients with atrioventricular block caused by transient or reversible conditions, as it carries a Class III recommendation with Level of Evidence B \((Glikson et al., 2021)\).

**Conclusion**

It is reasonable to suggest the use of dopamine and epinephrine in cases of severe heart block that do not respond to standard resuscitation techniques. In this case, the successful management of severe poisoning involving calcium channel blockers, beta-blockers, propafenone and simvastatin without the use of glucagon, insulin, intravenous lipid emulsion, or a pacemaker is noteworthy. It highlights the importance of personalized and comprehensive treatment approaches for patients presenting with cardiac complications. Each case should be assessed individually, and treatment plans should be tailored to the specific circumstances and requirements of the patient.

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**Conflict of Interest:** The authors report no conflict of interest.

**Informed Consent:** Not applicable, as the study was conducted retrospectively using medical records that had already been
supplemented with general consent. Prior to medical care, the patient's parents had provided a signed agreement, authorizing the use of the patient's medical data for educational and research purposes. This is in accordance with ethical guidelines for conducting research involving human subjects.

**Authors’ Contributions:** The first author processed data from the medical records and presented the case in a scientific forum. The second and third authors were directly involved in the patient's care and provided guidance in case presentation, and also assisted in the manuscript preparation. Their collective efforts were instrumental in the formulation of this comprehensive report. The division of responsibilities facilitated the thorough examination, treatment, and subsequent analysis of this multifaceted and critical case.

**Data Availability:** The authors declare that data supporting the findings of this study are available within the article.

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