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CASE REPORT

Refractory cardiogenic shock due to atomoxetine overdose rescued by venoarterial extracorporeal membrane oxygenation: A case report

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Abstract

Background: Atomoxetine, a selective norepinephrine reuptake inhibitor for attention-deficit hyperactivity disorder, may lead to severe complications, notably cardiac issues, upon overdose. We present a unique case of venoarterial extracorporeal membrane oxygenation (VA-ECMO) rescue for atomoxetine-induced cardiogenic shock.

Case Presentation: We report a 30-year-old man who, after ingesting a significant overdose of atomoxetine, experienced seizures and severe cardiogenic shock, necessitating VA-ECMO for resuscitation. While prior reports have noted cardiovascular complications like QTc prolongation and Takotsubo cardiomyopathy following atomoxetine overdose, this case is notable for its life-threatening circulatory failure, which required ECMO intervention. Swift recognition coupled with VA-ECMO initiation, endoscopic medication removal, intravenous lipid emulsion, and activated charcoal may have played a pivotal role in stabilizing the patient and facilitating recovery.

Conclusion: Healthcare practitioners should recognize the severe cardiac complications of atomoxetine overdose. Careful monitoring with ECG and echocardiography, along with providing intensive care, is crucial in managing critical cases.

KEYWORDS
atomoxetine, cardiac failure, extracorporeal membrane oxygenation, intravenous lipid emulsion, overdose

INTRODUCTION

Atomoxetine, marketed as Strattera®, is a selective norepinephrine reuptake inhibitor (SNRI) used to treat attention-deficit hyperactivity disorder (ADHD) in adults and children. Overdosing on atomoxetine can cause various adverse events. Notably, cardiovascular toxicity, including seizures,[1,2] QT interval prolongation,[3] and Takotsubo cardiomyopathy[4] are significant risks associated with its overdose. We present a case of a 30-year-old man who suffered seizures and refractory cardiogenic shock following an atomoxetine overdose, successfully treated with venoarterial extracorporeal membrane oxygenation (VA-ECMO). To the best of our knowledge, this report is the first to document cardiac failure resulting from atomoxetine overdose necessitating VA-ECMO, highlighting the drug's potentially fatal complications.

CASE PRESENTATION

A 30-year-old man arrived at our tertiary emergency medical center with generalized seizures following a 10-g atomoxetine overdose in a suicide attempt. He was discovered unconscious

beside 250 empty packs of 40-mg atomoxetine by his family, who promptly called for emergency medical service. He was on flunitrazepam, olanzapine, atomoxetine, and rikkunshito, which were prescribed for depression, and atomoxetine was individually purchased. The patient had no prior seizure history.

Before arrival, he had experienced several recurrent seizures. Vital signs at our center were as follows: Glasgow Coma Scale score of 3 (E1V1M1), heart rate of 50–60/min with wide QRS complexes, respiratory rate of 16/min, oxygen saturation of 95% on a 10-L/min face mask, body temperature of 36.5°C, and unmeasurable blood pressure with a weak peripheral pulse. The initial arterial blood gas analysis, conducted under a 10-L/min oxygen face mask, revealed a pH of 6.768; pCO_2, 94.5 mm Hg; pO_2, 179 mm Hg; HCO_3^-, 12.9 mmol/L; lactate, 20 mmol/L; sodium, 150 mmol/L; potassium, 3.8 mmol/L; and glucose, 130 mg/dL. Additional initial laboratory tests indicated a white blood cell count of 13.6×10^3/mL; hemoglobin, 17.5 g/dL; hematocrit, 55.6%; platelet count, 312×10^3/mL; aspartate aminotransferase, 40 IU/L; alanine aminotransferase, 221 U/L; urea, 10.1 mg/dL; creatinine, 1.25 mg/dL; ammonia, 279 μg/dL; creatine kinase, 261 U/L; and C-reactive protein, 0.03 mg/dL.

Electrocardiography revealed bradycardia at a rate of 53 bpm and a wide QRS interval of 238 ms with QT prolongation (QTc 595 ms) and an unrecognizable P wave (Figure 1A). Bedside echocardiography revealed decreased left ventricular systolic function with a visual ejection fraction (EF) of 20%, without any findings of Takotsubo cardiomyopathy. Generalized seizures and cardiogenic shock secondary to atomoxetine toxicity were suspected.

The patient was intubated for airway protection due to persistent unconsciousness. VA-ECMO was initiated 53 min after arrival because of refractory cardiogenic shock, even after a rapid intravenous infusion of isotonic crystalloids with

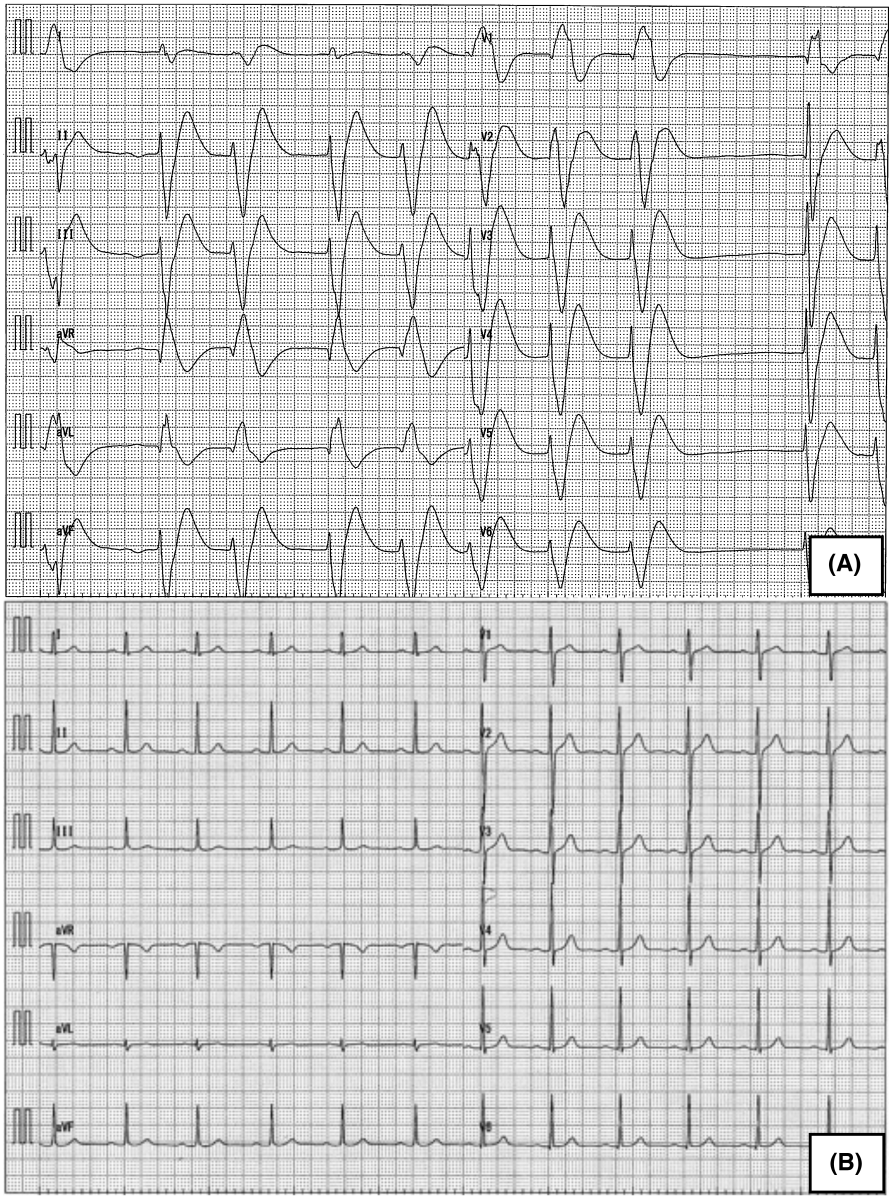

FIGURE 1 Electrocardiogram (10 mm/mV, 25 mm/s) on arrival (A) and on hospital day 2 (B).

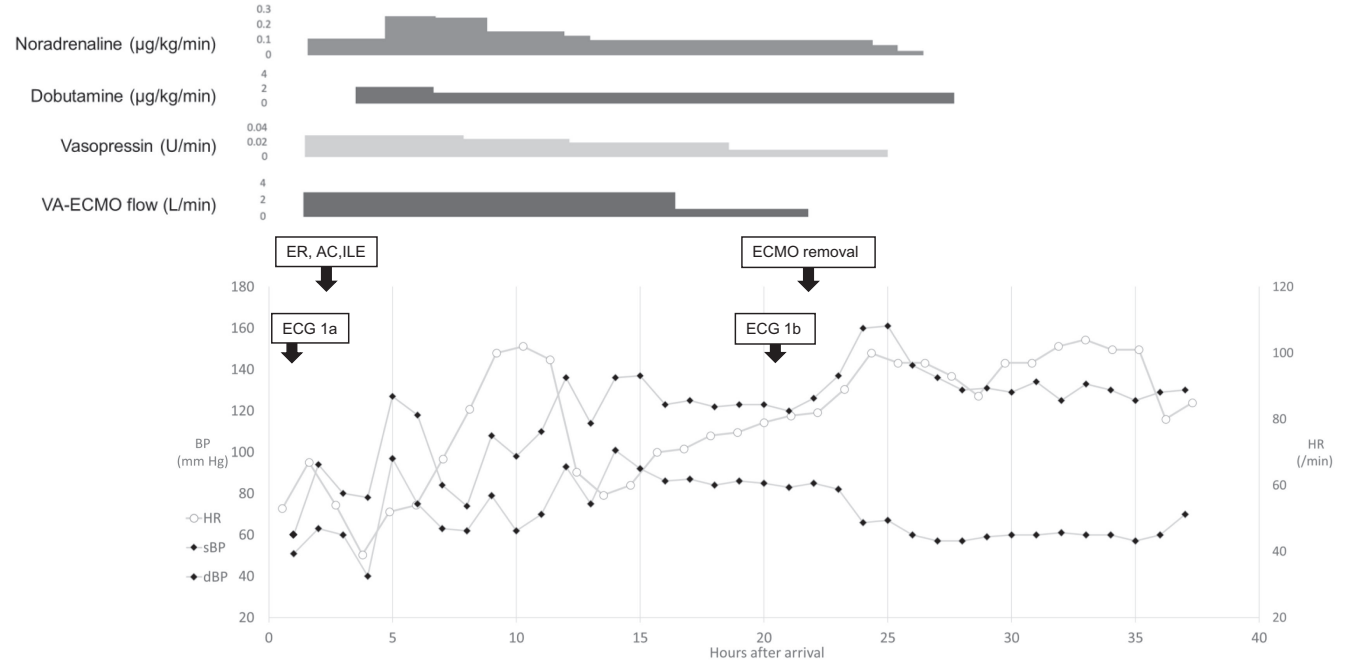

FIGURE 2 Progress chart during ICU admission. AC, activated charcoal; dBP, diastolic blood pressure; ECG, electrocardiogram; ER, endoscopic removal; HR, heart rate; ILE, intravenous lipid emulsion; sBP, blood pressure; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

a high dose of vasopressors and inotropes. A 22 Fr drainage cannula and 16 Fr return cannula were inserted peripherally into the right femoral vein and right femoral artery, respectively. A computed tomography (CT) scan following the introduction of VA-ECMO revealed a high-density area measuring 70 × 60 × 25 mm in the stomach, likely representing ingested tablets. Endoscopic examination showed fragments of drug tablets and drug clumps, and all visible substances were removed endoscopically. Activated charcoal (AC) (50 g) via a nasogastric tube and 40 g of intravenous lipid emulsion (ILE) was also administered. AC was given repeatedly three times in 4-h intervals. There were no immediate changes in vital signs and ECGs after the procedures above.

Within the first few hours of intensive care unit (ICU) admission, the patient required 0.1γ of noradrenalin, 0.03 U/min of vasopressin, and 4γ of dobutamine with 3 L/min of VA-ECMO support. Wide QRS arrhythmia gradually recovered by 20 h after arrival (Figure 1B), and bedside echocardiography showed recovery of left ventricular function with a visual EF of 30% and successful weaning of the vasopressors. Due to improvement in cardiac function and recovery from wide QRS arrhythmia and cardiogenic shock, decannulation and removal of VA-ECMO were successfully performed on hospital day 2 (20 h after the initiation of VA-ECMO) (Figure 2).

Despite lacking overt clinical signs of seizures, an initial continuous electroencephalogram (EEG) revealed a burst-and-suppression pattern. To complement midazolam's continuous infusion, fosphenytoin (1500 mg/day) and levetiracetam (3000 mg/day) were introduced on day 1. By day 2, the EEG pattern began improving, enabling cessation of midazolam infusion and successful extubation on day 4. Levetiracetam was stopped on day 8, coinciding with the patient's ICU discharge. Day 34 echocardiography confirmed a normal left ventricular EF of 72%. Despite a slight cognitive decline (Mini-Mental State Examination score: 28), the patient was transferred to a rehabilitation hospital on day 36 and was later discharged home post-rehabilitation.

DISCUSSION

Atomoxetine, a potent SNRI, enhances central nervous system noradrenergic neurotransmission by inhibiting the reuptake of norepinephrine into presynaptic neurons. This action elevates extracellular norepinephrine levels in the brain, effectively treating ADHD symptoms in children and adults. The half-life of atomoxetine is approximately 5 h in adults, though it can be extended in children and adolescents. Primarily metabolized by the hepatic CYP2D6 enzyme system, atomoxetine's elimination varies based on the administered dosage, with symptoms potentially persisting for days.[1,2]

Previous studies report various adverse effects from atomoxetine overdose, mainly impacting the central nervous system. These include seizures, drowsiness, agitation, hyperactivity, tremors, and hyperreflexia.[3] Cardiovascular events, notably QTc prolongation[5,6] and Takotsubo cardiomyopathy,[4,7] have also been observed, whereas reports on severe circulatory failure such as our case, are limited. A previous report described a case with QTc prolongation, multiple premature ventricular contractions (PVCs), and bradycardia (HR 30) with Takotsubo cardiomyopathy that required treatment with bisoprolol, lidocaine, and temporary pacing.[5] Another case of QTc prolongation was asymptomatic and did not require vasopressors, inotropes, antiarrhythmic medications, or mechanical support.[6] Compared to these reports of cardiovascular adverse events from atomoxetine

overdose, this case is significant for presenting severe cardiovascular shock, necessitating high-dose vasopressors and inotropes, as well as mechanical support by VA-ECMO.

Atomoxetine overdose is believed to cause cardiovascular events primarily through excessive synaptic norepinephrine concentrations.[1] The surge in catecholamines can induce conditions such as Takotsubo cardiomyopathy due to acute myocardial stress.[4] Additionally, some reports suggest that atomoxetine inhibits the human ether-a-go-go-related gene (hERG), which encodes a protein that forms potassium channels in the heart, leading to QTc prolongation.[3] Although these mechanisms are still hypothetical and require further research, they underscore the critical need for careful cardiovascular monitoring in patients receiving atomoxetine, particularly in overdose scenarios.

Importantly, atomoxetine overdose lacks a specific antidote, with management focusing on supportive care and monitoring vital signs and cardiac function. AC significantly lowers atomoxetine absorption and blood levels, mitigating toxic effects. When patients present early post-overdose (within 1–2 h), the suggested dose of AC is 50 g for adults and 1 g/kg for children.[1] Although there is limited evidence regarding the efficiency of lipid use in atomoxetine overdose, we employed ILE therapy based on atomoxetine's lipophilic nature and the utility of ILE as one of the approaches in cases of acute lipophilic drug intoxications.[8] Despite concerns raised by an in vitro study suggesting potential complications such as layering, agglutination in the tubing and circuits, cracking of stopcock valves, and an increased frequency of blood clots during ILE with ECMO, our case did not experience these issues.[9]

In a previous case, QTc prolongation persisted for 4 days, during which only atomoxetine was discontinued without the use of AC or ILE.[5] Given that our case experienced early stabilization and ECG normalization within 24 h, these treatments may have contributed to the early removal of VA-ECMO. It is important to note that cardiovascular improvement took approximately 12 h after AC and ILE treatment (Figure 2); thus, ECMO initiation should not be delayed when the patient is in a severe shock state. While further research is needed to establish the effectiveness of AC and ILE in atomoxetine overdose, our case and existing literature indicate that these treatments should be considered for managing severe cardiac adverse events due to atomoxetine overdose.

CONCLUSION

Our unique case demonstrates a critical overdose of atomoxetine leading to seizures and refractory cardiogenic shock. Prior studies noted cardiovascular events like QTc prolongation and Takotsubo cardiomyopathy; however, our case involved severe circulatory failure, requiring ECMO for effective resuscitation. Physicians should be aware that atomoxetine overdose can lead to severe cardiovascular events. This underscores the need for careful monitoring with ECG and cardiac echocardiography, as well as providing intensive care when necessary.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol: N/A.
Informed Consent: The patient provided consent for publication.
Registry and the Registration No. of the study/Trial: N/A.
Animal Studies: N/A.

INFORMED CONSENT

The patient provided consent for publication.

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