Air Medical Journal 38 (2019) 377–381

Contents lists available at ScienceDirect

Air Medical Journal

journal homepage: http://www.airmedicaljournal.com/

Case Report

Interfacility Critical Care Transport of an Elderly Patient With Confirmed Tricyclic Antidepressant Toxicity and Hemodynamic Collapse

Benjamin J. Lawner, DO, MS, EMT-P [1,2,*], Nsehniitooh Mbah, MD [4], Stephanie Bailey, RN, MSN, CFRN [3], Heather Erickson, RN, BSN, CFRN [3], Matthew Poremba, DO [1,2]

[1] Department of Emergency Medicine, Allegheny General Hospital, Pittsburgh, PA
[2] Department of Emergency Medicine, Temple University School of Medicine, Pittsburgh, PA
[3] LifeFlight Critical Care Transport Program, Allegheny Health Network, Pittsburgh, PA
[4] Emergency Medicine Training Program, Allegheny Health Network Educational Consortium, Pittsburgh, PA

Introduction

Tricyclic antidepressant (TCA) overdose asserts its dominance as a life-threatening and time-sensitive overdose. Expanded indications such as chronic pain management have once again thrust TCAs into the emergency medical spotlight. According to the 2015 data from the American Association of Poison Control Centers' National Poison Data System, TCA overdose accounted for over 4,000 patient exposures.[1] Lethality in the out-of-hospital setting is estimated at over 70%.[1] Once vital sign abnormalities occur, patients require rapid diagnosis and aggressive treatment. Lethality approaches 70% in patients who attempt suicide by ingestion of TCAs and who do not reach a health-care facility. Although the medical literature is replete with case reports, these overdoses remain exceedingly difficult to identify because of their varied clinical presentation. Patients presenting early in the course of their illness may manifest without vital sign abnormalities. Critical care and prehospital providers tasked with transporting these patients must remain vigilant with respect to signs and symptoms related to TCA overdose. Furthermore, effective treatment of this overdose may not be readily available to critical care transport teams. The care of TCA overdose patients in the transport environment requires a collaborative approach that anticipates patient needs, specific medications, and the real possibility of hemodynamic collapse. This case report reviews the initial presentation and medical care provided en route and highlights evidence-based treatment modalities for the care of patients with confirmed or suspected TCA overdose.

Case Report

A critical care transport team responded to an overdose patient at an outside hospital's emergency department. The patient was a 72-inch, 86-kg male patient with a past medical history significant for anxiety, coronary artery disease, hypertension end stage renal disease (ESRD), and severe depression. The patient reportedly overdosed on approximately 150 tablets of 100 mg nortriptyline. The exact formulation of the nortriptyline tablets was unknown. The patient was able to accumulate the medicine by not taking it as prescribed, and he reported the overdose to his wife. The wife arrived at home to find the patient slurring his speech and arousable to only verbal stimuli. An empty pill bottle was found upon emergency medical services arrival. The patient's mental status precipitously declined at the emergency department, and the patient was intubated for airway protection.

Air medical transportation was the preferred method of transport given the patient's hemodynamic compromise and time-sensitive illness. However, inclement weather prevented an immediate retrieval trip via helicopter. Therefore, the transport team traveled via ground to the referring hospital. The flight crew found the patient unresponsive and supine in a resuscitation bay. Initial vitals were recorded as a wide complex rhythm at a rate of 83, noninvasive blood pressure of 116/60, respirations of 20, SpO_2 of 100%, and end-tidal carbon dioxide of 22 mm Hg. Three liters of saline had already been infused, and the patient was on an infusion of norepinephrine at 0.1 μg/kg/min. The patient had not received additional sedation because intubation had occurred approximately 2.5 hours before critical care transport team arrival.

The patient remained nonresponsive to painful peripheral or central stimuli with a Glasgow Coma Scale of 3 (E1, V1, M1). He remained on assist control on the ventilator at a rate of 20 and had a tidal volume of 650 mL, a positive end-expiratory pressure of 5 cm H_2O, and a fraction of inspired oxygen of 40%. He maintained an oxygen saturation of 100% on the current ventilator settings. Three peripheral intravenous lines were in place and functioning. An initial arterial blood gas (ABG) obtained on 100% oxygen was as follows: pH of 7.27, pCO_2 of 58, pO_2 of 466, and HCO_3 of 26. His electrocardiogram showed a nonsinus rhythm

* Address for correspondence: Benjamin J. Lawner, DO, MS, EMT-P, Department of Emergency Medicine, Allegheny General Hospital, 320 East North Avenue, Pittsburgh, PA 15212.
E-mail address: blawner@ahn-emp.com (B.J. Lawner).

1067-991X/$36.00

https://doi.org/10.1016/j.amj.2019.05.009

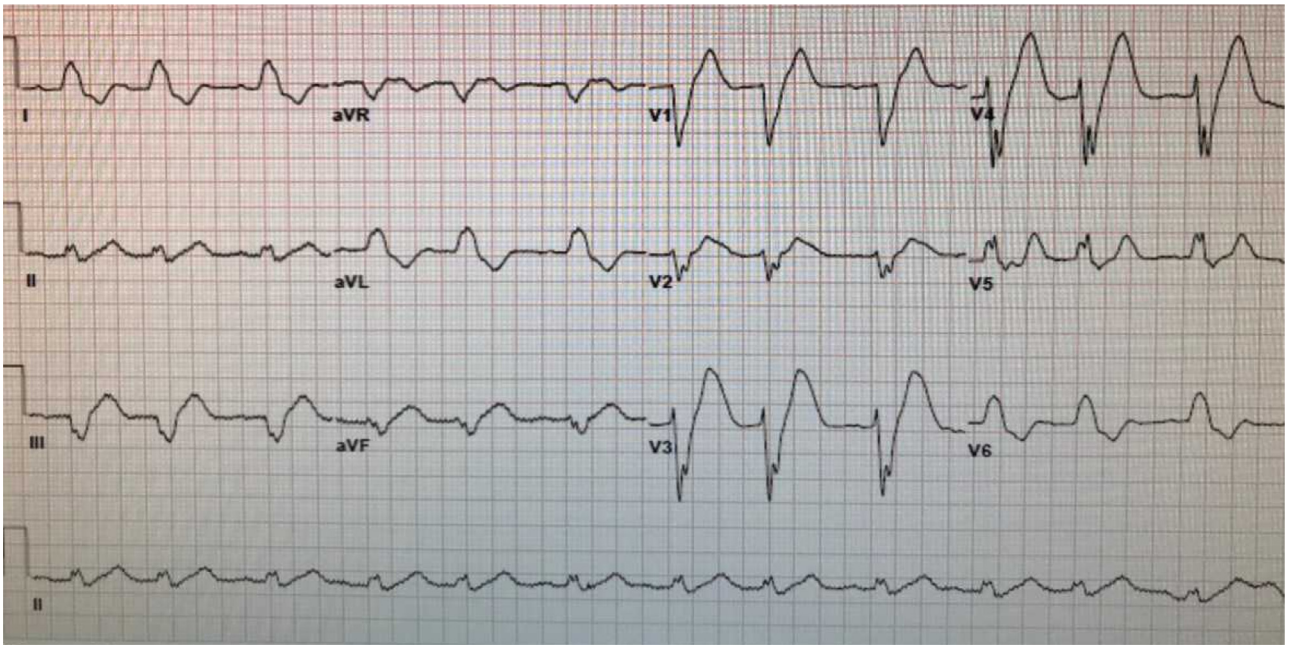

Figure 1. Patient's initial hospital electrocardiogram. The patient's electrocardiogram showed a persistent wide complex QRS and complete left bundle branch block.

and a significantly widened QRS complex of 0.2 milliseconds (Fig. 1). Within 12 minutes of flight crew arrival, the patient became hemodynamically unstable. His blood pressure dropped to 86/50 with heart rate of 86, SpO_2 of 100%, and end-tidal carbon dioxide of 22 mm Hg. The patient then exhibited several minutes of generalized tonic-clonic activity. In addition to boluses of sodium bicarbonate, the patient received 1 mg lorazepam intravenously. Seizure activity temporarily resolved, and the patient remained hypotensive. The norepinephrine drip was aggressively titrated to a dose of 0.3 μg/kg/min. Given the lengthy duration of ground transport, the flight crew contacted medical control for further recommendations. Systolic blood pressures of 80 to 90 mm Hg were achieved on the increased dose of norepinephrine. The patient had 2 more episodes of tonic-clonic seizures that were temporized by another 1-mg intravenous push of lorazepam. Medical command physician recommendations authorized repeated boluses of lorazepam for seizure activity and additional doses of sodium bicarbonate. Because of the end-stage renal disease, further boluses of saline were deferred. The medical control physician authorized an increased dose of norepinephrine if needed and instructed the flight crews to stock additional 50-mEq ampules of sodium bicarbonate for the return transport. The weather had cleared sufficiently, and the crew was able to make the return trip via air. The ABG was reviewed, and ventilator settings were adjusted to deliver a tidal volume of 6 mL/kg and a decreased concentration of inspired oxygen. The patient was transitioned without difficulty to the transport ventilator and placed on adaptive support ventilation settings with a fraction of inspired oxygen of 40%. Phenylephrine was obtained from the receiving facility in case the patient required additional vasopressor support. Six more ampules of sodium bicarbonate were retrieved from the referring emergency department.

The ABG before departure revealed a pH of 7.61, pCO_2 of 37, pO_2 of 45, and HCO_3 of 36.7. Poison control concurred with the treatment goal of targeting a pH of at least 7.5. During movement from the emergency department to the aircraft, the patient had another generalized seizure, which responded to 2.5 mg intravenous midazolam. Seizures persisted during transport, and the electrocardiogram continued to display a widened QRS complex. In flight, the patient received 5 more 2.5-mg doses of midazolam and 5 more 50-mEq ampules of sodium bicarbonate. Additional boluses and a subsequent infusion of midazolam were administered. The patient also received a bolus of levetiracetam. Continuous electroencephalographic (EEG) monitoring conducted in the intensive care unit revealed an increasing frequency of subclinical seizures. Propofol was added to the patient's anticonvulsant regimen, which suppressed the EEG activity.

In the receiving facility's intensive care unit, the patient was given a loading dose of levetiracetam and was placed on a midazolam drip. An intravenous infusion of 20% lipid emulsion was initiated because of persistent toxicity and hemodynamic compromise. Hemodynamic parameters remained stable for several hours after the lipid emulsion. The patient's electrocardiogram showed persistent QRS widening, which may have been secondary to underlying coronary artery disease and a previously unknown left bundle branch block. Boluses of hypertonic saline were administered, but there was no observable change in the patient's 12-lead electrocardiogram. Unfortunately, the patient experienced another precipitous decline and failed to respond to the additional doses of vasoactive medications including dopamine and epinephrine. Oxygen saturations dipped into the 80s, and the ventilator was further adjusted to compensate for changes secondary to developing pulmonary edema and possible adult respiratory distress syndrome. The patient remained hypotensive and bradycardic and died despite maximal medical therapy.

Discussion

TCA toxicity represents a time-sensitive and potentially life-threatening condition. The toxicity is multimodal, and a thorough understanding of the medication's mechanisms of action is critical to a successful treatment strategy. Sodium channel blockade may be responsible for the medication's ability to mitigate chronic and severe pain. However, in supratherapeutic states, the sodium channel blockade precipitates severe hypotension through interference with myocardial contractility. Furthermore, the medication has alpha-blocking and anticholinergic properties. The alpha blockade is also thought to contribute to the refractory hypotension observed in cases of overdose. The clinical presentation of severe and life-threatening overdose, as observed in this case, involves tachycardia, hypotension, seizures, and obtundation.

The mainstay of treatment for TCA overdose involves the use of intravenously administered sodium bicarbonate ($NaHCO_3$). $NAHCO_3$

administration induces alkalization of the urine and facilitates elimination of any unbound drug. Furthermore, $NAHCO_3$ may be effective at counteracting the sodium channel blockade that contributes to impaired myocardial contractility and the widened QRS complex. Boluses are administered until the QRS narrows or until clinical improvement is achieved. QRS duration in excess of 100 milliseconds is commonly used as a trigger for the initiation of bicarbonate therapy.[1] Other pertinent electrocardiographic findings associated with TCA toxicity include sinus tachycardia, a rightward electrical axis, and a terminal R wave in lead aVR[1,2] (Fig. 2). One study suggested that the presence of the terminal R wave predicts the onset of seizures and dysrhythmias in the setting of TCA overdose.[3] An infusion of sodium bicarbonate should be initiated once the QRS narrows sufficiently or below the 100-millisecond threshold.[1,4] Frequent blood gas measurements assist clinicians in monitoring the efficacy of treatment. A target arterial pH of 7.50 to 7.55 is recommended to ensure adequate serum alkalization.[1,4,5] Doses in excess of what is described in common treatment protocols may be required. This patient's QRS complex remained prolonged. Underlying left bundle branch block pathology combined with the severity of the patient's overdose could have contributed to the fixed and abnormal QRS duration. The patient received 17 total ampules of sodium bicarbonate throughout the entirety of his treatment course.

Hypertonic saline has been considered as an alternative treatment for patients who fail to respond appropriately to sodium bicarbonate boluses. Theoretically, hypertonic saline may have a role in combating the overwhelming sodium channel blockade present during critical overdoses. Data supporting this approach are unsurprisingly limited to animal studies and case reports. A decision to administer hypertonic saline must be informed by an understanding of its potential side effects, including worsening hyperchloremic acidosis and hypernatremia.[6]

Alpha receptor blockade contributes to the refractory hypotension noted in TCA overdose.[1,2] Receptor-specific agents such as norepinephrine and phenylephrine may be useful during resuscitation. The combined effects of sodium channel and alpha receptor blockade contribute to profound hemodynamic collapse,[1,2] and patients may require the administration of multiple vasopressors.[1,2] Vasopressor choice is informed by an understanding of TCA pharmacology. Alpha receptor agonists, such as norepinephrine and phenylephrine, are considered first-line therapies for overdose treatment.[4]

There have not been any studies to show that the choice of ventilator therapy can improve outcomes in the setting of TCA overdose. Serum alkalization is more rapidly achieved through intravenous bicarbonate therapy as opposed to increasing the rate of ventilation. Current recommendations related to respiratory therapies include compliance with ARDSnet lung protective guidelines such as maintenance of low tidal volumes, physiologic respiratory rates, and the application of positive end-expiratory pressure to avoid lung derecruitment and atelectasis.[1,2] A combined strategy of induced respiratory alkalosis and serum alkalization has been linked to profound metabolic alkalosis and increased mortality.[7]

Case studies and review articles highlight other potential therapies. Dialysis and hemoperfusion have not shown usefulness in TCA overdose because of the extremely large volume of drug distribution.[2,8] The use of intravenous lipid emulsion (ILE) may be of benefit in cases refractory to traditional therapy. A case report from 2014 described a case of lipid rescue in a 50-year-old male patient who presented to the emergency department with severe metabolic acidosis, shock, and respiratory failure.[9] In 2012, Harvey and Cave[10] published a case report that suggested that the use of ILE "curtailed" vasopressor requirements in a patient suffering from TCA toxicity and concurrent polysubstance ingestion. Varney et al[11] conducted a randomized controlled trial examining the use of bicarbonate and ILE in a swine model of TCA toxicity. Twelve swine received standard therapy comprised of a bicarbonate infusion, and the remaining 12 received a bolus and subsequent infusion of ILE. The 2014 study did not show any difference between the treatment groups in mean heart rate, mean arterial pressure, or cardiac output. Obvious limitations include the use of animal models and the omission of sodium bicarbonate in the experimental treatment cohort. High-quality human research is lacking, and the mechanism of ILE is not fully understood. It is thought ILE therapy functions as a "lipid sink" that effectively absorbs any remaining, unbound toxic ingestant.[5] Therefore, it may be reasonable to have a low threshold to initiate ILE in the setting of persistent hemodynamic stability.[10,12] The usual dosing regimen for lipid rescue consists of a 20% lipid emulsion solution administered as a 1 to 1.5 mg/kg intravenous bolus. The bolus is administered over 1 minute and is followed by an infusion at 0.25 to 0.5 mL/kg. The exact duration of the infusion is unknown, but it is acceptable to continue dosing until there is normalization of hemodynamic parameters (4). It is important to mention that isolated case reports comprise much of the clinical data surrounding TCA overdose treatment. Case reports also highlight the potential use of extracorporeal membrane oxygenation (ECMO) in the setting of life-threatening TCA overdose.[13,14] ECMO may act as "bridging" therapy in the setting of severe systolic dysfunction and myocardial suppression. There is simply not enough high-quality evidence to recommend routinely incorporating ECMO into TCA treatment algorithms. ECMO may be useful in the selective treatment of cardiac arrest or cardiogenic shock from polysubstance ingestion.[13]

Seizures in the setting of TCA overdose may be particularly difficult to treat. This patient did not respond to high doses of midazolam

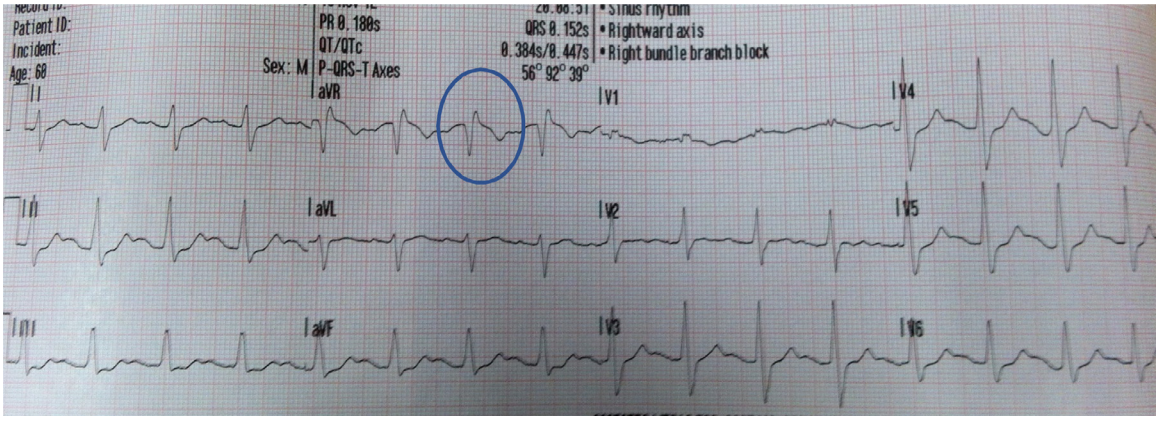

Figure 2. Classic electrocardiographic findings in the setting of TCA overdose. The circle encompasses a QRS complex in lead aVR. There is a terminally positive R wave, and the duration of the QRS is > 100 milliseconds. The other associated findings include tachycardia and a rightward axis.

- Obtain a 12 lead ECG
- Consult specialized resources early in the course of overdose (pharmacy, critical care, poison control)
- Bolus sodium bicarbonate until QRS duration < 100 ms
- Target sodium bicarbonate administration to a pH of 7.5 or greater
- Consider agents with alpha adrenergic agonist properties for vasopressor support (norepinephrine, epinephrine, phenylephrine)
- Avoid anticonvulsants with sodium channel blocking properties (lidocaine, phenytoin)
- Use benzodiazepines first line for the treatment of TCA associated seizures
- Consider intralipid infusion for patients failing to respond to sodium bicarbonate
- Avoid routine gastric decontamination / activated charcoal administration

Figure 3. Key strategies/benchmarks in the treatment of suspected TCA overdose.

and required a propofol infusion to suppress seizure activity. Because of its sodium channel blocking properties, the use of phenytoin is contraindicated in the setting of TCA overdose. Current guidelines recommend first-line treatment with benzodiazepenes.[1,4,15] Continuous EEG monitoring is recommended in the setting of ongoing sedation to monitor for subclinical seizures. In this patient's case, frequent EEG activity persisted despite aggressive midazolam dosing. Additional anticonvulsants were necessary to suppress EEG spikes.

Gastric decontamination may represent a potential therapeutic modality. Like other therapies, there are no high-quality clinical trials to support the use of activated charcoal. The large volume of distribution of TCAs, coupled with their anticholinergic properties, lends support to the theoretical therapeutic effect of gastric decontamination. Studies conducted in healthy volunteers showed that the administration of multiple-dose activated charcoal could increase the elimination of nortriptyline. Another small randomized trial looked at gastric lavage and activated charcoal in patients with suspected TCA overdose. Thirty-four patients received activated charcoal after gastric lavage, and the remaining 43 patients served as the control group. The trial examined peak plasma concentrations at specific intervals after the initiation of gastric decontamination. The authors did not detect a measurable difference in the "systemic absorption or elimination of TCA" in the cohort that received a 20-g dose of activated charcoal.[8,16] It is challenging to extrapolate those findings to patients who have ingested toxic amounts of the drug. Furthermore, the decision to administer charcoal must be considered in light of potential airway compromise. The rapid progression of TCA overdose often results in airway compromise and obtundation, and the potential aspiration of activated charcoal is a life-threatening complication. Therefore, transport crews should evaluate patients for impending respiratory failure when considering an unproven therapy that may not immediately impact hemodynamic parameters. Activated charcoal administration might be a reasonable option if prehospital providers can reliably verify the time of ingestion in a neurologically intact patient without evidence of electrocardiographic changes or hemodynamic compromise. The evidence-based guideline endorsed by the American Association of Poison Control Centers reflects the controversy surrounding the lack of available evidence. The guideline states that benefit of gastric decontamination is "unknown" and that "prehospital activated charcoal administration . . . should only be carried out . . . if no contraindications are present."[1,15]

Clearly, an aggressive, multimodal, and goal-directed approach is warranted in the treatment of TCA overdose. Figure 3 summarizes key components of a successful TCA overdose treatment strategy. Nortriptyline is a potent tricyclic antidepressant and demands vigilance with respect to ongoing treatment and monitoring. Mortality is high after the onset of hemodynamic compromise. Emergency clinicians should recognize signs suggestive of TCA ingestion and remain ready to initiate treatment with sodium bicarbonate, intravenous fluid, and vasopressors. Consider endotracheal intubation early in the patient's course because of the potential for hemodynamic collapse and obtundation. Ventilator strategies are planned in accordance with ARDSnet recommendations. Should standard therapies fail to result in clinical improvement, ILE can be considered as an adjunct therapy.[1,9,17]

Conclusion

TCA overdose remains a time-sensitive and critical condition. It must be promptly recognized if adverse outcomes are to be avoided. Prehospital and emergency clinicians can recognize TCA overdose by taking a thorough history, obtaining a 12-lead electrocardiogram, and conducting frequently neurological assessments. Sodium bicarbonate administration/therapy and rapid transport represent cornerstones of an effective treatment strategy. Sodium bicarbonate is titrated according to ECG findings and pH parameters. Vasopressors, especially alpha agonists, play a prominent role in management. The administration of intralipid can be considered in patients who fail to respond to standard therapy. Patients with abnormal vital signs and a deteriorating neurologic examination require advanced interventions such as vasopressor titration and endotracheal intubation. Critical care transport crews should consider the need for additional resources such as high doses of bicarbonate, benzodiazepines, and ABG results before medical evacuation.

References

1. Tsai V. Tricyclic antidepressant toxicity. emedicine online; 2017. https://emedicine.medscape.com/article/819204-overview. Accessed September 20, 2018.
2. Kerr GW, Mcguffie AC, Wilkie S. Tricyclic antidepressant overdose : a review tricyclic antidepressant overdose : a review. *Emerg Med J*. 2001;18:236–241.
3. Liebelt E, Francis P, Woolf A. ECG lead aVR versus QRS interval in predicting seizures and arrythmias in acute tricyclic antidepressant toxicity. *Ann Emerg Med*. 1995;26:195–201.
4. Salhanick S. Tricyclic antidepressant poisoning. UpToDate; 2018. www.uptodate.com. Accessed January 19, 2019.
5. Goldstein JN, Dudzinski DM, Erickson TB, Linder G. Case 12-2018: a 30-year-old woman with cardiac arrest. *N Engl J Med*. 2018;378:1538–1549.
6. Eken C. Hypertonic saline: an alternative therapy in TCA overdoses failed to respond sodium bicarbonate. *Clin Toxicol (Phila)*. 2009;3650:2–3.
7. Wrenn K, Smith B, Slovis C. Profound alkalemia during treatment of tricyclic antidepressant overdose: a potential hazard of combined hyperventilation and intravenous bicarbonate. *Am J Emerg Med*. 1992;10:553–555.
8. Dargan P, Colbridge M, Jones A. The management of tricyclic antidepressant poisoning: the role of gut decontamination, extracorporeal procedures, and fab antibody fragments. *Toxicol Rev*. 2005;24:187–194.
9. Perza MN, Schneider LA, Rosini JM. Suspected tricyclic antidepressant overdose successfully treated with lipids. *J Emerg Nurs*. 2013;39:296–298.

10. Harvey M, Cave G. Case report: Successful lipid resuscitation in multidrug overdose with predominant tricyclic antidepressant toxidrome. *Int J Emerg Med*. 2012;5:1–5.
11. Varney SM, Bebarta VS, Vargas TE, Boudreau S, Castaneda M. Intravenous lipid emulsion therapy does not improve hypotension compared to sodium bicarbonate for tricyclic antidepressant toxicity: a randomized, controlled pilot study in a swine model. *Acad Emerg Med*. 2014;21:1212–1219.
12. Goldstein JN, Dudzinski DM, Erickson TB, Linder G. Case 12-2018: a 30-year-old woman with cardiac arrest. *N Engl J Med*. 2018;378:1538–1549.
13. Koschny R, Lutz M, Seckinger J, Schwenger V, Stremmel W, Eisenbach C. Extracorporeal life support and plasmapheresis in a case of severe polyintoxication. *J Emerg Med*. 2014;47:527–531.
14. Goodwin D, Lally K, Null D. Extracorporeal membrane oxygenation support for cardiac dysfunction from tricyclic antidepressant overdose. *Crit Care Med*. 1993;21:625–627.
15. Woolf A, Erdman AR, Nelson L, et al. Tricyclic antidepressant poisoning: an evidence based consensus guideline for out-of-hospital management. *Clin Toxicol*. 2007;45:203–233.
16. Hulten B, Adams R, Askenasi R, et al. Activated charcoal in tricyclic antidepressant poisoning. *Hum Toxicol*. 1988;7:307–310.
17. Giwa A, Oey E. The return of an old nemesis: survival after severe tricyclic antidepressant toxicity, a case report. *Toxicol Rep*. 2018;5:357–362.