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Selected Topics: Toxicology

Successful Treatment of Amoxapine-Induced Intractable Seizures With Intravenous Lipid Emulsion

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□ **Abstract—Background: Amoxapine is a second-generation tricyclic antidepressant with a greater seizure risk than other antidepressants. If administered in large amounts, amoxapine can cause severe toxicity and death. Therefore, it is necessary to terminate seizures immediately if amoxapine toxicity occurs. However, intractable seizures often occur in these patients. We describe a case of intractable seizures caused by amoxapine poisoning, in which intravenous lipid emulsion (ILE) was used successfully. Case Report: A 44-year-old woman with a history of depression ingested 3.0 g of amoxapine during a suicide attempt. Although she was initially treated with intravenous diazepam, her seizures persisted. Levetiracetam and phenobarbital were then administered, but seizures persisted. Hence, ILE was injected for over 1 min. At 2 min after ILE administration, the patient's status seizures ceased. Recurrence of seizures was observed 30 min after ILE, and the seizures disappeared after re-administration of ILE. Why Should an Emergency Physician Be Aware of This?: ILE may be effective in amoxapine intoxication. Emergency physicians may consider ILE as an adjunctive therapy for amoxapine poisoning with a high mortality rate. ILE should be implemented carefully with monitoring of total dosage and adverse events. © 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)**

□ **Keywords—Tricyclic antidepressant; Intravenous lipid emulsion; Lipid sink; Lipophilic drug; Amoxapine**

Introduction

Tricyclic antidepressants (TCAs) are used to treat depression and are currently prescribed to patients. Owing to their widespread adaptation, such as their use in neuropathic and chronic pain, obsessive-compulsive, and attention-deficit hyperactivity disorders, TCA overdose is common and has lethal adverse effects, such as cardiotoxicity and seizure activity (1). Amoxapine is a second-generation TCA characterized by less cardiotoxicity than first-generation TCAs. In contrast, amoxapine overdose has a greater seizure risk than other antidepressants and requires critical care, as it is associated with a high fatality risk and has been reported to be associated with the highest mortality rate among antidepressants (2,3). Therefore, if amoxapine intoxication occurs, seizures must be terminated as soon as possible. However, treatment resistance generally manifests.

Anecdotal studies have suggested that intravenous lipid emulsion (ILE) therapy may effectively reduce toxicity from a variety of lipophilic drug overdoses that are resistant to standard treatments. Various in vitro and in vivo experiments have suggested that ILE reduces toxicity by incorporating the intoxication-causing substance

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into lipid emulsions (4). In the clinical setting, ILE administration has been temporally associated with successful resuscitation from cardiovascular toxicity caused by various multidrug therapies, such as combined bupropion and lamotrigine–induced cardiac arrest and amelioration of verapamil- and β-blocker–induced shock (5,6). Amelioration of coma caused by sertraline and quetiapine has also been reported; thus, ILE therapy may effectively alleviate central nervous system toxicity (7). Here, we report the first case of ILE treatment for refractory seizures caused by amoxapine overdose.

Case Report

A 44-year-old, 60-kg woman with a history of depression ingested 3.0 g of amoxapine during a suicide attempt. On admission, her heart rate was 158 beats/min; blood pressure was 110/62 mm Hg; temperature was 36.9°C; Glasgow Coma Scale score was 6; pupil diameter was 3.5 mm; and her pupils were equal, round, and reactive to light and accommodation. The patient intermittently experienced two 1-min tonic seizures and observed the risk of upper airway obstruction due to glossoptosis. She was initially treated with intravenous diazepam (10 mg), and her seizures subsided temporarily. The patient was rapidly administered lidocaine (50 mg), fentanyl (50 μg), and midazolam (4 mg), intubated and placed on a ventilator. After gastric tube insertion, the patient underwent gastric lavage, removing several tablets, and 40 g of activated charcoal was administered to bind the excess drug and subsequent decontamination (Figure 1).

Arterial blood gas analysis revealed the following: pH was 6.644; $PaCO_2$ was 81.1 torr, PaO_2 was 73.9 torr, HCO_3^- was 8.3 mmol/L, base excess was –33.7 mmol/L, and lactate was 30.0 mmol/L. Initial electrocardiogram showed sinus tachycardia (heart rate was 117 beats/min) with evidence of intraventricular conduction delay (QRS width was 110 ms) along with a prolonged corrected QT interval (Bazett's QTc was 457 ms). As the seizures continued every few minutes, levetiracetam (1000 mg) was administered; however, the seizures persisted. We attempted to curb seizures by infusing 0.33 mg/kg/h of midazolam and 1.66 mg/kg/h of propofol. However, seizures could not be suppressed, and the addition of phenobarbital (1000 mg) was anticonvulsant. Her temperature then increased to 41°C due to the extended duration of status seizures. In parallel with the drug treatment for seizures, we inserted a cool line catheter into the central line and initiated external cooling. In addition, blood alkalinization was performed by administering 80 mEq/L of sodium bicarbonate. However, repetitive seizures recurred. We believe that refractory status seizures were caused by amoxapine intoxication, and it was considered reasonable to start administering ILE for amoxapine, which is highly fat-soluble.

At 90 min after arrival, 100 mL of 20% lipid emulsion (Intralipos injection 20%; Otsuka Pharmaceutical Factory Inc.) was administered intravenously for over 1 min. At 2 min after ILE administration initiation, the patient's seizure activity ceased. Therefore, continuous amplitude-integrated electroencephalography (aEEG) monitoring of seizures was initiated. Next, rocuronium administration was initiated to prevent shivering through targeted temperature management. At this point, arterial blood gas analysis revealed the following results: pH was 7.157, $PaCO_2$ was 44.2 torr, PaO_2 was 309.0 torr, HCO_3^- was 15.0 mmol/L, base excess was –12.8 mmol/L, and lactate was 28.0 mmol/L. Despite this initial treatment, recurrence of seizures was observed at 60 min after ILE injection. Therefore, additional doses of 20% lipid emulsion were administered in 100-mL increments while monitoring for seizures. As a result, the seizures disappeared after four times of 20% lipid emulsion (100 mL each; total of 400 mL). At this point, arterial blood gas analysis revealed the following results: pH was 7.475, $PaCO_2$ was 32.8 torr, PaO_2 was 83.0 torr, HCO_3^- was 23.9 mmol/L, base excess was 1.2 mmol/L, and lactate was 14.2 mmol/L.

Once in the intensive care unit, in addition to maintaining deep sedation using midazolam and propofol to avoid hyperthermia and secondary brain damage, the target temperature was maintained with invasive cooling on rocuronium infusion for 24 h. No elevation of amylase or coagulation abnormalities was observed with ILE administration, and no pancreatitis or thrombosis was developed. Moreover, no epileptic seizures or abnormal EEG were observed after careful monitoring using aEEG. Sedation was discontinued on day 2 and aEEG monitoring was continued until day 3; however, there were no abnormal findings. The patient was extubated on day 10 of hospitalization, and the disturbance of consciousness was improved. She was transferred to a psychiatric medical ward and discharged on day 90 with a memory disturbance that remained as sequelae.

The toxicological results, which were not available during the emergency department stay, showed that the patient's serum amoxapine concentration was measured as 23.4 μg/mL at 30 min after arrival and 7.5 μg/mL after 5 h. This value is significantly higher than 67.4 $\pm$ 35.8 ng/mL, which is the maximum blood concentration of amoxapine 100 mg taken orally (8).

Discussion

We report a case of refractory status seizures induced by amoxapine overdose, which was unresponsive to ini-

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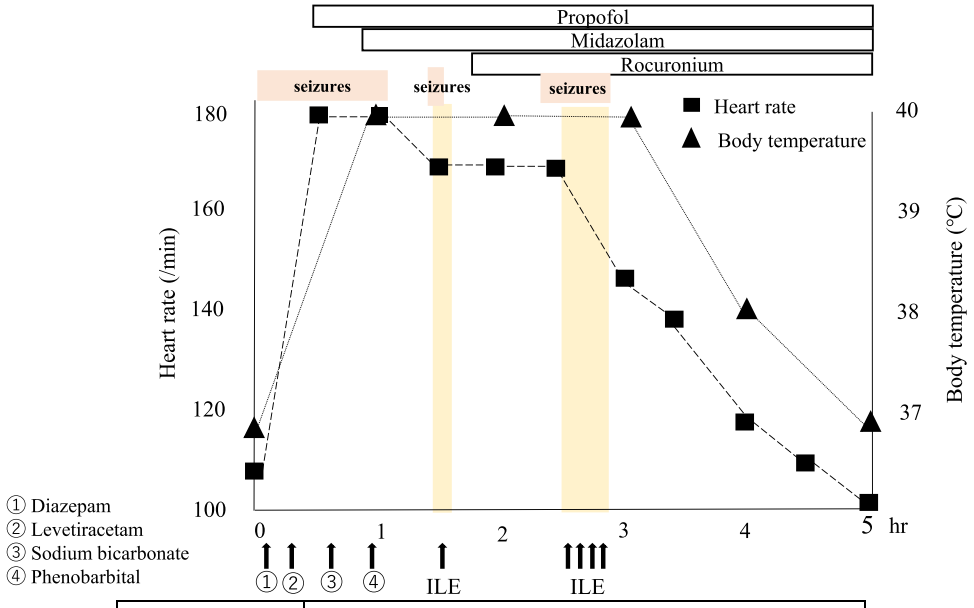

	Time After Admission					
	30min	90min	150min	210min	240min	300min
PH	6.644	7.157	7.475	7.507	7.572	7.570
$PaCO_2$ (mmHg)	81.1	44.2	32.8	34.6	31.4	33.0
PaO_2 (mmHg)	73.9	309.0	83.0	126.0	141.0	101.0
HCO_3^- (mmol/L)	8.3	15.0	23.9	27.3	28.9	30.2
Lac (mmol/L)	30.0	28.0	14.2	5.9	6.0	4.1
BE (mmol/L)	-33.7	-12.8	1.2	4.6	7.0	8.0
Na (mmol/L)	150	144	143	144	145	143
K (mmol/L)	6.1	3.9	3.5	3.0	2.6	2.7
Glu (mg/dL)	233	188	223	161	138	126

Figure 1. The first part of therapeutic processes of the case reported in this study. It shows epilepsy, medication, vital signs, blood gases, and blood levels of amoxapine within 5 h of patient's arrival. ILE = intravenous lipid emulsion.

tial anticonvulsant therapy, with a temporal relationship between overt seizure cessation and ILE. The mechanism of amoxapine-induced seizures is thought to involve the blockade of the physiological effect of gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the cerebral cortex that counterbalances neuronal excitation (9). This effect is observed at high doses and differs from GABA receptor antagonism (10). Amoxapine poisoning differs from other TCAs in that it often presents with intermittent epileptic seizures (3). These patients have shown resistance to benzodiazepine, which is most commonly used to treat status seizures, thus making it difficult to curb drug-induced seizures (11). This patient also exhibited intermittent epileptic seizures and did not respond to diazepam or midazolam, and other antiepileptic drugs failed to produce anticonvulsant effects and were considered an additional management strategy.

ILEs are effective for highly liposoluble drugs, and octanol/water partition coefficients of log $p \geq 2$ have been reported as a guide to their liposolubility (12). Amoxapine was highly liposoluble, with a log $p = 3.38$ (13). There are no reports of ILE use in treating amoxapine poisoning in the clinical or experimental literature. However, given the lipophilicity of amoxapine, ILE may suppress seizures by incorporating amoxapine into lipid emulsions. Therefore, we decided to administer ILE for refractory seizures that were difficult to control. As a result, seizures disappeared quickly. ILE has been reported to affect various types of drug poisoning within a few minutes, and the onset time of ILE's effect in this case is consistent with previous reports (14–17). It has also been suggested that the blood levels of TCAs do not correlate with toxicity or mortality (18). In other words, it is reasonable to assume that seizures correlate more with brain tissue drug concentrations than with blood concentrations during severe

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amoxapine intoxication. Therefore, it is logical to assume that the trapping of amoxapine from brain tissue into the lLE may reduce its concentration in brain tissue and ameliorate addiction. ILE has been reported to be associated with improvement in circulatory failure immediately after the administration of amitriptyline poisoning, a TCA with chemical properties similar to those of amoxapine (15). In addition, in an animal study examining the relationship between amitriptyline blood and tissue concentrations after ILE, the amitriptyline blood levels increased in the ILE groups compared with those in the non-ILE groups, while the concentrations in the brain and heart decreased (19). This suggests that ILE suppresses poisoning symptoms by decreasing the tissue distribution of the drugs. Based on these findings, it is possible that ILE administration transiently decreased the amoxapine concentration in the brain tissue because the drug was anticonvulsant, despite the abnormally high blood concentration in this case as well. However, as we did not measure the brain tissue concentrations in this case, we believe that the detailed mechanism is a subject for future study.

In this case, seizures recurred 60 min after ILE administration, although the patient was receiving rocuronium. As in the present case, there have been many reports of toxicity recurrence at the end of ILE administration. For example, it has been reported that the relapse of cardiotoxicity of bupivacaine occurred 40 min after ILE administration, and cardiotoxicity recurred after ILE administration for amitriptyline poisoning but improved after re-administration of ILE (16,17). The duration of ILE's effect was not determined. It has been theorized that ILE binds to drug molecules via electrostatic forces (20). These interactions are weak bonds that are susceptible to fluctuations in pH and temperature; thus, it is likely that ILEs do not bind to the drug strongly (21). Furthermore, lipids are rapidly metabolized, suggesting that lipid sink drugs can be redistributed in the tissue (22). Based on these facts, we inferred that ILE's effect is transient; hence, it is considered appropriate for repeated administration. ILE administration has been described in various guidelines, but there is no consensus on how to administer them. The American College of Medical Toxicology (ACMT) position statement suggests a bolus infusion of 1.5 mL/kg of 20% fat emulsion over 2–3 min, and if the response to the first bolus fails, consider a repeat bolus (23). In this case, ILE was re-administered with reference to this report, and seizures were controlled successfully. However, it has been suggested that the risk factors for adverse events associated with ILE are proportional to the infusion rate and total dose, and there have been reports of overdose due to repeated administration of ILE to poisoned patients, although no effect was achieved (24,25). There is no known maximum dose, but ACMT suggests a maximum dose of 10 mL/kg, and it may be practical to re-dose at 1.5 mL/kg to avoid exceeding that dose. In numerous cases of resuscitation with lipid emulsions, only a few adverse effects have been reported at doses below the maximum dose described above (23,26). In this case, the total dose was 7 mL/kg, and there were no adverse events, such as lung injury or pancreatitis, due to ILE administration.

This case report has some limitations. First, inadequate administration of sodium bicarbonate for acidemia may have caused the seizures to persist. Second, the ventilator management and appropriate coping strategies improved acid–base balance and stabilized hemodynamics. This correction of acid–base equilibrium and hemodynamic stabilization may also contribute to the anticonvulsant effects. Thus, it may be difficult to establish the effect of ILE alone, as the patient received other treatments at various times. However, in the present case, a temporal coincidence between ILE and resolution of seizures was observed, suggesting that ILE has a certain effect on amoxapine poisoning.

Why Should an Emergency Physician be Aware of This?

Lipid emulsion therapy use seemed to have a rapid effect in terminating the seizure activity of amoxapine toxicity. This may have prevented further clinical destabilization during the patient's clinical course. Emergency physicians may consider ILE as an adjunctive therapy for amoxapine poisoning with a high mortality rate. ILE should be carefully implemented with monitoring of total dosage and adverse events.

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