CASE REPORT

Unusual complications from amitriptyline intoxication

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SUMMARY

Although tricyclic antidepressants (TCAs) are frequently prescribed to patients with depression, these drugs can also be misused. A 21-year-old comatose patient was referred to our hospital presenting with ventricular tachycardia. Despite initial treatment including intravascular lipid emulsion, ventricular fibrillation occurred soon after arrival. Venoarterial extracorporeal membrane oxygenation and therapeutic hypothermia were administered. Refractory arrhythmia disappeared on the next day. A high concentration of amitriptyline was identified in his blood samples on arrival. Mechanical bowel obstruction followed after abdominal compartment syndrome caused by anticholinergic effects, and refractory seizure occurred due to TCA intoxication. Although seizure was brought under control with anticonvulsant agents, his Glasgow Coma Scale did not recover to the full score. MRI presented irreversible damage to the bilateral frontal lobe and insula. Amitriptyline has the potential to cause unusual serious complications, such as abdominal compartment syndrome, irreversible central nervous system disability and lethal arrhythmia.

BACKGROUND

Depression is a common disease in Japan. Tricyclic antidepressants (TCAs), including amitriptyline, are the most commonly prescribed drugs for patients with depression. However, these drugs can also be misused, leading to coma, lethal refractory ventricular arrhythmia and various other complications. With easy access to the TCAs, the number of patients with overdose intoxication is predicted to increase. We recently experienced a patient with unusual but lethal complications associated with amitriptyline intoxication.

CASE PRESENTATION

A 21-year-old man with a history of multiple TCA overdoses was brought to our hospital by ambulance. He was comatose and presented with ventricular tachycardia (VT) on ECG. His vital signs were as follows: Glasgow Coma Scale (GCS) score: E1 V1 M1 (Eye opening (E), best verbal response (V), best motor response (M)); heart rate: 150 beats per minutes; blood pressure: 66/41 mm Hg; respiratory rate: 10 breaths per minutes; oxygen saturation: not available. Both pupils were dilated, 6 mm, and fixed. There was no light reflex. Blood test results on arrival were as follows: pH 6.776, P_{CO_2} : 139 mm Hg, P_{O_2} : 13.1 mm Hg, HCO_3^- : 20.0 mmol/L, base excess: -18.9 mmol/L, anion gap: 35.5 mmol/L, glucose: 23.3 mmol/L, lactate:

15.76 mmol/L. Other electrolytes were almost normal. He also presented intermittent systemic seizures lasting a few seconds. Asynergy was not found by transthoracic echocardiogram. Hyperdynamic state in ventricle was recognised. Intubation and direct current shock (150 J, 200 J and 360 J) were administered rapidly. However, arrhythmia did not return to sinus. Although no information about his prescribed drugs was available, based on his previous history and his symptoms, we administered fluid therapy with 4 L crystalloid, and infused 7% bicarbonate phosphate (1250 mL), diazepam and magnesium, followed by 40 mg of intravenous lipid emulsion (ILE). Despite these efforts, his ECG changed to ventricular fibrillation (VF) 70 min after arrival. We started cardiopulmonary resuscitation and decided to initiate venoarterial extracorporeal membrane oxygenation (VA-ECMO). Epinephrine and amiodarone were administered. Down time between collapse and pump-on was 30 min. His urine test (triage) was positive for TCA, which had been prescribed for depression, so activated charcoal was administered via a nasogastric tube, although we did not know the interval from ingestion. Whole-body CT was within normal findings. The serum concentration of amitriptyline on arrival was 306.2 ng/mL.

After admission to intensive care, therapeutic hypothermia, targeting 33°C for 24 hours with VA-ECMO, was started according to the AHA guideline for the postcardiac arrest syndrome, because the patient did not present any motor findings. However, it was discontinued before 24 hours due to uncontrollable haemorrhage at the site of femoral catheter insertion. Refractory ventricular arrhythmia continued for 3 days. Abdominal CT on postadmission day (PAD) 3 revealed intestinal emphysema leading to the abdominal compartment syndrome (ACS). Intra-abdominal pressure was 23 mm Hg, and ACS was improved with conservative treatments by the next day. Afterwards, his ECG showed normal sinus rhythm naturally on PAD 3.

Nonetheless, several complications occurred such as mechanical bowel obstruction and refractory systemic seizure. Abdominal CT revealed bowel obstruction and strangulation on PAD 23 (figure 1). Since mechanical bowel obstruction did not improve with long intestinal tube, a laparoscopic small bowel resection was performed on PAD 43.

Regarding his central nervous system (CNS), although anticonvulsion drugs regulated refractory seizure, his comatose condition did not improve. MRI on PAD 21 showed that the bilateral frontal lobe and insula were damaged, which were not

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Figure 1 Abdominal CT of abdominal compartment syndrome.

compatible with hypoxic damage (figures 2 and 3). After extubation, he was not alert (GCS: E4 V2 M4). He was transferred to a rehabilitation hospital on PAD 54.

DISCUSSION

Amitriptyline, which is classified as a TCA, is commonly used to treat depression. TCAs including amitriptyline are highly bound to protein in the vasculature and are quite lipophilic with a large distribution volume, causing a long elimination half-life generally exceeding 24 hours; the elimination half-life of amitriptyline ranges from 31 to 46 hours. TCAs are absorbed rapidly in the gastrointestinal tract and metabolised via the first-pass effect.¹ Amitriptyline toxicity usually occurs within 2–6 hours after ingestion.² Typical findings caused by overdose

Figure 2 High intensity at the bilateral frontal lobe and insula in a diffusion-weighted image.

Figure 3 High intensity at the bilateral frontal lobe and insula in a fluid-attenuated inversion recovery.

are hypotension, seizure, CNS depression and arrhythmias such as QT prolongation.

Kerr *et al* reported that TCAs' toxic effects are caused by four primary pharmacological characteristics: anticholinergic action, direct α adrenergic block, inhibition of norepinephrine reuptake at nerve terminals and a membrane stabilising or quinidine-like effect on the myocardium.¹ Seizures usually occur due to gamma-aminobutyric acid antagonism and sodium channel blockade. Intestinal peristalsis caused by the anticholinergic effect may not frequently occur. However, some cases cause serious megacolon and intestinal perforation.^{3,4} Hypotension is induced by myocardial depression due to sodium channel blocking and α antagonism. Tachycardia, the most common cardiovascular symptom, is caused by anticholinergic action and inhibition of norepinephrine reuptake. Intraventricular conduction and QT prolongation leading to VT and cardiac arrest occur due to sodium channel blockade and potassium efflux blockade, respectively.

Our case presented three unique symptoms during the clinical course: (1) VT followed by VF, (2) mechanical bowel obstruction followed by ACS and (3) refractory seizure derived from irreversible brain damage.

First, our patient presented with VT and VF despite ILE. Bicarbonate administration was recommended as treatment of TCAs overdose by the guideline,⁵ and ILE is predicted as other treatment. As discussed above, TCAs are lipophilic with a large amount of distribution, which is suitable for ILE therapy. Weinberg *et al* first suggested the benefit of lipid emulsion for bupivacaine poisoning in a rat model in 1998.⁶ Rosenblatt *et al* reported the first case of successful human resuscitation using lipid therapy for intravenous bupivacaine toxicity in 2006.⁷ Afterwards, ILE has been applied for intoxication from several lipophilic drugs as well as verapamil,⁸ propranolol⁹ and TCAs. Levine *et al* reported a successful case of a patient with cardiac arrest after amitriptyline overdose treated with ILE.¹⁰ Abeyaratne *et al* reported a case of survival after amitriptyline poisoning with cardiac arrest and VT treated with three uninterrupted hours of direct current shocks and cardiac massage.¹¹

The potential benefit of ILE therapy is based on the lipid sink theory, in which rapid intravenous administration of lipid causes movement of lipophilic drugs down concentration gradients. Therefore, the lipophilic medication gets pulled from the toxicity site into the vascular compartment.¹² Although several successful cases were reported recently, ILE therapy for TCA intoxication is still controversial.

Second, mechanical bowel obstruction occurred, followed by ACS caused, which might be caused by an anticholinergic effect due to amitriptyline overdose. Analgesic or anaesthetic agents like fentanyl were not administered. Therapeutic hypothermia causes diarrhoea rather than ileus. Mehta *et al* reported malabsorption in a patient with tight adhesion and small intestinal volvulus caused by an overdose of aspirin, amitriptyline and diazepam.¹³ To our best knowledge, studies associated with the keywords 'amitriptyline,' 'bowel obstruction,' or 'ileus' and 'abdominal compartment syndrome' have never been published. This is the first case associated with bowel obstruction followed by ACS caused by amitriptyline intoxication.

Third, regarding the CNS, his comatose condition did not fully recover. An electroencephalogram did not present spike wave indicating epilepsy. Since blood examination (white cells, C reactive protein and procalcitonin), physical examination such as stiff neck or focal signs and head CT demonstrated normal findings, infectious diseases were not suspected. He was healthy 5 hours before he admitted to our hospital; therefore, neurodegenerative disease was not diagnosed. The MRI revealed unique findings, that is, high intensity signals at the bilateral frontal lobe and insula in T2-weighted and diffusion-weighted images, indicating cerebral oedema. This finding was not compatible with hypoxic brain damage. Bilateral lesions suggested metabolic dysfunction including drug intoxication.

As far as we know, few previous studies of irreversible brain damage caused by amitriptyline intoxication have been published. Although the majority of severe cases of amitriptyline intoxication present comatose within 24 hours, Roberge

and Krenzelok¹⁴ reported a unique case with a prolonged coma lasting more than 5 days and loss of brain stem reflexes. Tatli *et al*¹⁵ published another unique case of cerebellitis in a 4-year-old girl following accidental ingestion of TCAs. We cannot determine why our patient developed irreversible brain damage. Although VT occurred, the MRI findings were not typical of hypoxaemia. Overdose of amitriptyline might be associated with irreversible brain damage. Further studies on amitriptyline intoxication are needed.

Contributors TN and HM attributed the treatment of this patient. AN suggested thoughtful opinion for sophisticated manuscript. SN gave final approval to publish.

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REFERENCES

- Kerr GW, McGuffie AC, Wilkie S. Tricyclic antidepressant overdose: a review. *Emerg Med J* 2001;18:236–41.
- Brooks DE, Levine M, O'Connor AD, *et al*. Toxicology in the ICU: part 2: specific toxins. *Chest* 2011;140:1072–85.
- McMahon AJ. Amitriptyline overdose complicated by intestinal pseudo-obstruction and caecal perforation. *Postgrad Med J* 1989;65:948–9.
- Ross JP, Small TR, Lepage PA. Imipramine overdose complicated by toxic megacolon. *Am Surg* 1998;64:242–4.
- Body R, Bartram T, Azam F. *Guideline for the management of tricyclic antidepressant overdose*, 2009.
- Weinberg GL, VadeBoncouer T, Ramaraju GA, *et al*. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology* 1998;88:1071–5.
- Rosenblatt MA, Abel M, Fischer GW, *et al*. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. *Anesthesiology* 2006;105:217–8.
- Tebbutt S, Harvey M, Nicholson T, *et al*. Intralipid prolongs survival in a rat model of verapamil toxicity. *Acad Emerg Med* 2006;13:134–9.
- Harvey MG, Cave GR. Intralipid infusion ameliorates propranolol-induced hypotension in rabbits. *J Med Toxicol* 2008;4:71–6.
- Levine M, Brooks DE, Franken A, *et al*. Delayed-onset seizure and cardiac arrest after amitriptyline overdose, treated with intravenous lipid emulsion therapy. *Pediatrics* 2012;130:e432–e438.
- Abeyaratne DD, Liyanapathirana C, Gamage A, *et al*. Survival after severe amitriptyline poisoning with prolonged ventricular tachycardia and cardiac arrest. *BMC Res Notes* 2016;9:167.
- Cave G, Harvey M. Intravenous lipid emulsion as antidote beyond local anesthetic toxicity: a systematic review. *Acad Emerg Med* 2009;16:815–24.
- Mehta D, Mehta S, Mathew P. Unusual abdominal complications of a suicidal overdose of analgesic and psychotropic drugs in an elderly patient. *J Am Geriatr Soc* 1978;26:43–6.
- Roberge RJ, Krenzelok EP. Prolonged coma and loss of brainstem reflexes following amitriptyline overdose. *Vet Hum Toxicol* 2001;43:42–4.
- Tatli O, Karaca Y, Gunaydin M, *et al*. Cerebellitis developing after tricyclic antidepressant poisoning. *Am J Emerg Med* 2013;31:1419.e3–1419.e5.

Learning points

- ▶ Amitriptyline is a common tricyclic antidepressant, potentially causing critical complications, such as an abdominal compartment syndrome with bowel obstruction, irreversible central nervous system disability and lethal arrhythmia, in spite of intravenous lipid emulsion.
- ▶ Clinicians should be aware of these lethal complications from amitriptyline intoxication.

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