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Chewing the fat: A case report on intravenous lipid emulsion to reverse cardiotoxicity from intentional amitriptyline overdose

Tailler le bout de gras: Une étude de cas sur l'émulsion de lipides par voie intraveineuse pour inverser la cardiotoxicité émanant d'une overdose intentionnelle d'amitriptyline

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KEYWORDS

Tricyclic antidepressants;
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Abstract *Introduction:* Tricyclic antidepressant overdoses are a common presenting problem to emergency centres in South Africa.
Case history: A 20-year-old female was brought to the emergency centre in status epilepticus due to tricyclic antidepressant toxicity.
Discussion: Toxicity was manifested as severe haemodynamic instability that did not respond to standard therapy, and was subsequently treated with intravenous fat emulsion (ILE) therapy. The patient recovered with a survival to hospital discharge, neurologically intact.

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Abstract *Introduction:* Les overdoses d'antidépresseurs tricycliques sont un problème courant dans les centres d'urgences en Afrique duf Sud.
Profil du cas: Une femme de 20 ans a été amenée aux urgences dans un état épileptique suite à une toxicité aux antidépresseurs tricycliques.
Discussion: La toxicité était manifeste avec une grave instabilité hémodynamique qui ne répondait pas à la thérapie standard, qui a été ensuite traitée par une thérapie d'émulsion de graisse par voie intraveineuse (ILE). La patiente s'est rétablie avec survie à la sortie de l'hôpital, sans lésions neurologiques.

African relevance

- TCA overdose is a common and potentially fatal cause of overdoses presenting to South African emergency centers.
- Routine management includes cardiac monitoring and ensuring ventilation, sodium bicarbonate and seizure terminal – available in most emergency centers in South Africa.
- Despite issues around accessibility and affordability of ILE in South Africa, it should be considered a potentially life-saving drug in the context of TCA overdose and an effort should be made to ensure access to it.

What's new

- ILE is a relatively new and largely untested therapy in the treatment of TCA overdose; most evidence coming from case reports.
- This is the first report of successful ILE use in the treatment of TCA overdose in South Africa.
- The effect of treatment was dramatic and the patient recovered without any residual effects.
- As side-effects are relatively limited, ILE should seriously be considered in the treatment algorithm of TCA overdoses.
- More research is needed to examine this therapy and its potentially life-saving benefits in the treatment of TCA (and possibly other) overdoses.

Introduction

Tricyclic (TCA) antidepressant overdoses are a common presentation to emergency centres in South Africa where they constitute up to 20% of overdose cases.[1] These patients may prove particularly challenging to the attending physician, as overdoses with TCAs can exhibit significant adverse cardiovascular and neurologic effects that are difficult to treat. Traditional therapies include the use of benzodiazepines for seizures, sodium bicarbonate to reverse the toxicity, vasoactive medications to counteract the vasodilation of the toxicity, and gastrointestinal decontamination (to minimize the damage post ingestion).[2]

Intravenous lipid emulsion (ILE) is an emerging, but still unproven therapy for refractory cardiotoxicity due to lipid-soluble drugs. Its potential was first recognized in a rat model of bupivacaine toxicity and has gained credence in the clinical arena after reports of its successful use for bupivacaine and other drug toxicities.[3] The use of ILE for TCA overdose in humans has only been reported in a few case studies in the published literature.[4–6]

Case report

A 20-year-old female was found convulsing at home and brought to the emergency centre by ambulance. She presented in status epilepticus and was immediately given intravenous diazepam in an attempt to abort her seizure. Her seizure activity ceased within a minute. A wide complex rhythm was noted on cardiac monitor.

She was somnolent with no spontaneous eye opening and her GCS at this stage was 6/15 initial vital signs revealed a blood pressure of 92/64 mmHg, and a heart rate of 132 beats per minute (bpm).

A 12-lead ECG revealed a QRS duration 160 ms, a right bundle branch block, R-wave amplitude of 7 mm, and QTc 583 ms. She subsequently had another generalized tonic–clonic seizure and was given 100 ml 8.5% sodium bicarbonate, in addition to diazepam. Accompanying relatives volunteered a history of amitriptyline overdose. A third seizure in the emergency centre was terminated with another 10 mg bolus of diazepam. In view of the clinical presentation, the patient was intubated and mechanically ventilated after a respiratory arrest.

Initial arterial blood gas, prior to intubation, demonstrated the following values: pH 7.06, pCO_2 14.3 kPa, pO_2 8.5 kPa, HCO_3 23.9 mmol/l, BaseExcess −10.

The decision was made by treating physicians in the emergency centre to initiate ILE therapy as a specific treatment for possible TCA toxicity manifesting as haemodynamic instability and refractory status epilepticus.

ILE therapy was administered as follows: ILE 20%, 500 ml infusion (100 ml as a bolus, and the remaining 400 ml was infused over 15 min).

Following administration of ILE, the patient's blood pressure increased to 110/70 while a repeat ECG revealed a shortened QTc of 497 ms and QRS complex narrowing to 114 ms. At no point during her stay in the emergency centre, did the patient require cardiopulmonary resuscitation or the use of vasopressors.

The patient was subsequently transferred to a tertiary intensive care unit, where she required inotropic support with adrenaline for the first 30 h post admission due to haemodynamic

instability. Toxicology results confirmed a mixed overdose of tricyclic antidepressants and paracetamol level of 709 μmol/l; intravenous N-acetylcysteine therapy was subsequently commenced. She was extubated 3 days after admission and discharged to a general medical ward 4 days after her initial transfer.

Discussion

The traditional use of ILE is to provide nutrition in the form of free fatty acids to patients who require parenteral nutrition.[7] However, it has been demonstrated to be an effective amelioration for cardiovascular and central nervous system sequelae of local-anaesthetic and non-local-anaesthetic drug toxicity in animal models as well as showing significant promise in human subjects.

Tricyclic antidepressants have a variety of pharmacologic effects on the cardiovascular and central nervous system that are important when considering their potential toxicity.[6] TCAs are rapidly absorbed from the gut, are lipophilic, have a large volume of distribution, and the plasma component is significantly protein-bound. Intravenous lipid emulsion is presumed to reverse the toxicity of drugs via a number of proposed mechanisms.[7] Sequestration of lipophilic toxins to an expanded plasma lipid phase is credited as the predominant beneficial mechanism of action of ILE, the so-called "lipid sink" theory. The second proposed mechanism involves augmenting cardiac energy supplies.[8] Local anaesthetics and other drugs can impair fatty acid transport to cardiac mitochondria by inhibiting carnitine acylcarnitine translocase. Lastly, direct activation of the cardiac voltage-gated calcium channel is believed to occur, increasing cytosolic calcium and increasing cardiac performance.[7,8]

Serious consideration of ILE as a life saving therapy in amitriptyline toxicity is based on the first published case report[6] of a patient with vasopressor-refractory haemodynamic instability despite standard therapy. The authors reported that although ILE was administered at a time where the patient's conduction abnormalities had been reversed with previous administration of NaHCO3, the severe vasopressor-refractory shock had an almost immediate, and thus significant, response to ILE.

A separate case study published in 2010[8] reported rapid improvement in vital parameters, including blood pressure and GCS, of a patient with a mixed drug overdose following ILE administration. The patient's admission to high care was reduced to less than 24 h and subsequently recovered fully.

The use of ILE in TCA toxicity had been previously examined in laboratory rats[9] and rabbits[10] where it was demonstrated to have a beneficial haemodynamic effect with improved mortality. Human experience with ILE and TCAs had been previously limited to a single 1987 study[11] of healthy volunteers. This trial refuted the use of a lipid infusion in TCA toxicity based on similar plasma levels measured after 5 h in the two groups assigned to lipid and saline infusions respectively.

ILE has a safe track record based on its frequent and long-standing use in parenteral nutrition therapy.[7] Adverse effects have been isolated to one case of hyperamylaesmia[12] and one instance of acute lung injury.[13]

The use of ILE as an antidote is the subject of much recent academic and clinical debate despite its clinical safety.[14] Significant heterogenicity in patient presentations and published case reports makes general recommendations for use of ILE difficult, if not impossible. The American College of Medical Toxicology Position Statement on use of ILE[13] rests the decision to initiate LRT (lipid resuscitation therapy) solely on the discretion of the treating physician, however, they consider it a reasonable treatment option in cases where serious haemodynamic, or other instability from a xenobiotic with a high degree of lipid solubility exists; even if the patient is not in cardiac arrest.

Conclusion

Our case represents the first reported human use of intravenous lipid emulsion to successfully treat the life-threatening cardiotoxic effects of an intentional TCA (amitriptyline) overdose in South Africa. Although our patient did not go into cardiac arrest or require initial vasopressor support, the effect of ILE on the demonstrated cardiotoxicity, was almost immediately evident; she recovered fully without any adverse sequelae. ILE is not yet ready for routine use in the early stages of resuscitation, but many toxicologists would recommend it as a last-ditch effort when a lipophilic drug is causing cardiovascular collapse not improving with standard treatment. Although ongoing reporting and analysis of such cases will prove invaluable in determining the exact utility of ILE in the setting of drug toxicity, perhaps the strongest statement to this effect has been by Jeffrey Brent in a recent editorial[6,15]: "It is fair to say that based on what we known so far, no patient dying of cardiotoxic drug poisoning should do so without a trial of lipid rescue."

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Short answer questions

Test your understanding of the contents of this original paper (answers can be found at the end of the regular features section)

1. Intralipid emulsion has been used for the following purposes:
   a. Treatment of local anaesthetic overdose
   b. Treatment of non-local-anaesthetic overdose
   c. In total parenteral nutrition (TPN)
   d. In tricyclic antidepressant overdose
   e. All of the above

2. Overdose of tricyclic antidepressant is typically associated with all of the following, except:
   a. Convulsions
   b. Renal failure

c. Respiratory depression
d. Coma
e. Cardiovascular instability

3. The presumed mechanism of action of ILE in the treatment of tricyclic antidepressant toxicity:
   a. Sequestration of lipophilic toxins to an expanded plasma lipid phase
   b. Augmentation of cardiac energy supplies
   c. Direct activation of the cardiac voltage-gated calcium channel
   d. All of the above
   e. None of the above

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