

CASE REPORT

Glucagon in hemodynamic instability after tricyclic antidepressant overdose

S.M.Rombach¹, E.J. Wesselink², E.I. de Stoppelaar¹, E.R. Rijnsburger¹, C. Slagt³

¹ Department of Intensive Care Medicine, Zaans Medical Center, Zaandam, the Netherlands

² Department of Clinical Pharmacy, Zaans Medical Center, Zaandam, the Netherlands

³ Department of Anesthesiology, Pain and Palliative medicine, University Medical Center St. Radboud, Nijmegen, the Netherlands

Correspondence

S.M.Rombach – s.rombach@vumc.nl

Keywords - nortriptyline, intoxication, glucagon, hemodynamic instability

Abstract

A 38-year old man presented with hemodynamic instability after a nortriptyline intoxication. He was intubated and treated with fluids, sodium bicarbonate 8.4%, activated charcoal, sodium sulfate, intravenous lipid emulsion, norepinephrine and magnesium sulfate intravenously. Only after the addition of glucagon 10 mg intravenously, his hemodynamic condition improved. Glucagon should be considered early in severe tricyclic antidepressant overdose.

Introduction

Tricyclic antidepressants (TCAs) are prescribed in case of severe depression, despite the availability of a new generation of antidepressants with an improved safety profile. Tricyclic antidepressants block alpha-adrenergic receptors and have anticholinergic effects.¹ This may lead to sinus tachycardia, cardiac conduction abnormalities, vasodilation, arrhythmias, hypotension or even asystole. The anticholinergic effects of TCAs are a dry mouth, blurred vision, dilated pupils, hyperthermia and delayed gastric emptying. Neurological symptoms include drowsiness, coma, respiratory depression, seizures and delirium.¹

The following case report shows the example of a patient with severe TCA intoxication, refractory to initial treatment, who was treated with glucagon as rescue therapy.

Case report

A 38-year-old man was admitted to the emergency department after a suicide attempt taking fifty-five tablets of 25 mg nortriptyline (total of 1375 mg) and ten tablets of 10 mg zolpidem (total of 100 mg). His medical history revealed a gastric bypass two years ago and he was treated for a bipolar disorder. He presented, approximately 1.5 hour after ingestion, with somnolence, an obstructive airway, low blood pressure

(50/25 mmHg) and increased heart rate (>200 beats per minute), as well as a broad complex tachycardia (QRS 220 ms) on ECG (*figure 1*).

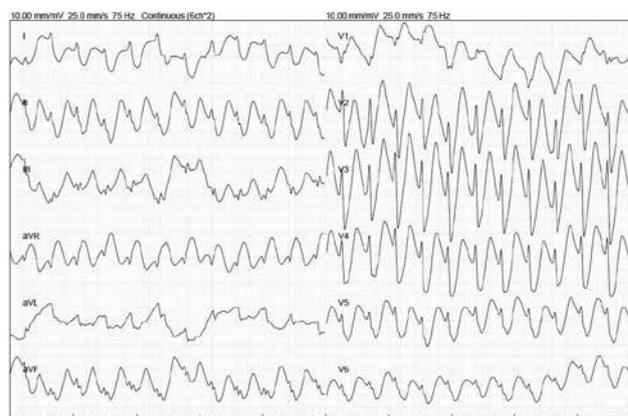


Figure 1. ECG at presentation.

He was intubated for airway protection. Thereafter the following interventions were applied: administration of fluids, sodium bicarbonate 8.4% to achieve a pH between 7.50 and 7.55, activated charcoal 50 gram every six hours, sodium sulphate 30 gram every six hours and treatment with intravenous lipid emulsion (Intralipid® 200 mg/ml, Fresenius Kabi, NL) to a total of 500 ml. Despite these interventions, the tachycardia and hypotension persisted. Subsequently norepinephrine (*figure 2*) and magnesium sulphate (2 grams) were initiated, however without clinical improvement. After the administration of 10 mg of glucagon intravenously, the blood pressure increased and the norepinephrine dose was rapidly decreased (*figure 2*). Glucagon 5 mg per hour was given continuously. A couple of hours later, short runs of ventricular arrhythmias (VT) were treated with magnesium sulphate and additional norepinephrine boluses.

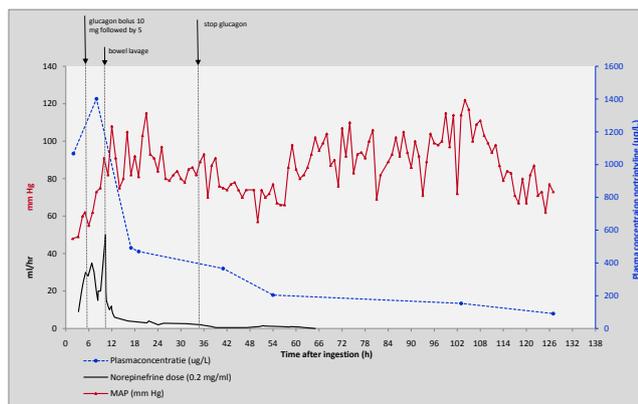


Figure 2. X-axis: time after ingestion of nortriptyline. Y-axis: mean arterial pressure (MAP, mmHg) and pharmacological agent as indicated.

During his ICU stay, he developed generalised seizures treated with clonazepam and propofol. Furthermore, he developed hyperthermia, for which active cooling was started. Further laboratory results revealed a high alanine transaminase (5230 U/l) and aspartate transaminase (10,378 U/l) without signs of rhabdomyolysis (creatinine kinase 47 U/l), indicating hepatotoxicity without evidence of liver failure.² In the next couple of days the liver enzymes returned to normal. At day 6 he was extubated. He suffered from short-term memory loss, but otherwise his long-term memory was intact and there were no signs of other neurological impairment.

At admission, the nortriptyline concentration was 1067 µg/l (two hours after ingestion, $t=2h$), and later on 1401 µg/l ($t=8h$), 492 µg/l ($t=17h$) and 470 µg/l ($t=19h$). Glucagon was stopped when he was hemodynamically stable (35 hours after ingestion). Sodium bicarbonate, active charcoal and magnesium sulphate were continued until the patient improved clinically, the half-life had passed and the drug levels were within the therapeutic range (at day 4).

Discussion

The major clinical symptoms of tricyclic antidepressant (TCAs) intoxication are ventricular arrhythmias and seizures. The therapeutic range of tricyclic antidepressants ranges from 50-150 µg/l. Toxic concentrations of >200-1000 µg/l are described.^{3,4} Although the level of the TCA concentration is generally higher in patients presenting with complications than without,⁵ the serum drug level does not necessarily predict the severity of symptoms.^{3,4} A prolonged QRS interval (>100 milliseconds) and a decreased level of consciousness (Glasgow Coma Scale <8) do predict a higher chance of developing complications.^{3,4} Good outcomes have been reported in patients with TCA overdose treated with sodium bicarbonate infusion, magnesium sulphate, charcoal, bowel lavage, and intralipid infusion.¹ The mainstay of treatment for TCA intoxication is sodium bicarbonate, adjusting the pH to 7.45-7.55.¹ Though observational studies and case

reports mention a rapid improvement in hypotension and cardiac arrhythmias following the administration of sodium bicarbonate, randomised trials have not been performed.⁶ When hypotension is not resolved after sodium bicarbonate and fluids, vasopressors or magnesium sulphate are indicated.¹ Recently the first randomised clinical trial on supplementation of magnesium sulphate was reported, resulting in a shorter length of stay at the intensive care unit and a trend towards a lower mortality rate.⁷

In refractory hemodynamic instability, intralipid therapy is generally recommended, however the clinical evidence for this therapy is limited.^{1,8}

Glucagon 10 mg intravenously can be considered in case of life-threatening hypotension or arrhythmias refractory to other measures.¹ To date, evidence is too limited to support routine use of glucagon in TCA overdose. There are three other cases that support its benefit.⁹⁻¹¹ Of note, in all cases, multiple interventions were applied, which makes it difficult to distinguish the effect of glucagon in TCA intoxication.¹² Our patient, similar to these three cases, received multiple treatments; however, eventually his blood pressure increased after addition of glucagon.

TCAs block alpha-adrenergic receptors and have anticholinergic effects.¹ This could explain why norepinephrine, a potent alpha-adrenergic vasoconstrictor, alone was not effective in increasing the blood pressure. Glucagon, also known for the treatment for beta blocker and calcium channel antagonists overdoses, increases the intracellular calcium concentration in the myocardium by stimulating adenyl cyclase, causing positive inotropic and chronotropic effects, independent of adrenergic receptors.¹¹ In heart failure, the positive inotropic effect of glucagon decreases sympathetic tone by decreasing the reflex sympathetic stimulation as a result of the improvement of cardiac activity and the concomitant improvement in the blood flow to various organs.¹³ Furthermore, glucagon stimulates the release of endogenous epinephrine from the adrenal medulla.¹³

The magic bullet for treating TCA intoxication has yet to be invented. The administration of Fab (antibody fragments) has been investigated as treatment for TCA intoxication. In a preliminary study seven patients were treated with Fab, resulting in a decreased QRS duration in two patients; however, patients with hypotension or refractory ventricular dysrhythmias were not included.¹⁴ The study is too small to draw any conclusions on its efficacy. Hemofiltration has been reported in only two cases with a severe TCA intoxication, both receiving multiple interventions.^{15,16}

Conclusion

Glucagon administration should be considered in case of severe TCA intoxication, when hemodynamic instability persists after treatment with sodium bicarbonate, magnesium sulphate and vasopressors.

Informed consent: the patient gave written informed consent; available on request.

Disclosure

All authors declare no conflict of interest. No funding or financial support was received.

References

1. Body R, Bartram T, Azam F, Mackway-Jones K. Guidelines in Emergency Medicine Network (GEMNet): guideline for the management of tricyclic antidepressant overdose. *Emerg Med J.* 2011;28:347-68.
2. Weibrecht K, Dayno M, Darling C, Bird SB. Liver aminotransferases are elevated with rhabdomyolysis in the absence of significant liver injury. *J Med Toxicol.* 2010;6:294-300.
3. Boehnert MT, Lovejoy FH. Value of the QRS Duration Versus the Serum Drug Level in Predicting Seizures and Ventricular Arrhythmias After An Acute Overdose of Tricyclic Antidepressants. *New Engl J Med.* 1985;313:474-9.
4. Hultén BA, Adams R, Askenasi R, et al. Predicting severity of tricyclic antidepressant overdose. *Clin Toxicol.* 1992;30:161-70.
5. Paksu S, Duran L, Altuntas M, et al. Amitriptyline overdose in emergency department of university hospital: Evaluation of 250 patients. *Hum Exp Toxicol.* 2014;33:980-90.
6. Vrijlandt PJ, Bosch TM, Zijlstra JG, Tulleken JE, Ligtenberg JJ, van der Werf TS. Sodium bicarbonate infusion for intoxication with tricyclic antidepressives: recommended in spite of lack of scientific evidence. *Ned Tijdschrift Geneesk.* 2001;145:1686-9.
7. Emamhadi M, Mostafazadeh B, Hassanijirdehi M. Tricyclic antidepressant poisoning treated by magnesium sulfate: a randomized, clinical trial. *Drug Chem Toxicol.* 2012;35:300-3.
8. Cave G, Harvey M. Intravenous lipid emulsion as antidote beyond local anesthetic toxicity: a systematic review. *Acad Emerg Med.* 2009;16:815-24.
9. Ruddy JM, Seymour JL, Anderson NG. Management of tricyclic antidepressant ingestion in children with special reference to the use of glucagon. *Med J Aust.* 1972;1:630-3.
10. Sener EK, Gabe S, Henry JA. Response to glucagon in imipramine overdose. *J Toxicol. Clin Toxicol.* 1995;33:51-3.
11. Sensky PR, Olczak SA. High dose intravenous glucagon in severe tricyclic poisoning. *Postgrad Med J.* 1999;75:611-2.
12. Teece S, Hogg K. Glucagon in tricyclic overdose. *Emerg Med J.* 2003;20:264-5.
13. Farah AE. Glucagon and the circulation. *Pharmacol Rev.* 1983;35:181-217.
14. Heard K, Dart RC, Bogdan G, et al. A Preliminary Study of Tricyclic Antidepressant (TCA) Ovine FAB for TCA Toxicity. *Clin Toxicol (Phila).* 2006;44:3:75-81.
15. Ozayar E, Degerli S, Gulec H. Hemodiafiltration: A novel approach for treating severe amitriptyline intoxication. *Toxicol Int.* 2012;19:319-21.
16. Frank RD, Kierdorf HP. Is there a role for hemoperfusion/hemodialysis as a treatment option in severe tricyclic antidepressant intoxication? *Int J Artif Organs.* 2000;23: 618-23.



NVIC CURSUS ECHOGRAFIE

De rol van echografie op de intensive care wordt steeds groter en wordt beschouwd als een zeer waardevolle aanwinst in de zorg voor kritisch zieke patiënten.

Opzet cursus

Op de 1^e dag wordt de basale echocardiografie behandeld volgens de principes van de R(apid) A(ssessment) by C(ardiac) E(cho).

De volgende onderwerpen komen aan bod:

- introductie van de echocardiografie;
- functie linker en rechter systeem;
- preload en vulling;
- pericard

De tweede dag start met een herhaling van dag 1 en worden de volgende onderwerpen behandeld:

- echografie van longen en pleura;
- echografie van de vaten

Veel nadruk ligt op 'hands on' sessies. Het streven is om per oefenstation met maximaal drie cursisten te werken.

Cursusdata 2016

Dinsdag 8 en woensdag 9 maart
Dinsdag 21 en woensdag 22 juni
Woensdag 14 en donderdag 15 september
Dinsdag 6 en woensdag 7 december

Doelgroepen

Alle artsen werkzaam in de acute geneeskunde of op de intensive care.

Inschrijven

U kunt zich voor deze cursus inschrijven via website: www.nvic.nl.

De inschrijfkosten bedragen:

€ 750 (incl. BTW) voor NVIC leden

€ 855 (incl. BTW) voor niet-leden

Diner, overnachting, ontbijt & lunch zijn bij het cursusgeld inbegrepen.

Accreditatie

Accreditatie is aangevraagd bij:

NIV, NVA, NVvH, NVALT, NVvN, NVN, NVVC & NVIC.

Locatie

OSG-VvAA

(Opleidingsinstituut Spoedeisende Geneeskunde VvAA)

Ringveste 7a, 3990 CG Houten

NVIC

Postbus 2124

3500 GC UTRECHT

T 030 - 282 38 38

E secretariaat@nvic.nl

W www.nvic.nl

Cursussecretariaat

OSG-VvAA

T 030 - 63 46 580

E cursus@nvic.nl