Submitted May 2018; Accepted September 2018

CASE REPORT

Loss of brainstem reflexes: not always an ominous sign

V.L. Winia[1], J. Horn[3], B. van den Bogaard[2,3]

[1]Department of Intensive Care, Netherlands Cancer Institute, Amsterdam, the Netherlands

[2]Department of Intensive Care, OLVG Oost, Amsterdam, the Netherlands

[3]Department of Intensive Care, Amsterdam UMC, location AMC, University of Amsterdam, Amsterdam, the Netherlands

Correspondence

V.L. Winia – v.winia@nki.nl

Keywords - **brainstem reflexes, intoxication, brain death**

Abstract

We present three cases of serious multidrug intoxications with absent brainstem reflexes that may imply diagnostic and prognostic challenges. Given the good neurological outcome in these patients and of earlier described cases in the literature, the absence of brainstem reflexes in intoxication is not necessarily a sign of a poor prognosis and should be used with caution in prognostication.

Introduction

Absent brainstem reflexes in the presence of known brain injury is often regarded as a sign of serious brainstem injury. In the Netherlands it is part of the brain death criteria used in organ donation procedures.[1] We present three patients with absent brainstem reflexes after severe drug intoxication with good neurological outcome. In the discussion we will describe the clinical course and treatment options after intoxications with the denoted drugs and present the available literature about absent brainstem reflexes after intoxication due to drugs.

Cases

Patient 1

A 67-year-old woman, with known depressive disorder and a history of multiple suicide attempts, presented to our emergency department after being found unconscious by her relatives. The paramedics had found her with a Glasgow Coma Score (GCS) of 3 and dilated pupils unresponsive to light. She vomited and had a seizure, after which she was sedated with midazolam and intubated.

Upon presentation in the emergency department (ED) she was hypotensive (blood pressure 85/61 mmHg) and tachycardic (pulse 91 beats/min), with a normal respiratory rate (12 breaths/min) and saturation (99%). Her pupils were deformed, moderately dilated and unresponsive to light. Corneal reflexes and oculocephalic reflexes were absent. Plantar reflexes were indifferent. CT of the brain did not show any abnormalities, specifically no signs of cerebral oedema or elevated intracranial pressure, and CT angiography of the brain excluded basilar artery thrombosis. ECG on admission showed a right axis, prolonged PQ interval (144 ms) and a broad QRS complex (160 ms). There was a strong suspicion of intentional intoxication with amitriptyline and as such activated charcoal and sodium bicarbonate were administered. Amitriptyline serum levels were found to be seriously elevated (amitriptyline >730 µg/l, nortriptyline 400 µg/l). On day 1 of her admission she had yet another seizure, for which she was started on levetiracetam and diazepam. There was a gradual improvement of her neurological performance, with return of brainstem reflexes within 24 hours, and she was taken off the ventilator on day 3 after admission. She was discharged to a regular ward on day 4 with minor symptoms of confusion. The course of the consecutive amitriptyline serum levels is shown in *table 1*.

Patient 2

A 28-year-old man, with a history of a complicated course after knee surgery, consisting of recurrent infections and septic shock, presented to our emergency department in coma. Upon presentation in the ED he had a GCS of 3 with pupils unresponsive to light, absent corneal reflexes and absent oculocephalic reflexes. There was no muscular tone and he had indifferent plantar reflexes. Haemodynamically he was stable (blood pressure 120/80 mmHg, pulse 110 beats/min), with a normal respiratory rate (15 breaths/min) and saturation (96%). Administration of 200 µg naloxone did not lead to neurological improvement, and he was intubated. The ECG was normal. Brain CT showed no abnormalities, and CT angiography of the brain excluded basilar artery thrombosis. EEG did not show any signs of epileptiform activity or encephalopathy. There was a

quick neurological recovery, with return of brainstem reflexes within several hours, after which he could be taken off the ventilator and discharged to a regular ward. On day 3 after his admission, toxicological testing was done, which showed levels of amitriptyline at the upper limit of normal (330 µg/l) and toxic levels of bromazepam (507 µg/l) (*table 1*). Repeated levels on day 9 were below detection point (< 50 µg/l).

Patient 3

A 58-year-old man, with an extensive medical history including depression, alcohol abuse, Child-Pugh B alcoholic liver cirrhosis, hypertension, atrial fibrillation and obstructive sleep apnoea syndrome, presented to our ED with reduced consciousness. His wife had found him snoring and unconscious, when she returned home after being out for two hours. Upon presentation in the ED he had a GCS of 3 with pupils responsive to light and corneal reflex present. He had normal blood pressure (115/85 mmHg) and pulse (80 beats/min). He was intubated because of bradypnoea (6 breaths/min) and a threatened airway. ECG showed atrial fibrillation, a left axis, prolonged QRS complex (130 ms) and negative T waves in the precordial leads. Serum ethanol level was 2.8 g/l. During the course of several hours his neurological status deteriorated, with dilated pupils, and absent pupil and corneal reflexes. Plantar reflexes were indifferent. Simultaneously, the QRS complexes broadened on his ECG (144 ms). CT of the brain showed no abnormalities.

There was a suspicion of intentional intoxication with venlafaxine and baclofen so activated charcoal was administered and continuous veno-venous haemofiltration (CVVH) was started. After several hours his pupil reflexes returned and he could be extubated on day 2. Intoxication was confirmed with both drugs, serum levels on admission were as follows: baclofen 1600 µg/l, venlafaxine 10502 µg/l, o-desmethylvenlafaxine (DM-venlafaxine) 418 µg/l.

Due to agitation he required sedation with midazolam after which he was reintubated. His sedation was consecutively switched to clonidine and dexmedetomidine because of ongoing agitation, and haloperidol and oxazepam were added. The course of the consecutive serum levels is shown in *table 1*. CVVH was stopped on day 3. Under suspicion of venlafaxine withdrawal, a dose of 75 mg once daily was started on day 4. He gradually became less agitated, after which the dexmedetomidine was stopped and he could be taken off the ventilator on day 6. He was discharged to a regular ward on day 7 with symptoms of delirium.

Discussion

These three cases show that severe intoxications can lead to coma with absent brainstem reflexes which, in the absence of known or proven brain injury, can result in diagnostic challenges. In patient 1 and patient 3 there was a strong suspicion of an intoxication, based on the previous medical history, but in case 2 there were no direct clues in that direction, leading to a delay in toxicological testing. Furthermore, these cases emphasise that severe intoxications with absent brainstem reflexes can pose a challenge in drawing conclusions about prognosis.

All drugs described in the above cases might lead to severe central nervous system depression when taken in overdose. Bromazepam and baclofen are both GABA receptor agonists and as such lead to inhibitory effects on the central neurotransmitters in the brain. Baclofen specifically targets the GABA-B receptor at spinal level and typically can lead to flaccidity.

Amitriptyline, a tricyclic antidepressant (TCA), and venlafaxine, a selective serotonin and noradrenaline reuptake inhibitor (SNRI), both lead to higher availability of central serotonin and can lead to serotonin syndrome, consisting of mental status changes, autonomic manifestations and neuromuscular hyperactivity. Both drugs are metabolised by the cytochrome P450 enzyme system and as such can potentiate effects when ingested in combination. Amitriptyline also has anticholinergic effects and can lead to anticholinergic syndrome in overdose.

Table 1. Consecutive drug serum levels from all three cases

	Day 1	Day 2	Day 3	Day 4	Therapeutic levels	Toxic levels
Patient 1						
Amitriptyline	> 730 µg/l	570 µg/l	390 µg/l	190 µg/l	100-300 µg/l (1)	>400 µg/l (1)
Nortriptyline	400 µg/l	390 µg/l	320 µg/l	230 µg/l		
Patient 2						
Amitriptyline			330 µg/l		100-300 µg/l	>400 µg/l
Bromazepam			507 µg/l		80-170 µg/l	>250 µg/l
Patient 3						
Baclofen	1600 µg/l	510 µg/l			80-600 µg/l	>1100 µg/l
Venlafaxine	10,502 µg/l	7522 µg/l			100-400 µg/l (2)	>1000 µg/l (2)
DM-venlafaxine	418 µg/l	592 µg/l				

Reference laboratory values for therapeutic and toxic levels from the Academic Medical Center and OLVG, Amsterdam. (1) Combined amitriptyline and nortriptyline; (2) combined venlafaxine and o-desmethylvenlafaxine (DM-venlafaxine)

The mainstay of the treatment of severe intoxications with the aforementioned drugs is supportive measures. In TCA overdose treatment with sodium bicarbonate is advised and in both severe SNRI and TCA overdose intralipid infusion might be effective to achieve faster elimination, although this is based on anecdotal evidence only.[2-6] In case of serotonin syndrome the admission of cyproheptadine might be effective to treat the symptoms, although evidence is scarce.[7]

The severe central nervous system depression leading to absent brainstem reflexes as described in our cases illustrates a challenge in clinical decision-making. Absent brainstem reflexes is one of the components of the protocol to establish brain death for organ donation and is generally associated with a poor prognosis.[1,8,9] Nonetheless earlier cases of severe intoxications leading to absent brainstem reflexes with good clinical outcome have been described. We will describe below the relevant literature regarding the drugs mentioned in our patients. Other drugs and toxins that can elicit absent brainstem reflexes can be found in *table 2*. Please note that the information in this table may not be complete and that other drugs or toxins might cause the same effects.

Table 2. Drugs and toxins that can elicit absent brainstem reflexes

Group	Drug/toxin	References
Antidepressants	Amitriptyline (tricyclic antidepressant) Venlafaxine (serotonin-norepinephrine reuptake inhibitor) Bupropion (dopamine agonist)	This article This article [22]
Benzodiazepines	Bromazepam Zolpidem	This article [23]
Barbiturates	Pentobarbital Thiopental	[24] [25]
Skeletal muscle relaxants	Baclofen	This article
Anti-epileptics	Valproic acid Carbamazepine	[26] [27]
Ethanol	Ethanol	[28]
Ethylene glycol	Ethylene glycol	[29,30]
Insecticides	Thiacloprid (neonicotinoid) Phorate (organophosphate)	[31] [32]
Synthetic cannabinoids	Synthetic cannabinoids	[33]

Several cases concerning amitriptyline intoxications have been published, some of which showing complete neurological recovery after 5 to 7 days.[10-14] One case even concerned a patient with out-of-hospital cardiac arrest after intentional overdose with amitriptyline, in which cardiopulmonary resuscitation was started 18 minutes after collapse.[11] Pulseless ventricular tachycardia was the initial rhythm, and there was a return of spontaneous circulation within 6 minutes after two shocks. Patient had absent brainstem reflexes on day 2, leading to concern about severe hypoxic ischaemic encephalopathy. However, at the end of the second day a cough reflex and sluggish pupillary reflexes were noted, and there was a complete neurological recovery by day 6. An overview of amitriptyline and nortriptyline serum levels from cases associated with absent brainstem reflexes can be found in *table 3*.

Table 3. Amitriptyline (AT) and nortriptyline (NT) serum levels from cases associated with absent brainstem reflexes

Case		Serum levels at presentation	Clinical course	References
38-year-old female	AT	1310 µg/l	Full recovery at day 5	[10]
	NT	38 µg/l		[10]
52-year-old male	AT	2800 µg/l	Full recovery at day 6	[11]
	NT	630 µg/l		[11]
46-year-old female	AT	2350 µg/l	Full recovery at day 5	[12]
62-year-old female	NT	2290 µg/l	Full recovery at day 3	[14]
38-year-old female	AT	2900 µg/l	Died after 2 weeks	[14]

Bromazepam coma is very common but rarely reported; there are some reports of prolonged coma and two cases specifically describing absent brain stem reflexes secondary to bromazepam intoxication with return of spontaneous ventilation on day 5 in one case.[15-17]

One earlier case concerning venlafaxine describes fixed dilated pupils in a comatose patient with combined overdose with carbamazepine and venlafaxine, who eventually recovers.[18] To our knowledge no cases of mere venlafaxine intoxication leading to complete absent brainstem reflexes followed by neurological recovery have been described.

We found several earlier cases with partial absent brainstem reflexes after intoxication with baclofen combined with other drugs.[19-21] One described an impressive case of a patient who presented in a comatose state after intentional overdose with baclofen, possibly combined with nabumatone, diphenhydramine and alprazolam.[21] She had a GCS of 3 and remained without brainstem reflexes until day 4, when neurology consultation was requested for brain death determination. She failed to fulfil the clinical criteria for brain death based on having a spontaneous breath after 5 minutes of apnoea testing. Surprisingly she opened her eyes on day 5 and continued to improve until her discharge from the ICU on day 15.

This last case illustrates the importance of utmost strictness in establishing brain death according to the current protocols. Apart from clinical neurological examination, of which the absent brainstem reflexes are a component, the Dutch brain death protocol also requires the case to fulfil preliminary conditions.[1] These conditions state that brain death can only be established in case of fatal brain injury with known cause and no possible treatment; and that this establishment can only be done with absolute certitude after it has been made plausible that there are no

other causes of unconsciousness and unresponsiveness. In light of these conditions the previously mentioned case from Kansal et al. would pose a serious challenge, considering a patient post cardiac arrest with possible hypoxic ischaemic encephalopathy.[11] To ascribe the clinical symptoms of absent brainstem reflexes in this case solely to the cardiac arrest and subsequent hypoxic ischaemic encephalopathy could have led to withdrawal of further treatment or proceeding to donation after brain death.

Hence, if there is no good explanation for the cause of a coma with absent brainstem reflexes or if intoxication cannot be ruled out, further diagnostic tests are required. A thorough toxicological screening and consultation of a clinical toxicologist should be performed. In case of a proven intoxication a patient should not be considered for potential donation after brain death, unless there is sufficient proof that toxins have been eliminated and no longer play a role in clinical symptoms of brain death. Furthermore, in unexplained coma it is justified to apprehend a longer expectant policy. As shown in both *table 1* and *table 2*, serum levels are not necessarily directly related to clinical symptoms or outcome. As such serum levels should not be used as exact cut-offs in decision making, but could contribute to the decision to await possible further recovery.

Conclusion

Several severe intoxications with drugs depressing the central nervous system might lead to a comatose state with absent brainstem reflexes. This is not necessarily a sign of a poor prognosis and as such we recommend caution in predicting unfavourable outcomes on this given fact alone; and above all we recommend patience in awaiting the course of the possibly intoxicated patient.

Acknowledgements

We would like to thank Eric Haak and Eric Franssen, hospital pharmacists (OLVG hospital) for performing various toxicological tests.

Disclosures

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

References

1. Nederlands Hersendoodprotocol. Besluit van 11 mei 2017, houdende vaststelling van het tijdstip van inwerkingtreding van het besluit van 10 februari 2017, houdende wijziging van tabel 4 in de bijlage bij het Besluit Hersendoodprotocol in verband met het herstel van een omissie (Stb. 2017, 74). Staatsblad van het Koninkrijk der Nederlanden. 2017;207.
2. Bradberry SM, Thanacoody HK, Watt BE, Thomas SH, Vale JA. Management of the cardiovascular complications of tricyclic antidepressant poisoning : role of sodium bicarbonate. Toxicol Rev. 2005;24:195-204.
3. Hillyard SG, Barrera-Groba C, Tighe R. Intralipid reverses coma associated with zopiclone and venlafaxine overdose. Eur J Anaesthesiol. 2010;27:582-3.
4. Eren Cevik S, Tasyurek T, Guneysel O. Intralipid emulsion treatment as an antidote in lipophilic drug intoxications. Am J Emerg Med. 201432:1103-8.
5. Blaber MS, Khan JN, Brebner JA, McColm R. "Lipid rescue" for tricyclic antidepressant cardiotoxicity. J Emerg Med. 2012;43:465-7.
6. Gosselin S, Hoegberg LC, Hoffman RS, et al. Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning. Clin Toxicol (Phila). 2016;54:899-923.
7. Graudins A, Stearman A, Chan B. Treatment of the serotonin syndrome with cyproheptadine. J Emerg Med. 1998;16:615-9.
8. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40:1816-31.
9. Nyam TE, Ao KH, Hung SY, Shen ML, Yu TC, Kuo JR. FOUR Score Predicts Early Outcome in Patients After Traumatic Brain Injury. Neurocrit Care. 2017;26:225-31.
10. Roberge RJ, Krenzelok EP. Prolonged coma and loss of brainstem reflexes following amitriptyline overdose. Vet Hum Toxicol. 2001;43:42-4.
11. Kansal A, Khan FA, Rana MH. "Complete" loss of brain stem reflexes - not always brain death! Beware of amitriptyline overdose. Crit Care Shock. 2017;20:17-20.
12. Yang KL, Dantzker DR. Reversible brain death. A manifestation of amitriptyline overdose. Chest. 1991;99:1037-8.
13. Choi KH, Lee KU. Serial Monitoring of Lead aVR in Patients with Prolonged Unconsciousness Following Tricyclic Antidepressant Overdose. Psychiatry Investig. 2008;5:247-50.
14. Franssen EJ, Kunst PW, Bet PM, Strack van Schijndel RJ, van Loenen AC, Wilhelm AJ. Toxicokinetics of nortriptyline and amitriptyline: two case reports. Ther Drug Monit. 2003;25:248-51.
15. Lakhal K, Pallancher S, Mathieu-Daude JC, Harry P, Capdevila X. Protracted deep coma after bromazepam poisoning. Int J Clin Pharmacol Ther. 2010;48:79-83.
16. Rudolf J, Kaferstein H, Neveling M, Stenzel C. Protracted course of bromazepam poisoning in advanced age. Dtsch Med Wochenschr. 1998;123:832-4.
17. Mouradian MD, Penovich PE. Spindle coma in benzodiazepine toxicity: case report. Clin Electroencephalogr. 1985;16:213-8.
18. Cordova S, Lee R. Fixed, dilated pupils in the ICU: another recoverable cause. Anaesth Intensive Care. 2000;28:91-3.
19. Miller JJ. Baclofen overdose mimicking anoxic encephalopathy: a case report and review of the literature. Ther Adv Drug Saf. 2017;8:165-7.
20. Ostermann ME, Young B, Sibbald WJ, Nicolle MW. Coma mimicking brain death following baclofen overdose. Intensive Care Med. 2000;26:1144-6.
21. Sullivan R, Hodgman MJ, Kao L, Tormoehlen LM. Baclofen overdose mimicking brain death. Clin Toxicol (Phila). 2012;50:141-4.
22. Stranges D, Lucerna A, Espinosa J, et al. A Lazarus effect: A case report of Bupropion overdose mimicking brain death. World J Emerg Med. 2018;9:67-9.
23. Kuzniar TJ, Balagani R, Radigan KA, Factor P, Mutlu GM. Coma with absent brainstem reflexes resulting from zolpidem overdose. Am J Ther. 2010;17:e172-4.
24. Druda DF, Gone S, Graudins A. Deliberate Self-poisoning with a Lethal Dose of Pentobarbital with Confirmatory Serum Drug Concentrations: Survival After Cardiac Arrest with Supportive Care. J Med Toxicol. 2018 Aug 2. [Epub ahead of print]
25. Grattan-Smith PJ, Butt W. Suppression of brainstem reflexes in barbiturate coma. Arch Dis Child. 1993;69:151-2.
26. Auinger K, Müller V, Rudiger A, Maggiorini M. Valproic acid intoxication imitating brain death. Am J Emerg Med. 2009;27:1177.e5-6.
27. De Rubeis DA, Young GB. Continuous EEG monitoring in a patient with massive carbamazepine overdose. J Clin Neurophysiol. 2001;18:166-8.
28. Paul M, Schwan C, Dück MH, Wedekind C. Severe ethanol-intoxication mimics symptoms of intracranial hypertension. Anasthesiol Intensivmed Notfallmed Schmerzther. 2003;38:366-9.
29. Marik PE, Varon J. Prolonged and profound therapeutic hypothermia for the treatment of "brain death" after a suicidal intoxication. Challenging conventional wisdoms. Am J Emerg Med. 2010;28:258.e1-4
30. Nahrir S, Sinha S, Siddiqui KA. Brake fluid toxicity feigning brain death. BMJ Case Rep. 2012; doi: 10.1136/bcr-02-2012-5926.
31. Zuercher P, Gerber D, Schai N, Nebiker M, König S, Schefold JC. Calypso's spell: accidental near-fatal thiacloprid intoxication. Clin Case Rep. 2017;5:1672-5.
32. Peter JV, Prabhakar AT, Pichamuthu K. In-laws, insecticide--and a mimic of brain death. Lancet. 2008 ;371:622.
33. van Gorp F, Wejden LC, Stienstra NA, Kuck EM, Haas LEM. Severe neurological symptoms following synthetic cannabinoid intoxication. Neth J Med. 2017;75:158-60.