From unknown poisoning to carbamazepine poisoning

Natasha Simonovska,[1,2] Andon Chibishev,[1,2] Niko Bekarovski,[1,2] Aleksandra Babulovska,[1,2] Biljana Ivanova,[1] Kiril Naumovski,[1,2] Kristin Kostadinovski[1,2]

[1]University Clinic for Toxicology; [2]Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia

Abstract

In the 2020 annual report of the American Association of Poison Control Centers, 2562 toxic exposures to carbamazepine have been reported, 908 resulted in hospitalization, and among these about 5-6% were life-threatening or resulted in significant disability. A 15-year-old female patient was brought under suspicion of alcohol poisoning. The result of alcoholemia was 11.0 mg/dL and the toxicological screening for THC, opiates, methadone, tramadol, amphetamine, MDMA, cocaine, benzodiazepines, buprenorphine was negative. At admission she was comatose (GCS=6), with metabolic acidosis, hypotension, rare short-term partial seizures, isochoric and later dilated pupils, body temperature was 36.4°C, with oxygen saturation from 89 up to 93%. Toxicological analysis were immediately extended. After three hours of admission, a result was obtained where the plasma concentration for carbamazepine was 167mmol/L. The patient was quickly prepared for hemodialysis which was performed for four hours. After 8 hours of admission the patient woke up with stable vital parameters.

Correspondence: Natasha Simonovska, University Clinic for Toxicology, Clinical Centre, "Mother Teresa", Faculty of Medicine, Ss Cyril and Methodius University, Vodnjanska 17, 1000 Skopje, Republic of North Macedonia.
Tel.: +389.71277295.
E-mail: N.Simonovska@yahoo.com

Key words: toxicity; carbamazepine; renal dyalisis.

Contributions: NS, contributed to the conception of the work; NS, BI, KN cared for the patient. All authors participated in the design of the work, drafted the work, or critically reviewed it. All authors approved the final version for publication.

Conflict of interest: the authors declare no conflict of interest.

Availability of data and materials: all data underlying the findings are fully available.

Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals.

Consent for publication: informed consent was obtained from the patient and her parent included in this study.

Acknowledgements: the authors are grateful to the University Clinic for Nephrology for facilitating this work, the physicians from the University Clinic for Toxicology who contributed to the examination of the patient, and Lenche Danevska for English proofreading of the manuscript.

Received for publication: 20 Februaary 2023.
Accepted for publication: 16 May 2023

Licensee PAGEPress, Italy
Emergency Care Journal 2023; 19:11270
doi:10.4081/ecj.2023.11270

Introduction

In 2020, the American Association of Poison Control Centers reported 2562 toxic exposures to carbamazepine. Of these, 1257 were isolated ingestions and 908 were treated in a health care facility. There was one death, and 52 patients experienced major toxicity, defined as life-threatening or resulting in significant disability.[1]

Data from the US Poison Control Centers documented 4149 toxic carbamazepine exposures in 2012, 14% of which had at least a moderate effect. Carbamazepine has been used for many years for the treatment of both partial and generalized seizures, as well as trigeminal neuralgia. It has also been used as a mood stabilizer and for treatment of neuropathic pain syndromes. Toxicity due to carbamazepine overdose was first described in 1967 and continues to be responsible for a large proportion of life-threatening cases among anticonvulsant poisonings.[2]

Initial signs of overdose with Carbamazepine include lethargy, nystagmus, ataxia and dysarthria. Anticholinergic effects as evidenced by decreased bowel motility, urinary retention and sinus tachycardia are common. Increasing intoxication leads to fluctuating level of consciousness, seizures, coma and respiratory depression. Patients with an underlying seizure disorder are more susceptible to seizures. Increased muscle tone, hyperreflexia and myoclonus are reported. The latter has been confused with seizure activity.[3] Cardiovascular effects include hypotension (secondary to reduced myocardial contractility), sinus tachycardia, bradyarrhythmia, widened QRS complex and atrioventricular conduction delay. Cardiogenic pulmonary edema may occur. Aspiration pneumonitis may occur from inhalation of vomitus.[4] Mydriasis with sluggish reaction to light is reported as well.[5] Death from overdose is infrequent but can result from severe cardiovascular toxicity, status epilepticus or aspiration pneumonitis.[4] Specifically, in a review of 427 patients, seizures were statistically associated with a fatal outcome.[6]

Oxcarbazepine was primarily used in the treatment of epilepsy, but now it is prescribed for other indications, too, *e.g.* neuropathic pain. It can also be used as mood stabilizer in management of bipolar affective disorders. Oxcarbazepine is a structural

derivative of carbamazepine, with the advantage of being less myelotoxic and not being a CYP3A inducer, resulting in less drug interactions. Side effects are dose dependent. Most common are hyponatremia, dizziness, somnolence, agitation, headache, ataxia, nausea, vomiting and difficulty in concentration. Rare adverse effects include anaphylaxis, angioedema, toxic epidermal necrolysis, Stevens-Johnson syndrome, photosensitivity and suicidality. Unlike other antiepileptic drugs, it does not seem to be proconvulsant in overdose.[7]

Case Report

A 15-year-old female patient, weight 51kg, was brought by ambulance to the University Clinic for Toxicology in Skopje. The family said they did not have precise information about what happened. Allegedly, the patient was out with her friends the night before and she might have drunk more than was good for her. When she returned home, her family talked with her, but the next day, they could not wake her up. She was unconscious with occasional seizures and vomited. The last communication was approximately 9 hours before admission at our Clinic. She had a history of depressive episodes regularly treated with Escitaloparm of 5 mg/day. On admission, she was comatose (GCS=6), with isochoric pupils and rare, short-term partial seizures. Blood pressure was 90/60 mmHg, body temperature was 36.4°C, with oxygen saturation on room air from 89 up to 93%, with clear lungs, soft abdomen and ECG with sinus rhythm HR=100/min, QRS=100 msec, QTc=410 msec, without other changes. In the meantime, the result of alcoholemia showed 11.0 mg/dL (value <100mg/dL-low level) and the toxicological screening in urine sample for tetrahydrocannabinol (THC), opiates, methadone, tramadol, amphetamine, 3,4-methyl-enedioxy-methamphetamine (MDMA), cocaine, benzodiazepines, buprenorphine was negative. Biochemical analyses were normal except for increased white blood cells up to 24.4×10^9/L (normal value 4.00-9.00×10^9/L). The family informed us that the patient had been sick the previous week. Polymerase chain reaction (PCR) test for covid-19 was negative. On admission blood gas analyses were performed with oxygen support by face mask (PH:7.19; pCO2:5.39 kPa; pO2: 9.3kPa; base excess (BE): -12.5; cHCO3: 15.3-decompesated metabolic acidosis). Firstly, the patient was treated with crystalloids: sodium chloride (0.9% NaCl) with a dose regime 2.5 mL/kg/h intravenous (iv) infusion, sodium hydrogen bicarbonate (1 mmol/kg), ceftriaxone 2 gr/day. Two hours after admission, the pupils were dilated (4 millimeters). We assumed differential diagnostic that the reason of comatose state of the patient could be caused both by non-toxicological trigger, both by other toxic agent. A neurological examination was performed by neurologist, and, in addition to the confirmed comatose state, a positive Babinski was also seen. CT brain was with normal finding. Although the time of the possible intake of the drug was unknown, we adhered to the ABCDE approach to the poisoned patient. Activated charcoal was given at a dose of 50 g via nasogastric tube.

We have been in contact with her parents continuously and have informed them that it was almost certain that alcohol as they stated at the admission of the patient was not the cause of her unconsciousness. We explained them our differentially diagnostic approach and which conditions could lead to comatose state. Among other things, it was emphasized that it might be an acute overdose with some other toxic agent. In the meantime, we received information from her father that he found empty boxes of Carbamazepine at home. It was possible for us to determinate carbamazepine concentration with the available fluorescent immunoassay (FIA) method. After three hours of admission, plasma carbamazepine concentrationwas 167 mmol/L (reference value: 17.00-50.00 mmol/L). A nephrologist was called and the patient was quickly prepared for hemodialysis. A right femoral catheter was placed and hemodialysis was performed in duration of four hours. The same evening, 8 hours after admission, the patient woke up and she was with stable vital parameters, no seizures, improvement of gas analyses. The next day, 22 hours after admission, verbal contact was established with the patient, and she confirmed that she took 20 tablets Carbamazepine 200 mg with suicidal idea. These tablets were used from her grandmother. A chest x-ray and abdominal ultrasonography were also performed and reported normal findings. Ninety-six hours after admission, plasma carbamazepine concentration was again analyzed and the levels were 47.11 mmol/L. As soon as patient's condition was stabilized, she was discharged from hospital on the sixth day, and referred to a psychiatrist.

Discussion

An interesting data for healthcare workers who operate in emergency (either in pre-hospital either in hospital phase) is published in one study by Lee *et al*. They reported the results of patients with altered mental status in whom the cause could not be determined via blood and imaging tests, and the altered mental status in 31.5% of these patients was found to be caused by poisoning. This finding is similar to that of previous studies showing that 19–31% of patients visited the emergency room for altered mental status due to poisoning.[8]

Any symptomatic patient can indicate a potential drug overdose. Altered mental status, gastrointestinal complaints, cardiovascular compromise, seizures, and temperature-related disorders can all be toxin-related.[9]

In our case, the diagnosis was unclear and the data obtained did not correlate with the results of the initial toxicological analyses.

Airway, breathing, circulation (ABCs) is central to the management of unknown poisoned patient.[9,10] In patients who have unknown overdoses, a toxidrome can assist in making a diagnosis and is also useful for anticipating other symptoms that may occur.[10]

A comatose state in a patient could be caused by either non-toxicological trigger (*e.g.* intracranial hemorrhage, stroke, hypoglycemia, sepsis, etc.) or by toxic causes. Numerous drugs and toxins (salicylates, iron, metformin, methanol/ethylene glycol may determine coma and metabolic acidosis, etc.). Metabolic acidosis can result from the ingestion of a substance that is either an acid or has an acidifying metabolite.[11] Borron in his study mentioned the association of metabolic acidosis with toxins such as metformin, ethylene glycol, and methanol.[12]

Ingestions of other anticholinergic agents (*e.g.* tryciclic antidepressants, anti-histamines, anti-psychotics…) than carbamazepine may yield similar clinical signs and symptom.[13] Spagnolo *et al.* reported in their article the need for physicians to be aware of the potential emergence of tropicamide as a drug of misuse, to prevent further harm.[14] Tropicamide is an antimuscarinic ophthalmic solution used to produce short-acting mydriasis and cycloplegia. It is feared that tropicamide abuse may become more frequent.[15] Tropicamide has been recently anecdotally reported to be recreationally misused from online sources.[16] From 2013 in Italy, a diverted use of tropicamide has been suspected by some pharma-

cists, who observed an abnormal increase in eye drop sales. In its annual report for 2014, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) identified intravenous tropicamide administration as a new practice in opioid abusers.[17] Sympathomimetic toxicity (*e.g.* cocaine, MDMA, amphetamines, mephedrone) may look clinically indistinguishable from carbamazepine toxicity though the neuromuscular effects may be more prominent with carbamazepin.[18] Also serotonin syndrome (*e.g.* SSRI) may have similar vital sign abnormalities (*e.g.* tachycardia and clonic disorders) and CNS depression though the hyperreflexia is more pronounced in serotonin syndrome.[19] Other antiepileptic agents (*e.g.* phenytoin or valproic acid) can lead to CNS depression and nystagmus though these agents do not tend to have the cardiovascular toxicity associated with carbamazepine overdose.[20]

Coma, anticholinergic syndrome, and unexpected acts are seen in patients with acute and chronic exposure. Ozhasenekler *et al.* in their study reported that the physical examinations of all patients showed respiratory depression in 4% while convulsion, ataxia and diplopia were found in 6%, dysarthria in 10%, vertigo in 12%, mydriasis in 18% and sinus tachycardia in 63% of patients.[21]

In our case report, there was impairment of consciousness, partial convulsions, delayed mydriasis.

Basic treatment of carbamazepine poisoning is supportive, and there is no antidote. Primary decontamination with activated charcoal is widely used. Active charcoal decreases absorption of carbamazepine across intestine. Thus, its plasma half-life decreases, too. Duration of coma may extend a few days because carbamazepine absorption delays across gastrointestinal tract. Hence, an aggressive approach is required for removal of carbamazepine and its metabolites. Gastric lavage with active charcoal was shown to be useful.[22]

Early gastrointestinal decontamination is recommended. Activated charcoal should be administered.[22] Prevention of ongoing absorption and control of any seizures are also priorities. There should be a low threshold for intubation as pulmonary aspiration is a significant concern and intubation facilitates decontamination. Seizures are an indicator of a poor outcome and must be aggressively managed; initially with a benzodiazepine, followed by a barbiturate if benzodiazepines are ineffective.[23] IV fluids should be administered to hypotensive patients, but care must be taken not to overload the patient as hypotension is typically due to poor myocardial contractility. Due to sodium channel blocking properties, cardiac toxicity is well recognized although quite rare. Sodium bicarbonate should be given if broad-complex cardiac dysrhythmia occurs.[24] Multiple dose activated charcoal (MDAC) is recommended following any large or symptomatic ingestion.[25] Intubated patients should receive MDAC via nasogastric tube (ensuring bowel sounds are present). Due to an anticholinergic action on the gut motility must be monitored as ileus may occur. In severe cases extracorporeal elimination is recommended; intermittent hemodialysis is preferred but intermittent hemoperfusion or continuous renal replacement therapies are acceptable alternatives if hemodialysis is not available. Urinary retention may require catheterization.[2]

Early hemoperfusion (HP) administered directly by emergency doctors to patients with carbamazepine poisoning can significantly reduce plasma carbamazepine concentration and accelerate the elimination from the body. In addition, HP treatment can significantly relieve impaired consciousness, respiratory depression and seizure after carbamazepine poisoning.[26]

Despite the low quality of the available clinical evidence and the high protein binding capacity of carbamazepine, the workgroup suggested extracorporeal removal in cases of severe carbamazepine poisoning.[27] Hemodialysis is simple, cheap and is a widely used procedure. It is easier to apply compared to HP. Hemodialysis is more advantageous than HP because of lower cost, simplicity, easier accessibility and paucity of side effects related to procedure (thrombocytopenia, coagulopathy, hypothermia, hypocalcemia). Consequently, it has been shown that standard hemodialysis may also be a good therapeutic option in cases HP is not available in patients with carbamazepine poisoning presenting with coma and convulsion.[21]

In our patient, although the time of the possible intake of the drug was unknown, we adhered to the ABCDE approach of the poisoned patient. Activated charcoal was given at a dose of 50 g. On the first day of admission, plasma carbamazepine concentration was 167 mmol/L. After hemodialysis, the same evening the patient woke up without convulsions.

Conclusions

Approach to an unconscious patient with unknown etiology and a patient with unknown poisoning can be diagnostically and therapeutically difficult, but at the same time a great challenge as well. In the presented case collecting patient's history was essential to differentiate and identify the correct diagnosis as much as verifying the correlation among suspected causes and clinical manifestations. In our patient hemodialysis has been performed without complications and this procedure may be helpful and considered in severe carbamazepine poisoning.

References

1. Gummin DD, Mowry JB, Beuhler MC, et al. 2020 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 38th Annual Report. Clin Toxicol (Phila) 2021;59:1282-501.
2. Ghannoum M, Yates C, Galvao TF, et al. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila) 2014;52:993-1004.
3. Weaver DF, Camfield P, Fraser A. Massive carbamazepine overdose: clinical and pharmacologic observations in five episodes. Neurology 1988;38:755-9.
4. Tibballs J. Acute toxic reaction to carbamazepine: clinical effects and serum concentrations. J Pediatr 1992;121:295-9.
5. Rockoff S, Baselt RC. Severe carbamazepine poisoning. Clin Toxicol 1981;18:935-9.
6. Schmidt S, Schmitz-Buhl M. Signs and symptoms of carbamazepine overdose. J Neurol 1995;242:169-73.
7. Kalogera V, Galopoulos D, Eleftheriotis G, et al. Patient survival after acute voluntary poisoning with a huge dose of oxcarbazepine and olanzapine. Med Arch 2018;72:303-5.
8. Lee JS, Cha YS, Yeon S, et al. Changes in diagnosis of poisoning in patients in the emergency room using systematic toxicological analysis with the national forensic service. J Korean Med Sci 2021;36:e118.
9. Parris MA, Calello DP. Found down: approach to the patient with an unknown poisoning. Emerg Med Clin North Am 2022;40:193-222.
10. Chandran J, Krishna B. Initial management of poisoned patient. Indian J Crit Care Med 2019;23:234-40.
11. Judge BS. Metabolic acidosis: Differentiating the causes in the

poisoned patient. Emerg Med Clin North Am 2022;40:251-64.
12. Borron, S.W. Acid–base balance in the poisoned patient. In: Jeffrey Brent et al., eds. Critical Care Toxicology. Springer, Cham. 2017. p. 325-58.
13. The Royal Children's Hospital Melbourne. Clinical Practice Guidelines. Anticholinergic Syndrome. Accessed August, 2017. Available from: https://www.rch.org.au/clinicalguide/guideline_index/Anticholinergic_Syndrome/
14. Spagnolo PA, Badiani A, Nencini P. Polydrug abuse by intravenous use of heroin and tropicamide-containing eyedrops. Clin Neuropharmacol 2013;36:100-1.
15. Bozkurt M, Karabulut V, Evren C, et al. Intravenous abuse of tropicamide in opioid use disorder: presentation of 2 cases. Subst Abus 2015;36:170-3.
16. Bersani FS, Corazza O, Simonato P, et al. Drops of madness? Recreational misuse of tropicamide collyrium; early warning alerts from Russia and Italy. Gen Hosp Psychiatry 2013;35:571-3.
17. Ponté C, Pi C, Palmaro A, Jouanjus E, Lapeyre-Mestre M. French Addictovigilance Network. Early signal of diverted use of tropicamide eye drops in France. Br J Clin Pharmacol 2017;83:1791-800.
18. Kolecki P. Medscape. Drugs & diseases > emergency medicine. sympathomimetic toxicity. Accessed 02 March, 2021. Available from: https://emedicine.medscape.com/article/818583-overview
19. Chiew AL, Buckley NA. The serotonin toxidrome: shortfalls of current diagnostic criteria for related syndromes. Clin Toxicol (Phila) 2022;60:143-58.
20. Murty S. Antiepileptic Overdose. Indian J Crit Care Med 2019;23:290-95.
21. Ozhasenekler A, Gökhan S, Güloğlu C, et al. Benefit of hemodialysis in carbamazepine intoxications with neurological complications. Eur Rev Med Pharmacol Sci 2012;16:43-7.
22. Mohamed AM, Adnan A, Seifert SA, et al. An endoscopic end to coma. Toxicol Comm 2017;1:6-9.
23. Spiller HA, Carlisle RD. Status epilepticus after massive carbamazepine overdose. J Toxicol Clin Toxicol 2002;40:81-90.
24. American College of Medical Toxicology. Sodium Bicarbonate Shortage Recommendations. Acessed 15 August 2017. Available from: https://www.acmt.net/wp-content/uploads2022/06/PRS_170815_Sodium-Bicarbonate-Shortage-Recommendations.pdf
25. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. J Toxicol Clin Toxicol 1999;37:731-51.
26. Yang X, Xin S, Zhang Y, Li T. Early hemoperfusion for emergency treatment of carbamazepine poisoning. Am J Emerg Med 2018;36:926-30.
27. Ouellet G, Bouchard J, Ghannoum M, Decker BS. Available extracorporeal treatments for poisoning: overview and limitations. Semin Dial 2014;27:342-9.