SciMedCentral

Journal of Pharmacology & Clinical Toxicology

Case Report

Treatment of Severe Carbamazepine Intoxication with Intravenous Lipid Emulsion Therapy

Mucahit Avcil, Yunus Emre OZLUER*, Kıvanc Karaman, Mucahit KAPCI and Burcak KANTEKIN

Department of Emergency Medicine, Adnan Menderes University Hospital, Turkey

***Corresponding author**

Yunus Emre OZLUER, Resident of Emergency Medicine, Adnan Menderes University Hospital, Department of Emergency Medicine, Aydın, Turkey, Email: emreozluer@gmail.com

Submitted: 09 March 2015

Accepted: 12 June 2015

Published: 16 June 2015

ISSN: 2333-7079

Keywords

- Carbamazepine
- Intoxication
- Intravenous lipid emulsion
- Treatment

Abstract

Carbamazepine (CBZ) is a widely prescribed anticonvulsant agent. It is used in treatment of epilepsy including general tonic-clonic, simple partial and complex partial seizures, neuropathicpains, especially in trigeminalneuralgia, central diabetes insipidus, attention-deficit and hyperactivity disorders and bipolar disorders. CBZ overdose is usually associated with cardiac, neurologic and respiratory problems. By this time, several treatment modalities such as oral multiple doses of activated charcoal, conventional hemodialysis (HD), high-flux hemodialysis (HFHD), continuous venovenous hemodiafiltration (CVVHDF), albumin-enhanced CVVHDF with high and low dialysate flow, resin hemoperfusion(HP), plasma exchange (PE) and charcoal HP have been performed in treating acute CBZ toxicity, however traditional supportive care is stil considered the primary treatment for CBZ intoxication.

We would like to report a case of severe CBZ poisioning who was treated with ILE therapy.

INTRODUCTION

Intravenous lipid emulsion (ILE) is a potentially lifesaving treatment of lipophilic drug intoxications [1-11]. The history of ILE treatment is not very far. Its use is first reported in reduction of thiopental anesthetic duration in rats in 1962 and was described in *in vitro* and *in vivo* studies with chlorpromazine and rabbitblood in 1974 [12,13]. First humancases of ILE totreat acute drugtoxicity as a rescue orantidotal therapy were published in 2006 [14] and also these first cases of ILE therapy were used to treat deliberate overdose [15,16]. To date intravenous lipids have been used successfully to treat cardiac toxicity associated with a variety of lipid-soluble drugs, such as local anesthetics, calcium channel blockers, beta blockers, tricyclicantidepressants, andcocaine [17-20].

CASE REPORT

24–year-oldmale, transferred from a secondary care hospital to our emergency medicine clinic for further evaluation and treatment, 7 hours after intentionally ingesting seven 400 mg controlled-release carbamazepine (CBZ) tablets (Tegretol-CR® 400 mg, a total of 2.8 g). It has been acknowledged that this was not patient's medication. Gastriclavage and decontamination with activated charcoal was given *via* nasogastric tube at previous hospital. At his presentation to the emergency room, he had decreased level of conciousness and agitation. He was also confused and Glasgow Coma Scale (GCS) was 12. His he art rate was 104 bpm and blood pressure was 100/60 mmHg. The remainder of the physical examination was normal. On laboratory examination, serum CBZ level was 30 µg/mL (Normal range 4-12 µg/mL). ECG showed QTc prolongation with 474 ms and the patient then was transferred to intensive care unit for monitorization due to the risk of ventricular tachyarrhytmias and cardiac arrest. 100 ml of Clinoleic® 20% (Baxter Healthcare Limited, Norfolk, England) was given as a bolus and an infusion dose of 100 ml per hour was maintained for four hours. Multiple doses of activated charcoal and intravenous hydration with % 0.9 NaCl was given additionally. After intravenous bolus of lipid emulsion patient's GCS improved to 14, he regained conciousness and his confusion resolved in approximately 60 minutes. Serum CBZ level declined to 23.1 µg/mL on 8th hour, 17.6 µg/mL on 24th hour and 8 µg/mL on 32th hour of the initiation of the first bolus dose of intravenous lipidemulsion, respectively (Figure 1). In addition, QTc declined to 412 ms on 5th hour (after the infusion of lipid emulsion stopped), 388 ms on 9th hour and 394 ms on 10th hour, respectively. During ILE, none of possible complications occurred and patient was discharged from ICU to

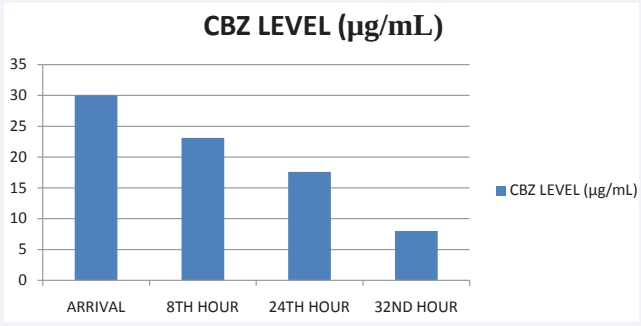

Figure 1 CBZ levels on arrival and after ILE therapy.

ward on 3rd day with GCS 15 and without any neurologic and cardiac complications.

DISCUSSION

Carbamazepine (CBZ) is a widely prescribed anticonvulsant agent. It is used in treatment of epilepsy including general tonic-clonic, simple partial and complex partial seizures, neuropathic pains, especially in trigeminal neuralgia, central diabetes insipidus, attention-deficit and hyperactivity disorders and bipolar disorders. CBZ overdose is usually associated with cardiac, neurologic and respiratory problems. Diversity of manifestations is wide such as ataxia, coma, seizures, dysrhytmias, respiratory depression [7]. Hemodynamic instability hypotension, conduction delays and QTc (corrected QT time in ECG) prolongation (>420 ms) have been reported and there is no specific antidote.

Our patient had QTc prolongation (474 ms) in his initial ECG and this situation has been the main reason for us to administer ILE therapy despite the risk of complications such as fat overload syndrome [21-23], hypervolemia, hyperamylasemia, hemolysis, icterus, seizures, inreasedclottingtimesand ARDS [23].

CBZ is slowly absorbed from gastrointestinal system and also has inhibitory action on bowel motility. Thus the peak CBZ level is accomplished within 10-30 hoursafter oral ingestion [10].

In overdose situations the duration to reach to the peak serum level of controlled-release CBZ form is much longer up to 70 hours. Because CBZ may induce its own metabolism, the half-life is also variable [5]. Therefore multiple doses of activated charcoal should be administered in all cases unless there are contraindications such as ileus. Our patient had a nasogastric tube and he had no signs and symptoms of ileus. Thus we administered acitivated charcoal every 6 hours in 1 g/kg doses.

According to the circulating level of carbamazepine, poisoning can be classified in four stages: potentially catastrophic relapse with levels < 11 µg/mL, disorientation and ataxia at levels of 11-15 µg/mL, combative-ness and hallucinaitons at levels of 15-25 µg/mL and convulsions and coma at levels> 25 µg/mL [24]. Although, total carbamazepine concentrations and toxic manifestations are not directly correlated [5] and severity of toxicity is assessed on the basis of the clinical status and not the serum CBZ concentration [2]. Our patient's serum CBZ level was 30 µg/mL, he did not have any seizures and he was not in coma with GCS 12. Also after bolus infusion of ILE his conciousness and general condition improved.

ILE is used traditionally for parenteral nutrition treatment. Rosenblatt et al. [25] made the first clinical study with ILE treatment of systemic toxicity from local anesthetics (bupivacaine). After reports in local anesthetic toxicity, ILE was began to use in other lipophilic drug intoxications such as beta blockers, calcium channel blockers, parasiticides, herbicides and several psycho tropicagents [20,26]. In addition, ILE is also recommended in the Advanced Cardiac Life Support guidelines for cardiac arrest secondary to beta blockers when conventional resuscitative therapies have failed. Over the decades, publications emphasized the benefit of ILE in lipophilic drug intoxications. Dagtekin et al. performed ILE therapy for serotonin syndrome due to the ingestion of venlafaxine, lamotrigine and diazepam [27,28]. In a caseseries [29], ILE was used to treat acute toxicity caused by lipophilic drugs such as dosulepin, olanzapine, amitriptyline, verapamil, quetiapine, bupropion, lamotrigine and diltiazem. However, we could not find the use of ILE therapy to treat acute carbamazepine intoxication.

In 1998, Weinberg defined the widely accepted 'lipid sink' theory to explain the mechanism of elimination of lipid soluble drugs. According to this theory, the infusion of ILE creates a distinct lipid compartment within the bloodstream and 'entraps' lipophilic drugs into plasma and lowers their tissue concentrations, thereby reducing toxicity. We think that our patient's serum CBZ levels correlated with lipid sink theory because after completion of ILE therapy in 4 hours serum CBZ level declined almost %50 despite the fact that CBZ serum half life is between 12-20 hours.

Azak et. al reported a case of CBZ intoxication treated with HD which there was a reduction of 5% of CBZ after 3 h of HD [30]. Koh et. al used HFHD in a case with CBZ intoxication and reported approximately 40% reduction of CBZ level after 3 h of HFHD [5]. In 2011 Li et. al reported reduction of 31% in second session of resin HP [2] where Goktas et. al used CVVHDF in a case with severe CBZ intoxication which they achieved reduction of 82% of drug level after 24 h [6]. In addition, Kozanoglu et. al reported a case of a pediatric patient (3 years old) who had taken a lethal dose of CBZ and was treated with PE. They had reduction of 24% after 12 h of PE therapy [9]. In our case, initial serum CBZ level was 30 µg/mL and after 8 hours of inititiation of ILE therapy, it declined to 23.1µg/mL with a reduction of 23% and on 24th hour CBZ level measured 17.6 µg/mL (42% reduction). ILE therapy seems like a good treatment option since it is easy to access, effective, safer and cheaper than other treatment modalities mentioned above.

We accept that a de facto relation between the use of ILE and normalisation of QTc interval and improvement in GCS in our patient in short notice cannot be proved by this single observation but this recovery suggests a potential therapeutic benefit. Further experimental and clinical studies are required to elucidate the importance of this treatment option. Furthest acknowledgement can be obtained at www.lipidrescue.org.

REFERENCES

1. Tetiker T, Sert M, Koçak M. Efficacy of indapamide in central diabetes insipidus. Arch Intern Med. 1999; 159: 2085-2087.

2. Li TG, Yan Y, Wang NN, Zhao M. Acute carbamazepine poisoning

treated with resin hemoperfusion successfully. Am J Emerg Med. 2011; 29: 518-522.

3. Graudins A, Peden G, Dowsett RP. Massive overdose with controlled-release carbamazepine resulting in delayed peak serum concentrations and life-threatening toxicity. Emerg Med (Fremantle). 2002; 14: 89-94.

4. Yaylacı S, Demir MV, Acar B, Sipahi S, Tamer A. Successful treatment of excessive dose of carbamazepine. Indian J Pharmacol. 2012; 44: 417-418.

5. Koh KH, Tan HH. High-flux haemodialysis treatment as treatment for carbamazepine intoxication. Med J Malaysia. 2006; 61: 109-111.

6. Goktas U, Kati I, Yuce HH. Management of a severe carbamazepine overdose with continuous venovenous hemodiafiltration. Am J Emerg Med. 2010; 28: 260.e1-2.

7. Askenazi DJ, Goldstein SL, Chang IF, Elenberg E, Feig DI. Management of a severe carbamazepine overdose using albumin-enhanced continuous venovenous hemodialysis. Pediatrics. 2004; 113: 406-409.

8. Chung YK, Chang KY, Park HS, Kim MH, Lee KM, Lim TS, et al. Severe carbamazepine intoxication unresponsive to albumin-enhanced continuous venovenous hemodiafiltration with low dialysate flow. Hemodialysis International. 2014; 18: 552-561.

9. Kozanoglu I, Kahveci S, Asma S, Yeral M, Noyan A, Boga C, et al. Plasma-exchange treatment for severe carbamazepine intoxication: a case study. J Clin Apher. 2014; 29: 178-180.

10. Isik Y, Soyoral L, Karadas S, Emre H, Cegin MB, Goktas U. Effectivity of one session charcoal hemoperfusion treatment in severe carbamazepine poisoning. Iran Red Crescent Med J. 2013; 15: 749-751.

11. Eren Cevik S, Tasyurek T, Guneysel O. Intralipid emulsion treatment as an antidote in lipophilic drug intoxications. Am J Emerg Med. 2014; 32: 1103-1108.

12. Russell RL, Westfall BA. Alleviation of barbiturate depression. Anesth Analg. 1962; 41: 582-585.

13. Krieglstein J, Meffert A, Niemeyer DH. Influence of emulsified fat on chlorpromazine availability in rabbit blood. Experientia. 1974; 30: 924-926.

14. Jamaty C, Bailey B, Larocque A, Notebaert E, Sanogo K, Chauny JM. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol (Phila). 2010; 48: 1-27.

15. Sirianni AJ, Osterhoudt KC, Calello DP, Muller AA, Waterhouse MR, Goodkin MB, et al.Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. Ann Emerg Med. 2008; 51: 412-415.

16. Harchelroad FP, Palma A. Efficacy and safety of intravenous lipid therapy in a beta blocker overdose. 634. Clinical Toxicology. 2008; 46: 245.

17. Weinberg G. Lipid rescue resuscitation from local anaesthetic cardiac toxicity. Toxicol Rev. 2006; 25: 139-145.

18. Young AC, Velez L, Kleinschmidt KC. Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. Resuscitation. 2009; 80: 591-593.

19. Stellpflug SJ, Harris CR, Engebretsen KM, Cole JB, Holger JS. Intentional overdose with cardiac arrest treated with intravenous fat emulsion and high-dose insulin. Clin Toxicol (Phila). 2010; 48: 227-229.

20. Arora NP, Berk WA, Aaron CK, Williams KA. Usefulness of intravenous lipid emulsion for cardiac toxicity from cocaine overdose. Am J Cardiol. 2013; 111: 445-447.

21. Perez A, Wiley JF. Pediatric carbamazepine suspension overdose-clinical manifestations and toxicokinetics. Pediatric Emergency Care. 2005; 21: 252-254.

22. Hojsak I, KolaÄek S. Fat overload syndrome after the rapid infusion of SMOFlipid emulsion. JPEN J Parenter Enteral Nutr. 2014; 38: 119-121.

23. Goulet O, Girot R, Maier-Redelsperger M, Bougle D, Virelizier JL, Ricour C. Hematologic disorders following prolonged use of intravenous fat emulsions in children. JPEN J Parenter Enteral Nutr. 1986; 10: 284-288.

24. Unei H, Ikeda H, Murakami T, Tanigawa K, Kihira K. Detoxication treatment for c arbamazepine and lithium overdose. Yakugaku Zasshi. 2008; 128: 165-170.

25. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. Anesthesiology. 2006; 105: 217-218.

26. Weinberg GL. Lipid emulsion infusion: resuscitation for local anesthetic and other drug overdose. Anesthesiology. 2012; 117: 180-187.

27. Cave G, Harvey M, Graudins A. Intravenous lipid emulsion as antidote: a summary of published human experience. Emerg Med Australas. 2011; 23: 123-141.

28. Dagtekin O, Marcus H, Müller C, Böttiger BW, Spöhr F. Lipid therapy for serotonin syndrome after intoxication with venlafaxine, lamotrigine and diazepam. Minerva Anestesiol. 2011; 77: 93-95.

29. Presley JD, Chyka PA. Intravenous lipid emulsion to reverse acute drug toxicity in pediatric patients. Ann Pharmacother. 2013; 47: 735-743.

30. Azak A, Koçak G, Huddam B, Duranay M. Is conventional hemodialysis enough to manage carbamazepine intoxication?. Blood Purif. 2012; 33: 225-226.

Cite this article

Avcil M, OZLUER YE, Karaman K, KAPCI M, KANTEKIN B (2015) Treatment of Severe Carbamazepine Intoxication with Intravenous Lipid Emulsion Therapy. J Pharmacol Clin Toxicol 3(3):1052.