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Severe Carbamazepine Toxicity Treated with Continuous Venovenous Hemofiltration at Palestine Medical Complex: Two Case Reports

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Abstract: Carbamazepine intoxication is not uncommon and accounts for many cases of poisoning among anticonvulsive medications users. Since there is no specific antidote for carbamazepine overdose, management is limited to gastric decontamination and supportive therapy. With its high protein binding, the role of extracorporeal elimination in carbamazepine intoxication is still questionable. Here two cases of severe carbamazepine intoxication are presented; the cases were brought to the emergency department after the ingestion of 12,000 mg of controlled release carbamazepine for the first case, and unknown amounts of the same drug for the second case. Both cases were presented with altered mental status, convulsion, and high serum carbamazepine levels of more than 20 mcg/mL. They were intubated and treated with continuous venovenous hemofiltration, after which carbamazepine levels declined significantly along with subsequent clinical improvement and complete neurological recovery. Both cases were discharged home for further psychiatric care.

Keywords: carbamazepine, poisoning, continuous renal replacement therapy

Introduction

Carbamazepine is an anticonvulsant drug that is commonly used in the management of partial and generalized seizures, bipolar disorder, and neuropathic pain.[1] Carbamazepine toxicity was first reported in 1967 and is still a leading cause of anticonvulsant medication toxicity.[2] In the United States of America, for instance, 3185 and 3139 cases were reported in 2018 and 2019, respectively.[3,4] Significant toxicity usually occurs with serum levels above 40 mcg/mL in adult patients, but toxicity can be seen even with serum levels above 20 mcg/mL.[2] When compared to adults, pediatric populations are more susceptible to toxicity-related side effects and symptoms at lower serum levels.[5] Toxicity in pediatrics can be seen with serum levels above 12 mcg/kg, but life threatening toxicity is usually seen if serum level exceeds 28 mcg/kg.[6] In severe toxicity, carbamazepine may induce cardiac arrhythmias, neurological dysfunction, respiratory depression, renal toxicity, and significant anticholinergic symptoms.[7,8] Carbamazepine toxic exposure is associated with a dose higher than 20 mg/kg; however, severe neurological toxicity usually manifests when the ingested dose is more than 50 mg/kg.[2,5,9,10] Supportive therapy and gastrointestinal decontamination are the mainstays of treatment.[5] Extracorporeal elimination may be used in severe cases, but the role of this method in eliminating carbamazepine is still questionable as carbamazepine is highly protein-bound (70–80%).[2] However, several case reports were published on successful treatment using extracorporeal elimination.[11,12] Here, two cases of severe carbamazepine toxicity are presented, that were managed successfully using continuous venovenous hemofiltration (CVVH).

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Case 1

A 30-year-old woman with a history of bipolar disorder on treatment with carbamazepine, presented to the emergency department (ER) at Palestine Medical Complex (PMC) one hour after the ingestion of 62 controlled release carbamazepine (CR-CBZ) tablets of 200 mg each in a suicidal attempt.

Upon arrival to the ER, the patient denied any complaints. She was fully awake with a Glasgow Coma Scale (GCS) of 15 with no neurological deficit detected. The body temperature was 36.6 °C. She was hemodynamically and respiratory wise stable with a blood pressure of 121/64 mmHg, pulse rate of 77 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 96% on ambient air.

The clinical examination was unremarkable. Electrocardiography demonstrated sinus rhythm with a normal Q-T interval. Laboratory investigations, including urine toxicology screen, were normal except for a serum carbamazepine level of more than 20 mcg/mL (normal value is 4–12 mcg/mL) at presentation. A nasogastric tube was inserted, and gastric lavage was performed, with a few particles of the ingested tablets seen during the procedure. Activated charcoal was given in a dose of 50 g every 6 hours for 24 hours. After one hour of observation in the ER, the patient became drowsy with slurred speech and confused. The pupils were dilated (4 millimeters) with a fixed upward gaze. She subsequently developed encephalopathy and coma with a GCS of 3. She was immediately intubated and transferred to the Intensive Care Unit (ICU). At ICU evaluation, the patient had ophthalmoplegia and demonstrated dystonic posture with repeated myoclonic activities and a decerebrate in response to pain. She was started on intravenous levetiracetam 500 mg twice daily after a loading dose of 1500mg, and intravenous midazolam 10mg/hour infusion after a loading dose of 10 mg with subsequent deterioration in the hemodynamic status that necessitate vasopressor initiation 6mcg/min. At this point, with rapid clinical deterioration, and with severe neurological and cardiovascular decompensation, a decision was made to start the patient continuous renal replacement therapy (CRRT) using CVVH mode to help with drug elimination. After 19 hours of steady CVVH therapy, the carbamazepine level declined to 9.8 mcg/mL. The patient started to show some clinical improvements in the form of absent dystonic posturing, reactive pupils, and withdrawal to tactile stimuli, in addition to hemodynamic improvement with weaning of vasopressors. However, she continued to have frequent episodes of myoclonic seizures that eventually subsided in the next 2 days with increasing levetiracetam dose to 1000 mg twice daily and continuous drug elimination with CVVH therapy. She continued to show dramatic clinical improvement during her ICU stay and was extubated at day 5 of admission, and midazolam was stopped. She was transferred to the general ward for a complete recovery of her neurological function and was discharged home on levetiracetam 1000 mg twice daily and clonazepam 0.5 mg at bed time. The patient did not show any long-term sequelae and was referred to psychiatric clinic for further psychiatric evaluation.

Case 2

A previously healthy 14-year-old boy presented to our hospital after being found drowsy in his bedroom, surrounded by different empty medication sachets, which contained more than 50 tablets of 200 mg controlled-release carbamazepine and 20 tablets of 10 mg enalapril in a suicidal attempt. Initially, he was brought to a local emergency service where he underwent gastric lavage with activated charcoal and was transferred to our hospital. On presentation to the ER, the patient was agitated with a GCS of 13, and he was hemodynamically stable Electrocardiography showed sinus rhythm with no abnormality detected. A few hours later, the patient developed periodic tonic-clonic movements with progressive cognitive impairment. He was transferred to the ICU for further monitoring and support. He continued to have tonic-clonic seizures without response to intravenous midazolam 5mg/hour after a loading dose of 10 mg, the patient was then subsequently sedated with propofol and intubated. His serum carbamazepine level was found to be higher than 20 mcg/mL. The patient's blood pressure decreased to 80/45 mmHg; he was adequately resuscitated with fluids and subsequently started on intravenous norepinephrine 1mcg/min to normalize his blood pressure.

Twelve hours later, he did not show any clinical improvement for which he was placed on CRRT using CVVH mode. After 48 hours of CVVH therapy, the carbamazepine level dropped to 9.81 mcg/mL. At this time, the patient became conscious and showed significant neurological improvement with no signs of seizures. The hemodynamic parameters were also stabilized, and norepinephrine and midazolam were stopped. Three days later, he was successfully extubated and transferred to medical floor. A few days later, the boy was clinically well and was discharged home with continuing psychiatric care.

Discussion

Carbamazepine is a commonly used medication with a target therapeutic serum level of 4 to 12 mcg/mL (17 to 51 micromole/L).[2] Carbamazepine toxicity is common and severe toxicity is usually associated with ingestion of more than 50 mg/kg.[9] It is important to keep in mind that the pharmacokinetic properties of carbamazepine might be different with overdose compared to chronic therapeutic use. For example, peak concentration occurs 3–12 hours after the ingestion of extended-release forms, while after an overdose, absorption can be erratic and prolonged, with peak serum concentrations occurring over 96 hours.[13] This might be attributed, in part, to the anticholinergic effect of carbamazepine, which leads to slower bowel motility. Carbamazepine's half-life with initial dosing is reported to be 25–65 h, which decreases to 12–17 h with repeated or continued dosing, while it can be as long as 35 hours following a single overdose.[2] Therefore, carbamazepine elimination after exposure to a high dose may be prolonged and erratic, which makes treatment more challenging. The management of carbamazepine intoxication is usually supportive, along with gastric decontamination and activated charcoal.[5] Charcoal in a single dose is preferable to multi-dose.[14] However, multi-dose charcoal may be used in serious, life-threatening intoxication and was proven to significantly shorten serum carbamazepine half-life.[6,15] The above mentioned cases presented with signs of severe toxicity including hemodynamic instability, respiratory depression, seizures, and altered mental status. Therefore, multiple doses of charcoal were given. Most importantly, in light of the above-mentioned critical scenarios of both cases, CVVH was initiated. It is worth mentioning that the role of extracorporeal elimination of carbamazepine is still questionable since carbamazepine is highly protein bound.[2] However, the current recommendations of The Extracorporeal Treatments In Poisoning workgroup (EXTRIP) supports its use in severe cases.[2] Several case reports have been published demonstrating successful treatment using extracorporeal elimination with varying elimination rates.[11–16] The highest clearance was reported with hemoperfusion (96.9 mL/min), followed by hemodialysis and CRRT.[2] Selecting one mode of extracorporeal elimination over another depends on both the pharmacokinetic and pharmacodynamic properties of the drug and the resources of the facility. Hemoperfusion is considered a costly technique and the hemoperfusion cartridges are not readily available in many regions of the world, including the settings of this case series. Intermittent hemodialysis is cheaper, readily available, fast in removing toxins, and with the newer high-flux and high-efficiency synthetic membranes it seems to have comparable effects to hemoperfusion.[2] However, considering the significant risk for hypotension with hemodialysis, CRRT is preferred in critically ill patients with hemodynamic instability and those on mechanical ventilation, which is frequently seen in patients with severe carbamazepine toxicity as evident in our two reported cases. CRRT is also more effective in removing large molecules than intermittent hemodialysis, and it is ideal for toxins or drugs with rebound release effect ensuring continuous elimination.[16] Among the different modes of CRRT, CVVH is the most effective in removing drugs with a molecular size up to 40 KDa.[12] Carbamazepine has a small molecular weight (236 Da) and relatively low volume of distribution, which is expected to be readily removed by CVVH.[2,16] However it is highly protein-bound around (70–80%) at therapeutic plasma concentration which makes it poorly removable with extracorporeal elimination.[2] Still, CRRT appears to be capable of removing carbamazepine, which is not commonly thought to remove protein-bound molecules.[17] The degree of protein binding in overdose is expected to be less than in the treatment dose, so an enhanced elimination is likely to happen with CRRT, considering that it is being applied over several hours[2,18] Therefore, CRRT was the preferred approach in our two cases especially that hemoperfusion was not available, and hemodialysis is hard to conduct for mechanically ventilated patients in our ICU settings. The patients' clinical conditions showed dramatic improvement after several hours of CRRT, with concomitant significant and rapid reduction in serum drug level below <10 mcg/mL. Therefore, CRRT was stopped as both findings are considered indications for extracorporeal elimination cessation according to the EXTRIP workgroup.[2] However, in our approach we faced some limitations including the lack of appropriate neurological monitoring in our facility such as continuous electroencephalogram (EEG) and the inability to measure Carbamazepine level in the effluent bags in order to determine the rate of drug elimination.

In conclusion, although it comes third after hemoperfusion and hemodialysis, CRRT seems to be effective in removing carbamazepine as demonstrated by our two cases. However, further studies are needed to confirm the extent of carbamazepine removal by measuring serial serum and effluent carbamazepine levels. We suggest considering CRRT therapy for patients with severe carbamazepine toxicity in similar settings where hemoperfusion is not available and hemodialysis is impractical.

Informed Consent

This case series was approved by the Research Ethical Committee of Birzeit University. Informed consents to publish have been obtained from both patients, and also from the patient's parents for the second case.

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Disclosure

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