Massive Carbamazepine Overdose: Any Role of Hemodialysis?: Case Report

İleri Derecedeki Karbamazepin Doz Aşımlarında Hemodiyaliz Uygulanmalı mı?

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ABSTRACT Massive carbamazepine (CBZ) overdose is associated with life-threatening hemodynamic complications that present challenges for clinicians. We describe the highest-reported dose of CBZ intoxication in a patient who survived and discuss early hemodialysis option in a CBZ-poisoned patient. Although hemodialysis is reported to increase the elimination of CBZ despite its partiall effectiveness due to the poor water-solubility of CBZ, massive CBZ overdose can induce an acute renal failure and renal function should be monitored closely, and the data obtained from this case that standard low-flux HD might be used and is effective in the management of acute CBZ overdose in patients with associated electrolyte disorders and acute renal failure.

Key Words: Anticonvulsants; poisoning; carbamazepine; renal dialysis

ÖZET İleri derecedeki karbamazepin (CBZ) doz aşımı, yaşamı tehdit edici hemodinamik komplikasyonlarla seyrettiğinden klinisyenler için önemli sorunlar oluşturur. Hayatta kalan bir hastada bildirilmiş en yüksek dozda CBZ intoksikasyonunu sunuyor ve CBZ ile zehirlenmiş bir hastada erken hemodiyaliz seçeneğini tartışıyoruz. Literatürde hemodiyalizin CBZ atılımını artırdığı fakat ilacın suda zayıf çözünürlüğü nedeniyle kısmen etkisiz olduğu bildirilmekle birlikte; ileri derecedeki CBZ dozaşımı akut böbrek yetmezliğine neden olabilir, bu nedenle böbrek fonksiyonları yakın takip edilmelidir ve bu vakadan elde edilen veriler, özellikle eşlik eden elektrolit bozuklukları ve akut böbrek yetmezliği gelişmesi durumunda, ileri derecedeki CBZ dozaşımlarında standart düşük akımlı hemodiyalizin etkili olduğunu desteklemektedir.

Anahtar Kelimeler: Antikonvülzanlar; zehirlenme; karbamazepin; böbrek diyalizi

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CASE REPORT

A 24-year-old woman presented to the Emergency Department (ED) with a history of carbamazepine (CBZ) overdose. She had taken 280 controlled-release CBZ tablets (200 mg) and 30 oxaprozin tablets (600 mg) one hour before admission. The patient complained of dizziness and severe nausea and vomited several times shortly after her arrival in the ED. Nine years previously, she had been diagnosed with epilepsy and was taking CBZ, but otherwise she had no remarkable past-medical history. She was not taking any recreational drugs, and had not previously taken an intentional overdose or expressed any suicidal thoughts. On presentation, she was alert and cooperative. Her Glasgow Coma Scale (GCS) score was 15/15.

Vital signs were: Temperature 37.0°C, blood pressure 130/100 mmHg, pulse 96 beats/min, and respiratory rate 14 breaths/min. Physical examination revealed multiple superficial lacerations on both dorsal forearms. Findings on examination of the heart, lungs, vascular system and abdomen were unremarkable. An electrocardiogram revealed a sinus tachycardia (100 beat/min). Following a gastric lavage with suction, a single dose of activated charcoal (50 g) was given and orders were written for repeated doses of 25 g every 4 h. Her laboratory findings were within normal limits. Arterial blood gas measurements revealed no evidence of a metabolic acidosis. Over the next few hours, she became increasingly drowsy and her GCS score fell to E2M4V1. The patient was endotracheally intubated for airway protection. On the 4th hour, it was noted that her bowel sounds were lost and had minimal abdominal distention. Further treatment with multidose activated charcoal was discontinued due to early signs of large bowel obstruction. Serial CBZ levels were determined as 9.37 μg/ml at the 1st h and 36.86 μg/ml (therapeutic drug level: 5-12 μg/ml) at the 6th hour. Twelve hours later, laboratory tests showed a serum creatinine level as 2.85 mg/dl, sodium as 131 mEq/l, potassium as 6.0 mEq/l and glucose as 142 mg/dl. It was thus decided to perform hemodialysis in ED. Her CBZ plasma concentration was 23.7 μg/mL upon completion of hemodialysis (HD). Computerised tomography of the brain revealed no intracranial abnormalities. Acetominophen levels were not significantly raised on immediate testing. She was admitted to the intensive care unit for ventilation and supportive care. She was extubated without any neurological sequelae on the third day. The patient was asymptomatic upon discharge seven days after admission, and a psychiatric follow-up arranged.

DISCUSSION

CBZ is a well-known and widely used iminostilbene derivative anticonvulsant with a chemical structure closely related to the cyclic antidepressants.[1] It is an antiepileptic drug widely used for the treatment of complex partial[2] and simple seizures, depressive disorders, migraine, trigeminal neuralgia, and bipolar affective disorder.[3] The drug accounted for more than 30% of all anticonvulsant drug overdoses.[4] It is absorbed erratically after oral administration because of its lipophilic nature. It has a large volume of distribution; peak plasma levels occur 4-8 hours[2] postingestion but may take up to 96 hours to reach the peak levels.[5] The primary site of metabolism is the liver; its metabolite is also active, which may increase the duration of the symptoms of toxicity.[2] CBZ poisoning is characterized by neurological and cardiovascular disorders. Mortality rate is approximately 2-13%, particularly resulting from cardiovascular toxicity.[5] Patients with a CBZ overdose who arrive in the ED without a history of access to CBZ may present a difficult diagnosis. Ophthalmoplegia, absent pupillary response, deep coma, and unstable cardiovascular status may suggest a number of neurovascular accidents, including brain stem infarct and stroke.[6] Acute CBZ intoxication is associated with ataxia, nystagmus, dystonia, mydriasis and sinus tachycardia.[3] The clinical features of toxicity after acute CBZ overdose are dose-related and correlate well with serum levels.[7] Levels ≥12 μg/l are associated with ataxia and nystagmus, and levels ≥ 40 μg/l are associated with coma, respiratory depression and seizures.[6] Chronic CBZ overdose can result in headache or diplopia. Although not formally studied, sodium bicarbonate should be administered if the QRS duration exceeds 100 msec. CBZ-induced seizures usually respond to benzodiazepines.[8] Idiosyncratic adverse events are common. Hypersensitivity syndrome may occur and is characterized by fever, lymphadenopaty, erythroderma, leucocytosis and hepatic involvement[9] and erythema multiforme in patients receiving CBZ.[10] Furthermore, CBZ and other antiepileptic drugs may affect the serum thyroid hormone concentrations in prepubertal children[11] and adults.[8] In epileptic children, obesity[12] growth retardation, hyperandrogenism and polycystic ovary syndrome may occur during the antiepileptic treatment course.[13] The kidney is rarely involved, water retention due to inappropriate secretion of antidiuretic hormon being the most frequent adverse reaction. Acute renal failure may appear been related as an advers reaction to CBZ, mostly as a tubulointerstitial nephri-

tis in relation with hypersensitivity and formation of immune complexes,[14] although tubular necrosis caused by CBZ has also been reported.[15,16] Our patient ingested 933 mg/kg of controlled-release CBZ. The highest dose reported in a survivor is 640 mg/kg.[17] Treatment of CBZ intoxication is mainly supportive care.[3] Multiple-dose activated charcoal has a therapeutic role in the management of patients with CBZ overdose.[7] Whole-bowel irrigation has been advocated as a method of decontamination after CBZ overdose. It is technically more difficult in the intubated and ventilated patient, and is further complicated if ileus develops as a result of the anticholinergic effects of CBZ.[8] In this patient, early signs of large bowel obstruction and decreased gastrointestinal motility limited the utilizing of activated charcoal. Clinicians must be careful to monitor for the development of intestinal ileus, a potential complication of severe CBZ intoxication, if using either therapies.[18] In the management of acute CBZ overdose, different therapeutic interventions such as charcoal hemoperfusion (HP), HD[6] and plasma exchange[19] have been reported to be effective with supportive measures, although the indications for their use are not well defined. Enhanced elimination may be indicated in several types of patients, such as patients who fail to respond adequately to full supportive care. The amount of xenobiotic absorbed or its high concentration in serum indicates that serious morbidity or mortality is likely. Patients with concomitant electrolyte disorders can be treated by HD, such as our case.[8] Charcoal HP and high-efficiency HD have been reported to reduce serum concentrations by 25 to 50%.[6] In this case serum, CBZ level fell %36 after low-flux HD with clinical improvement. The decision for a therapeutic intervention for drug removal is obliged to be based on clinical findings, especially of neurological and cardiac involvement, rather than solely blood CBZ level.[20] Some authors have suggested that HP was superior to HD, but this has been challenged. Low-flux HD might also be used and is equally effective in the management of acute CBZ overdose especially when HP is unavailable.[21] Schuerer et al. reported clearance rates similar or better than those attributed to hemoperfusion by using high-efficiency HD.[22] This fits the known toxico-kinetic effect of CBZ in overdose. Additionally, the metabolite, CBZE, which less than 50% is protein-bound, is increasingly being implicated as a key part of the toxicity of this drug in overdose and would be a good candidate for removal by HD. Finally, the advantage to HD is that it lacks the side effects associated with HP, such as hypocalcemia, thrombocytopenia, coagulopathies and hypothermia.[6]

CONCLUSION

In conclusion, massive CBZ overdose can induce an acute renal failure, therefore renal function should be monitored closely. Our data support effectivity of standard low-flux HD with supportive measures in the management of acute CBZ overdose in patients with electrolyte disorders and acute renal failure.

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