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Carbamazepine and the active epoxide metabolite are effectively cleared by hemodialysis followed by continuous venovenous hemodialysis in an acute overdose

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Abstract

Hemodialysis (HD) and continuous venovenous hemodialysis (CVVHD) have an unproven role in the management of carbamazepine overdose. Albumin-enhanced CVVHD may accelerate carbamazepine (CBZ) clearance, but no pharmacokinetic data has been reported for traditional CVVHD without albumin enhancement. In addition, it is unclear whether the active CBZ-epoxide metabolite is removed with either mode of dialysis. We present a case of CBZ intoxication successfully managed with sequential HD and CVVHD. The CBZ half-life during CVVHD was 14.7 hours, compared with the patient's endogenous half-life of 30.8 hours. The CBZ-epoxide half-life was 3.2 hours during HD. We conclude that HD and CVVHD provide effective clearance of CBZ and the epoxide metabolite and should be considered in the management of an acute toxic ingestion.

Key words: Pharmacokinetics, carbamazepine, hemodialysis, CVVHD, overdose

INTRODUCTION

Carbamazepine (CBZ) overdose and toxicity can lead to neurologic dysfunction, respiratory compromise, cardiac arrhythmias, and death.[1] Initial management of acute ingestion involves limiting absorption of the drug utilizing gastric lavage and oral activated charcoal. Development of an ileus from the anticholinergic effects of CBZ can delay absorption so that peak serum levels may be seen up to 96 hours postingestion.[2] Traditionally, extracorporeal therapies were considered of limited utility given that at therapeutic concentrations CBZ is about 80% to 85% protein-bound and has a large volume of distribution estimated between 0.5 to 2 L/kg.[3] Case reports of charcoal hemoperfusion, high-flux hemodialysis (HD), and albumin-enhanced continuous venovenous hemodialysis (CVVHD) have shown some success,[4–9] but typically only describe serum levels of the drug, which are widely influenced by variable hepatic metabolism and renal excretion. Since dialysate levels of CBZ rarely have been measured, improved clearance with HD and CVVHD is inferred but not substantiated. Furthermore, little is known about whether extracorporeal therapy effectively removes the major active metabolite, carbamazepine-10,11 epoxide (CBZ-E).

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We describe a case of acute CBZ overdose that was successfully managed by HD followed immediately by CVVHD and report pharmacokinetic analysis of CBZ and its epoxide metabolite for both modalities.

CASE REPORT

A 32-year-old, 48 kg female was brought to an emergency department 2 hours after ingestion of 32 g of CBZ in an apparent suicide attempt. She had not been taking CBZ chronically. Upon presentation she was obtunded and unresponsive with a Glasgow Coma Scale of 3. Her initial blood pressure was 132/88 mmHg with a heart rate of 94/minute, respiratory rate of 14/minute, and oxygen saturation level of 95% on room air. Cardiopulmonary exam was unremarkable. Bowel sounds were absent. She was noted to have flaccid muscle tone, and exhibited diffuse hyporeflexia. Occulocephalic and corneal reflexes were absent.

Gastric lavage was not performed. A nasogastric tube was placed followed by administration of 50 g of activated charcoal. Over the next several hours, the patient had 3 tonic clonic seizures, became hypoxic, and required intubation. She became hypotensive to 74/46 and was treated with volume resuscitation and intravenous vasopressor therapy. Initial serum drug levels 2.5 hours after ingestion were: CBZ 32.9 μg/mL (therapeutic 4 to 12 μg/mL), ethanol 190 mg/dL, and acetaminophen 45 μg/mL (therapeutic range: 10 to 30 μg/mL). Urine screening for pregnancy and drugs of abuse was negative. An ECG revealed a normal QRS interval at 86 ms.

Subsequent serum CBZ concentrations were: 42.7 ug/mL at 4 hours postingestion, 67 μg/mL at 11 hours and >80 μg/mL; at 16 hours. Other lab work revealed sodium 143 mmol/L, bicarbonate 23 mmol/L, creatinine 0.8 mg/dL, and calcium 8.7 mg/dL with normal liver function tests except for an ALT of 42 IU/L.

Due to the continued rise in serum CBZ concentrations with associated neurologic impairment and cardiovascular instability, the patient was transferred to our institution and HD was initiated 23 hours after ingestion with a F-200 NR dialyzer (Fresenius Medical Care North America, Waltham, MA, USA) (surface area 2.0 m^2, ultrafiltration coefficient 62 mL/h/mmHg) with a blood flow rate of 350 mL/min and a dialyzate flow rate of 700 cc/min. Treatment was continued for 3 hours. This was followed immediately by CVVHD using a Braun Diapact with a F-160 NR dialyzer, a blood flow rate of 200 mL/min, a dialyzate flow rate of 4000 mL/h (83 mL/kg/h), and a regional citrate anticoagulation protocol.[10] No net ultrafiltration was performed with either therapy.

The CVVHD was discontinued after 38 hours of therapy at which point she was awake and interactive, extubated, and off vasopressors. At the time of CVVHD discontinuation, the serum CBZ level was 11.5 μg/mL. The EEG monitoring revealed no epileptiform activity. She remained nonoliguric throughout her course. She was discharged on hospital day five with no residual sequela.

Pre/postdialyzer and effluent samples were collected during HD and CVVHD and were assayed for CBZ and CBZ-E by a fluorescence polarization immunoassay. Clearance by HD and CVVHD was determined with the equations:

$$\text{Clearance (HD)} = \frac{\text{Pre dialyzer conc} - \text{post dialyzer conc}}{\text{Pre dialyzer conc}} \times \text{Blood flow rate}$$

$$\text{Transmembrane clearance (CVVHD)} = \frac{\text{Effluent CBZ concentration}}{\text{Prefilter CBZ concentration}} \times \text{Dialyzate flow rate}$$

CBZ half-life was determined from the slope of the regression line of the serum CBZ concentration-time profile for each segment of therapy/no therapy (Fig. 1).

Calculated CBZ clearance during HD was 77.2 mL/min based on samples taken during the last hour when concentrations were within the assay range of the laboratory. At the beginning of HD, CBZ levels could not be accurately quantified by the clinical laboratory as levels were above the upper limits of the assay (>80 μg/mL). As a result, CBZ half-life during HD could not be accurately estimated. Total CBZ-E clearance was 147 mL/min at the start of HD and 63.4 mL/min at the end of HD. The

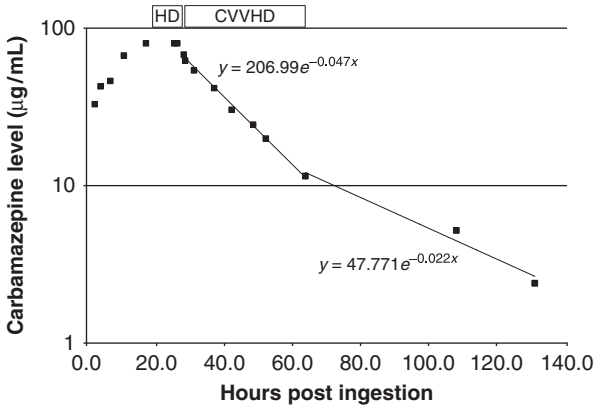

Figure 1 Serum carbamazepine levels during hemodialysis, continuous venovenous hemodialysis, and after extracorporeal therapy was ended. Regression lines during continuous venovenous hemodialysis (CVVHD) and after therapy are shown.

apparent half-life of CBZ-E during HD was 3.2 hours. During CVVHD, CBZ and CBZ-E saturation coefficients were 0.36 and 0.70, resulting in CVVHD transmembrane clearances of 24.0 mL/min and 46.4 mL/min respectively. CBZ half-life was 14.7 hours during CVVHD therapy. Once CVVHD was discontinued, the patient's endogenous half-life of CBZ was 30.8 hours.

DISCUSSION

We describe a case of severe acute CBZ ingestion with neurologic, respiratory, and cardiovascular compromise that was successfully managed with HD followed by CVVHD, a sequence of therapies not previously reported in the literature. Initial dosing of CBZ results in a half-life of 25 to 65 hours, while chronic dosing leads to autoinduction of the hepatic cytochrome P450 enzyme CYP3A4 with a decreased half-life of 12 to 17 hours.[11] Hepatic metabolism of the drug produces the active CBZ-E metabolite that is about 50% protein bound[12] and has a half-life of 6.9 hours.[13] Several reports indicate that toxicity can occur with elevated CBZ-E levels, even in the setting of therapeutic CBZ levels.[14–16]

Our patient, who had not been taking CBZ chronically, had an endogenous CBZ half-life of 30.8 hours, similar to numerous reports of 31 to 37.7 hours with single dose ingestion.[2,11,17] CVVHD greatly enhanced CBZ clearance with a 50% reduction in half-life of the drug, thereby potentially reducing the ICU stay. The sieving coefficient of 0.36 obtained during CVVHD suggests a larger fraction of unbound CBZ than would be anticipated at therapeutic concentrations, 0.15 to 0.2. This is likely due to saturation of protein binding sites in the setting of an acute intoxication. The sieving coefficient of CBZ-E was 0.70, essentially twice that of the parent compound and was also amenable to removal through CVVHD therapy with a shorter half-life than what has been reported in the literature.[13,18] Thus, while charcoal hemoperfusion was originally thought to be needed for CBZ removal, our data indicate that CVVHD can be an effective alternative therapy, particularly in hemodynamically unstable patients.

Askenazi published a case report[4] of albumin-enhanced CVVHD with an albumin concentration of 4.5 g/dL in the dialyzate. They observed a CBZ half-life between 7 and 8 hours, which was twice as fast as we attained in our study using albumin-free dialyzate. Askenazi used a dialysate flow rate of 3 L per 1.73 m^2, compared with our dialyzate flow rate of 4.4 L per 1.73 m^2. However, direct CBZ dialytic clearance was not measured in their case report and the patient's native CBZ clearance was unknown, thus making it difficult to determine the relative benefit of that therapy. In the in vitro assessment of albumin enhanced CVVHD, Churchwell et al. reported that increased dialyzate flow substantially improved CBZ clearance independently of whether 2.5% or 5% albumin enhanced dialyzate was used.[19] Therefore, CVVHD with high dialyzate flow, but without albumin enhancement as shown in the present study, can provide significant clearance without the incremental costs.

Kielstein et al.[8] reported a CBZ clearance of 59 mL/min in one of the only studies containing pharmacokinetic data in high-flux HD. However, this is likely an underestimate, as they used a batch dialysis system, in which a subsequent study[20] revealed contamination of fresh dialyzate with spent dialyzate when used for toxin removal in a patient like ours, who did not have renal failure.

In summary, our data show that both HD and CVVHD greatly enhance overall clearance of CBZ and its metabolite, CBZ-E. We suggest that both modalities be considered in cases of acute large quantity CBZ ingestion associated with significant neurologic, respiratory or cardiovascular impairment.

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