Case report

Continuous venovenous hemodiafiltration to treat controlled-release carbamazepine overdose in a pediatric patient

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Summary
Carbamazepine (CBZ) intoxication is an important issue in acute poisoning practice. Highly protein-bound, CBZ is not removed efficiently through conventional hemodialysis. We describe the use of continuous venovenous hemodiafiltration (CVVHDF) in a 2-year-old boy who developed general tonic clonic seizure and respiratory depression due to controlled-release formula of CBZ overdose (peak drug level of >20 μg·ml⁻¹, therapeutic range: 5–10 μg·ml⁻¹). Serum CBZ concentrations fell to 0.25 μg·ml⁻¹ at the end of hemodiafiltration. The patient recovered rapidly and was discharged from hospital 4 days from the time of ingestion with no complications or neurologic impairment.

Keywords: anticonvulsants; carbamazepine; poisoning; overdose; haemodiafiltration

Introduction
Carbamazepine (CBZ) is an anticonvulsant prescribed for all types of epilepsy (1). At toxic levels (>16 μg·ml⁻¹), complications such as cardiac dysrhythmia, seizures and coma have been reported. In addition, it has been reported that children may be at greater risk for these effects at lower serum levels than adults (2,3). The clinical picture is variable and does not always correlate with CBZ serum concentration. Controlled-release formulations of CBZ have a delay of over 48 h between the time of ingestion and peak serum CBZ concentrations. Highly protein-bound, CBZ is not removed efficiently through conventional hemodialysis.

We describe the use of continuous venovenous hemodiafiltration (CVVHDF) in a 2-year-old boy who developed general tonic clonic seizure and respiratory depression from controlled-release formulation of CBZ overdose.

Case report
A 2-year-old 12-kg boy presented to the emergency department 20 h after ingesting five 400-mg controlled-release CBZ tablets (Tegretol-CR® 400 mg, a total of 2 g, approximately 166 mg·kg⁻¹). The medication had been prescribed for his grandmother for treatment of seizure disorder. The child
had a generalized tonic clonic seizure before admission. At presentation BP was 110/60 mmHg and heart rate 92 b min⁻¹. He was unconsciousness with flexion withdrawal to noxious stimuli. Both pupils were reactive. Serum CBZ level was higher than 20 µg ml⁻¹. CBZ concentrations were determined using a fluorescence polarization immunoassay (Abbott Axsym, 13885–96, Texas, USA). Initial blood gas analysis, serum biochemistry and creatine phosphokinase levels were in the normal range. Complete blood count revealed leukopenia (3.2 × 10⁹ l⁻¹) and neutropenia (5.3 × 10⁹ l⁻¹). A 12-lead electrocardiogram revealed sinus rhythm, normal pulse rate, QRS and QT. The patient was given bowel irrigation, gastric lavage and decontamination with oral activated charcoal (1 g l⁻¹ 6 h) via a nasogastric tube. He was managed conservatively because of adequate vital signs. Unfortunately, after 2 h of observation, pupils became nonreactive and midriatic. He had a generalized tonic clonic seizure lasting 1 min and a respiratory arrest. He was intubated and ventilated in PICU. Pupils regained reactivity and minimal respiratory effort was observed. Because of no further neurological improvement and instability, a double-lumen catheter was placed into the left femoral vein and CVVHDF (Hospal Prisma CFM 960917, Colorado, USA) was initiated at the 46th hour of ingesting CBZ at a blood flow rate of 80 ml·min⁻¹ using a dialysate rate of 1000 ml·h⁻¹. Pediatric lines were primed with isotonic and dialysate included glucose (Dienal 1.36). After a 10 h session of hemodiafiltration, the filter and circuit became clotted. Twelve hours later, the circuit was replaced and a second 8 h session of hemodiafiltration was performed since he remained comatose and had ingested the controlled-release form of CBZ. Blood samples were taken before the first and second sessions of CVVHDF, but the serum CBZ could not be measured one because of a failure in the laboratory computer system. The patient became increasingly responsive and extubated himself spontaneously.

No complications occurred during hemodiafiltration. Serum CBZ concentrations fell to 0.25 µg ml⁻¹ at the end of hemodiafiltration. The patient recovered completely and was discharged from hospital on the fifth day.

Discussion

This is a case of poisoning with controlled-release CBZ, a drug with delayed peak serum concentrations, which is rarely seen in childhood. Admission of the patient to hospital was at 20 h after ingestion, and even though the initiation of VVHDF was at 46 h, the patient recovered completely.

Carbamazepine is a drug that has an important anticonvulsant effect in therapeutic doses and strong proconvulsant effect in overdoses (4). In therapeutic doses, the pharmacokinetics of CBZ change according to the type of preparation. Immediate-release CBZ has a slow and erratic absorption over several hours, while controlled-release CBZ has slower absorption (5). After an overdose of CBZ, peak serum concentrations may be delayed up to 70 h postingestion. Additionally, elevated serum concentrations of CBZ may persist because of continued absorption from the gut because of gastrointestinal hypomotility.

Critical clinical problems associated with CBZ overdose are coma, respiratory depression and ventricular arrhythmias. Seizures are seen in 18% of all cases. In one review of 427 patients with CBZ overdose, the occurrence of seizures was the only clinical parameter statistically associated with a fatal outcome (6). Our patient presented with a generalized tonic-clonic seizure as the first sign before hospital admission in a comatose state. Cardiac toxicity or hypotension were not observed.

In cases in which large amounts of CBZ have been ingested as in our case, whole bowel irrigation is part of the decontamination procedure. Activated charcoal is known to bind to CBZ and prevents absorption from the gut. In addition, it enhances CBZ elimination by interrupting the enterohepatic circulation of the drug. Multiple doses of activated charcoal have been recommended by the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists as useful in enhancing clearance of CBZ in severe or life-threatening cases of poisoning (7).

Spiller (4) suggested management decisions should be made according to clinical presentation instead of drug concentrations. We were not able to measure the serum CBZ concentration at the end of the first hemodiafiltration session, but because of lack of improvement in neurological and clinical status we decided to repeat the session.
Several modalities have been used for enhanced clearance of CBZ. Because CBZ is highly protein-bound (80%) and has a large volume of distribution, conventional hemodialysis which is a diffusion-based technique, may not be efficient in acute CBZ toxicity (8). For enhanced clearance charcoal hemoperfusion or albumin-enhanced CVVHD are recommended which may be more effective in removing highly protein-bound substances (9,10). Use of high-flux dialyzers and plasmapheresis have also been advocated (11,12).

Solute removal in continuous dialysis therapeutic techniques is achieved either by convection, diffusion or a combination of these two techniques. Convective techniques depend on solute removal by solvent drag, while diffusion-based techniques are based on the principle of a solute gradient between the blood and the dialysate. The CVVHDF process, used in our patient, utilizes both diffusion and convection. CVVHDF is a more difficult and expensive technique than other continuous renal replacement therapies. However, combining convection and diffusion allows flexibility in enhancing clearance by increasing the volume of ultrafiltrate or the dialysate flow rates. The advantage of this process over diffusive techniques alone is that convective transfer contributes to the clearance of larger molecules such as cytokines and drugs. Because it is a continuous procedure and can be controlled easily, it has a significant advantage in a hemodynamically unstable child (13).

In conclusion, we report a case of, initially unrecognized poisoning with controlled-release CBZ. Although we could not always measure serum CBZ levels we suggest that CVVHDF may be an alternative to enhance the clearance of CBZ. Serum concentrations of CBZ fell after CVVHDF was instituted and the patient’s clinical condition improved. Clinicians should be aware of the availability of CR formulations of CBZ and that significantly delayed gastrointestinal tract absorption may result from overdose, particularly when inadequate gastrointestinal tract decontamination has been performed.

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**References**


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