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Lack of effect of high-volume continuous veno-venous haemofiltration with dialysis in massive carbamazepine overdose

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Summary

A 32-year-old man, with a long history of chronic pain and bipolar disorder, was admitted to our emergency department 2 h after a mixed overdose, predominately consisting of carbamazepine. Following no clinical improvement after four days of ventilation on our intensive care unit (ICU), high-volume continuous veno-venous haemofiltration with dialysis was instituted to enhance the elimination of the carbamazepine. It had no significant effect on the patient's clinical status or serum carbamazepine level. It was discontinued after 48 h. He spontaneously recovered and was discharged uneventfully from ICU after 7 days.

BACKGROUND

Owing to the wide availability of carbamazepine, which is prescribed to the paediatric and adult patients usually as an anticonvulsant, there are many cases of its overdose. Various treatment options to enhance the elimination of this highly protein-bound molecule have been reported. These include high-volume continuous veno-venous haemofiltration with dialysis (CVVHDF), which should be more effective with small, less protein-bound molecules. We report the lack of effect of CVVHDF in a patient with a massive carbamazepine overdose.

CASE PRESENTATION

A 32-year-old man, with a long history of chronic pain and bipolar disorder, was admitted to our emergency department 2 h after a mixed overdose of carbamazepine (44.8 g, estimated 631 mg/kg), clonazepam (3.5 mg) and chlorpromazine (300 mg). He was admitted to the general intensive care unit (ICU) for ongoing supportive care. Within 24 h his Glasgow Coma Scale score began to fluctuate from 13 to 5, and he developed intermittent agitation. He developed type 1 respiratory failure, a degree of hypotension and was felt to be at risk of aspiration.

INVESTIGATIONS

Arterial blood gas analysis, with the patient breathing 60% oxygen, revealed pH 7.37, pCO_2 4.97 kPa, pO_2 6.93 kPa and FiO_2 0.6) and was intubated and ventilated and started on inotropes. Chest x-ray showed patchy infiltrates and his PaO_2/FiO_2 ratio was <26.7 kPa. Creatinine kinase was elevated at 3000 µ/l, C reactive protein of 240 mg/dl and QTc prolonged at >450 m. Carbamazepine level on admission was 33 mg/l (therapeutic level 4–10 mg/l). Paracetamol and salicylate were not detected.

DIFFERENTIAL DIAGNOSIS

The diagnosis of a mixed overdose, predominately carbamazepine, leading to neurological and respiratory depression and signs of acute respiratory distress syndrome (ARDS) was made.

TREATMENT

The patient was intubated and ventilated. Inotropes were instituted to maintain adequate perfusion and the ARDSnet ventilation protocol followed. Vigorous rehydration and standard ICU care bundles were instituted. Owing to lack of clinical progress, high-volume CVVHD was started on day 3 of admission and continued for 48 h with little effect. He slowly improved, was extubated on day 7, and discharged for further psychological treatment from the medical team on day 9.

OUTCOME AND FOLLOW-UP

The patient had no medical squelae from this overdose and is still receiving help with his underlying medical conditions.

DISCUSSION

Carbamazepine is an anticonvulsant, also prescribed as a mood stabiliser, structurally related to tricyclic antidepressants. It is highly protein bound (approximately 80%) with a volume of distribution of 1–2 l/kg. As well as being hepatically metabolised, it causes autoinduction, within 5–7 days, of CYP3A4, which metabolises carbamazepine itself. It has a normal half-life of 24–48 h, which is shortened by autoinduction. Its inactive metabolites are excreted renally. Our patient had been prescribed carbamazepine for a number of years, hence autoinduction would have occurred prior to presentation.

Signs and symptoms of carbamazepine toxicity are dose-related and can be predicted by serum levels. With

ingestion of >20 mg/kg signs are predominately neurological including ataxia, nystagmus, mydriasis, movement disorders and the anticholinergic toxic syndrome. Ingestion of doses >50 mg/kg lead to more severe neurological depression. The dose in this case was estimated as 631 mg/kg.

The treatment of such a large dose is uncertain. There are case reports describing charcoal lavage, charcoal haemoperfusion,[1] and CVVHDF against albumin.[2] These treatments either inhibit gut absorption or are recognised methods to remove large molecular weight, highly protein-bound substances from the blood. In addition, there are case reports that high flow, standard CVVHDF can be effective with carbamazepine toxicity in the adult and paediatric population.[3 4] In light of the patients' depressed neurological state, rising inflammatory markers and lack of improvement the decision was taken to follow this route and institute high flow, standard CVVHDF, since this was the most easily available option open to us. Serum carbamazepine levels were measured daily during his admission.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Carbamazepine (mg/l)	33	35	32	29	33	33	23

CVVHF was performed over days 3 and 4 of admission and made little impact on measured serum levels. The carbamazepine level of the filtrate fluid was 10 mg/l giving a maximum clearance of 720 mg/day, approximately 16% of the total dose. Interestingly following an overdose with initial serum levels of 22.6 mg/l, Chetty *et al*[3] achieved greater than 50% clearance after 4 hours of CVVHDF.

The lack of effect of CVVHDF in our case may be due to a number of reasons. The degree of toxicity was much higher in our case, swamping the ability of native enzymes to metabolise carbamazepine. This would have been allied to the probable redistribution to many compartments such as muscle and bone. Equilbrilation among multiple, saturated compartments would have been a prolonged process. It is also possible that the type of filter membrane, dialysate and CVVHDF machine may have affected carbamazepine removal.

In this case, CVVHDF made no discernable difference clinically or to serum carbamazepine levels. It is probable that further autoinduction, allied to time led to the elimination of carbamazepine.

In light of the pharmacokinetics of carbamazepine, in particular its highly protein-bound nature, it is unlikely that CVVHDF will significantly enhance its elimination following such a large overdose.

Learning points

- Carbamazepine overdose can lead to neurological depression, convulsions and a decreased ability to protect ones airway.
- Carbamazepine is a highly protein-bound molecule, with a large volume of distribution.
- Its elimination theoretically should be enhanced by methods such as charcoal haemoperfusion, which are known to effectively remove such molecules.
- Continuous veno-venous haemofiltration with dialysis should be less effective at removing such molecules.

Competing interests None.

Patient consent Obtained.

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