CASE REPORT

Overdose with antiepileptic drugs: the efficacy of extracorporeal removal techniques

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SUMMARY

Drug overdose is a growing problem among adolescents. Clinical severity depends on the drug and ingested amount, which in some cases may be life-threatening. We present a clinical case of a previously healthy teenage girl who ingested 16.4 g of carbamazepine and 14.5 g of valproic acid. She presented with profound disturbance of consciousness and toxic levels of both drugs, raised in the first hours after the ingestion. She was successfully treated with charcoal haemoperfusion followed by continuous venovenous hemodiafiltration. Overdose with the two drugs separately is common, but there are no reports of intoxication by simultaneous ingestion. High levels of carbamazepine and valproic acid can lead to severe systemic effects and management is made difficult by the absence of specific antidotes. Extracorporeal removal techniques are a good therapeutic option in these cases as they enhance the clearance by reducing the half-life of both drugs thereby preventing serious complications.

BACKGROUND

Adolescence is a period in life of high risk behaviour, during which more suicide attempts happen than at any other time in life.^{1 2} Drug overdose is one of the leading methods of adolescents' suicide attempts in developed countries but only in a few cases is it life-threatening.^{2 3} Clinical severity of drug overdose depends on the drug and amount taken. The challenge in the management of poisoned patients is to identify, at an early stage, those who are most at risk of developing serious complications and who might benefit from extracorporeal elimination techniques.⁴

Carbamazepine (CBZ) and valproic acid (VPA) are both widely used in the treatment of epilepsy. Isolated CBZ or VPA overdose is common and also observed in paediatric emergencies.^{5–11} However, there are no reports of intoxication by simultaneous ingestion of both drugs.

The serum therapeutic range for CBZ is between 4 and 12 µg/mL.^{5 6} Toxicity increases as plasma concentration rises above therapeutic range; if it goes higher than 40 µg/mL, serious complications such as respiratory depression, apnoea, coma and ventricular arrhythmias can occur.^{12 13} Children and adolescents may be at greater risk at lower serum levels than adults.^{6 14} VPA therapeutic levels range between 50 and 100 µg/mL. Toxic effects are associated with blood levels above that range and central nervous system depression is frequent with levels beyond 180 µg/mL.¹⁵ Toxicity of VPA is mainly manifested by neurological symptoms, and can lead to respiratory depression, coma and even

death.^{7 9 16 17} Both drugs are extensively bound to serum proteins and neither one has an antidote; the optimal treatment for intoxication is not clear and should depend on clinical presentation.⁴ Cases of isolated overdose by CBZ or VPA have been successfully treated with extracorporeal methods, but few cases are described in paediatric age.^{5 7 18}

CASE PRESENTATION

A 16-year-old girl was admitted to the emergency department of a local hospital 3 h after ingesting an estimated amount of 16.4 g of CBZ (27 prolonged release tablets of 400 mg and 28 of 200 mg) and 14.5 g of VPA (29 prolonged release tablets of 500 mg). She had no previous diseases and had never threatened or attempted suicide. After an argument with her mother, she ingested the tablets (part of her father's regular medication) and, 3 h later, her parents found her unconscious. Spontaneous emesis was not noticed.

She presented to the emergency department with fluctuations in conscious state, Glasgow Coma Scale (GCS) between 5 and 8; her vital signs were: axillary temperature 34.5°C, arterial blood pressure 114/46 mm Hg, heart rate 77 bpm, respiratory rate 19/min and peripheral oxygen saturation 100% (breathing room air). A gastric lavage was performed without direct visualisation of the tablets and activated charcoal administered via a nasogastric tube. The patient was kept under neurological status and vital signs monitored; activated charcoal was administered every 4 h.

INVESTIGATIONS

Five hours after ingestion, laboratory data showed CBZ levels of 43.1 µg/mL and VPA levels of 111.5 µg/mL. Drug serum concentrations were determined using a Vitros 5.1 FS system. CBZ concentration was determined by a kinetic two-point test and VPA by an immunomultipoint kinetic test. The patient's blood cell count was normal as were her blood gases, aminotransferases and ammonia. Blood urea nitrogen was 4.7 mmol/L and creatinine 53 µmol/L. Coingestion with drugs of abuse was excluded. Twelve-lead ECG did not reveal arrhythmia and brain CT was normal.

The patient remained comatose in the following hours, with irregular response to stimuli. Ten hours after ingestion the drug concentration had increased (CBZ=43.9 µg/mL; VPA=183 µg/mL). The paediatric retrieval team was called and the patient was taken to the nearest paediatric intensive care unit (PICU) after being intubated with an uncuffed

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endotracheal tube to secure the airway and started on invasive ventilation.

On PICU admission, 14 h after intoxication, she remained unconscious (GCS=6), on invasive ventilation with 21% oxygen, peripheral body temperature 35.8°C, blood pressure 116/86 mm Hg and heart rate 97/min.

TREATMENT

The patient was kept on intestinal decontamination with activated charcoal every 6 h during the first 24 h after admission. In order to accelerate bowel elimination she was also put on enteral macrogol. Fifteen hours after ingestion, because of no neurological improvement, drug serum concentrations were evaluated again with increasing VPA (283 µg/mL) and maintained toxic levels of CBZ (40 µg/mL). A dialysis catheter was placed and charcoal haemoperfusion (CHP) was performed for 4 h with a blood flow rate of 200 mL/min. A remarkable decrease of CBZ levels (18.6 µg/mL) and VPA (90.5 µg/mL) was observed (figure 1). After the procedure, platelets decreased from 167 000/µL to 45 000/µL. In the next 48 h, continuous venovenous hemodiafiltration (CVVHDF) was performed with a blood flow rate of 150 mL/min, effluent filtration rate of 2000 mL/h and fluid replacement of 600 mL/h (=11.8 mL/kg/h). During CHP and CVVHDF, drug levels were monitored every 6 to 8 h. Both techniques were performed with Prismaflex.

In the first hours of PICU admission the patient presented with charcoal aspiration and increased oxygen demand up to 25%. Her chest X-ray showed bilateral basal hypotransparency (figure 2) and she was started on ceftriaxone.

At the end of CVVHDF, CBZ level was 17.8 µg/mL and VPA was 119 µg/mL; these levels continued decreasing in the next hours (figure 1). At this time, platelets had increased to 51 000/µL.

There was no need for blood transfusion and serum electrolytes remained within normal physiological range: at the end of procedure sodium was 137 mmol/L, potassium 4.1 mmol/L, magnesium 0.79 mmol/L, calcium 2.2 mmol/L and phosphorus 1.45 mmol/L. Ammonia was 18 µmol/L.

Ninety hours after drug ingestion, the patient became increasingly responsive and was extubated at 120 h. She completed 5 days of ceftriaxone and continued on oral amoxicillin for five additional days.

OUTCOME AND FOLLOW-UP

There was complete neurological recovery and the patient was discharged to the local hospital on the eighth day, for mental

Figure 2 First day chest X-ray showing aspiration bilateral pneumonia.

support by paedopsychiatrist. A week later she was considered mentally stable and was discharged home, keeping regular appointments with the paedopsychiatrist.

DISCUSSION

A clinical case of severe CBZ and VPA overdose due to a suicide attempt is presented. Suicide attempts are common during adolescence and girls present with higher rates than boys.¹⁻³

To the best of our knowledge, this is a unique case of simultaneous ingestion of CBZ and VPA both, in such a high amount. This case illustrates the difficulties in the management of a life-threatening toxic ingestion with two different drugs that are extensively bound to serum proteins. Both drugs' intoxications have to be managed with supportive measures since there are no specific antidotes or treatment guidelines.^{6 16 17 19 20}

The main symptom of this patient was central nervous system depression, explained either by CBZ or VPA toxicity or probably by the additional effect of both drugs together. Risk of toxicity rises as CBZ and VPA plasma concentration increases; serious complications can occur with concentrations of CBZ over 40 µg/mL and VPA over 180 µg/mL.^{12 13 15} In this case, toxic levels of both drugs were reached just before CHP initiation.

The decision for active therapeutic intervention for drug removal must be based on clinical findings rather than the drug serum level alone.⁶ Extracorporeal methods can be an important tool in the management of intoxications.⁴ Their effectiveness increases with intoxication severity and with higher serum drug levels.^{9 18} Elimination of a drug by extracorporeal techniques is determined by toxin properties: molecular weight, protein binding, volume of distribution and the extracorporeal method.⁴ CBZ has a molecular weight of 236 Da and a slow absorption rate that, in cases of overdose, becomes erratic and can be largely extended with peak levels occurring up to 100 h after ingestion.^{5 12-14 21} Additionally, elevated serum concentrations of CBZ may persist due to a continued absorption from the gut because of gastrointestinal hypomotility (anticholinergic side effect of this drug).^{6 10 13 14 19} CBZ is 75 to 90% protein bound but, in concentrations higher than therapeutic, the percentage of free molecules circulating in blood is greater.^{5 6 19} VPA has a molecular weight of 144 Da, a faster absorption rate than CBZ, with peak level occurring 1-4 h after ingestion,

Figure 1 Carbamazepine (CBZ) and valproic acid (VPA) serum concentration evolution before, during and after the treatment with charcoal haemoperfusion (CHP) and continuous venovenous hemodiafiltration (CVVHDF). Therapeutic levels of CBZ=4-12 µg/mL and of VPA=50-100 µg/mL.

which in cases of overdose is usually delayed.^{7 16} In therapeutic ranges it is 90% protein bound, but in higher levels, VPA protein-binding capacity decreases.^{7 9 16 17} The relatively low concentrations of both drugs during the first hours can be explained by their slow absorption rate worsened by the fact that both are prolonged release formulations.

Solutes with molecular weight below 500 Da, such as CBZ and VPA, are easily removed by haemodialysis (HD). However, diffusive removal of a drug by HD requires that it is protein unbound in order to cross the dialysis membrane, which makes CBZ and VPA elimination difficult by this technique.^{4 14 19 22} Their elimination becomes possible since protein binding capacity is surpassed, justifying successful published cases of HD use in similar cases.^{6 9 16 22}

To enhance CBZ or VPA clearance in cases of intoxication, CHP, CVVHDF or a combination thereof, have been reported to be effective along with supportive measures. CHP is preferred since it is the most effective way of removing CBZ and VPA, although it is not easily accessible.^{5–7 10 11 13 14 17 19–23}

The decision to perform CHP should be taken with caution because of its side effects, cost and the level of expertise involved. There is no indication for its initiation, unless there are signs of severe intoxication or clinical deterioration.⁴ In this case, 15 h after ingestion, persistently increasing serum drug levels above toxic range and the maintenance of neurological depression led to the decision of starting CHP. This technique promotes blood circulation through an activated charcoal-containing cartridge added to the circuit of a HD machine.^{4 24} It has the advantage of removing toxins that are highly bound to serum proteins as activated charcoal competes with plasma proteins for drug binding.^{10 16 18 24} In our case, CHP led to a reduction of 53% in CBZ and 68% in VPA concentration, similar to other described cases.^{7 13 17} This technique enhances the body drug clearance, reducing possible side effects and leading to a faster recovery of consciousness, with short intubation and hospitalisation periods.

This technique is associated with complications such as thrombocytopenia, leucopenia, hypocalcaemia, reduction of fibrinogen and hypothermia. These are caused by the adsorption of cells and complement to the activated charcoal.^{4 13 24} In this case the only complication was thrombocytopenia, spontaneously resolved after procedure ending.

CVVHDF has also been efficient in treating these intoxications.^{6 9 14 16 18 19 22} During CVVHDF, fluctuating levels of both drugs were noticed. In fact, CHP has shown to be more effective than hemodiafiltration.^{13 20} In other published cases, two or three sessions of CHP were performed in the same patient with good results.^{10 17} However, the sudden decrease of platelets made us choose CCVHDF after CHP. The other advantage of CVVHDF is the use of diffusion and convection techniques, both of which allow the removal of plasmatic solutes.

We also included multiple doses of activated charcoal, as this is part of the decontamination procedure in cases of massive intoxication with digested drugs such as CBZ and VPA.²⁵ It has been proven to be more effective with CBZ than with VPA due to the prolonged absorption period of the first drug. Actually, we noted a small CBZ level decrease, while VPA level continued to increase. Administration of activated charcoal is effective in the first 24 h after ingestion enabling its binding to the toxin, preventing absorption of the molecule from the gut and also interrupting enterohepatic circulation.^{10 13 14 20 22 25 26} If the patient has neurological depression, it is safer to withhold treatment with activated charcoal until the airway is secured with an endotracheal tube.²⁵ In this case, intubation with a cuffed tube

should have been considered earlier to maintain a secure airway and prevent charcoal aspiration. By following these procedures, aspiration pneumonia might be avoided.

This case illustrates severe intoxication with CBZ and VPA with serious neurological depression that had a good outcome without other end-organ lesions. We consider that CHP and CVVHDF reduced coma time and may have contributed to avoiding other serious complications.

Extracorporeal removal with CHP and CVVHDF should be considered as an important part of the management of any patient with neurological compromise due to CBZ and VPA toxicity.

Learning points

- ▶ Suicide attempts are examples of risk behaviours practiced during adolescence.
- ▶ Before activated charcoal administration, the physician must guarantee a secure airway and intubate with a cuffed endotracheal tube when necessary.
- ▶ In the management of intoxicated patients, paediatricians should be able to early identify those who might potentially benefit from extracorporeal elimination techniques.
- ▶ Carbamazepine and valproic acid are common anticonvulsant drugs that, in severe overdose, can lead to serious complications, have no specific antidote and may be managed with charcoal haemoperfusion followed by continuous venovenous hemodiafiltration.

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