Continuous Veno-Venous Haemodiafiltration in Sodium Valproate Overdose Complicated by Cerebral Oedema: A Case Report

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ABSTRACT

A case of severe sodium valproate overdose is presented in which continuous venovenous haemodiafiltration was used. However, following the commencement of dialysis and a fall in the serum valproate levels, the patient developed cerebral oedema. This case demonstrated a poor correlation between serum valproate and its toxic effects and the lack of benefit of continuous venovenous haemodiafiltration in the management of sodium valproate overdose. (Critical Care and Resuscitation 2002; 4: 173-176)

Key words: Sodium valproate overdose, continuous veno-venous haemodiafiltration, cerebral oedema

Renal replacement therapies have previously been advocated to enhance the elimination of valproate (VPA) following an overdose. The rationale has been to rapidly decrease the serum levels and thus decrease its toxic effects.

Recommended indications for renal replacement therapy during sodium valproate intoxication have included plasma levels above 700 mg/L, rapid clinical deterioration, evidence of hepatic dysfunction and continued drug absorption.

We present a case where continuous venovenous haemodiafiltration (CVVHDF) was instituted for a sodium valproate overdose in which there was rapid clinical deterioration and a serum VPA level of greater than 700 g/L. While the serum level fell during dialysis, the patient became unconscious and developed cerebral oedema. This case illustrates the poor correlation between serum VPA levels and toxic effects and a lack of benefit of CVVHDF in this setting.

CASE REPORT

A 20-year-old man was admitted to hospital 9 hours after the ingestion of 40 g of sodium valproate (80 x 500 mg tablets). He had a past history of head injury, following which he developed epilepsy, depression, obsessive compulsive disorder and multiple episodes of self-harm.

He presented to the emergency department with a Glasgow coma score (GCS) of 8, pulse of 115 beats per minute and arterial blood pressure of 110/80 mmHg. His serum VPA level was 846 mg/L. The patient was observed clinically and did not receive oral activated charcoal.

At approximately 17 hr following the ingestion of sodium valproate he became obtunded with a GCS of 3 at which stage he was intubated and 50 g of activated charcoal was administered via a nasogastric tube. His serum VPA level had increased to 1094 mg/L and a
serum ammonia level taken at this stage was 144 µmol/L. A computed tomography (CT) scan of the head was performed which showed no evidence of cerebral oedema. The patient was transferred to the intensive care unit where CVVHDF was instituted after a third serum VPA estimation revealed a level of 1136mg/L.

He was treated with CVVHDF for the next 24 hr (1 litre cycles of Baxter® 5 L dialysate, 600 mL per hour prediluting replacement with the same solution, and 200 mL per hour blood flow via a Kimal dialysis machine) during which his serum VPA (figure 1) and ammonia levels (figure 2) quickly fell.

Four hours after the initiation of CVVHDF, the patient’s serum VPA level decreased to less than 500 mg/L. However, as he remained unconscious, a head CT scan was performed (36 hr after the first CT scan), which demonstrated cerebral oedema (figure 3).

His intracranial pressure was not monitored, so an arbitrary mean arterial pressure of 80 mmHg was targeted using a noradrenaline infusion in an attempt to maintain a satisfactory cerebral perfusion pressure. A tracheostomy was performed. His mental state slowly improved and by day 7 a head CT scan showed a reduction in the amount of cerebral oedema (figure 4). Additional complications during his stay in the intensive care unit included an episode of atrial fibrillation, paroxysmal supraventricular tachycardia, Staphylococcus aureus ventilator-associated pneumonia, bone marrow suppression with lymphopenia (0.13 x 10⁹/L), thrombocytopenia (44 x 10⁹/L) and transient elevation of the plasma ALT (405 U/L) and alkaline phosphatase (245 U/L), all of which resolved. The patient was decanulated 11 days after admission and was discharged to the ward with no clinical neurological defects.

DISCUSSION
Sodium valproate is a short-chain dicarboxylic acid that is 90% protein bound, has a half-life of 15 hr¹⁴ and has an apparent volume of distribution that ranges from 0.1 to 0.4 L/kg, at therapeutic levels.¹⁵ When taken as an overdose its absorption may be slow and erratic,
especially when slow-release products are ingested, and the concentration of free drug increases as the protein binding sites become saturated.

During therapy with sodium valproate the most common side effects are nausea, vomiting, ataxia, tremor and sedation. However, an overdose of sodium valproate (with serum VPA levels greater than 450mg/L) may be potentially lethal due to metabolic acidosis and coma. The coma is multifactorial with the contributory factors including hyperammonaemia, high anion gap lactic acidosis, direct sedative effects, cerebral oedema and mitochondrial dysfunction. Hypernatraemia, hypocalcaemia and hypophosphataemia may also occur. Pancreatitis, elevated hepatic transaminases and bone marrow suppression may complicate both overdose and therapeutic dosing. Nevertheless, fatalities associated with sodium valproate overdose are rare.

Various forms of renal replacement therapies have been used for the extra-corporeal removal of VPA during an overdose, but they have never been studied in the setting of a controlled trial and all the available clinical evidence is based on case reports. Haemodialysis, haemoperfusion and a combination of the two all appear to reduce the serum levels of VPA effectively but whether it influences the outcome of an overdose is less clear. In the case we report, CVVHDHF caused a reduction in the serum VPA levels, but cerebral oedema developed despite levels falling rapidly and coma persisted despite serum VPA levels returning to the therapeutic range.

The management of sodium valproate overdose remains largely supportive. While oral activated charcoal is usually administered to reduce gastrointestinal adsorption, one study suggested that use of activated charcoal beyond one hour of the ingestion imparted no benefit. However, the use of slow-release preparations and reports of slow absorption over many hours suggest that activated charcoal might be beneficial in many cases if given several hours after ingestion. Naloxone has been advocated to reverse coma, and L-carnitine has been given to prevent hepatotoxicity, however there is little objective evidence to support their routine use in sodium valproate overdose.

Although rapid correction of serum VPA levels with renal replacement therapies have been advocated in severe overdose of sodium valproate, in the case reported, cerebral oedema was not directly related to serum VPA levels, and CVVHDF was not associated with any clinical benefit. We believe that the place of renal replacement therapies in the management of sodium valproate overdose is not clearly defined.

REFERENCES