Case Report

Effectiveness of hemodialysis in a case of severe valproate overdose

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Abstract

A case of severe sodium valproate overdose is presented in which medicinal management failed to reverse coma of the patient. High-flux hemodialysis was then used to eliminate sodium valproate. This case demonstrated the effectiveness of hemodialysis in not only decreasing valproate levels very rapidly but also as an effective anti-coma management.

Keywords: Anti-coma management, high-flux hemodialysis, hyperammonemia, valproate overdose.

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Introduction

Valproic acid (VPA) is currently not only used in epilepsy treatment but also in the treatment of bipolar disorders and migraine prophylaxis.[1] Although some side effects of VPA are not dose-dependent, toxic effects are associated with daily doses above 1,800 mg and blood levels above 100 µg/ml.[2] Prospective studies are lacking with regard to the management of poisoned patients, and the available data are mainly from case reports or small retrospective studies. We present a case of sodium valproate overdose where hemodialysis was used because of rapid clinical deterioration and a serum VPA level greater than 1,000 µg/ml.

Case Report

A 21-year-old man with a history of bipolar disorder, who was on sodium valproate 400 mg twice a day since 3 years, had an alleged history of consumption of about 30 g sodium valproate (150-170 tablets, 200 mg each). He complained of headache 1 hour later and was shifted to a government hospital where gastric lavage with activated charcoal 50 g was done. He became agitated and drowsy 4 hours after the episode and was shifted to our hospital for further management. On examination, the patient was comatose and not responding to painful stimuli with Glasgow Coma Scale (GCS) 6/15 (E1V2M3), pupils bilaterally constricted, 1 mm, sluggishly reacting to light with plantars flexor, respiratory rate was 10-12/min, SpO_2 92% on 10 L of oxygen with face mask, ABG showing acute respiratory and metabolic acidosis and pO_2 52 mm Hg [Table 1]. His blood sugar was 62 mg%, so 25% dextrose 100 ml was administered. The patient was intubated with 8.0 mm portex endotracheal tube and put on volume-controlled ventilation with tidal volume 8 ml/kg, respiratory rate 18/min and FIO_2 0.5. The SpO_2 level increased to 98%, with ABG showing correction of respiratory acidosis and pO_2 98 mm Hg [Table 1]. His heart rate was 118/min and blood pressure in the right forearm was 84/60 mm Hg. He was given fluid bolus of 1 L normal saline, after which his blood pressure increased to 102/64 mm Hg. His other systemic examination had normal findings.

The patient was injected naloxone 1.5 mg IV stat, and 0.5 mg repeated every 10 min for a total of 12 mg, but his comatose condition persisted. Nine hours after ingestion, his valproate levels were 1,060 µg/ml (normal, 50-100) and serum ammonia 98 µg/dl (normal, 9-33). He

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Table 1: ABG.

ABG	On admission	Post intubation	After hemodialysis	Day 2 on T piece	Post extubation
pH	7.14	7.29	7.41	7.46	7.42
pCO_2 mm Hg	68	38	39	36	42
pO_2 mm Hg	52	98	90	84	86
HCO_3 mEq/l	17	18.6	23	25	24
Lactate (0.7-2.1 mEq/l)	2.2	1.9	1.2	1.1	1.1
Anion gap	31	29	10	5	5
Osmolar gap	28	28	12	NA	NA

NA - Not Available

Table 2: Valproate levels

	Pre-Hemodialysis	Post-Hemodialysis	Day 2	Day 3	Day 4
Valproate level μg/ml (reference range, 50-100)	1,060	200	108	65	46

Table 3: Investigations

	Day 1	Day 2	Day 3
Hemoglobin (11.5-15.5 g/dl)	14.3	13	14
Total leucocyte count (TLC) (400-11,000 mm^3)	7,800	11,900	7,900
Platelet count (1.5-4.0 109/L)	2.0	1.28	1.05
International Normalised Ratio (INR) (0.8-1.2)	1.1	-	-
Partial thromboplastin time (PTT) test / control (sec)	27.1/33	-	-
Blood urea/ Serum creatinine (10-50/0.5-1.3 mg/dl)	22/1.2	42/1.2	-
Sodium/potassium/calcium (135-145/3.5-5.0/8.4-10 meq/L)	153/4.6/11	149/3.4/8.9	141/4.1
Uric acid (3-7.6 mg/dl)	6.8	4.9	-
Serum bilirubin total (0.2-1.0 mg/dl)	0.2	1.3	-
Aspartate aminotransferase/Alanine aminotransferase (AST/ALT) (5-40/5-40 IU/L)	28/25	15/16	-
Serum ammonia μg/dl (normal, 9-33 μg/dl/L)	108	28	14
Alkaline phosphatase (normal, 39-117 U/L)	74	75	-
Blood sugar random (mg/dl)	118	132	116

was started on l-carnitine with 5-g bolus IV followed by 750 mg four hourly for 24 hours. Urgent high-flux hemodialysis (HD) with FX80 dialyzer (helixone, 1.8 m^2, Fresenius Medical Care), blood flow rate 350 ml/min and ultrafiltration rate 450 ml/hr for duration of 4 hours was performed, using right femoral venous access. Post dialysis, his valproate levels dropped to 200. His other investigations are shown in Table 3.

Post dialysis, he became more conscious and was extubated after about 24 h of admission to hospital. He was observed closely for any deterioration in consciousness along with valproate levels [Table 2] and serum ammonia levels [Table 3]. His oral feeding was started on the 3rd day and was discharged to high-dependency unit the next day. His psychiatric counselling was done on the same day and then discharged on day 5 with advice for regular follow-up to psychiatric out-patient department (OPD).

Discussion

VPA is an 8-carbon 2-chain fatty acid mainly used as primary and adjuvant drug in epilepsy treatment. Recently, it has also been finding use in acute and maintenance therapy of bipolar disease, for migraine prophylaxis and as adjunctive therapy for treatment of alcohol and other sedative-hypnotic withdrawal syndromes.[3]

Mechanism of therapeutic action and toxicity

VPA increases the levels of gamma-amino butyric acid (GABA) and prolongs the recovery of inactivated sodium channels, thereby causing central nervous system (CNS) depression. This may partially contribute to its anticonvulsant activity. VPA may also cause impairments in fatty-acid metabolism and disrupt the urea cycle, leading to hyperammonemia.[3]

VPA is well absorbed from the gastrointestinal tract. However, time to maximum concentration (T_{max} and C_{max}), which represents the rate of absorption, depends on the preparation from VPA syrup (34.2 mg/L, 0.9 h) and VPA capsule (31.4 mg/L, 2.2 h) to enteric-coated delayed-release tablet (26.0 mg/L, 3.4 h) and finally, extended-release tablet (11.8 mg/L, 19.7 h).[4] In our case, the patient took enteric-coated delayed-release preparation, and thus he started deteriorating after 4 hours of ingestion, and serum levels taken 9 hours after ingestion were very high.

VPA is a small molecule (MW 144.2) and is highly protein bound (85-90%). It has a half-life of 10-20 hours (mean, 15 h) and has an apparent volume of distribution (Vd) that is in the range of 0.1-0.4 L/kg, at therapeutic levels. After an overdose, at serum concentrations of more than 300 μg/mL, protein-binding sites are saturated and only 35% binds to protein, increasing the free fraction of VPA and Vd.[4] Low molecular weight and decreased protein binding during toxicity make valproate make it ideal for removal through extracorporeal circulation. Hemodiafiltration (HDF) and high-flux HD are effective in reducing serum valproate levels during valproate toxicity.[5,6]

VPA overdose most commonly presents with nausea and vomiting closely followed by CNS symptoms of headache, ataxia, decreased level of consciousness, confusion and coma. With serum levels more than 850 µg/ml, hypotension, cardiac arrest, respiratory depression requiring intubation has been reported.[4] The coma is multifactorial, with the contributory factors including hyperammonemia, high anion gap lactic acidosis, direct sedative effects, cerebral edema and mitochondrial dysfunction.[7] Pancreatitis, elevated hepatic transaminases and bone marrow suppression may complicate both overdose and therapeutic dosing. Laboratory manifestations include hypernatraemia (sodium salt of valproate), hypocalcaemia, hyper or hypophosphataemia, high anion and osmolar gap. Our patient showed hypernatraemia, high anion and osmolar gap.

Cerebral edema is a delayed presentation and usually occurs 48-72 hours after ingestion, even as serum levels are decreasing. The disruption of the osmotic gradient, caused by elevated serum ammonia levels is thought to be the precipitating cause of the edema.[3] Our patient did not show secondary deterioration, may be due to early institution of hemodialysis, and hence correction of hyperammonemia.

The management of sodium valproate overdose remains largely supportive. Oral activated charcoal 1 mg/kg can be administered to reduce gastrointestinal adsorption, especially if presented within the first hour.[3] In our patient, charcoal 1 mg/kg was used.

Medical management for coma using naloxone and l-carnitine has been described in isolated case reports.[8,9] Naloxone acts as a GABA antagonist. Our patient did not show any improvement with naloxone.

Long-term use of VPA is associated with depletion of serum carnitine levels. l-Carnitine supplementation is indicated in patients with concomitant hyperammonemia, encephalopathy, and/or hepatotoxicity.[3,9] We used l- carnitine in our patient.

Hemodialysis, haemoperfusion, and a combination of the two, all appear to effectively reduce the serum levels of valproate. VPA because of its low molecular weight (144.2) is highly dialysable, which is partially opposed by its high protein binding. In a meta-analysis, it was found that low-efficiency or low-flux HD removes only 20% of administered dose at therapeutic levels.[10] However, in toxic levels due to saturation of plasma protein binding sites, clinically significant removal of valproate can be done with dialysis.[4] High-flux HD and HDF are effective in reducing serum valproate levels both during toxic and therapeutic states.[5,6,11]

Recommended indications for renal replacement therapy during sodium valproate intoxication are plasma levels above 700 µg/ml, rapid clinical deterioration, evidence of hepatic dysfunction, and continued drug absorption.[3] In our patient, we used high-flux HD without haemoperfusion and found significant drop in both serum valproate and serum ammonia levels.

In conclusion, the use of renal replacement therapies seems the most effective treatment for valproate overdose and should be strongly considered besides other supportive therapies in a patient with refractory coma and serum valproate levels above 700 µg/dl.

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