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Combining Extracorporeal Elimination with Carbapenems in a Patient with Severe Valproic Acid Toxicity: A Case Report

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Abstract

Introduction: Valproic acid (VPA) toxicity causes a wide range of neurological manifestations, spanning from mild lethargy to life-threatening cerebral edema. Extracorporeal elimination, mainly hemodialysis enhances plasma clearance of VPA. Meanwhile, Carbapenems interact with VPA leading to reduction in its plasma concentration. Previous cases reported utilizing either one of these two modalities in VPA toxicity. In this case, we combined the use of both hemodialysis and carbapenem antibiotic in treating a patient with severe VPA poisoning.

Case Report: A 41-year-old male brought to the emergency department after being found unresponsive in his room. He was in deep coma with Glasgow Coma Scale (GCS) 3/15. He was intubated and placed on mechanical ventilator. Physical examination revealed loss of all brainstem reflexes. He was shifted to the medical intensive care unit. Blood test showed unquantifiable high serum VPA concentration >4000 umol/L (Therapeutic Range: 350 - 690 umol/L). Hemodialysis was done and 1-gram ertapenem was administered. Later on, day 1, patient started to breathe over the ventilator. On day 2, patient underwent another session of hemodialysis and another dose of ertapenem was given. He became fully awake, with GCS 15/15 and valproate level came down to 1760 umol/L then later day 2 to 800 umol/L. The patient was successfully extubated, and history was taken which revealed that he took 300 tablets of 500 mg valproic acid (total 150 g) for suicidal attempt.

Conclusion: Carbapenems may add additional benefit to extracorporeal elimination in patients with life threatening valproic acid toxicity. Further studies are needed to establish the role of carbapenem in VPA poisoning.

Keywords: Valproic acid; Extracorporeal elimination; Carbapenems; Toxicity; Drug interaction

Abbreviations: VPA: Valproic Acid; GABA: Gamma-Aminobutyric Acid; CPMs: Carbapenem Antibiotics; ED: Emergency Department; GCS: Glasgow Coma Scale

Introduction

Drug overdose toxicity is considered one of the most common causes of morbidity and mortality all over the world [1,2]. 2016 annual report of the American Association of poison control center's stated that 8.4% of the patients exposed to drug overdose required hospitalization, and 4.8% of them admitted to the intensive care unit. Among adults, analgesics were the most common group of medications accounted for overdose toxicity by 12%, followed by sedatives/hypnotics and antidepressants which counted for almost 10%, 7% of the total exposures, respectively [3]. Moreover, sedatives/antipsychotics were accounted for the highest incidence of fatalities [3].

Valproic acid (VPA) is a branched-chain carboxylic acid act by enhancing gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter [4]. VPA was introduced in the United States in 1978 as an anti-epileptic for partial and generalized seizure. Later, VPA therapeutic indications extended to include treatment for acute mania, bipolar disorder, and migraine headache. VPA therapeutic serum concentration range from 350 to 700 µmol/L (50 to 100 mg/l) [5].

VPA toxicity manifested by a wide range of neurological manifestations ranged from mild lethargy and drowsiness, extended to life threatening cerebral edema. Additionally, severe VPA toxicity may be associated with hyperammonemia, metabolic acidosis, hypotension and/or respiratory depression [6,7]. Several case reports showed successful treatment of VPA toxicity with extracorporeal elimination [8], especially if VPA concentration is above (>6250 µmol/L (900 mg/L). Furthermore, few case reports showed successful treatment of VPA toxicity patient with carbapenem antibiotics (CPMs) utilizing the previously known drug interaction between VPA and carbapenems [9-11]. As per our best knowledge this is the first case reporting the use of these two modalities combined (besides the usual supportive care) in treatment of a patient with severe VPA toxicity.

Case Report

A 41-year-old male south Asian patient recently landed in Qatar working as construction laborer brought to the emergency department (ED) by ambulance after finding him unresponsive in his room as per patient roommate. The roommate gave a history that the patient took sodium valproate tablets (amount unknown at that time) and he brought a strip of the drug with him. Additionally, he gave a history of heroin addict back in patient's country and previous hospital admission for the addiction. No history of trauma or seizures.

In emergency department (ED), the patient was found to be deeply comatose with Glasgow Coma Scale (GCS) 3/15 and equal pinpoint non-reactive pupils with no neck rigidity. Patient was intubated immediately to secure his airway and placed on mechanical ventilator. Vital signs upon admission were blood pressure of 118/74 mmHg, heart rate of 112 beats /min, temperature of 36°C and respiratory rate of 21 breath/minute, and oxygen saturation of 95% on room air. Physical examination showed that all brainstem reflexes were lost and he didn't show any triggering on mechanical ventilator, no jaundice or

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any skin rash, cardiovascular, lungs and abdominal examination were unremarkable. Multiple naloxone doses were given in view of suspicion of opioid toxicity with no improvement noted in his GCS.

The patient remained hemodynamically stable and was shifted directly to the Medical intensive care unit for further care. Blood tests were sent which revealed normal results of complete blood count, liver/kidney functions and electrolytes apart from Serum valproic acid (VPA) level came to be undetected >4000 umol/L (Therapeutic Range: 350-690 umol/L). Arterial blood gas analysis showed mixed metabolic and respiratory acidosis with an anion gap of 16 and ammonia of 79 umol/L (normal 21-71 umol/L). An urgent computed tomography was ordered and showed no gross intracranial abnormalities. After the results of VPA came, a single dose of charcoal 50 grams was given through nasogastric tube, a double-lumen internal jugular was inserted and hemodialysis was started for 2 hours. Additionally, patient also received 6 grams of L-carnitine as loading then 3 grams every 8 hours with 1 gram of ertapenem given daily. Repeated VPA level on day 1 still shown >4000 umol/L. Later on day 1, the patient starts to cough with suctioning and also starts triggering the ventilator.

On day 2 early morning patient underwent another session of hemodialysis for 5 hours and another dose of ertapenem with the continuation of L-carnitine. The patient became fully awake, obeying commands with GCS 15/15 and his VPA level came to be 1760 umol/L then later on day 2, came down to 800 umol/L. Patient was extubated successfully and when we took the history in detail he confessed that he took 300 tablets of VPA 500 mg (150 grams) for suicide. Patient said that he tried to suicide because of financial problems. On day 6, repeated level came to be 123 umol/L (Figure 1).

The patient was seen by the psychiatrist and transferred from the intensive care unit to the psychiatry hospital on day 5 for further assessment and care. On day 7, valproic acid 500 mg once daily was restarted. After being mentally stable for 2 the patient was discharged home with follow up in the psychiatry outpatient clinic.

Discussion

Retrospective studies showed a reduction in valproic acid (VPA) serum level upon the addition of Carbapenem antibiotics (CPMs) to patients taking valproic acid products. Meropenem, ertapenem, and imipenem caused up to 82%, 72% and 51% reduction in VPA serum concentration respectively [12]. Seizure incidence has been also reported with the combined use of VPA and CPMs secondary to decrease activity of VPA [13]. Rapid and significant fall in VPA serum concentration occurred within few days reaching to sub-therapeutic concentrations after starting on a CPM antibiotic [14]. After discontinuation of the culprit CPM; VPA levels normalized usually within days, and in some patients, it may take up to 2-4 weeks [15].

Mechanisms of VPA-carbapenem interaction are not clear yet, however the main hypothesis is decrease in enterohepatic recirculation (enteric hydrolysis) of valproate glucuronide [16]. Other potential mechanisms are reduced intestinal absorption [17], increase in glucuronidation of VPA [18] and increase in valproate glucuronide renal clearance [19]. Notably, concomitant use of VPA and meropenem for almost 2 weeks did not cause apparent interaction in a patient with cirrhosis. Reduced hepatic glucuronidation and biliary drug secretion because of hepatic impairment led to reduced VPA clearance and so antagonizing the carbapenem effect [20].

On the other side, several cases were reported about the intentional use of this interaction in the treatment of VPA overdose [9,10].

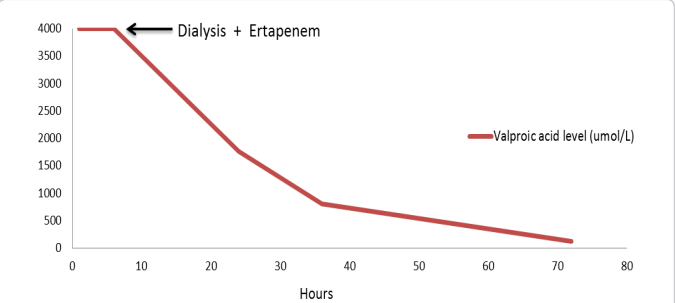

Figure 1: Effect of dialysis plus ertapenem on valproic acid level.

Khobrani et al. have reported the intentional use of meropenem in an intubated unresponsive patient with VPA overdose, which showed successful neurologic recovery and rapid VPA serum level reduction [9]. In another reported case, a patient with altered mental status who was found to have elevated VPA serum concentration. Ertapenem was used among other general measures e.g. charcoal administration. Like the previous case report; this patient's mental status improved and VPA serum level was significantly decreased [10].

Although no clinical studies were conducted to evaluate the use of extracorporeal elimination in VPA toxicity, many case reports showed the effectiveness of either hemodialysis or hemofiltration in treating severe VPA toxicity cases [21-24]. Owing to the small molecular weight of VPA (144 daltons), extracorporeal elimination considered the treatment of choice in severe VPA toxicity in severe valproic acid toxicity defined as serum VPA concentration >1300 mg/L (9000 µ mol/L), presence of cerebral edema and/or shock [25].

In the present case, patient was comatosed with unrecordably high VPA serum concentration treated by simultaneous use of hemodialysis and a carbapenem (ertapenem). Complete neurologic recovery from baseline coma status in addition to significant reduction of VPA serum concentration from unquantifiable high value may be attributed to the combined use of extracorporeal elimination and carbapenem antibiotic. Further systematic studies are needed to clearly identify the role of VPA-carbapenem interaction in the management of VPA toxicity either individually or combined with extracorporeal elimination.

Conclusion

Carbapenems may add additional benefit to extracorporeal elimination in patients with life threatening valproic acid toxicity. Further studies are needed to establish the role of carbapenem in VPA poisoning.

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