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Use of Meropenem to Treat Valproic Acid Overdose

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Keywords: Meropenem, Carbapenem, Valproic Acid, Divalproex, Overdose, Toxicity

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Use of Meropenem to Treat Valproic Acid Overdose - Abstract

Overdose of valproic acid (VPA) or its derivatives can cause significant toxicities such as hyperammønemia or altered mental status. While levocarnitine has been used historically to manage VPA-associated hyperammonemia, no standard of therapy exists to manage VPA toxicity. We present a case of VPA overdose managed with meropenem in addition to levocarnitine. A 38-year old female presented to the emergency department after intentionally ingesting 20 tablets of extended release divalproex sodium. She received a 4-gram loading dose of levocarnitine. She developed altered mental status, and a repeat VPA level yielded a result of 278 µg/mL. She was given 1 gram of meropenem and her subsequent VPA level was 193 µg/mL. Approximately eight hours after the initial dose, another 1 gram of meropenem was administered. Additionally, she received 1 gram of levocarnitine every four hours for a total of six doses. A repeat VPA level returned at 62 µg/mL. The patient was transferred to the intensive care unit for further management. Carbapenem antibiotics inhibit acylpeptide hydrolase in the gastrointestinal tract. Inhibition of this enzyme prevents the reabsorption of metabolized VPA and therefore causes increased elimination. Our patient demonstrated a rapid lowering of VPA levels after administration of meropenem.

Keywords: Meropenem, Carbapenem, Valproic Acid, Divalproex, Overdose, Toxicity

Use of Meropenem to Treat Valproic Acid Overdose – Main Text

Introduction:

Valproic acid (VPA[1]) and its derivatives are often used to treat neurological and psychiatric conditions such as seizure disorders and bipolar disorder[1]. Overdose of VPA and its derivatives can have significant repercussions including cerebral edema, hyperammonemia, and respiratory depression[2]. Current literature has described the use of carnitine supplementation to treat VPA-associated hyperammonemia; however, no standard of therapy for treatment of VPA overdose has been established[3]. Carbapenem antibiotics have been reported to lower VPA levels and use of VPA with these agents is contraindicated due to likely VPA failure[4-8]. We present a case of a woman with intentional VPA overdose who was given meropenem in addition to levocarnitine.

Case Description:

A 38-year-old woman with a past medical history of bipolar disorder presented to the emergency department (ED). The patient reports having auditory hallucinations compelling her to commit suicide for the past three days. Empty prescription bottles of multiple VPA formulations were brought by emergency medical services, however, the patient reports taking approximately 20 tablets of quetiapine and 20 tablets of extended release divalproex sodium roughly 45 minutes prior to coming to the emergency department.

Her vitals on presentation included a blood pressure of 127/81 mmHg, heart rate of 101 beats/minute, respiratory rate of 24 respirations/minute, and oxygen saturation

[1] VPA – Valproic Acid

of 96% on room air. Her measured weight was 119.1 kg. Her initial laboratory workup revealed a VPA level of 82 µg/mL and undetectable ammonia level (Figure 1). Her liver function tests were within normal limits. Her urine toxicology screen was negative for illicit substances, alcohol, aspirin, and acetaminophen. An electrocardiograph revealed normal sinus rhythm with a QRS interval of 66 milliseconds and a QTc of 433 milliseconds.

At initial presentation, the patient's mental status was intact, and she was alert and oriented. Upon examination, she was found to be diaphoretic, anxious, and expressing suicidal thoughts and ideation. The patient received 50 grams of activated charcoal by mouth. Subsequently, the patient's mental status deteriorated and sequential workup yielded an elevated VPA level of 278 µg/mL. Meropenem 1 gram was administered intravenously (IV). Three hours after administration, a serum VPA level of 193 µg/mL and an ammonia level of 41.1 µMol/L were detected. In addition, the patient was given a loading dose of 4 grams (33 mg/kg) of IV levocarnitine. Another 1-gram dose of IV meropenem was given eight hours after the previous dose. Approximately one hour after the second dose of meropenem was administered, repeat serum levels were obtained and yielded a VPA level of 62 µg/mL and an ammonia level of 51.0 µMol/L. Levocarnitine 1 gram (8 mg/kg) IV every four hours was scheduled for a total of six doses.

The patient was transferred to the intensive care unit. No further doses of meropenem were given. Nearly 24 hours after presentation to the ED, her VPA level was 12 µg/mL and her ammonia level was 34.0 µMol/L. The patient was managed by the

critical care team for the remainder of her hospitalization. After five days of hospitalization, she was transferred to an inpatient psychiatric facility.

Discussion

VPA and its metabolites are heavily metabolized in the liver, conjugated with glucuronic acid, and eliminated through bile[9]. The presence of acylpeptide hydrolase enzyme in the gastrointestinal tract removes the glucuronic acid group from VPA and causes reabsorption and recycling of the drug after metabolism leading to a longer half-life and consistent serum concentrations[9]. Carbapenems have been proposed to irreversibly inhibit the activity of the acylpeptide hydrolase enzyme therefore preventing reabsorption of VPA[10]. This leads to increased elimination, shorter half-life, and lower serum concentrations[4]. All carbapenems show this interaction; however, the extent of VPA lowering appears to be lowest with imipenem[4-7]. Higher daily doses of meropenem have not been shown to have an increased effect in lowering VPA serum concentrations[5]. Because carbapenems irreversibly inhibit acylpeptide hydrolase, administering a higher dose of VPA to re-establish serum concentrations is not advised. A minimum of seven days after cessation of meropenem is needed to see an increase in VPA levels[5]. Limited literature is available to outline the optimal use of carbapenem antibiotics in the setting of VPA overdose. In our case, meropenem was chosen due to formulary status. Higher doses of carbapenems have not been shown to have a greater effect in lowering VPA serum concentrations[6-7]. This effect has also been shown to be independent of VPA daily dosage or baseline VPA serum concentration[5-7].

Conclusion

Management of valproic acid in the setting of overdose has not been fully established. We present a unique case of utilization of meropenem to acutely lower VPA serum concentrations after an intentional overdose. Our patient demonstrated rapid lowering of VPA serum concentrations after administration of two 1-gram doses of meropenem. While unconventional, use of carbapenem antibiotics may provide a new avenue in managing VPA overdose and toxicity.

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Figure 1: Laboratory Progression of Valproic Acid Overdose

Caption: Time course of valproic acid and ammonia levels in correlation with meropenem administration

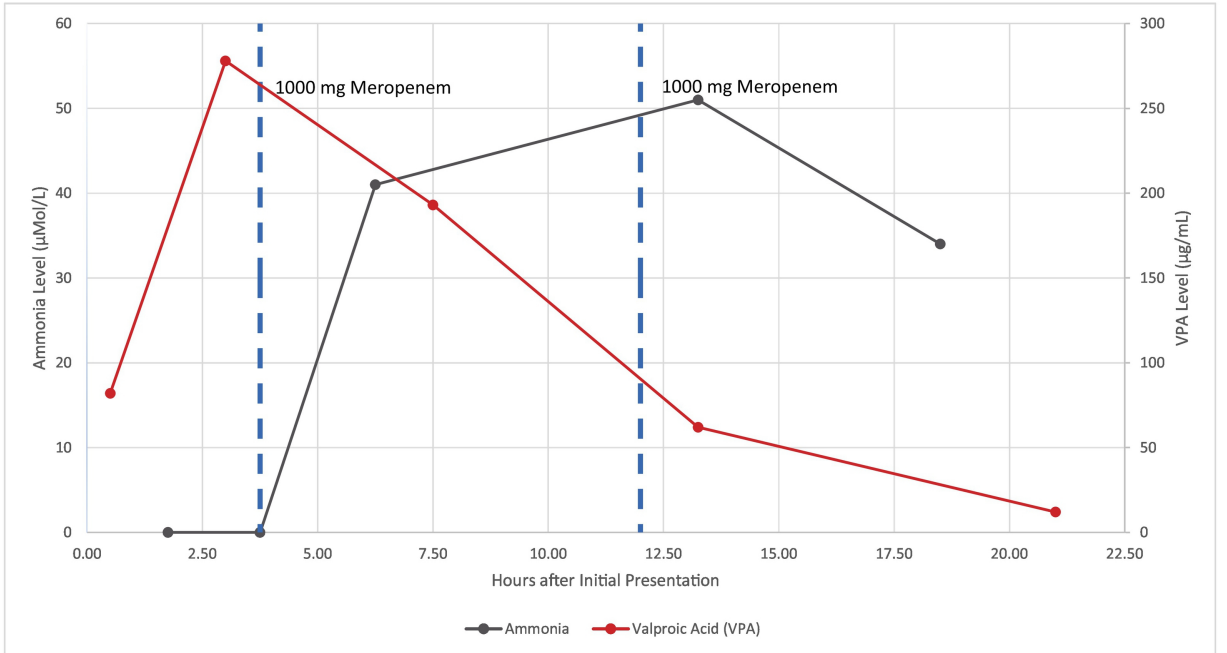
1000 mg Meropenem
1000 mg Meropenem
Ammonia Level (µMol/L)
VPA Level (µg/mL)
Hours after Initial Presentation
Ammonia
Valproic Acid (VPA)
0
10
20
30
40
50
60
0
50
100
150
200
250
300
0.00
2.50
5.00
7.50
10.00
12.50
15.00
17.50
20.00
22.50

Figure 1