THE USE OF ERTAPENEM FOR REDUCING TOXIC VALPROIC ACID CONCENTRATIONS

Patrick Dougherty, PharmD, BCPS, BCEMP[1]; Lauren Antal, PharmD[2]

[1]TidalHealth Peninsula Regional, Salisbury, MD; [2]University of Maryland Eastern Shore School of Pharmacy and Health Professions, Princess Anne, MD

Background

• Valproic Acid (VPA) overdoses commonly cause central nervous system (CNS) depression and hyperammonemia, with more severe effects possible, including bone marrow suppression, cerebral edema, and coma.[1-5]
• Typical management consists of supportive measures, administration of levocarnitine for hyperammonemia, and renal replacement therapy (RRT).[1-5]
• Carbapenems interact with VPA by inhibiting the enzyme acylpeptide hydrolase, which causes an enhanced elimination of VPA from the body.
• Presented are two cases where administering ertapenem significantly reduced elevated VPA concentrations in addition to other standard therapies.

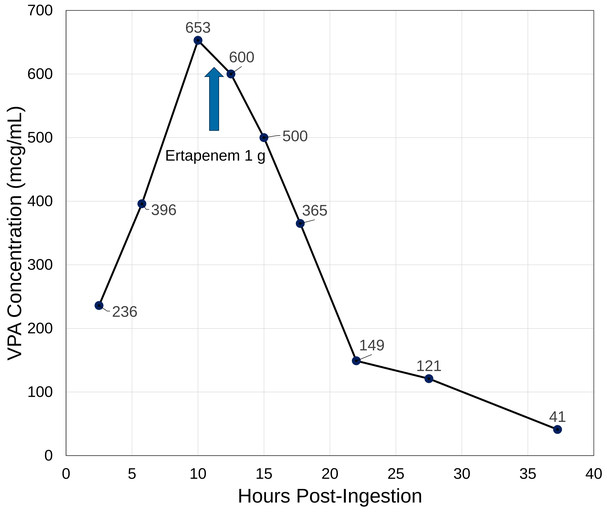
Case Reports

• 1. 28 year-old male, history of bipolar disease, blindness, & suicidal ideation, intentionally ingested 30-40 tablets each of haloperidol 5 mg and divalproex sodium EC 500 mg in a suicidal gesture 2 hours prior to ED arrival
• Levocarnitine 72.7 mg/kg loading and 15 mg/kg maintenance doses every 4 hours
• Ertapenem 1 g 11 hours after arrival (12.5 hours post-ingestion)
• VPA concentrations 500 and 365 mcg/mL two and five hours after administration of the ertapenem
• Discharged to psychiatric service; length of medical stay: 3 days

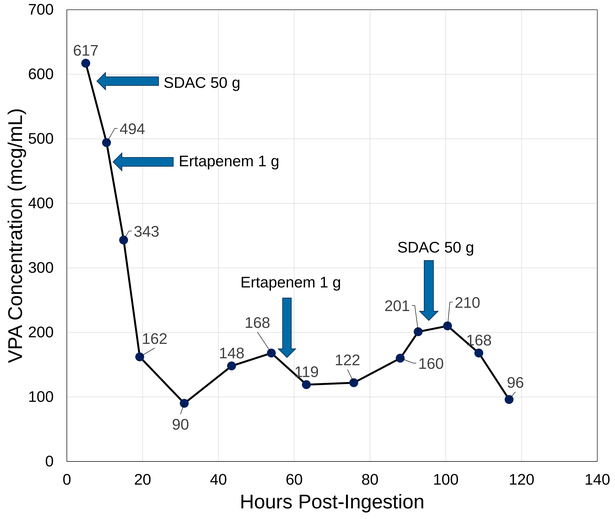
• 2. 61 year-old female, history of bipolar disorder, atrial fibrillation, sick sinus syndrome, and COPD intentionally ingested approximately 200 tablets of divalproex sodium ER 500 mg in a suicidal gesture 5 hours prior to ED arrival
• Previous history of hyperammonemia from therapeutic VPA dosing
• Unresponsive, hypothermic, hypotensive, and bradypneic requiring IV fluid, external warming, and endotracheal intubation in the ED
• SDAC administered twice: 6 & 96 hours post-ingestion
• Levocarnitine 90.4 mg/kg loading dose & 13.4 mg/kg maintenance doses every 4 hours
• Ertapenem 1 g at 7.5 & 52.5 hours after arrival (12 & 57 hours post-ingestion)
• Repeat VPA concentrations trended down, peaked again at 168 mcg/mL & 210 mcg/mL at 54 & 92 hours post-ingestion
• Ammonia concentrations peaked at 1,311 mcmol/L (15 hours post-ingestion) & 168 mcmol/L (108 hours post-ingestion)
• CRRT & norepinephrine infusion hospital days 2-9
• Hemoglobin 7.6 g/dL, Platelets 19 k/cmm at 92 hours post-ingestion, transfused 1 unit PRBCs & 2 units platelets
• Endoscopy hospital day 8: unremarkable
• Discharged to psychiatric service; length of medical stay: 22 days

Valproic Acid Concentrations & Doses of Ertapenem

Case 1

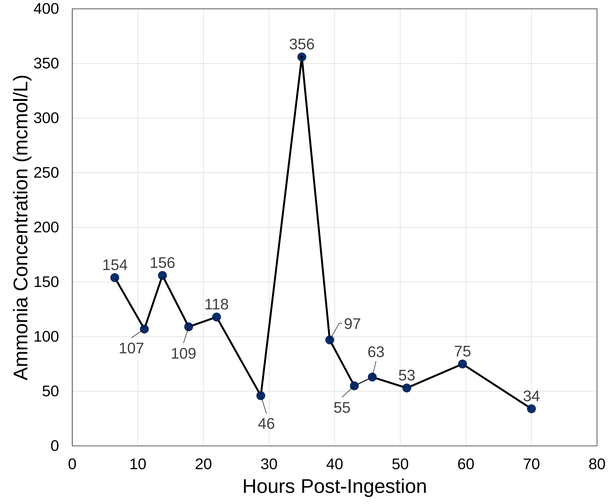


Case 2

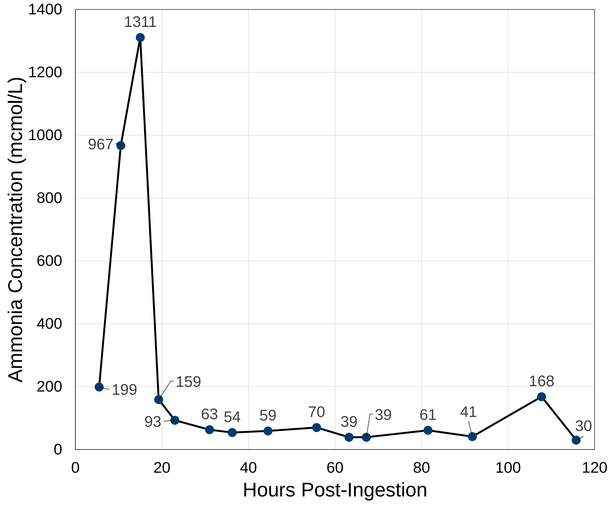


Ammonia Concentrations

Case 1



Case 2



Discussion

• Valproic acid overdose can cause significant toxicity, which requires management with conventional therapies of supportive care and levocarnitine.
• Administering ertapenem in these cases was valuable to help rapidly decrease toxic VPA serum concentrations without significant risk.
• The second peak in VPA concentration was mitigated with a second dose of ertapenem in Case 2.
• A third dose of ertapenem 1 g IV might have mitigated the third peak in Case 2.
• SDAC might have prevented absorption of VPA in Case 1, as well as impacted the second VPA concentration peak in Case 2.
• Overdoses of extended-release divalproex sodium can cause delayed peaks in valproic acid concentrations.
• Overdoses of both enteric-coated and extended-release divalproex sodium can cause delayed peaks in ammonia concentrations.
• Serial laboratory analyses of VPA & ammonia concentrations were trended & assisted with knowing when to re-dose ertapenem and continue with levocarnitine administration.

Conclusion

• In addition to supportive care and levocarnitine for hyperammonemia, a carbapenem should be administered to symptomatic patients with toxic concentrations of VPA.
• More than one dose of the carbapenem may be needed if VPA concentrations rebound.
• Consider administering a dose of the carbapenem whenever the VPA concentrations increase in the setting of an overdose, particularly from ER formulations of divalproex sodium.

References

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