ToxTidbits

Maryland Poison Center
UNIVERSITY OF MARYLAND SCHOOL OF PHARMACY

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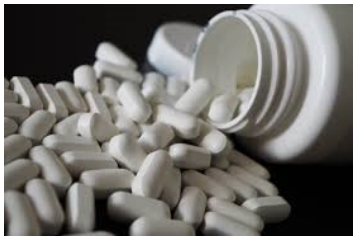
The Maryland Poison Center's Monthly Update: News, Advances, Information

Carbapenems for Valproic Acid Toxicity



Valproic acid (VPA) is an interesting toxin. It's a carboxylic acid (-oic) that is used for seizures, bipolar disorder, and migraine prophylaxis. The most common finding in overdose is coma. Metabolic complications including hyperammonemia, hypernatremia, hypocalcemia, and metabolic acidosis can occur. Beyond supportive care, other key interventions include multidose activated charcoal, l-carnitine, hemodialysis, and possibly carbapenems.

There is a significant interaction between carbapenem antibiotics and valproic acid that is so profound that the interaction is listed as a warning in the prescribing information for carbapenem antibiotics. Multiple case-series have identified a reduction in serum VPA concentrations ranging from 52% to 90% after starting a carbapenem. Associated seizure rates range from 33% to 48% *(Kaohsiung J Med Sci, 2017:130-6; Ther Drug Monitoring, 2012:599-603).* Increasing the dose of VPA is not adequate to overcome the interaction.

Multiple mechanisms of interaction have been postulated, including decreased absorption of VPA, enhanced glucuronidation of VPA by inducing UDP glucuronyl transferase, and reduction of the deconjugation of VPA-glucuronide by inhibiting deconjugation enzymes *(Ther Drug Monitoring, 2016:587-92).* Absorptive changes are possible, but unlikely to be the primary mechanism of action given that the interaction occurs with intravenous or oral VPA. Enzyme induction usually takes days to weeks. Published data suggest that reduction in VPA concentrations of 60 -80% is within 24 hours and the duration of action is up to one-week post discontinuation of a carbapenem *(Ther Drug Monitoring, 2016:587-92*; *J Clin Pharm Ther, 2018:723-5)*. Taken together, the primary mechanism is likely the inhibition of VPA-glucuronide deconjugation resulting in improved fecal elimination.

There is very limited literature on the use of carbapenems for acute overdose of VPA. Most of the data surrounds the drug interaction. In one case report, a patient who overdosed on VPA was given a short course of meropenem for aspiration pneumonia. The half-life of the VPA reduced from 9 hours to 4 hours *(J Clin Pharm Ther, 2018:723-5)*. There are no systematic evaluations or outcomes data for the use in overdose and you are unlikely to find the recommendation in a text book.

The primary concern about the use of carbapenems for VPA toxicity is the risk of seizures from a subtherapeutic serum VPA concentration. It would be reasonable to avoid this combination in a patient receiving VPA for epilepsy, especially considering the long duration of the interaction.

The bottom line: activated charcoal, L-carnitine and dialysis remain standard therapies for VPA toxicity. However, if serious toxicity persists despite these measures, call the Maryland Poison Center for further recommendations including the use of nontraditional treatments.

Jimmy Leonard, PharmD
Clinical Toxicologist

Did you know?

Severe lung illness has been reported with e-cigarette use.

As of September 6th of this year, 450 cases (including 5 deaths) of severe lung illness possibly associated with e-cigarette use have been reported in 33 states, including Maryland. Patients have described a gradual onset of coughing, shortness of breath, and/or chest pain, with some requiring intubation. Vomiting, diarrhea, fatigue, fever, and weight loss have also been reported. Many of the vaping products tested by states or the FDA have been identified as containing tetrahydrocannabinol (THC), a psychoactive component of marijuana. Most of those samples also contained Vitamin E acetate, an oil. Currently, it's not certain what specific products or chemicals are causing the illnesses.

When patients present with pulmonary illness of unclear etiology, ask about the use of e-cigarettes. Report all suspected cases to the poison center and your local health department. CDC guidelines can be found at **https://emergency.cdc.gov/han/han00421.asp** .

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