IOWA POISON CONTROL CENTER

Poison HOTLINE

1-800-222-1222

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Did you know ……

There is a national critical shortage of IV lorazepam. Due to this, there is now a shortage of IV diazepam. The IPCC commonly recommends benzodiazepines (BDZs) for many symptoms including seizures, hypertension, tachycardia, and agitation.

To preserve the remaining IV BDZ supply, the IPCC will be recommending the use of oral BDZs such as lorazepam or diazepam for more minor symptoms for the time being. For patients who are unable to take oral medication and require IV sedation or who have more severe symptoms, the IPCC will now be recommending the use of IV phenobarbital.

For patient specific treatment recommendations for your poisoned patient, please call the IPCC at **1-800-222-1222**.

POISON Help 1-800-222-1222

Carbapenems for Valproic Acid

Traditional treatment of valproic acid (VPA) toxicity has historically been primarily supportive care with the addition activated charcoal, levocarnitine, and/or hemodialysis in some cases. Carbapenems may have a role in the treatment of VPA overdoses. To understand the role of carbapenems, particularly meropenem and ertapenem, VPA's enterohepatic circulation must be understood.

VPA Absorption and Enterohepatic Circulation
VPA is metabolized in the liver through conjugation with glucuronide. VPA-glucuronide is then excreted through urine and bile. A gastrointestinal enzyme, acylpeptide hydrolase, can separate VPA-glucuronide and allow the VPA to be reabsorbed from bile in the gastrointestinal tract.

The Effects of Carbapenems on VPA
Carbapenems have been shown to inhibit acylpeptide hydrolase. This prevents the breakdown of VPA-glucuronide into VPA and prevents its reabsorption thereby inhibiting enterohepatic circulation. This increases the rate of VPA elimination.

Clinical Implications
Research suggests this interaction causes a reduction in the level of VPA within 24 hours after administration of a single dose of meropenem can result in a decreased duration of hospitalization.

Obstacles and Future Research
This is an off-label use of meropenem and ertapenem - an ongoing clinical trial in phase 4 underway with the goal to evaluate VPA toxicity as a new FDA approved indication for meropenem. The interaction between VPA and carbapenems can last up to a week; subtherapeutic levels and seizures are a potential risk in patients receiving VPA for epilepsy. Of note, some hospitals require infectious disease approval of administration of carbapenem antibiotics.

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References:
Caitlin Thomas, James Priano, Tracey L. Smith. Meropenem as an antidote for intentional valproic acid overdose, The American Journal of Emergency Medicine, Volume 38, Issue 3, 2020, Pages 690.e1-690.e2.
Nguyen, P., Chevillard, L., Gouda, A.S. *et al.* L-carnitine does not improve valproic acid poisoning management: a cohort study with toxicokinetics and concentration/effect relationships. *Ann. Intensive Care* **12,** 7 (2022).
Thomas C, Priano J, Smith TL. Meropenem as an antidote for intentional valproic acid overdose. Am J Emerg Med. 2020 Mar;38(3):690.e1-690.e2. doi: 10.1016/j.ajem.2019.09.011. Epub 2020 Jan 8. PMID: 31980292.

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