Drug Monitor

Brain Death After Valproic Acid Overdose

Case series suggest that severe complications rarely result from overdoses of valproic acid, especially with ingestions of less than 400 mg/kg and peak serum levels below 450 µg/mL. So it was unusual, say physicians from the University of California, Davis, when a 19-year-old man died of cerebral edema after taking an intentional overdose of extended-release valproic acid (333 mg/kg), venlafaxine (3 g), and risperidone (60 mg).

Upon initial evaluation, approximately 90 minutes after the overdose, the patient was lethargic but awake. Electrocardiography and chest radiography results were normal. He was given 50 g of activated charcoal with sorbitol.

At this time, his valproic acid level was 305.4 µg/mL and his ammonia level was 379 µg/dL. By 11 hours postingestion, the ammonia level had dropped to 76 µg/dL, but six hours later it had risen again to 193 µg/dL. Despite lactulose therapy, the ammonia level continued to climb, spiking from 338 µg/dL at 48 hours to 1,191 µg/dL at 65 hours.

At 90 hours, the ammonia level was back down to 117 µg/dL but the patient's overall condition had deteriorated. By 110 hours, he had fixed, dilated pupils and extensor posturing. A computed tomography scan showed cerebral edema and possible tentorial herniation. He was pronounced brain dead at 120 hours.

The role of the coingestants in this reaction was uncertain, say the physicians. While combinations of valproic acid and other antiseizure drugs have been linked to hyperammonemic encephalopathy, risperidone and venlafaxine haven't.

The physicians say this case reinforces the importance of ongoing gastric decontamination in patients with valproic acid levels that persist or increase after acute overdose. They support previous endorsements of carnitine supplementation—though they add that this substance isn't always stocked in sufficient quantities to supply the recommended doses.

Source: *Ann Emerg Med*. 2005;45:337–338 (letter).

Post-PCI Fluvastatin for Diabetics

The recent Lescol Intervention Prevention Study (LIPS) demonstrated that long-term statin therapy significantly reduces major adverse cardiac events following a first successful percutaneous coronary intervention (PCI). Since patients with diabetes are well known to be at higher risk for cardiac problems than are nondiabetic patients, the LIPS researchers performed a subgroup analysis comparing patients with and without diabetes—with dramatic results. They found that fluvastatin essentially negates the rise in cardiac risk caused by diabetes after PCI.

Of 1,677 patients, 844 received fluvastatin (120 with diabetes and 724 without) and 833 received placebo (82 with diabetes and 751 without). Among placebo patients, diabetes nearly doubled the risk of major adverse cardiac events after PCI. By contrast, the risk was about the same for diabetic and nondiabetic patients taking fluvastatin. Overall, fluvastatin reduced cardiac risks by roughly 50% in diabetic patients.

The researchers stress that, while the drug's benefits were sustained for several years, they took about 18 months to appear, suggesting that prolonged therapy is needed to slow atherosclerotic progression in this high risk group.

Source: *Am Heart J*. 2005; 149:329–335.

Drug-Disease Interactions in Elders

Four in 10 frail, elderly inpatients are at risk for drug-disease interactions, say researchers from the VA's multicenter Geriatric Evaluation and Management (GEM) trial. Among the 397 subjects, the most common potential interactions were between calcium channel blockers (CCBs) and heart failure (12.3%), beta-blockers and diabetes (6.8%), aspirin and peptic ulcer disease (5.5%), beta-blockers and peripheral vascular disease (PVD) or Raynaud disease (5.5%), and beta-blockers and chronic obstructive pulmonary disease (5.3%). The risk of interaction was higher for patients aged 75

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or older and those with multiple comorbidities—even after the researchers controlled for other characteristics, including number of drugs.

The researchers note that the clinical significance of some interactions may be questionable. In some cases, the dangers could be mitigated by using certain drugs within the class (such as the newer dihydropyridine CCBs) or by coprescribing other drugs (such as gastroprotective agents along with aspirin). And for some elders with diabetes or PVD, the benefits of beta-blockers might outweigh the risks. Nevertheless, the researchers believe the prevalence of drug-disease interactions among elders in this study suggests an opportunity for health care providers to intervene to prevent adverse events. ●

Source: *Ann Pharmacother*. 2005;39:412–417.