Drug Monitor

Hypoglycemia in the Hospital

Is tight glycemic control better for a hospitalized patient—reducing the risks of hyperglycemia—or is that very control putting the patient at risk for dangerous hypoglycemia? Research has not yet answered the question, leaving clinicians to find the fine line between too much control and not enough.

Many studies, including a large one that was ended early, have found hypoglycemia is common during hospitalization and is strongly associated with death. However, those studies have been done mostly among critically ill patients who are older and sicker. Researchers from Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY, theorized that it might be the comorbidities, not the drug treatments, that were responsible for seemingly hypoglycemia-related deaths. They designed a retrospective observational study to determine whether hypoglycemia was associated with higher risk of death in noncritically ill patients.

The researchers analyzed data from a cohort of 31,970 patients, of whom 3,349 (11%) had at least 1 episode of hypoglycemia. Those with hypoglycemic events were older; had a lower body mass index; had more comorbidities, including diabetes; and received more insulin, sulfonylureas, or thiazolidinediones (as opposed to metformin). Roughly similar proportions developed "spontaneous hypoglycemia" (not associated with glucose-lowering treatment) and drug-associated hypoglycemia (1,714 vs 1,635).

In-hospital mortality was 4 times higher among patients with hypoglycemia (4.39% [147 of 3,349] vs 1.06% [304 of 28,621]). The risk of death was significantly higher among patients with hypoglycemia whether or not the patient had diabetes. However, patients without diabetes but with hypoglycemia had about double the mortality rate of patients with diabetes and hypoglycemia (5.88% vs 2.97%).

The association between hypoglycemia and mortality was "markedly different" among subjects who developed it spontaneously vs those who developed it after glucose-lowering treatment, the researchers say. Among patients who were not on insulin treatment, those with hypoglycemia had significantly higher mortality, compared with those who did not develop hypoglycemia. By contrast, the risk of death was similar among those treated with insulin or oral antidiabetic drugs, regardless of whether hypoglycemia developed.

When the researchers subdivided the groups by drug class, they found that patients who developed hypoglycemia associated with sulfonylureas or insulin did not have an increased risk of mortality compared with normoglycemic patients taking the same drugs. The researchers say the lower rate of death among patients receiving metformin, thiazolidinediones, and sulfonylureas likely reflects that oral drugs are discouraged during hospitalization. After adjusting for patient demographics and comorbidities, the association between spontaneous hypoglycemia and mortality was eliminated, the researchers say.

Their findings suggest that hypoglycemia in hospitalized patients may be a marker of disease burden rather than a direct cause of death, the researchers conclude. They add that their results should reassure clinicians who manage glucose levels in hospitalized patients.

Source: *Am J Med.* 2011;124(11):1028-1035. doi:10.1016/j.amjmed.2011.07.11.

Giving Valproic Acid Another Chance

Valproic acid has several effects on the blood, some of them serious, such as pancytopenia. When a patient develops valproate-induced pancytopenia and alternatives don't work, no guidelines exist on whether it's safe to restart the valproate, says a physician who cared for a patient in just such a situation.

The patient, a 73-year-old man with a lifelong history of bipolar illness, had done well with conventional doses of valproic acid for 10 years, with nearly complete control of his mood symptoms. He had only minor thrombocytopenia, although he had other conditions, including coronary artery disease, diabetes, hypertension, osteoporosis, and benign prostatic hypertrophy. In addition to the valproic acid, he was taking sertraline, epoetin alfa, terazosin, finasteride, omeprazole, aspirin, and calcium, none of which were new.

When he developed pancytopenia, his valproic acid dosage was 500 mg bid with no recent dosage adjustments. His serum level was 62.1 µg/mL. Serum B_{12} and folate levels were within normal limits, and he had no history of hematologic problems.

The physician discontinued the valproic acid and substituted lithium carbonate. All cell lines returned to normal within a week.

Initially the patient did well, but within 6 months his manic symptoms

DRUG MONITOR

and paranoid delusions returned. Over the next year, his medical team tried lamotrigine, gabapentin, quetiapine, risperidone, haloperidol, and loxapine. Finally, bolstered by reports of a possible dose-dependent relationship between the drug and hematologic problems, they decided to cautiously reintroduce valproic acid, titrated to achieve somewhat lower serum levels (40-50 µg/mL).

The patient's symptoms promptly improved and remained well controlled on a combination of valproic acid and lamotrigine. His blood counts also remained stable within normal ranges.

The author notes that valproate-induced hematologic abnormalities generally arise early in therapy. A late adverse event such as his patient's might be explained by dosage or medication changes, but there had been none. That the pancytopenia resolved quickly suggested that it was not due to an underlying problem such as leukemia. And only 1 other drug—omeprazole—is associated with pancytopenia. Even though the patient had been taking valproate for some time, the rapid resolution of symptoms pointed to that drug.

While pancytopenia is serious and can be fatal, mandating caution, the author says it's "encouraging to note that it may not represent an absolute contraindication to carefully restarting valproate therapy with close hematologic monitoring."

Source: *Am J Geriatr Pharmacother.* 2011;9(5):351-353. doi:10.1016/j.amjopharm.2011.09.003.

For additional Drug Monitor content, check out the exclusive online edition of Drug Monitor at: **www.fedprac.com**