Drug Monitor

ONLINE EDITION

Too Much Heparin?

Half of patients with ST-segment elevation myocardial infarction (STEMI) who are treated with unfractionated heparin and fibrinolytics have received an excess dose of heparin, according to a study by researchers from Duke University, Durham, NC and University of Cincinnati, Cincinnati, OH.

Using the national registry Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) database, the researchers identified 758 patients with STEMI who were treated with fibrinolytics and adjunctive, unfractionated heparin therapy between April 2005 and December 2006. Defining an excess bolus dose of heparin as one that is greater than 60 U/kg and an excess infusion dose as one that is greater than 12 U/kg/h (based on the currently recommended initial doses), they found that 368 patients (49%) received an excess bolus or infusion dose. More than one third of these 368 patients received "major" excess dosing (defined as a bolus dose greater than 70 U/kg or an infusion dose greater than 15 U/kg/h). In addition, about 44% of patients received an initial bolus dose that exceeded the currently recommended upper limit of 4,000 U and 17% received an initial infusion dose that exceeded the currently recommended upper limit of 1,000 U.

Women, older patients, patients with low body weight, and patients with renal insufficiency were more likely to receive excess dosing. Those who received major excess dosing had higher unadjusted rates of major bleeding and transfusion than patients who did not receive excess dosing.

The study provides one of the first characterizations of unfractionated heparin dosing among fibrinolytic-treated patients with STEMI in contemporary practice, the researchers say. They note that proper dosing of both fibrinolytic and antithrombotic medications is critical for patients with STEMI because the therapeutic window is limited and seemingly small deviations in the intensity of anticoagulation can influence bleeding complications and clinical outcomes significantly.

Although several studies have shown that adherence to dosing guidelines is "far from ideal," the researchers say, their results are particularly concerning given that patients with STEMI who were already at higher risk for bleeding (such as women with low body weight) also were more likely to receive excess heparin dosing. The researchers suggest that one factor contributing to the nonadherence may be the lack of weight-based dosing—which was evidenced by a preponderance of patients who were given a combination of a 5,000-U bolus and a 1,000-U/h infusion. They say it isn't clear whether this "one-dose-fits-all" approach is related to underrecognition of STEMI dosing guidelines or is a response to the intense time pressure of rapid reperfusion, which may deter clinicians from taking the time to measure a patient's body weight to guide dosing.

The researchers note that hospital size and academic status were not associated with excess heparin dosing—and that their estimates of overdosing are likely conservative.

Source: *Am J Med.* 2008;121(9):805–810. doi:10.1016/j.amjmed.2008.04.023.

Megestrol Acetate and Adrenal Insufficiency

Although megestrol acetate (MA) is FDA approved to stimulate appetite in patients with advanced breast or endometrial cancer or cachexia related to AIDS, the drug is commonly prescribed off label to malnourished, elderly patients who experience unintentional weight loss. Unfortunately, adrenal insufficiency—a previously reported but often overlooked adverse effect of the drug—may be hard to detect in older patients, due to subtle and diverse signs and symptoms, warn researchers from University of Missouri Kansas City, Plaza Primary Care and Geriatrics, and Saint Luke's Internal Medicine, all in Kansas City, MO.

They describe the case of an 80-year-old woman with dyspnea who was admitted to their university-affiliated community medical center (CMC). Before admission, the patient had been treated in a psychiatric facility for major depression with psychotic features. Her general physical function had begun to decline at that facility, however, and because she was losing weight, treatment with MA 400 mg/day was initiated there to stimulate her appetite and improve her nutrition. She had been taking the MA for one month before her CMC admission.

During the CMC hospitalization, her dyspnea worsened and she was transferred to the intensive care unit, where she was intubated. Her blood pressure dropped. After infectious, cardiac, and neurologic causes of hypotension were ruled out, a cosyntropin stimulation test was performed to rule out adrenal insufficiency—and it indicated a suboptimal response.

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Based on those findings, the MA was discontinued and the patient's clinicians initiated steroid replacement therapy. Her blood pressure normalized and she improved slowly. She was weaned from the ventilator several weeks later and discharged to a skilled nursing facility. Two months later, her strength and respiratory function were improved and the results of a repeat cosyntropin stimulation test were normal.

The authors point out that, in chronically ill, malnourished, elderly patients, adrenal insufficiency may present with vague symptoms, such as depression and reduced appetite, making the diagnosis difficult. They advise maintaining a high degree of suspicion when MA is being prescribed. In their own case presentation, adrenal insufficiency was not suspected initially because the presentation was unusual, the patient's clinical history was complicated by comorbidities, and she had not been taking MA for an extended period of time. Although they stopped the MA immediately in their patient (because MA stores in fat deposits and a natural tapering effect of the drug occurs), the authors recommend tapering MA in patients who have cushingoid features or if they are at high risk for addisonian crisis.

The authors also recommend that patients who need more than 12 weeks of treatment with MA should have their free cortisol levels checked at 12 weeks and biweekly thereafter. They recommend empiric therapy with stress doses of corticosteroids during periods of illness in patients who are receiving MA, and they urge clinicians to make patients taking MA and their families aware of the signs of adrenal emergency.

Source: *Am J Geriatr Pharmacother.* 2008;6(3):167–172. doi:10.1016/j.amjopharm.2008.08.004.