Decreased Kidney Function Increases Bleeding Risk with Enoxaparin

Patients with moderate renal impairment have a sharply increased risk of major bleeding during treatment with enoxaparin, suggests a report in the Archives of Internal Medicine.

From June through November 2009, 164 patients at the authors' Veterans Administration Medical Center were treated with enoxaparin sodium (1 mg/kg every 12 hours or 1.5 mg/kg once daily). On the basis of a creatinine clearance of 30–50 mL/min, 59 patients were classified as having moderate renal impairment. Episodes of major bleeding—causing death, hospitalization, longer hospital stay, or emergency department visit—were compared for patients with moderate renal impairment versus normal renal function (creatinine clearance over 80 mL/min).

Twenty-two percent of patients with moderate renal impairment had major bleeding episodes while taking enoxaparin, compared with 5.7 percent of those with normal renal function. The odds ratio for major bleeding in the moderate renal impairment group was 4.7, decreasing to 3.9 on multivariable adjustment for other risk factors.

Indepently of renal function, the risk of major bleeding was higher in patients receiving enoxaparin as bridge therapy: 13.7 percent, compared with 8.1 percent for those receiving new anticoagulation, thromboembolism, evaluated as a secondary outcome, was similar between groups.

Enoxaparin, a low-molecular-weight heparin, allows simplified dosing without the need for laboratory monitoring. Even though enoxaparin is excreted by the kidneys, there is no recommended dose adjustment for patients with moderate renal impairment.

This study finds a fourfold increase in major bleeding with enoxaparin in patients with moderate renal impairment. More research is needed to establish appropriate dosing of this important and widely used anticoagulant in patients with reduced kidney function [DeCarolis DD, et al. Enoxaparin outcomes in patients with moderate renal impairment. Arch Intern Med 2012; 172:1713–1718].

Reducing the burden of ESA administration
Consider the first once-monthly, non-EPO ESA offering less-frequent dose administration.

INDICATION AND LIMITATIONS OF USE
OMONTYS® (peginesatide) Injection is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

OMONTYS® is not indicated and is not recommended for use in patients with CKD not on dialysis, in patients receiving treatment for cancer and whose anemia is not due to CKD, or as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia. OMONTYS® has not been shown to improve symptoms, physical functioning, or health-related quality of life.

IMPORTANT SAFETY INFORMATION

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, PREVENTION OF TUMOR PROGRESSION OR RECURRANCE. Chronic Kidney Disease:

In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.

• No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.

• Use the lowest OMONTYS® dose sufficient to reduce the need for RBC transfusions.

Contraindications
OMONTYS® is contraindicated in patients with uncontrolled hypertension and in patients who have had serious allergic reactions to OMONTYS®.

Warnings and Precautions
Increased mortality, myocardial infarction, stroke, and thromboembolism:

• Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality. A rate of hemoglobin rise of >1 g/dL over 2 weeks may contribute to these risks.

• In controlled clinical trials of ESAs in patients with cancer, increased risk for death and serious adverse cardiovascular reactions including myocardial infarction and stroke was observed.

• There is increased mortality and/or increased risk of tumor progression or recurrence in patients with cancer receiving ESAs.

• In controlled clinical trials of ESAs, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.

• In 2 trials of OMONTYS, patients with CKD not on dialysis experienced increased specific cardiovascular events.

Hypertension (see Contraindications): Appropriately control hypertension prior to initiation of and during treatment with OMONTYS. Reduce or withhold OMONTYS if blood pressure becomes difficult to control.

Serious allergic reactions (see Contraindications): Serious allergic reactions have been reported with OMONTYS. Immediately and permanently discontinue OMONTYS and administer appropriate therapy if a serious allergic reaction occurs.

Lack of or loss of response to OMONTYS: Initiate a search for causative factors. If typical causes of lack or loss of hemoglobin response are excluded, evaluate for antibodies to peginesatide.

Dialysis management: Patients receiving OMONTYS® may require adjustments to dialysis prescriptions and/or increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

Laboratory monitoring: Evaluate transferrin saturation and serum ferritin prior to and during OMONTYS treatment. Administer supplemental iron therapy when serum ferritin is less than 100 ng/mL, or when serum transferrin saturation is less than 20%. Monitor hemoglobin every 2 weeks until stable and the need for RBC transfusions is minimized. Then, monitor monthly.

Adverse reactions
Most common adverse reactions in clinical studies in patients with CKD on dialysis treated with OMONTYS were dyspnea, diarrhea, nausea, rash, and arteriovenous fistula site complication.

Please see accompanying Brief Summary.

C CB plus ARB Improves Outcomes in Hypertension and CKD
In high-risk older adults with hypertension and chronic kidney disease (CKD), adding a calcium channel blocker (CCB) to high-dose angiotensin II receptor blocker (ARB) yields further reductions in cardiovascular events, reports a trial in Kidney International.

The multicenter “OlmoSarnt and Calcium Antagonists Randomized” (OSCAR) trial included 1078 older Japanese adults with hypertension and baseline cardiovascular disease and/or diabetes. In the main trial, patients were randomly assigned to upward titration of ARB or to the addition of a CCB to ARB therapy. The current study was a prespecified subgroup analysis assessing treatment responses according to baseline estimated GFR (eGFR).

On the basis of an eGFR of less than 60 mL/min/1.73 m², 355 patients had CKD; in almost all, eGFR was 30–59 mL/min/1.73 m². In patients with or without CKD, blood pressure was lower with CCB plus ARB than with high-dose ARB.

Among CKD patients, the primary composite outcome of cardiovascular events and noncardiovascular death was about twice as high in the high-dose ARB group: 30 versus 16 events, hazard ratio 2.25. In particular, the rates of cerebrovascular and heart failure events were higher in CKD patients receiving high-dose ARB, compared with CCB plus ARB. By contrast, for patients without CKD, the primary event rate was similar between treatment groups.

The subgroup interaction was significant, with high-dose ARB being an independent prognostic factor for primary events among...