

# Advances in Hematology

Section Editor: **Craig M. Kessler, MD**

*Current Developments in the  
Management of Hematologic Disorders*

## Adjusting the Dose of Low Molecular Weight Heparins in Renally Impaired and Obese Patients

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### **Why were studies of dosing for low molecular weight heparins in renally impaired patients needed?**

Low molecular weight heparins (LMWHs) are preferentially eliminated from the body renally. For the most part, clinical trials of treatments for acute coronary syndromes and venous thromboembolism (VTE) have excluded patients with a creatinine clearance (CrCl) of less than 30 mL/min, or who have a serum creatinine of more than 2.0 mg/dL, because very little pharmacokinetic data were available for this patient group and dosing guidelines for renally impaired patients were not available. Also, patients with renal insufficiency, whether treated with an LMWH or unfractionated heparin (UFH), are at high risk of bleeding, and no specific guidelines existed that would help avoid this problem.

Often, the US Food and Drug Administration (FDA) approves dosing regimens for patients with renal insufficiency based on small trials in patient groups that are not necessarily the patient group that the clinician is treating. For example, a pharmacokinetic study might be conducted in dialysis patients with no known disease. Blood concentrations are measured and dosing is recommended based on that data. For LMWHs, the equivalent measurement is anti-factor Xa concentration, which measures the anticoagulant effect rather than the drug concentration. Most of the data we have on dosing of LMWHs in patients with renal insufficiency are from small studies. These small studies did suggest that there is a longer half-life of the drug for most LMWHs, and therefore some dosing adjustment would be required for renally impaired patients. Another study examining prophylactic enoxaparin (Lovenox, Aventis) at a dose of 40 mg/day suggested that some small dosing adjustment would be necessary, but these data were available only in abstract form at the time we started our study.

### **Could you describe the retrospective study that you conducted?**

We conducted a retrospective study of the data collected in the Thrombosis in Myocardial Infarction (TIMI) 11b trial and the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) trial. When

these trials were conducted, the impact of renal impairment was not necessarily taken into account because doing so requires measuring serum creatinine and body weight, and determining CrCl, amounting to a potentially cumbersome process. There may have been patients enrolled in these studies with a CrCl of less than 30 mL/min. In the TIMI 11b trial, a serum creatinine of 2 mg/dL was used in the inclusion criteria, and older patients with a serum creatinine of 2 are likely to have a CrCl of less than 30 mL/min. We decided to try to retrospectively evaluate the safety and efficacy of patients with renal insufficiency who were enrolled in these studies and had a CrCl of less than 30 mL/min. Although anti-factor Xa levels were not measured in these studies, we were more interested in measuring bleeding and efficacy outcomes, specifically in terms of prevention of death/myocardial infarction (MI) and the need for urgent revascularization procedures.

### **Could you discuss the recent dosing change made to the enoxaparin product label?**

As of December 2003, the enoxaparin label includes recommendations for both treatment and prophylaxis dosing adjustment. For patients with a CrCl less than 30 mL/min, the recommended venous thromboembolism prophylaxis dose is 30 mg once daily, and the recommended treatment dose is 1 mg/kg once daily.

### **On what data is this change based?**

Other than the small pharmacokinetic study of 40 mg once daily described above, additional data were gathered using larger doses. These data are unpublished but included in the product label. A study was conducted by Dr. Sanderink and is now data on file with Aventis. The pharmacokinetic data used in the study were from previous studies in patients that received prophylaxis dosing and in renally impaired but otherwise healthy patients who received either 1.5 mg/kg/day or 1 mg twice per day of enoxaparin.

In the first study, patients received enoxaparin 1 mg/kg every 12 hours for 7 doses. The minimum and maximum anti-factor Xa concentrations were compared between 9 pa-

tients with CrCl less than 30 mL/day and 21 healthy control patients. According to their findings, the minimum concentration (trough) of anti-factor Xa was approximately 132% higher in patients with significant renal impairment. Therefore, the trough levels were approximately 1 IU/mL. The peaks increased by approximately 50% and were approximately 1.6 IU/mL. The half-life in healthy volunteers was approximately 6.8 hours, compared with approximately 10 hours for renally impaired patients. Based on these data, the recommended adjustment for enoxaparin in renally impaired patients was a 50% reduction.

In another study of patients receiving 1.5 mg/kg once daily for 7 doses, anti-factor Xa levels were measured on day 7. This study included 7 patients with CrCl less than 30 mL/min and 19 healthy control patients. In patients with CrCl less than 30 mL/min, the trough concentrations were low, approximately 0.5 IU/mL. However, the peak concentration was increased by about 35%, measuring approximately 1.8 IU/mL, on average. Therefore, the manufacturer's recommended dosing adjustment for renally impaired patients who receive 1.5 mg/kg/day is reduced approximately 35% to 1 mg/kg/day.

### **What was the patient population in your retrospective study?**

The combined databases of the TIMI 11b and ESSENCE studies included several thousand patients with acute coronary syndromes. Of these patients, only 143 had renal insufficiency with a CrCl of less than 30 mL/min.

### **What were your study findings?**

Renally impaired patients experienced a 14-day death/MI or need for urgent revascularization rate of 18%, compared with approximately 16% in patients without significant renal insufficiency. Also, the renally impaired patient group had a 6-fold higher risk for major bleeding (approximately 7.5%, compared to 1.2%). The rate of any bleeds was almost 18% in renally impaired patients, compared with less than 10% in patients without significant renal impairment.

We also compared enoxaparin and UFH in patients with renal insufficiency. While the occurrence of death/MI and the need for urgent revascularization was higher in patients receiving UFH, the difference was not statistically significant. Bleeding was higher in the enoxaparin-treated patients (7.5% versus 5.8%), but again, this difference was not statistically significant in our small sample.

### **Has LMWH dosing been studied in dialysis patients?**

Single-dose trials of anticoagulation for patients undergoing hemodialysis have been conducted with different LMWHs. However, the studies cited for treatment dosing in the enoxaparin label change did not include dialysis patients. Significant drug accumulation could occur should unadjusted doses be given repeatedly. However, a brief period of treatment dosing, such as 1 or 2 doses, may be possible but has not been adequately studied. For example, in the recent Superior Yield of the New Strategy of Enoxaparin, Revas-

cularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial of patients with acute coronary syndromes, which also excluded patients with significant renal impairment, patients were treated for approximately 21 hours before proceeding to coronary angiography and revascularization. Heparins are not usually continued after revascularization so the possibility of using short-term treatment dosing of enoxaparin in patients with renal insufficiency should be evaluated prospectively. For now, patients with significant renal impairment receiving renal replacement therapy who have CrCl less than 10 mL/min should probably receive unfractionated heparin.

### **Based on your study and other available data, what dose adjustment would you recommend for renally impaired patients?**

For acute coronary syndrome patients, the typical dose recommended in patients who are not renally impaired is 1 mg/kg twice per day. For renally impaired patients with a CrCl of 10–29 mL/min, the recommendation is now 1 mg/kg once per day. For VTE patients, there are 2 dosing options. The 1 mg/kg twice per day recommendation has been reduced to 1 mg/kg/day, as has the second option of 1.5 mg/kg/day. Ultimately, the proper adjustment depends on the patient. For patients whose CrCl is less than 30 mL/min, the typical dose is 1 mg/kg/day.

### **In your retrospective study, was age examined in terms of potential differences in LMWH dosing?**

Not specifically. In our statistical analysis, we controlled for age, diabetes, and other risk factors so that we could look at differences in renal function only. However, age was not examined as a separate outcome.

### **Does the dosing of LMWHs need to be adjusted for obese patients?**

In our retrospective study, approximately 1,800 of 7,000 patients were obese. The dosing in the TIMI 11b and ESSENCE studies was based on weight, which is the current recommendation. However, the very large dose that would be required for very obese patients is a concern among physicians. For example, the highest weight patient in the study was 159 kg. Rounding this to 160, the recommended weight-based dose would be 320 mg of enoxaparin.

Some centers have decided to cap the maximum dose at 150 mg twice per day, in part because of safety concerns and in part because enoxaparin is available at a maximum of 150 mg in a prefilled syringe. Some physicians choose to give their more obese patients UFH instead because of this limitation.

There are no pharmacokinetic data indicating differences in safety or efficacy of LMWH in obese patients compared with nonobese patients that would lead to changes in dosing. However, it is important to note that the patients volunteering for LMWH studies are essentially healthy obese patients. There are some data on 180-kg patients who have received dalteparin, and there is no difference in the pharmacokinetic

data compared with nonobese patients—peak concentrations and clearance are the same, and there is no accumulation. One concern among physicians has been that obese patients have a higher risk of bleeding, but according to our findings, this is not the case.

### **Approximately 30% of patients in your retrospective study were obese—is this typical of cardiology studies?**

Yes. The average cardiology patient weighs approximately 80–85 kg. Obesity is a risk factor for acute coronary disease. The results that were seen in the primary studies of enoxaparin in obese patients should be typical of the obese population in general. However, for VTE, where there is a higher rate of oncology patients and patients tend to be lighter in weight, data for the treatment of obese patients is still needed.

### **In what other areas are studies needed, where dosing adjustments for obese patients are concerned?**

There is an urgent need for a better understanding about the most appropriate LMWH dose level for super-morbid obese patients undergoing bariatric surgery, and for 500–600-lb patients in need of medical prophylaxis. In bariatric surgery, many different prophylactic modalities are used, including elastic stockings, intermittent pneumatic compression, and heparin. Enoxaparin given at a dose of 40 mg/day would be an appropriate medical prophylaxis for a morbid obese patient who has pneumonia at this time because data are lacking. However, many clinicians would question why a 500-lb patient and an 80-lb patient should be given the same dose. Since we are accustomed to dosing for treatment in terms of mg/kg, some people would think that prophylaxis should also be dosed in terms of mg/kg. But the original studies on enoxaparin prophylaxis employed a fixed dose. In addition, larger weight patients tend not to volunteer for studies unless it is for bariatric surgery. The bariatric surgery population would be a good patient group to include in a future study.

### **What do you typically tell physicians who inquire about dosing adjustments for obese patients?**

Typically, I recommend to physicians that they approach the patient as an individual to whom they are trying to give the best care. If the physician thinks that a regimen other than the FDA-approved regimen is needed, then he/she should discuss this with the patient, and document in the patient medical record why a different dose is needed.

Some physicians, seeing that an 80-kg patient is being given 40 mg of enoxaparin in the hospital setting, would give a 250-kg patient 125 mg of enoxaparin. Other physicians who would try to measure the anti-factor Xa concentration in the patient. The latter approach is recommended in the American College of Chest Physician guidelines published in 2001.

In the prophylactic setting, enoxaparin should be undetectable 24 hours and less than 0.6 IU/mL less than 6 hours after dose administration. Therefore, one approach to identifying the correct dose would be to increase the dose until a detectable concentration is measured at 4–8 hours. This is a reasonable approach, although dose adjusting would be difficult here, since it would need to be done prospectively.

LMWHs are cleared renally. Their clearance is not affected by body weight and is similar in obese and nonobese patients. Therefore, clearance is most likely not part of the difficulty in treating obese patients. Patients with morbid obesity are at high risk for VTE. Physicians treating such patients should balance this risk with treatment, and approach the patient as an individual, particularly considering the lack of data.

### **Why did you use a composite endpoint in your study?**

The primary composite endpoint was first instituted for acute coronary syndrome trials around 1995. Early trials looked at mortality as a single endpoint. However, as therapies were added and as the effectiveness of combination therapies began improving, it became difficult to study mortality as a single endpoint in a reasonable number of patients. To avoid this difficulty, investigators began using prespecified composite endpoints. For the original trials, it is possible to then look at individual endpoints as a secondary analysis. Composite endpoints are very common; in fact, one recent cardiology trial looked at 4 different endpoints combined together, and others have used 5 or 6. Using a composite endpoint decreases the number of patients needed, and ideally, all components should be clinically meaningful. Death is clinically meaningful; stroke is commonly included. In our study, the need for urgent revascularization reflects the need for increased medical services because of failed drug therapies, so this was included in the composite endpoint.

### **Suggested Reading**

Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the management of patients with unstable angina). Available at: [http://www.acc.org/clinical/guidelines/unstable/update\\_index.htm](http://www.acc.org/clinical/guidelines/unstable/update_index.htm). Accessed April 19, 2004.

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