Low-Molecular-Weight Heparin Use in Special Populations

PETER N. JOHNSON, PHARMD; KELLY M. SMITH, PHARMD

Because many obese patients and patients with underlying renal dysfunction require surgical intervention, it is important to examine the dosage recommendations and monitoring required with low-molecular-weight heparins.

Low-molecular-weight heparins (LMWHs) are an attractive alternative for prevention and treatment of thromboembolic conditions. Three LMWHs currently available in the United States include enoxaparin, dalteparin, and tinzaparin. Due to their favorable pharmacokinetic properties and alternative route and frequency of administration compared with unfractionated heparin, the popularity of these agents has increased over the past several years. Derived from enzymatic depolymerization of unfractionated heparin, LMWHs exert their main pharmacologic effect by a conformational change in antithrombin III.1-3

Low-molecular-weight heparins are approximately one third of the molecular weight of unfractionated heparin; so their smaller fragments have difficulty in inhibiting thrombin whereas both unfractionated heparin and LMWHs inhibit factor Xa.1 Thus unfractionated heparin and LMWHs have a similar mechanism of action. Several proposed pharmacokinetic benefits of LMWHs versus unfractionated heparin include reduced binding to proteins, macrophages, and epithelial cells; longer half-life; and 100% bioavailability when given subcutaneously.1,4

This pharmacokinetic profile gives a more predictable dose response with LMWHs. These agents are usually administered in a fixed dose for prophylaxis or treatment effect making it often unnecessary to monitor laboratory values in healthy patients regularly.1 However, a number of questions exist regarding LMWH use in some special patient populations. Few of the large randomized clinical trials have focused on overweight and obese patients and patients with underlying renal dysfunction.

OBESITY

When considering the initiation of a patient on a LMWH, it is important to use the proper dosing weight to maintain efficacy of prophylaxis and treatment of thromboembolic events yet prevent adverse effects. It is estimated that 97 million Americans are overweight or obese; the National Heart, Blood, and Lung Institute defines obesity as a body mass index (BMI) \(>30\, \text{m}^2\).5 Low-molecular-weight heparins distribute mainly in the intravascular space, therefore, the volume of distribution (CrCl <30 mL/min). Because many of these patients may require surgical intervention, it is important to examine the dosage recommendations and monitoring required in these special populations.

Few of the large randomized clinical trials have focused on overweight and obese patients with underlying renal dysfunction.
national units/kg of tinzaparin in 37 healthy obese volunteers and found consistent pharmacokinetic parameters compared to patients with a normal weight. Thus this study supports the rationale that obese patients have a similar distribution of the LMWHs as patients with normal weight.

Some of the earlier work on the pharmacokinetics of LMWHs with total body weight in healthy volunteers has suggested that peak anti-Xa activities correlate with total body weight.1-3 One study comparing 10 healthy and 10 obese patients receiving weight-based doses of dalteparin found a nonsignificant difference in the mean volume of distribution between the two groups and a higher clearance in the obese patients.7 Smith and Canton8 performed a retrospective, open-label study in 21 obese patients and found that 4 of 10 patients on daily administration of dalteparin had an anti-Xa less than the target range of 1-2 international units/mL, suggesting that these patients also had a higher clearance. Pharmacokinetic differences have been observed in obese patients including higher renal clearance.

Controversy remains over whether obese patients receiving LMWHs should have a cap on the total dose of LMWH to be administered or receive fixed weight dosing. Some have argued that with the higher clearance seen with LMWHs that establishing a dosing cap might predispose obese patients to increased risk of thromboembolic complications. One study in patients receiving fixed doses of LMWHs for prophylaxis for hip and knee surgery suggested that patients with a higher BMI had a positive correlation with the risk of postoperative venous thromboembolism.9 Another study in obese patients receiving fixed-dose deep vein thrombosis (DVT) prophylaxis with enoxaparin found a negative correlation between total body weight and anti-factor Xa activity, suggesting that fixed dosing and dosing caps might lead to subtherapeutic dosing in obese patients.10 Thus, evidence exists to support that dosing caps may dispose patients to higher rates of thromboembolic conditions. Despite these two studies, many institutions have used dosing caps to prevent adverse effects. Few dosing recommendations are available for obese patients.

Few studies have focused on prevention or treatment of DVT with LMWHs in patients with a total body weight of >150 kg and BMI >50 kg/m². Dose capping in these patients is particularly a controversial issue. With the lack of clear recommendations in these patients, some sources have suggested following anti-Xa levels. Recommendations for monitoring in this patient population are to obtain an anti-Xa level within 3-7 days after the start of therapy, with a change in dose, or every 2-4 weeks.2 Because of the lack of evidence in using LMWHs in patients with a total body weight >150 kg and BMI >50 kg/m², it may be prudent to use unfractionated heparin to prevent and treat thromboembolic conditions.

**RENAL FAILURE**

Low-molecular-weight heparins are almost totally excreted by the kidneys. Nearly all of the large randomized con-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal surgery</td>
<td>40 mg subcutaneous daily</td>
<td>2500 international units subcutaneous daily or 5000 subcutaneous daily postoperatively</td>
<td>N/A</td>
</tr>
<tr>
<td>Hip/knee replacement surgery</td>
<td>30 mg subcutaneous every 12 h</td>
<td>2500 international units subcutaneous daily or 5000 subcutaneous daily postoperatively</td>
<td>N/A</td>
</tr>
<tr>
<td>During acute illness</td>
<td>40 mg subcutaneous daily</td>
<td>5000 international units subcutaneous daily</td>
<td>N/A</td>
</tr>
<tr>
<td>Prophylaxis of ischemia with unstable angina and non-Q wave myocardial infarction with concomitant aspirin therapy</td>
<td>1 mg/kg total body weight subcutaneous every 12 h</td>
<td>120 international units/kg total body weight subcutaneous every 12 hours*</td>
<td>N/A</td>
</tr>
<tr>
<td>Inpatient treatment DVT with or without PE with concomitant warfarin therapy</td>
<td>1 mg/kg total body weight subcutaneous every 12 h</td>
<td>N/A</td>
<td>175 international units/kg total body weight subcutaneous daily</td>
</tr>
<tr>
<td>Outpatient treatment of DVT with or without PE with concomitant warfarin therapy</td>
<td>1 mg/kg total body weight subcutaneous every 12 h or 1.5 mg/kg total body weight subcutaneous daily</td>
<td>N/A</td>
<td>175 international units/kg total body weight subcutaneous daily</td>
</tr>
</tbody>
</table>

*Maximum 10,000 international units subcutaneous every 12 hours.

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Abbreviations: DVT=deep vein thrombosis, FDA=Food and Drug Administration, N/A=not approved by the Food and Drug Administration, and PE=pulmonary embolism.

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trolled trials involving patients who have received LMWHs have excluded patients with renal failure. Compared with healthy volunteers, patients with a creatinine clearance (CrCl) /10 mL/min have a half-life 1.5-2/1003 that of healthy patients. 11 Most of the pharmacokinetic studies in patients receiving LMWHs have identified a strong correlation between anti-factor Xa and renal function. In patients with a CrCl /10 mL/min, one study found a linear relationship with anti-factor Xa levels such that patients with renal dysfunction had greater accumulation of anti-factor Xa concentrations.12 Renal dysfunction is associated with accumulation of LMWH and thus prolongation of antithrombotic activity.

If patients with a CrCl /30 mL/min have increased levels of anti-factor Xa, they could have an increased risk of bleeding. In a retrospective analysis of patients with renal insufficiency and obesity from the Efficacy Safety Subcutaneous Enoxaparin in Non-Q-wave Coronary Events and Thrombolysis in Myocardial Infarction 11B, patients with a CrCl /30 mL/min had a significant increase in risk for major hemorrhage (P<.001).13 Another retrospective analysis of patients with renal dysfunction receiving multiple doses of enoxaparin identified a 2.3 relative risk of bleeding (P<.01) and a 15.0 relative risk for major hemorrhage (P<.001).14 As LMWHs are mainly excreted by the kidneys, patients with underlying renal dysfunction appear to be at a higher risk of adverse events.

With a higher risk of bleeding seen with LMWH patients with renal dysfunction, dosage recommendations exist for patients with severe renal dysfunction (CrCl <30 mL/min). In light of the potential adverse effects of LMWHs in patients with renal dysfunction, established dosage recommendations according to each manufacturer exist, which may help to guide therapy in this patient population (Tables 1 and 2).

**TABLE 2**

<table>
<thead>
<tr>
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Abbreviations: DVT=deep vein thrombosis, FDA=Food and Drug Administration, N/A=not approved by the Food and Drug Administration, and PE=pulmonary embolism. *Maximum 10,000 international units subcutaneous every 12 hours.

**TABLE 3**

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<tr>
<th>Condition of VTE</th>
<th>Anti-factor Xa Concentrations1-3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>Treatment (twice daily dosing)</td>
<td>0.4-1.1</td>
</tr>
<tr>
<td>Treatment (daily dosing)</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Abbreviation: VTE=venous thromboembolism. *Anti-factor Xa concentrations measured as international units/mL.

In healthy patients receiving fixed doses of LMWHs, laboratory monitoring is typically not recommended. However, in
patients with a total body weight >150 kg or BMI >50 kg/m² or renal dysfunction, close monitoring may be necessary to adequately access the risk for adverse effects. As LMWHs do not affect thrombosis, monitoring activated partial thromboplastin time is not beneficial. One should regularly assess all patients receiving LMWHs with blood urea nitrogen (BUN)/SrCr to evaluate renal function and with complete blood count to evaluate signs of bleeding. Because of a similar risk of heparin-induced thrombocytopenia as unfractionated heparin, LMWHs should be discontinued in patients with signs and symptoms of bleeding or a platelet count <100,000. Thus all patients should at least receive periodic assessment with a hemogram and basic metabolic panel.

In the special populations of obesity and renal dysfunction, it may be necessary to follow anti-factor Xa levels. A number of published trials have included assessment of anti-Xa concentrations. Although increased anti-factor Xa activity has been shown to decrease the development of thrombus, it is unclear what level of anti-factor Xa must be achieved to affect thrombus formation. Several chromogenic anti-factor Xa assays are available; however, a large degree of variability exists in the assays making it difficult to interpret this laboratory marker in practice. There are no clear-cut consensus guidelines or recommendations for assessing anti-factor Xa levels. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy does not recommend routinely assessing anti-factor Xa levels in healthy individuals. It may be necessary to obtain these levels in patients who are obese or have renal dysfunction because of the risk for adverse effects. Anti-factor Xa concentrations should generally be obtained 4 hours after the third dose of subcutaneous LMWHs. Proposed recommendations used to assess anti-factor Xa concentrations are shown in Table 3. More studies must be performed to determine if each LMWH should have its own anti-Xa concentration.

THE BOTTOM LINE

Low-molecular-weight heparins are not interchangeable; each one of the available agents exhibits different pharmacokinetic parameters. In general, all patients receiving LMWHs should be dosed based on total body weight. For patients with a BMI >50 kg/m² or >150 mg/kg, avoid LMWHs because of the lack of clear safety data. Extreme caution should also be used in patients with renal dysfunction; LMWHs are usually not recommended in patients with a CrCl <30 mL/min. The manufacturer’s instructions should be used for specific dosage recommendations of LMWHs in patients with renal dysfunction. In obese patients or patients with renal dysfunction who are receiving LMWHs, there must be explicit monitoring. All patients should have regular assessment of BUN/SrCr to follow renal function and platelet counts to assess the development of bleeding or heparin-induced thrombocytopenia. Caution should be used in following anti-factor Xa levels to assess efficacy of prophylaxis or treatment of thrombembolitic conditions and prevention of adverse effects because no consensus guidelines have been established.

REFERENCES