Unexpectedly High PTT Values After Low-Dose Heparin Prophylaxis

Thromboembolic (TE) prophylaxis using low-dose unfractionated heparin (LD-UFH), ie, 5000 IU given subcutaneously twice or 3 times daily is effective, has low bleeding risk, and is generally not expected to prolong partial thromboplastin times (PTTs). Laboratory monitoring or dose adjustments based on weight or renal function are not considered necessary. An index case at our institution prompted us to review this conventional view and investigate the frequency and circumstances when significant PTT prolongations occur in hospitalized patients receiving LD-UFH for TE prophylaxis.

Report of a Case. A 73-year-old woman with diabetes, hypertension, hyperlipidemia, and chronic renal failure was treated on the inpatient medicine service for hypertensive emergency associated with chest pain and shortness of breath. She was placed on LD-UFH therapy, 3 times daily, for TE prophylaxis on hospital day 1 and improved steadily. On hospital day 11 she was to be discharged, when she was noted to be severely hypotensive. Evaluation revealed a large retroperitoneal hemorrhage with active bleeding from a lumbar artery branch, which was stopped by embolization treatment. The patient was transfused 14 red blood cell units during this episode. She was eventually discharged in stable condition to a skilled nursing facility on hospital day 69 following a complicated course. The first PTT value, 10 days after the start of LD-UFH therapy, when the retroperitoneal hemorrhage was recognized, was 105.4 seconds (reference range <37.6 seconds [STA-Compact, STA PTT automate reagent; Diagnostica Stago Inc, Parsippany, New Jersey]). Therapy with UFH was stopped, and PTTs were shortened to 35.5 seconds within 19 hours. The cause of the retroperitoneal bleeding and whether LD-UFH played a direct role could not be determined. However, the high PTT result, which was at the upper end of the therapeutic range for UFH at our institution (75-108 seconds, corresponding to anti-Xa levels of 0.3-0.7 U/mL), was alarming considering the life-threatening bleeding episode, caused confusion about the validity of the result, and raised questions about the most appropriate therapeutic action.

Comment. This case prompted us to look for patients receiving LD-UFH with prolonged PTTs. During the 6-month period since the original case, we identified an additional 15 patients at our hospital with peak PTTs 1.5 times above baseline or greater that were temporally associated with LD-UFH therapy (Figure). In 4 of the 16 patients, PTT or anti-Xa testing was performed by outside reference laboratories on split samples, confirming the high PTTs at our institution in 3 of the 4 cases. These figures likely represent a low estimate, since we do not routinely perform PTT testing during LD-UFH administration. Shared relevant characteristics of the 16 patients included 3-times-daily LD-UFH dosing (100%), Asian ethnicity (63%), low body weight (median, 56.8 kg; range 39.0-71.0 kg), decreased renal function (63% with estimated glomerular filtration rate <60 mL), low albumin level (median 3.1 mg/dL; range, 3.0-3.7 mg/dL [reference range, 3.2-4.6 mg/dL]), and total plasma protein level (median, 6.5 mg/dL; range 3.6-7.1 mg/dL [reference range, 6.2-8.1 mg/dL]). Each of the patients had at least 1 of these attributes in addition to TID dosing. With the exception of the index case, none of them experienced significant bleeding incidents.

Elevated PTTs during LD-UFH administration have been described previously. It is likely that the heparin-responsive coagulation instrument–reagent combination used in our clinical laboratory, which is common in the United States nowadays, was a factor in the relative frequency with which we observed this phenomenon. However, the patients we identified had at least 1 attribute in addition to 3-times-daily dosing that is known to increase and prolong heparin action, ie, low body weight, low plasma protein concentration, and impairment of renal function. Physicians who use LD-UFH should be aware of the possibility of significant PTT elevations in patients with these attributes.

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**Financial Disclosure:** None reported.


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**Orlistat and Acute Kidney Injury: An Analysis of 953 Patients**

Obesity is a significant health problem that is growing in prevalence.1,2 Orlistat (Xenical; Roche, Basel, Switzerland), an inhibitor of pancreatic lipases that limits the intestinal absorption of dietary fat, has proven effective in augmenting weight loss.3,4 In the United States, orlistat is available over the counter and by prescription. Single-person case reports have recently suggested that orlistat may cause oxalate-induced acute kidney injury (AKI).5,6 The putative mechanism is similar to enteric hyperoxalaturia in which unabsorbed dietary fat binds enteric calcium and reduces its ability to bind and sequester oxalate in the gut. This results in excessive absorption of free oxalate and subsequent deposition in the renal parenchyma.6 To explore the relationship between orlistat and AKI, we conducted a before-and-after-analysis of incident orlistat users.

**Methods.** The province of Ontario, Canada, has a single-payer universal health insurance program that covers all residents and has emigration rates of less than 1% per year. We conducted this study using 6 of Ontario’s linked health care databases. Detailed descriptions of these databases are provided in the eAppendix (http://www.archintermed.com).

Orlistat is available in Ontario by prescription and is an insured benefit of the provincial formulary for residents older than 65 years and those who receive disability benefits or social assistance. Using the Ontario Drug Benefits database, we identified all such patients who filled their first prescription for orlistat between January 1, 2002, and March 31, 2008. For each new orlistat user, we identified AKI events occurring in the 12 months before and after the initial orlistat prescription, including acute di-

**Results.** During the 87-month accrual period, we identified 953 new users of orlistat. The Table displays their demographic and baseline data. In the 12 months preceding the initial orlistat prescription, 5 patients expe-