Low-Molecular-Weight Heparin Administration in Patients with End-Stage Renal Disease—A Comment

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The data presented by Brophy and colleagues[1] are a good beginning to our understanding of the pharmacokinetics of enoxaparin in patients requiring dialysis. Still, there are too many unanswered questions based on the small number of patients, administration of a single dose of enoxaparin, and pharmacokinetic simulation used to support their conclusions.

Other researchers[2] discussed the use of low-molecular-weight heparins (LMWHs) in patients with renal insufficiency. Patients with impaired renal function who receive multiple doses of LMWH have higher anti-Xa levels, reduced drug clearances, and prolonged drug half-lives. Clear guidelines on dosage adjustments for LMWHs given to patients with end-stage renal disease (ESRD) have not been published.

Investigators retrospectively evaluated the frequency of bleeding and use of blood products in patients with renal insufficiency compared with those with normal renal function who received multiple doses of LMWH.[3] Patients with renal insufficiency were more likely to have bleeding complications and require transfusions than those with normal renal function. Our own (limited, unpublished) experience using multiple doses of LMWH in patients with renal dysfunction led us to believe that these patients are at higher risk for hemorrhage compared with patients with normal renal function.

As very few patients receive a single therapeutic dose of LMWH, it is premature to state that monitoring and dosing adjustments are unnecessary in patients with ESRD who receive multiple doses of LMWH.

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Authors' Reply

We are pleased that our article[1] generated important discussion on the pharmacokinetics of enoxaparin in patients with end-stage renal disease (ESRD). We thank Dr. Lile and Drs. Kalus and Spencer for their commentaries, as they reemphasize the limitations of our study.

We first want to provide a correction to our data. Due to a typographical error on page 173, line 12, we incorrectly reported the weight-based apparent clearance (Cl/F) and range as 0.13 ml/minute/kg and 0.13–0.25 ml/minute/kg, respectively. The correct Cl/F should have read 0.19 ml/minute/kg, and the reported range should have read 0.14–0.33 ml/minute/kg. This error does not affect the conclusion that our data are similar to those reported in another study.[2]

Dr. Lile restated the main talking points listed in our discussion. In addition, he cites a published review article[3] that describes the literature of various low-molecular-weight heparins (LMWHs) and their need for dosage adjustment in patients with renal dysfunction. His commentary states, "Patients with impaired renal function who receive multiple doses of LMWH have higher anti-Xa levels, reduced drug clearances, and prolonged drug half-lives." This statement may be only partly supported by the literature. In fact, this review article cited only

one multiple-dose study involving nadroparin that was conducted in elderly subjects with presumed age-related renal dysfunction.[4] There are several problems with this study that make it difficult to interpret its clinical significance. For example, it was not conducted in patients with ESRD; the elderly group in this study had a mean creatinine clearance (Cl_{cr}) of 62 ml/minute, which is hardly renal dysfunction. Second, although the trough anti-factor Xa concentration for the elderly group (mean 0.20 IU/ml) is statistically different than that of the young, healthy group (mean 0.08 IU/ml), both concentrations are well below the therapeutic range at the end of therapy. Although this difference may be statistically significant, it is likely not clinically relevant.

Another study assessed anti-factor Xa concentrations of tinzaparin after 10 days of dosing in patients with age-related renal dysfunction.[5] Patients were grouped according to their creatinine clearances: group 1, Cl_{cr} > 50 ml/minute; group 2, Cl_{cr} 40–49 ml/minute; group 3, Cl_{cr} 30–39 ml/minute; and group 4, Cl_{cr} 20–29 ml/minute. All subjects received 10 days of therapeutic tinzaparin dosing (175 IU/kg subcutaneously once/day). The results demonstrated that there was no accumulation of tinzaparin in patients with age-related renal dysfunction. There were no intergroup or intragroup differences in the mean peak anti-factor Xa concentrations measured on days 2, 5, 7 and 10 of therapy, and none of the subjects recorded a supratherapeutic anti-factor Xa concentration throughout the duration of the study. Finally, there was no correlation between creatinine clearance and anti-factor Xa concentration.

Dr. Lile mentions his personal experience with bleeding episodes in patients with ESRD and cites a retrospective chart review.[6] As we discussed in our paper, bleeding is not uncommon in this population, which already is prone to bleeding episodes due to their underlying uremic state. These patients often require transfusions for many reasons, including blood loss through dialysis and anemia of chronic renal failure. We urge caution in trying to draw firm conclusions from this retrospective chart review.[6] Although these data are suggestive, there are many potential explanations for the increased bleeding rates in the subjects with renal insufficiency observed in the chart review, including more frequent surgeries (25% of patients) compared with the normal renal function group (2%). Clearly, further study is necessary.

Table 1. Predicted Peak Anti-factor Xa Concentrations at Steady-State

Subject No.	Predicted Peak Anti-Factor Xa Concentration
1	1.17
2	1.12
3	0.98
4	1.23
5	0.91
6	0.96
7	1.22
8	1.23
Mean (95% CI)	1.10 (0.99–1.21)
Median	1.15
CV (%)	12

CI = confidence interval; CV = coefficient of variation.

Drs. Kalus and Spencer raise many good points on which we would like to elaborate. Single-dose pharmacokinetic studies often are used to collect pilot data to aid in developing subsequent multiple-dose studies. This was the intention of our study. We agree that our results do not provide the final answer to this question but, in fact, are preliminary data to help begin the process of answering the question.

Second, Drs. Kalus and Spencer correctly point out that the therapeutic range for anti-factor Xa concentrations is defined only for 4 hours after the dose of LMWH (peak concentration). Our study reported the average steady-state concentration data for the entire dosing interval. The predicted steady-state peak concentration at 4 hours can be estimated crudely from our data by simply multiplying the observed peak after a single dose by the accumulation ratio of 1.6 (Table 1). This calculation yields a mean estimated peak steady-state anti-factor Xa concentration of approximately 1.10 IU/ml (95% confidence interval 0.99–1.21), which is at the upper end of the therapeutic range at our institution (0.50–1.20 IU/ml). Three of the eight subjects are predicted to have peak steady-state anti-factor Xa concentrations slightly above the therapeutic range. The clinical implications of this are unknown since hemorrhagic events have not been correlated to supratherapeutic anti-factor Xa concentrations.[7, 8]

Finally, Drs. Kalus and Spencer suggest that the coefficient of variation (CV) for the reported apparent clearance (32%), half-life (41%), and volume of distribution (32%) is "marked." We respectfully disagree and believe that their point

is overstated. Generally, a CV of 30% or less in human studies is considered low variability; 30–40% variability is moderate and certainly acceptable. Our CV data are consistent with other trials[2, 9, 10] cited in our article.

In summary, our pilot study provided preliminary data for designing further clinical trials of enoxaparin in patients with ESRD. We acknowledge the limitations of our single-dose study, and we agree that further research is needed to develop more specific enoxaparin dosing guidelines in patients with ESRD.

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