Coagulation effects of low molecular weight heparin compared with heparin in dogs considered to be at risk for clinically significant venous thrombosis

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Abstract

Objective – Compare the effects of 3 anticoagulation protocols on anti-factor Xa activity (AXa).
Design – Prospective, randomized, double-blind study.
Setting – University veterinary teaching hospital.
Animals – Eighteen dogs considered to be at risk for venous thrombosis.
Interventions – Each dog was randomly assigned to 1 of the following 3 groups (n = 6/group) and was treated for 24 hours: low-dose heparin (LDH), high-dose heparin (HDH), and dalteparin (DP). Dogs in the LDH group received a constant rate infusion (CRI) of unfractionated heparin (UFH) at 300 U/kg/d, the HDH group received a bolus of 100 U/kg of UFH IV, then a CRI of 900 U/kg/day, and the DP group received 100 U/kg DP SC at 0, 12, and 24 hours.
Measurements and Main Results – A total of 54 samples for activated partial thromboplastin time (aPTT) and AXa assays were collected at 0, 4, and 28 hours. Six samples had an AXa > 0.1 U/mL, 5 of those were from the HDH group at hour 4. Two samples from the HDH group at hour 4 had a prolonged aPTT (93 and 200 seconds) and the highest AXa (0.6 and 1.0 U/mL, respectively). Four additional dogs in the HDH group did not complete the study due to hemorrhage; none of the dogs completing the study showed signs of hemorrhage.
Conclusions: Neither DP nor LDH increased AXa to values considered therapeutic in humans (0.5–1 and 0.35–0.75 U/mL, respectively), and both protocols appear to be inadequate to increase AXa in dogs with clinical illness. HDH increased AXa to this range in 2 of 6 dogs, but had unpredictable effects on aPTT and resulted in hemorrhage in some dogs.

Keywords: anti-coagulate, blood clot, canine, hypercoagulable

Introduction

The incidence of venous thrombosis in critically ill humans cared for in intensive care units ranges from 10% to 30% within the first week following admission. Venous thrombosis is an especially significant cause of morbidity and mortality in this population because these patients often have less cardiovascular reserve to tolerate circulatory compromise. To further complicate the matter, diagnosis of venous thrombosis in critically ill humans is difficult and unreliable. Only 16% of critically ill humans show symptoms before death, and one-half to two-thirds of thrombotic episodes are provoked by an acute trigger. Furthermore, these patients are frequently unable to communicate their symptoms due to sedation, mechanical ventilation, or serious injury.

Like their human counterparts, critically ill dogs may be uniquely prone to thrombotic complications. For example, mortality of dogs with primary immune-mediated hemolytic anemia has been estimated to be 26–70%, and venous thrombosis and pulmonary thromboembolism may account for 30–60% of these deaths. Venous thrombosis and pulmonary thromboembolism...
are felt to contribute to morbidity and mortality in other critically ill veterinary patients and prophylactic measures have been evaluated.\textsuperscript{13–18} For the past 40 years, unfractionated heparin (UFH) has been used in humans to prevent venous thrombosis because it is affordable, available, and effective at preventing clot formation.\textsuperscript{19,20} The primary mechanism of anticoagulation of UFH is through its binding to antithrombin (AT), creating a conformational change in that molecule that increases its binding affinity to thrombin. Once bound, the AT-heparin complex inactivates thrombin, thus decreasing the propensity of thrombus formation. UFH also binds to other activated coagulation factors (including factors XII, XI, X, and IX), further enhancing its anticoagulant action.\textsuperscript{21} The actions of thrombin and other factors of the intrinsic and common coagulation cascade affected by UFH can be monitored via measurement of the activated partial thromboplastin time (aPTT).\textsuperscript{19,21,22} The acceptable therapeutic target for this assay in humans is to prolong the aPTT by 1.5–2.5 times baseline.\textsuperscript{19,23,24} This target range has also been suggested by veterinary authors as an appropriate goal of heparin therapy in dogs.\textsuperscript{25–29} However, when using UFH the aPTT test has limited value in predicting heparin activity as defined by anti-factor Xa activity (AXa) because the 2 assays are not linearly correlated when using that product.\textsuperscript{30,31}

More recently, low-molecular-weight heparin (LMWH) has been adopted as the standard of care for primary prophylaxis for human patients at risk of venous thrombosis.\textsuperscript{19,32} In contrast to UFH, LMWH is more homogeneous in size, has a more predictable dose-response relationship and a longer duration of action. UFH is heterogeneous in size and binds to proteins and other molecules in the body, increasing its rate of metabolism and making it more difficult to predict its duration of action. Therapy with LMWH is associated with fewer complications such as heparin-induced thrombocytopenia and requires less monitoring due to the standardized dose and predictable response in humans. Success with this product in human medicine has prompted interest in studying the use of LMWH in dogs for the prevention of venous thrombosis.\textsuperscript{33}

The response to LMWH cannot be monitored by measuring the aPTT because its effect specifically targets activated factor X and at therapeutic doses (as defined by AXa activities of 0.5–1 U/mL) LMWH has little effect on factor II or other components of the intrinsic coagulation pathway. Factor Xa inhibition is due to binding to heparin-activated AT, and AT is a required cofactor for LMWH to exert a significant anticoagulant effect. AXa assays are the primary means of measuring the anticoagulant effect of LMWH in the plasma of humans and dogs and can also be utilized to monitor the effect of UFH.\textsuperscript{19,34,35} The AXa assay is chromogenic and measures the inhibition of a calibrated concentration of factor Xa to hydrolyze a test substrate when combined with a measured quantity of patient plasma.\textsuperscript{36,37}

The established therapeutic range for humans with the AXa assay is 0.5–1 U/mL when using LMWH and 0.35–0.75 U/mL when using UFH.\textsuperscript{38} In humans, this range corresponds with a 2-fold increase in the aPTT when using UFH, and is valid for monitoring therapy with that product. Because the dose-response relationship between LMWH and AXa inhibition is so predictable in humans, therapeutic monitoring is not routinely necessary unless the patient is obese, or has renal failure or some other disorder that may alter metabolism of the drug.\textsuperscript{19} Currently, ex vivo studies in dogs have validated the use of AXa assays and the correlation between AXa and aPTT has been established with the use of UFH and LMWH.\textsuperscript{37} Although only healthy dogs have been evaluated, there appears to be a statistical relationship between the 2 assays but the 2 are not linearly correlated across a wide range of values. However, in dogs treated with UFH, the aPTT typically does not increase to the same degree as it does in humans at similar plasma heparin levels.\textsuperscript{31} These experiments have only been conducted in healthy dogs; the relationship between AXa and aPTT has not been evaluated in dogs with spontaneous disease that might increase their thromboembolic risk.\textsuperscript{22,35}

As veterinary use of LMWH increases, the need to evaluate its safety and efficacy in canine patients becomes more important as there is currently little evidence-based information available to support its use. The study reported here compared the effects of LMWH against 2 different UFH protocols on AXa and aPTT in dogs that were treated with anticoagulant therapy by their attending clinician because they were judged to be at risk of venous thrombosis. Our hypothesis was that, when administered to sick dogs, dalteparin (DP) (100 U/kg, SC, q 12 h) would provide higher AXa activity than a constant rate infusion (CRI) of UFH at 900 U/kg/day.

**Materials and Methods**

**Selection of participants**

Client-owned dogs presented to North Carolina State University Veterinary Teaching Hospital and judged by their attending clinician to require anticoagulant therapy for thromboprophylaxis were evaluated for suitability for this study. Dogs with diseases or conditions that have been previously associated with a risk of thrombosis were considered for inclusion.\textsuperscript{3–18,30–42} Once identified, the principle investigator (K.S.) evaluated each animal to determine eligibility. Exclusion criteria

included signs of active hemorrhage, clinician estimation that the dog would not survive for at least 48 hours after enrollment and body weight of <5 kg. Permission with informed consent was granted by all owners and the protocol was approved by the institutional animal care and use committee. Because group allocation and drug preparation was conducted by our pharmacy staff during business hours, dogs were enrolled into the study from Monday to Friday between 8 AM and 5 PM. More than three-fourths of the dogs that presented during these hours were enrolled into the study.

**Experimental protocol**

Once enrolled, dogs were randomly assigned to 1 of 3 treatment groups: a DP group that received dalteparin at a dosage of 100 U/kg SC at 0, 12, and 24 hours, a high-dose heparin (HDH) group that received UFH at 100 U/kg IV immediately followed by a CRI of 900 U/kg/day via a syringe pump injecting into an IV fluid line, and a low-dose UFH (LDH) control group that received UFH at a dosage of 300 U/kg/day also by CRI. Dogs in each protocol were treated for 24 hours.

All personnel directly associated with the study were blinded as to treatment, and group allocation was performed by the pharmacy staff. A computer randomization program was used to randomize the 3 groups. Each group was required to have 6 individuals. A log was then created that had 18 rows, and the group letters were written in 1 column. As each dog presented, its name was written down, 1 name per row, beside a group letter, in sequential order. If an enrolled dog was dropped from the study due to complications, that dog’s group letter was written in at the end of the log and recycled. All dosages of placebo, DP, and UFH were formulated to identical volumes with the same vehicle (sterile saline) and appearance by the pharmacy staff. Dogs not in the DP group received an equivalent volume of sterile saline SC twice daily. All dogs were treated with an IV loading dose of either sterile saline or UFH 100 U/kg, and dogs in the DP group were given sterile saline as a CRI with a syringe pump.

During the study, all dogs were monitored for signs of bleeding by monitoring catheter bandages, incision sites, and packed cell volumes. If incisions or catheter sites were noted to have excessive bleeding, or if the packed cell volume decreased more than 5 percentage points, treatment was discontinued and the dog was withdrawn from the study.

Blood samples were collected from a central catheter before initiating treatment at time 0, and at 4 and 28 hours after treatment began. All blood sampling was performed using a previously published technique after clamping the IV line close to the sampling port at the central catheter hub, 6 mL of blood was removed and set aside as a purge sample. Another syringe was used to draw the sample for analysis for AXa assay and aPTT, and the purge sample was returned to the patient. A 22-G needle was used for all procedures. The sample was divided into 2 calcium citrate vacutainer tubes for submission to the Clinical Pathology Laboratory. The calcium citrate tubes were centrifuged within 30 minutes and the plasma decanted and placed into 2 aliquots. The first was used for the aPTT assay, which was determined via electromechanical clot detection Start 4 and the second plasma aliquot was immediately frozen at −62.2 °C (−80 °F) until it was sent, packed in dry ice, to the Comparative Coagulation Section Laboratory at Cornell University for AXa assay. All AXa assays were performed within 3 months of sample collection.

**Data analysis**

The distribution of results for both assays was not normal; therefore, nonparametric analysis methods were used. Values for the AXa assays that were below the lower limit of detection (0.1–0.2 U/mL, depending on hemolysis) were converted to 0 for analysis. Any sample that did not clot in the aPTT assay was recorded as 200 seconds. An overall treatment effect for repeated measures was evaluated with the Cochran-Mantel-Haenszel (CMH) statistic. When there was a significant overall treatment effect identified, a one-way ANOVA using Wilcoxon scores was used to generate the Kruskal–Wallis statistic to compare treatment effects at each time point.

**Results**

Thirty dogs were identified and enrolled in this study over a period of 14 months. Enrolled dogs were afflicted with a variety of disorders (Table 1). Twelve dogs of the originally identified 30 enrolled were disqualified at different points of the study. Most of these were dropped before the collection of the 28-hour sample and thus the post-treatment data were incomplete for these individuals and not included for analysis. This resulted in a total group of 18 dogs for the study; the study design of 6 dogs per group. Of 10 dogs allocated to the DP group, 4 were eliminated due to sample handling error (n = 2) or death from unrelated causes (n = 2); of 14 dogs allocated to the HDH group, 8 were eliminated due to sample handling error (n = 1), death from unrelated causes (n = 2), hemorrhage (n = 4), or treatment with a blood substitute that interfered with the AXa assay (n = 1). All six dogs allocated to the LDH group completed the study. No dog that completed the study developed clinically evident thrombosis.
The AXa and aPTT results at 4 and 28 hours from dogs that completed the study in each of the 3 groups were compared with baseline values. While there was no overall effect of treatment on the aPTT, treatment had a significant overall effect on the AXa assay (CMH statistic, \( P = 0.02 \)). This was due to the response by the HDH group at 4 hours, when those dogs had significantly higher AXa activity (0.4, 0–1.0 [median, range]) than the other 2 treatments (0, 0–0.1) (one-way ANOVA, \( P = 0.01 \)).

Samples from 2 dogs in the HDH group had AXa activities of 0.55 and 0.6 U/mL at hour 4 which were within the recommended human therapeutic range (0.35–0.75 U/mL) for AXa. Those same samples also had a 1.6- and 5.4-fold prolongation, respectively, in the aPTT (Figures 1 and 2) at the same time point. The hour 4 AXa value from a third dog in the same group exceeded the human therapeutic range slightly (1.0 U/mL); this sample did not form a clot in the aPTT assay.

One dog in the HDH group had subtherapeutic AXa values and a 2.1-fold elevation of the baseline aPTT at 4 hours; this same dog continued to have a subtherapeutic AXa and a 4.7-fold elevation of the aPTT value at 28 hours.

No dog in the DP and LDH groups had elevated AXa activity, hence these dogs did not achieve a response in the therapeutic range established for humans. No significant changes were seen in the aPTT at any time in the LDH group and only 1 dog in the DP group had a clinically significant increase in aPTT at hour 28 (increase to 31 seconds or 1.9-fold elevation over baseline).

### Discussion

In this study, the dose of UFH that increased the AXa to values recommended for humans was associated with marked prolongation of the aPTT in 4 of 6 dogs that

**Table 1:** Activated partial thromboplastin time (aPTT), anti-factor Xa activity (AXa), and predisposing condition of dogs completing the study

<table>
<thead>
<tr>
<th>Group</th>
<th>Condition</th>
<th>Hour 0 (aPTT [seconds]/AXa [U/mL])</th>
<th>Hour 4 (aPTT [seconds]/AXa [U/mL])</th>
<th>Hour 28 (aPTT [seconds]/AXa [U/mL])</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDH</td>
<td>Immune-mediated hemolytic anemia (IMHA)</td>
<td>16.5/&lt;0.1</td>
<td>26.3/&lt;0.55</td>
<td>17.4/&lt;0.1</td>
</tr>
<tr>
<td>HDH</td>
<td>Pancreatitis</td>
<td>17.4/&lt;0.1</td>
<td>19.9/&lt;0.25</td>
<td>15.8/&lt;0.1</td>
</tr>
<tr>
<td>HDH</td>
<td>Heart worm disease following parasite extraction</td>
<td>12.5/&lt;0.1</td>
<td>12.7/&lt;0.2</td>
<td>12.2/&lt;0.1</td>
</tr>
<tr>
<td>HDH</td>
<td>Pancreatic islet cell tumor resection</td>
<td>19.6/&lt;0.1</td>
<td>No clot/1</td>
<td>23.8/&lt;0.1</td>
</tr>
<tr>
<td>HDH</td>
<td>SIRS</td>
<td>23.3/&lt;0.2</td>
<td>50.6/&lt;0.2</td>
<td>109.3/&lt;0.2</td>
</tr>
<tr>
<td>HDH</td>
<td>Cholecystoduodenostomy</td>
<td>17.1/&lt;0.1</td>
<td>92.8/&lt;0.6</td>
<td>17.9/&lt;0.1</td>
</tr>
<tr>
<td>DP</td>
<td>Severe PLE</td>
<td>17.6/&lt;0.1</td>
<td>20.0/&lt;0.1</td>
<td>19.0/&lt;0.1</td>
</tr>
<tr>
<td>DP</td>
<td>Adrenalectomy</td>
<td>13.3/&lt;0.1</td>
<td>14.2/&lt;0.1</td>
<td>17.0/0.4</td>
</tr>
<tr>
<td>DP</td>
<td>IMHA</td>
<td>15.4/&lt;0.1</td>
<td>15.6/&lt;0.1</td>
<td>16.2/&lt;0.1</td>
</tr>
<tr>
<td>DP</td>
<td>PSS ligation</td>
<td>16.3/&lt;0.1</td>
<td>17.7/&lt;0.1</td>
<td>31.0/&lt;0.1</td>
</tr>
<tr>
<td>DP</td>
<td>Pancreatitis</td>
<td>19.1/&lt;0.1</td>
<td>20.3/&lt;0.1</td>
<td>16.5/&lt;0.1</td>
</tr>
<tr>
<td>DP</td>
<td>Anemia and severe protein loss</td>
<td>16.0/&lt;0.1</td>
<td>17.0/&lt;0.1</td>
<td>19.5/&lt;0.1</td>
</tr>
<tr>
<td>LDH</td>
<td>Adrenalectomy (pheochromocytoma)</td>
<td>11.7/&lt;0.1</td>
<td>11.7/&lt;0.1</td>
<td>15.6/&lt;0.1</td>
</tr>
<tr>
<td>LDH</td>
<td>IMHA</td>
<td>12.2/&lt;0.1</td>
<td>14.2/&lt;0.1</td>
<td>13.2/&lt;0.1</td>
</tr>
<tr>
<td>LDH</td>
<td>PSS ligation</td>
<td>21.3/&lt;0.1</td>
<td>24.9/&lt;0.1</td>
<td>23.4/&lt;0.1</td>
</tr>
<tr>
<td>LDH</td>
<td>Pancreatitis</td>
<td>8.6/&lt;0.1</td>
<td>9.4/&lt;0.1</td>
<td>8.4/&lt;0.1</td>
</tr>
<tr>
<td>LDH</td>
<td>Pancreatitis and hyperadrenocorticism</td>
<td>18.9/&lt;0.1</td>
<td>24.7/&lt;0.1</td>
<td>19.5/&lt;0.1</td>
</tr>
<tr>
<td>LDH</td>
<td>Severe hyperadrenocorticism</td>
<td>12.3/&lt;0.1</td>
<td>22.7/&lt;0.1</td>
<td>11.4/&lt;0.1</td>
</tr>
</tbody>
</table>

HDH, high-dose heparin, LDH, low-dose heparin, DP, dalteparin; PSS, portosystemic shunt; SIRS, systemic inflammatory response syndrome; PLE, protein losing enteropathy.
Figure 2: Anti-factor Xa (AXa) assay results. Shaded areas indicate the therapeutic target ranges for humans treated with unfractionated heparin (UFH) (dark shaded) and low-molecular-weight heparin (LMWH) (light shaded). The darkest area represents overlap of the 2 ranges. HDH, high-dose heparin, LDH, low-dose heparin, DP, dalteparin.

completed the study, and hemorrhage in an additional 4 of the total of 14 dogs enrolled in the HDH group. The LDH protocol did not prolong the aPTT or AXa and that dosage appears to be inadequate. Dosages of DP that have been used for prevention of aortic thromboembolism in cats did not produce measurable AXa activity in the dogs in this study. As expected, the dose of DP used in this study did not affect the aPTT, but it also did not increase AXa at either time point evaluated, suggesting that the dose was insufficient to produce clinical benefit in sick dogs.

High-dose UFH increased the aPTT greater than twice baseline in 3 of 6 dogs that completed the study. This effect was present at 4 hours after the CRI was started and had disappeared at 28 hours, 4 hours after administration was terminated, in all but 1 dog. Two of the 4 dogs that were dropped from the HDH group because of hemorrhage were removed after 4 hours and had an aPTT measurement at that time. Both results were prolonged to twice baseline (36.6 and 38.6 seconds), consistent with results in the dogs in this study. This effect was present at 4 hours after the CRI was started and had disappeared at 28 hours, 4 hours after administration was terminated, in all but 1 dog. Two of the 4 dogs that were dropped from the HDH group because of hemorrhage were removed after 4 hours and had an aPTT measurement at that time. Both results were prolonged to twice baseline (36.6 and 38.6 seconds), consistent with results in the dogs in this study.

The trend toward re-prolongation of aPTT in the HDH group at hour 4 may be attributable to the additive effect of the loading dose of UFH in addition to the CRI. The trend toward re-prolongation of aPTT in the HDH group from hour 4 (38.5 seconds, range 12.7–200 seconds) to hour 28 (17.6 seconds, range 12.2–109.3 seconds) could be due to rapid dissipation of the drug effect after withdrawal or may reflect some other fundamental change in the underlying condition or response to the drug.

While 4 dogs in the HDH group were dropped from the study due to hemorrhage before collection of the 28-hour sample, 2 dogs in this group that completed the study had essentially no prolongation of their aPTT or elevation of AXa. This wide range of results demonstrates the unpredictability of individual response to that drug and highlights the need for therapeutic monitoring when the therapeutic goal is to calibrate the dose to prolong the aPTT by a prescribed amount. It is possible that this range is a reflection of the individual variation in heparin response, the inconsistency of heparin composition, or the particular disease process in these dogs. Because of the unpredictable response to UFH, dosing nomograms are routinely used to guide therapy in humans and have been recommended for use in dogs.

This study was conducted in dogs with spontaneous disease and that were considered by their attending clinician to be at risk of venous thrombosis. That judgment was based on clinical evaluation alone, as funding and equipment did not allow for more objective determination of hypercoagulability. The low dose of UFH used in the LDH group was chosen as a comparative dose in this study because it reflected the common clinical practice at our institution for patients at risk of thrombosis, precluding the use of negative controls in this study. This LDH dose has been used in our veterinary teaching hospital as standard treatment for dogs in disseminated intravascular coagulation and had been extrapolated by many clinicians here as a primary prophylaxis in dogs at risk of venous thrombosis. In our institutional experience, this dose typically could be explained by the possibility that the doses were too low to interfere with appropriate coagulation.

Although by itself the loading dose of heparin used here may not prolong the aPTT beyond 1–2 hours, the prolongation of aPTT in the HDH group at hour 4 may be attributable to the additive effect of the loading dose of UFH in addition to the CRI. The trend toward re-prolongation of aPTT in the HDH group from hour 4 (38.5 seconds, range 12.7–200 seconds) to hour 28 (17.6 seconds, range 12.2–109.3 seconds) could be due to rapid dissipation of the drug effect after withdrawal or may reflect some other fundamental change in the underlying condition or response to the drug.
does not prolong the aPTT, an observation in line with the results of this study.

The HDH dose was selected based on Hellebreker’s work that demonstrated that SC UFH at a dosage of 1000 U/kg/day, divided every 6 hours will elevate a normal dog’s aPTT by roughly twice normal.25 The IV loading dose of 100 U/kg was chosen based on Green’s demonstration that when given IV, this dosage will elevate the aPTT to 1.8 times the baseline in normal dogs 1 hour after administration.26 Prior work using constant infusions of UFH in rabbits demonstrated that a constant infusion titrated to prolong the aPTT by 1.5–2.5 times normal had less recurrence of thrombi or bleeding than the same dose given via intermittent injections.46

The DP dose was selected because it was routinely used at our institution at the time of study design, based on reports of its use in cats.44,45 Although experimental studies suggested that healthy dogs may need a higher dose or more frequent administration of DP, this lower dose was selected because of concerns about any potential untoward effects of the higher doses in sick client-owned dogs.47 The sampling times of 4 and 28 hours were chosen based on recommendations of the testing laboratory as well as the observation that heparin activity of SC administered DP may be well maintained for 4 hours in healthy dogs.48 The authors are not aware of any published clinical studies evaluating the effects of DP in dogs with conditions that may predispose them to venous thrombosis.

There were several significant limitations to this study. First, with no reliable epidemiological data on thrombosis risk in a broad range of critical illness in dogs, inclusion in the study was based on the enrolling clinician’s assessment that the dog was at an increased risk of forming a venous thrombus, regardless of the underlying cause. There is currently no standardized method of determining risk for venous thrombosis in dogs; however, evaluating dogs with tests such as thromboelastography might help more accurately to identify dogs that are hypercoagulable rather than relying on clinical judgment alone.49

Second, the small number of subjects with multiple disease processes makes it difficult to discern the relative impact of disease process and drug on the coagulation parameters. Enrolling larger numbers of subjects, evaluating patients with only 1 disease process, and evaluating hypercoagulable dogs with varying dosages of LMWH would provide a better understanding of how the different types of heparin compare and what dosage is the most appropriate.

Third, budget limitations required utilizing normal pharmacy scheduled hours so dogs that presented after hours or on weekends could not be included in the patient population pool, thus reducing the number of subjects in the study. Budget constraints also permitted only 3 blood samples to be evaluated within a 28-hour period of time. More frequent sampling and longer monitoring would provide a better understanding of when the anticoagulants had their peak and trough effects, and would give us information on managing dogs that develop complications.

In conclusion, although this study was not designed to compare efficacy or outcome, none of the dogs developed clinically apparent thrombosis. The results demonstrated that the LDH and DP protocols used here were too low to increase AXa activity or prolong the aPTT, and the effect of UFH in the HDH protocol on aPTT was unpredictable in that the same dose that caused hemorrhage or marked prolongation of the aPTT in some dogs had no effect on aPTT in others. Additionally, the dose of UFH that elevated the AXa to the human therapeutic range was associated with marked prolongation of aPTT. The human therapeutic target for AXa was not met for any dog in the LDH or DP groups. Because of these disparities, future studies with LMWH should be designed to evaluate the heparin activity produced by higher doses than the dose of DP that was used here, as originally suggested by Mischke53 based on work in healthy dogs. If UFH is used in clinical studies, the HDH protocol is indicated but requires close therapeutic monitoring.

Footnotes
a Fragmin, Pharmacia, Kalamazoo, MI.
b Unfractionated heparin, Baxter Healthcare Corporation, Deerfield, IL.
c Diagnostica Stago, Parsippany, NJ.
d Rotachrom Heparin, Diagnostica Stago, Asnieres-sur-Seine, France, distributed in the United States by American Bioproducts Company, Parsippany, NJ.
e SAS/STAT using PROC NPAR1WAY, SAS Corporation, Cary, NC.
f Oxyglobin, Biopure Corporation, Cambridge, MA.

References