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Antithrombotic Effect of Enoxaparin in Clinically Healthy Cats: A Venous Stasis Model

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Background: Systemic arterial thromboembolic events are a serious complication of cardiac disease in cats.

Objectives: To determine if enoxaparin induces an antithrombotic effect in cats at a dosage of 1 mg/kg SC q12h and if this antithrombotic effect is predicted by anti-Xa activity.

Animals: Fourteen clinically healthy cats were divided into 3 groups: control (4 cats), treated and assessed at 4 hours (5 cats), and treated and assessed at 12 hours (5 cats).

Methods: A venous stasis model was used and the extent of thrombus formation estimated by measuring thrombus weight and accretion of ^{125}I-fibrinogen. Plasma anti-Xa activity was measured in treated cats.

Results: There was a significant reduction in thrombus formation in the 4 h group compared with control (median weight, 0.000 versus 0.565 mg/mm, $P < .01$; median %^{125}I-fibrinogen accretion, 0.0 versus 42.0%, $P < .01$). There was a reduction in thrombus formation in the 12 h group (median weight, 0.006 mg/mm, $P = .09$; median %^{125}I-fibrinogen accretion, 3.83%, $P = .09$) but this reduction was not significant. The median percent thrombus inhibition for treated cats was 100.0% at 4 hours and 91.4% at 12 hours. Plasma anti-Xa activity was not significantly correlated with thrombus formation.

Conclusions and Clinical Importance: This pilot study demonstrates that enoxaparin, when administered at a dosage of 1 mg/kg SC q12h, produces an antithrombotic effect in a venous statsis model in clinically healthy cats. Furthermore, this study demonstrates that anti-Xa activity is a poor predictor of enoxaparin's antithrombotic effect.

Key words: Anti-Xa; Cardioembolic; Feline; LMWH; Lovenox; Thrombosis.

Systemic arterial thromboembolic disease has been reported frequently in the cat, most often associated with underlying cardiac disease (ie, cardiogenic embolism).[1–4] Many antithrombotic drugs have been considered in the prevention of thromboembolic disease in cats, with the low-molecular weight heparins (LMWH) gaining particular interest over the past decade. Because of the greatly decreased inhibitory effect of LMWH on thrombin, common hemostatic tests are not altered with LWMH therapy. For this reason, the methodology used to evaluate LMWH therapy is a chromogenic anti-Xa assay.[5] Pharmacokinetic modeling of 2 LMWH, dalteparin, and enoxaparin, has been evaluated in cats utilizing plasma anti-Xa activity.[6] The conclusion from this study was that the dose and dosing frequency of these LMWH required to maintain anti-Xa activity within the target range in humans are much higher than currently suggested.[7] The hypothesis of this study was that enoxaparin, when used at a common dosage (1 mg/kg SC q12h) for 5 consecutive days, would result in a measurable antithrombotic effect utilizing a venous stasis model in clinically healthy cats. A secondary objective of this study was to assess the ability of anti-Xa activity to predict the antithrombotic effect of enoxaparin in healthy cats.

Abbreviations:

^{125}I-fib	^{125}I-fibrinogen
AT	antithrombin
LMWH	low-molecular weight heparins
TEG	thromboelastography
TFPI	tissue factor pathway inhibitor
UH	unfractionated heparins

Materials and Methods

Animals

Fourteen clinically healthy purpose-bred cats (5 intact males, 9 intact females, 12–18 months of age, weighing 2.0–6.8 kg) were divided into 3 groups. Four untreated cats served as a control group whereas the remaining 10 cats were each treated with enoxaparin (Lovenox)[a] 1 mg/kg SC q12h for 5 consecutive days (10 doses). A venous stasis model was created in each of the 14 cats. Five of the treated cats were modeled 4 h after their 10th dose of enoxaparin (4 h) whereas the remaining 5 treated cats were modeled 12 h after their 10th dose (12 h). These time points were chosen to approximate the peak and trough periods of anti-Xa activity. The research protocol was approved by the Purdue University Animal Care and Use Committee.

Venous Stasis Model

The venous stasis model used was a modification of previously published animal models to determine the antithrombotic effects of various LMWH.[8,9] Anesthesia was induced with ketamine (15 mg/kg IM), acepromazine (0.02 mg/kg, 0.1 mg maximum dose, IM), and atropine (0.54 mg/cat IM) and maintained with isoflurane in oxygen in a rebreathing system. The cats were placed in dorsal recumbency and the abdomen aseptically prepared. A blood sample was collected at this time by inserting a 22-gauge needle into the jugular vein and blood was collected directly into 3.8% sodium citrate at a ratio of 9 parts blood to 1 part citrate. A skin incision was made from 2 cm caudal to the xyphoid to 3 cm cranial to the pubis. The peritoneum was incised and the abdominal viscera were dis-

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placed cranially and to the left in order to access the caudal vena cava. The cava was isolated using untied sutures just caudal to the left renal vein and cranial to the external iliac veins. Any small side branches noted in this segment were ligated. Five μCi of ^{125}I-fibrinogen (^{125}I-fib)[b] was administered IV and allowed to circulate for 2 minutes to ensure complete distribution. Tissue thromboplastin[c] (500 μg/kg) then was administered IV and after 45–60 seconds the previously placed sutures around the cava were tied creating an estimated 5 cm isolated static venous segment. Stasis was maintained in situ for 30 minutes then the segment was removed to quantify thrombus formation. The cats were humanely euthanized after collection of the static venous segment.

The venous segment was thoroughly rinsed with physiologic saline and placed in a plastic tube. The total amount of ^{125}I-fib within the venous segment then was determined using a gamma well counter.[d] The segment was carefully incised and the thrombus placed on a preweighed, lined plastic weigh boat, and weighed to determine the wet weight of the thrombus. The thrombus and liner then were placed in a plastic tube and returned to the gamma well counter to determine the amount of ^{125}I-fib within the thrombus. The gamma counts for all samples were measured in duplicate.

Calculations

Normalized Thrombus Wet Weight. The wet weight of the thrombus was divided by the length of the venous segment to allow for comparisons among groups.

$$\text{Normalized weight (mg/mm)} = \frac{\text{wet weight of thrombus (mg)}}{\text{length of venous segment (mm)}}$$

Accretion of ^{125}I-Fib. The amount of ^{125}I-fib accumulation within the thrombus was determined by normalizing the amount of ^{125}I-fib within the thrombus to that within the entire venous segment. This calculation accounts for any difference in venous segment size and allows for comparisons between groups.

$$\%\text{Accretion of } ^{125}\text{I-fib} = \frac{\text{venous segment (cpm)} - \text{thrombus (cpm)}}{\text{venous segment (cpm)}} \times 100$$

Percent Thrombus Inhibition. To approximate the potential for thrombus inhibition by enoxaparin, the amount of accreted ^{125}I-fib in the control group was used as a theoretical baseline and used to determine the percentage of thrombus inhibition in each of the treated cats at peak (4 h) and trough (12 h) time points.

$$\%\text{ Thrombus inhibition} = \frac{\text{mean }\%^{125}\text{I-fib control} - \%^{125}\text{I-fib treated}}{\text{mean }\%^{125}\text{I-fib control}} \times 100$$

Anti-Xa Assay

Citrated blood samples were centrifuged immediately at 3000 *g* for 10 minutes at room temperature. Plasma was stored at −80 °C until assayed. Samples were shipped on dry ice to the Cornell Comparative Coagulation Laboratory where anti-Xa activity was determined using a previously published technique.[6] The detection limit for this assay is 0.05 IU/mL and any sample <0.05 IU/mL was assigned the value of 0.00 IU/mL.

Statistical Analysis

Due to small sample sizes, data were assumed to be nonnormally distributed. To compare medians among groups, the Kruskall-Wallis ANOVA with Wilcoxon rank-sum test was used. A Spearman's rank correlation coefficient (r_s) was calculated to determine if anti-Xa activity correlated with accretion of ^{125}I-fib. A *P*-value of ≤.05 was considered statistically significant. Statistical analysis was carried out using a commercial software program.[e]

Results

Median normalized thrombus weight was significantly decreased in 4 h cats compared with control cats (0.000 mg/mm; 0.565 mg/mm, $P < .01$). Median normalized thrombus weight in the 12 h cats did not reach statistical significance when compared with controls (0.006 mg/mm; 0.565 mg/mm, $P = .09$) (Table 1, Fig 1).

As expected, median $\%^{125}$I-fib accretion followed the same pattern and was significantly decreased in 4 h cats (0.00%; 42.0%, $P < .01$) but not in 12 h cats (3.83%; 42.0%, $P = .09$) (Table 1, Fig 1).

Median percent thrombus inhibition was 100.0% in the 4 h cats and 91.4% in the 12 h cats. Four of the 4 h cats (80%) and 2 of the 12 h cats (20%) had 100% thrombus inhibition (Table 1, Fig 2).

Plasma anti-Xa activities were variable in the 4 h cats, ranging from 0.35 to 1.4 IU/mL with a median of 0.75 IU/mL. Anti-Xa activity was 0.00 IU/mL in all cats in the 12 h group. Plasma anti-Xa activity was not significantly correlated with accretion of ^{125}I-fib ($r_s = -0.575$, $P = .082$) (Table 1, Fig 3).

No bleeding complications were noted during the study nor was excessive bleeding encountered during creation of the model.

Discussion

Data from this study demonstrates that enoxaparin results in a measurable antithrombotic effect in a venous stasis model in clinically healthy cats using a dosage of 1 mg/kg SC q12h. This effect was statistically significant 4 h but not 12 h after the final dose. However, the 12 h treatment group was influenced by the small sample size and 1 cat that had a much larger thrombus than the other 4 cats. Our study also showed no significant correlation between anti-Xa activity and antithrombotic effect in treated cats, rendering anti-Xa activity at any given point in time a poor predictor of the antithrombotic effect of enoxaparin in this species. In fact, undetectable anti-Xa activity was associated with $\%^{125}$I-fib accretion rates of 0.00, 0.00, 3.83, 12.20, and 52.46% in treated cats. Although our sample size was small and a larger study may have identified statistical significance, the relationship is weak as illustrated in Fig. 3 in which the data points fall along both axes making a true relationship unlikely. Our data are similar to other animal model data in the literature.[8,10–14]

After administration of enoxaparin, 4/5 (80%) cats in the 4 h group had no thrombus formation whereas the 5th cat had minimal thrombus formation. In the 12 h group, 4/5 (80%) cats had minimal (2/5), or no thrombus

Table 1. Demographic and thrombotic data of study population

Groups	Gender	Weight (kg)	N Thromb Wt (mg/mm)	^{125}I-fib Accretion (%)	Throm Inhib (%)	Anti-Xa (IU/mL)
Control	2 MI, 2FI					
Median		5.12	0.565	41.95	NA	NA
Peak	2 MI, 3 FI					
Median		4.20	0.000*	0.000*	100.00	0.75
Trough	1 MI, 4 FI					
Median		3.78	0.006	3.83	91.35	0.00

*$P < .01$ compared with control.

MI, male intact; FI, female intact; N Thromb Wt, normalized thrombus weight; ^{125}I-fib accretion, percent accretion of ^{125}I-fibrinogen; Throm Inhib, percent thrombus inhibition; Anti-Xa, plasma anti-Xa activity; NA, not applicable.

(2/5) formation. Although 4/5 (80%) cats in the 4 h group had anti-Xa activity within or above the target range for peak anti-Xa activity in humans[15], 0/4 (0%) of the cats in the 12 h group had measurable anti-Xa activity when a demonstrable antithrombotic effect was present.

One cat in the 12 h group formed a thrombus considerably larger than those observed in the other cats. If this cat is removed from data analysis, the median normalized thrombus weight and %^{125}I-fib accretion at 12 hours are significantly lower than those of the controls (0.003 mg/mm, 1.9%; 0.565 mg/mm, 42.0%, $P = .02$, .02, respectively), which correlates with 95.5% thrombus inhibition. Removal of this cat also would change the correlation between plasma anti-Xa activity and accretion of ^{125}I-fib ($r_s = -0.517$, $P = .154$). However, there is no justifiable reason to remove this cat and it was included in final data analysis. Possible explanations for the aberrant results in this cat include variable pharmacokinetic or pharmacodynamic responses to enoxaparin or an inherent prothrombotic condition in this individual cat. Given that this cat was only evaluated 12 hours after receiving enoxaparin, we cannot conclude that an antithrombotic effect would not have been seen at 4 hours. Additionally, our study was not longitudinal, and we cannot determine what size thrombus would have formed in this individual cat with no enoxaparin treatment.

Several animal model studies have demonstrated a clear antithrombotic effect of LMWH.[8,10–14] However, given the negligible effect of LMWH on standard hemostatic tests, the only way to estimate the clinical activity of these fractionated heparins has been by measuring their ability to inhibit factor Xa. Although many of the studies did demonstrate a correlation between peak anti-Xa activity and antithrombotic effect after IV administration in acute studies, this finding was not demonstrated in other animal studies that included SC administration or evaluation of different fractions of heparin.[8–14,16–18] Additionally, before our study, there were no animal model studies that evaluated antithrombotic effect when anti-Xa activity would be expected to be at its lowest (trough).

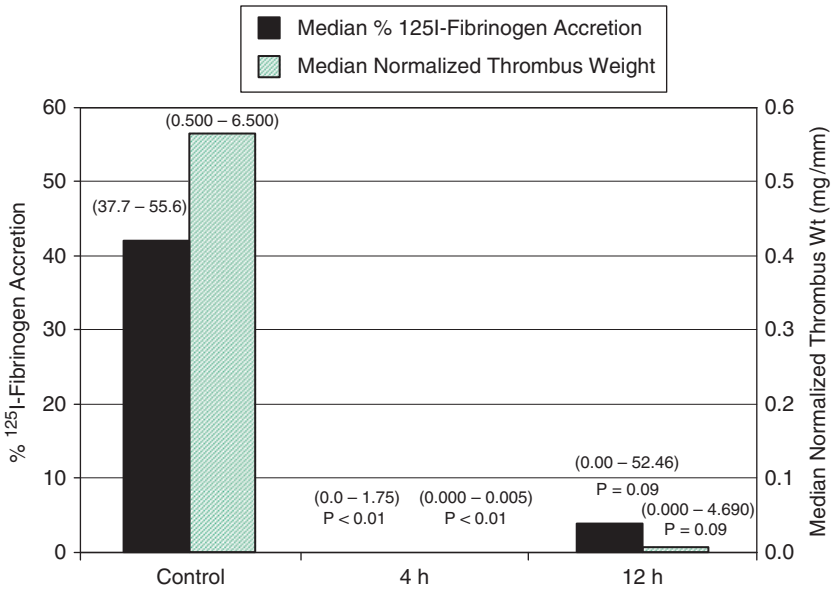

Fig 1. Median %^{125}I-fibrinogen accretion and median normalized thrombus weight for the control, 4 and 12 h groups. Result ranges are shown in parenthesis above each bar. *P*-values for difference from control group.

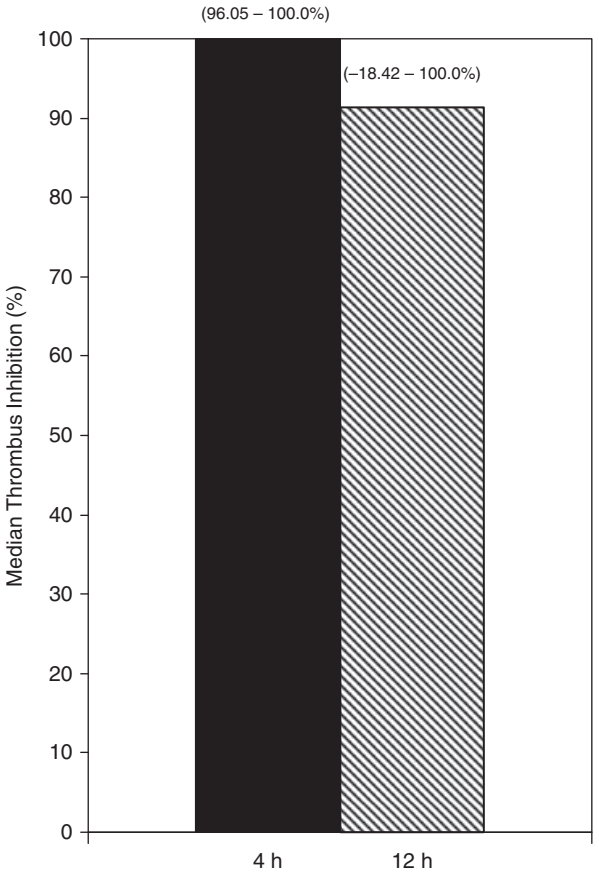

Fig 2. Median percent thrombus inhibition in 4 and 12 h cats. Result ranges for percent inhibition are shown in parentheses above each bar. One cat in the 12 h group had a larger thrombus than the median for the control group resulting in a negative thrombus inhibition value.

Once the antithrombotic effect of LMWH had been established in animal models, in vitro studies were carried out using human plasma spiked with variable concentrations of LMWH. A clear concentration-dependent effect on anti-Xa activity was found and, based on this data and

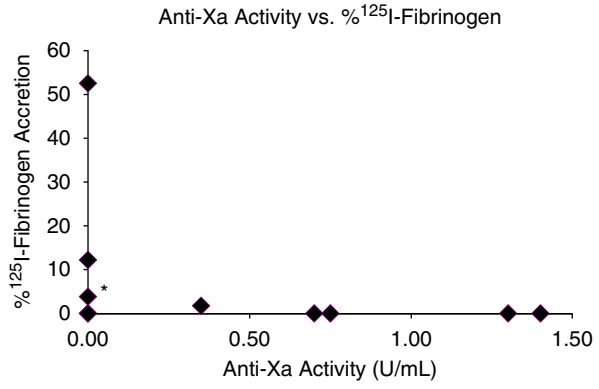

Fig 3. Measured anti-Xa activity for individually recorded $\%^{125}$I-fibrinogen in treated cats. *This plotted point represents 2 cats in the 4 h group.

negligible effects on other hemostatic tests, the anti-Xa assay was adopted as the method of choice to monitor LMWH in clinical trials of humans.[16] The LMWH have been proven repeatedly to be at least as effective and safe as unfractionated heparins (UH) in humans for the prevention of deep venous thrombosis or venous thromboembolism, thrombosis in acute coronary syndrome patients and percutaneous coronary intervention patients as well as in treatment of deep venous thrombosis and pulmonary embolism.[19–25]

Pharmacokinetic studies in humans have demonstrated that when LMWH are administered SC, anti-Xa activity peaks 3–5 hours after administration and then steadily declines. Elimination half-lives are 3–6 hours and are not dose dependent so that time to peak is unchanged regardless of whether drug administration is once or twice daily.[15,26] Once daily dosing of LMWH has been reported to effectively prevent thrombotic events even though anti-Xa activity was very low 6 hours after treatment.[27] Additional experimental studies have demonstrated that anti-Xa activity is often immeasurable 10–12 hours after administration.[28]

In the majority of clinical trials in humans, anti-Xa activity was only measured approximately 4 hours after treatment to estimate peak anti-Xa activity. The anti-Xa activity reached in these patients at 4 hours became the target range for peak anti-Xa activity or ''therapeutic peak anti-Xa activity'' for clinical use. Recommended ranges for peak anti-Xa activity with different LMWH dosing protocols have been suggested in humans. When total body weight (TBW)-adjusted enoxaparin is administered twice daily for thrombotic treatment, peak anti-Xa activity at 4 hours is recommended to be 0.6–1.0 IU/mL, with increased risk for bleeding if activity is >1.0 IU/mL.[15] No accepted range for peak anti-Xa activity has been established for thromboprophylaxis. However, mean peak anti-Xa activity at 4 hours of 0.42 IU/mL has been reported with median trough activity of 0.03 IU/mL (0.00–0.188) in normal humans receiving standard prophylaxis protocols.[29] Clinical trials in humans have not always been able to demonstrate a correlation between peak anti-Xa activity and thrombotic events or hemorrhagic complications.[16] Because of the uncertainty over this relationship, routine clinical monitoring of peak anti-Xa activity is not recommended in humans. Monitoring generally is limited to specific patient groups (eg, obese patients, renal failure patients) because they are potentially more prone to overdosing when TBW-adjusted protocols are used.[30–32] The minimal effective anti-Xa activity in humans remains unknown, and our results demonstrate that enoxaparin induces an antithrombotic effect in the absence of measurable anti-Xa activity.

The LMWH also have been shown to have antithrombotic effects beyond factor Xa inhibition including release of tissue factor pathway inhibitor (TFPI), fibrinolytic activity, rheologic effects, and release of endogenous heparans.[33–35] Some have proposed that these additional effects, especially release of TFPI, provide a beneficial antithrombotic effect when anti-Xa activity decreases to very low or immeasurable levels. Our study

demonstrates that enoxaparin continues to induce an antithrombotic effect at a time when anti-Xa activity was not measurable.

Only a few studies have evaluated the pharmacokinetics of LMWH in cats. The first study evaluated a TBW-adjusted protocol of dalteparin by measuring anti-Xa activity in a small number of cats.[f] It demonstrated that when dosed at 100 IU/kg SC once daily for 5 days, anti-Xa activity 4 h after administration was within the target range for peak anti-Xa activity for humans. One cat had anti-Xa activity measured at multiple time points and had a pattern similar to humans in whom peak activity was achieved after 4 h and then steadily declined, falling below the target range for peak anti-Xa activity between 4 and 8 h and becoming unmeasurable after 8 hours. A later study evaluated the pharmacokinetics of dalteparin and enoxaparin with the goal of maintaining anti-Xa activity within the therapeutic peak (4 h) range of 0.5–1.0 IU/mL in humans for the entire 24 h study period.[g] Both drugs were administered q6h and it was determined, by a pharmacokinetic model, that the predicted peak anti-Xa activity in cats treated with dalteparin and enoxaparin (0.99 and 0.95 IU/mL, respectively) would be achieved after 2 hours. An additional pharmacokinetic study of dalteparin determined that when administered q12h, 50% of cats achieved peak anti-Xa activity after 4 hours and then activity returned to baseline by 6 hours.[h] The remaining 50% of cats never developed measurable anti-Xa activity.

A more recent pharmacokinetic study by Alwood et al[6] evaluated TBW-adjusted treatment protocols for dalteparin (100 IU/kg SC q12h) and enoxaparin (1 mg/kg SC q12h) by measurement of multiple hemostatic markers including anti-Xa activity and thromboelastography (TEG). The pattern of anti-Xa activity was similar to the first study using cats and studies of humans in which peak activity was reached 4 hours after administration and then decreased until activity was undetectable after approximately 8 hours for both dalteparin and enoxaparin. However, median peak anti-Xa activity was 0.29 and 0.43 IU/mL on day 5 for dalteparin and enoxaparin, respectively, which is less than the target range for peak anti-Xa activity in humans.[15] Based on a pharmacokinetic model, the authors concluded that these drugs should be administered at 150 IU/kg q4h and 1.5 mg/kg q6h for dalteparin and enoxaparin, respectively, to maintain anti-Xa activity within the target range of peak anti-Xa activity for humans over the entire treatment period. However, as mentioned previously, this therapeutic range in humans only applies to the peak 4 h time point. Additionally, these anti-Xa activities were derived from large clinical trials in humans whereas similar clinical trials are not available for cats. Peak anti-Xa activity in our study (median, 0.75 IU/mL; range, 0.35–1.4 I U/mL) was higher than that reported by Alwood and colleagues but our trough anti-Xa activity actually was lower. The explanation for this finding is not apparent and it simply may reflect the variability of anti-Xa activity that also has been noted in humans. Alwood and colleagues also failed to demonstrate any significant changes in TEG after LMWH administration. Two studies in humans have identified dose-response changes to TEG parameters with enoxaparin therapy.[36,37] Although the 1st study did identify a correlation between these changes and peak anti-Xa activity[36], the magnitude of TEG changes was not always predicted by anti-Xa activity in the 2nd study, resulting in the conclusion that TEG is not useful for monitoring LMWH therapy.[37] We did not perform TEG in our study and cannot draw conclusions regarding changes in TEG parameters in this modified venous stasis model. Evaluation of TEG in a large clinical trial should be considered.

Although our data demonstrate that enoxaparin induces an antithrombotic effect in a venous stasis model in healthy cats, we cannot draw conclusions regarding the clinical efficacy of the dosage used in this study or any other. Prospective, dose-finding clinical trials in cats are necessary to make these determinations. These studies also could be used to estimate the appropriate target range for peak anti-Xa activity in cats as well as to evaluate the ability of other methodologies to accurately reflect effective therapeutic protocols for LMWH. One retrospective clinical study compared dalteparin to warfarin for prevention of recurrent cardiogenic embolism in cats, and demonstrated a comparable recurrence rate and median survival time between treatment groups.[i]

There were some notable limitations to our study. The small sample size may not accurately reflect the general population and resulted in an underpowered study. However, we believe our data proves a mechanistic effect and use of a larger number of animals may be considered inappropriate. Additionally, the cats in our study ranged widely in body weight, with 3 cats weighing $\leq$2.5 kg and normalcy was determined solely on the basis of physical examination findings. Additionally, a venous stasis model may not be appropriate to study a disease characterized by arterial thromboembolism. However, the underlying mechanism for this condition is static blood within a dilated cardiac chamber with subsequent thrombus formation.[38] The embolus that originates from the intracardiac thrombus creates a physical obstruction of the arterial tree in which the arterial wall is normal. We believe an arterial thrombosis model would be inappropriate because the initiating event is arterial endothelial damage associated with high shear flow. Therefore, we believe that a venous stasis model is appropriate for investigating cardioembolic disease in clinical veterinary medicine. Another limitation is the lack of a longitudinal study design. Thrombus size was compared among groups instead of within individual animals before and after therapy. This limitation was unavoidable due to the experimental design. Antithrombin (AT) activity was not measured in this study and AT activity can decrease after UH and LMWH therapy. Lower AT activity may result in a decreased LMWH-induced antithrombotic effect. The injection of tissue thromboplastin in this model may have resulted in decreased AT activity because large amounts of thrombin would have been generated. Therefore, if AT activity had been higher, a greater antithrombotic effect from enoxaparin may have been identified. Lastly, we used acepromazine as part of our anesthetic protocol. This

anesthetic protocol was chosen because it does not interfere with platelet studies in cats.[39–41] However, there is a published report of acepromazine decreasing ADP induced, but not collagen-induced, platelet aggregation in dogs.[42] The same anesthetic protocol was used for all cats in our study and if there was a negative effect on platelet function from the acepromazine, it should not have impacted comparisons among groups.

This pilot study demonstrates that enoxaparin does result in a measurable antithrombotic effect for at least 12 hours in a venous stasis model in clinically healthy cats when administered at a dosage and dosing interval less than that suggested from previous studies in the literature. Furthermore, this study demonstrates that random, time-matched anti-Xa activity is a poor predictor of the antithrombotic effect of enoxaparin in healthy cats. Future clinical trials are necessary to determine the clinical efficacy of this class of drugs and to more clearly elucidate appropriate monitoring methodologies for these drugs.

Footnotes

[a] Sanofi-aventis U.S. LLC, Bridgewater, NJ
[b] GE Healthcare, Pittsburgh, PA
[c] STA Neoplastine CI 10, Diagnostica Stago Inc, Parsippany, NJ
[d] Gamma Counter 7000, Organon Teknika Corp, Durham, NC
[e] STATA, v. 10.1, Stata Corp, College Station, TX
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