Use of low molecular weight heparin in cats: 57 cases (1999–2003)

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Objective—To determine duration of administration, complications, and frequency of aortic thromboembolism associated with administration of low molecular weight heparin (dalteparin) in cats.

Design—Retrospective study.

Animals—57 cats treated with dalteparin.

Procedure—Data were recorded from the medical records of cats treated with dalteparin, and owners were contacted by telephone for information regarding ease of administration and possible adverse effects.

Results—Dalteparin was easily administered by owners. Median dose was 99 U/kg (45 U/lb) once or twice daily. Bleeding complications were infrequent. Of 43 cats with cardiomyopathy that received owner-administered dalteparin for a median follow-up time of 172 days, 8 cats developed documented or possible arterial thromboembolism.

Conclusions and Clinical Relevance—Dalteparin was easily administered by owners and was well tolerated by cats. Whether dalteparin administration can reduce the frequency or severity of arterial thromboembolism is not yet known. (*J Am Vet Med Assoc* 2004;225:1237–1241)

Aortic thromboembolism is a common and serious consequence of feline cardiomyopathy. Aortic thromboembolism has been reported to affect 33% to 50% of cats with hypertrophic cardiomyopathy, the most common form of cardiomyopathy in cats.[1,2] In 100 cases dating from 1977 to 1993, only 37% of cats survived an episode of aortic thromboembolism long enough to be discharged.[3] In a 2003 study of 127 cats, 35% survival was reported, reiterating the continued poor prognosis associated with aortic thromboembolism.[4] Among cats surviving an initial aortic thromboembolism, many cats do not regain limb function and recurrence rates as high as 45% to 75% have been reported.[4-6] At present, no safe drug with proven efficacy in preventing aortic thromboembolism has been identified. Retrospective and prospective studies do not clearly document that aspirin is effective in preventing aortic thromboembolism in cats. In 2 retrospective studies of cats treated with warfarin, aortic thromboembolism recurred in 42%[6] and 44%[3] of cats. Warfarin administration requires careful monitoring by owners and frequent coagulation measurement to minimize the risk of bleeding.

Low molecular weight heparins (LMWHs) in human clinical trials are safe and effective in preventing and treating venous,[7-9] arterial,[10] and intracardiac[11,12] thromboembolism. There are important pharmacologic differences between LMWHs and unfractionated heparin. Unfractionated heparin binds to both thrombin and antithrombin III, resulting in the inhibition of thrombin and other coagulation enzymes including X, XII, XI, and IX. The shorter molecules of LMWHs cannot bind simultaneously to thrombin and antithrombin III and therefore do not inhibit thrombin. Instead, LMWHs selectively inhibit factor Xa to reduce the likelihood of thrombus formation, while minimally affecting clotting times. Relative to unfractionated heparin, LMWHs also bind less to macrophages, plasma proteins, and platelets.[13,14] Reduced binding of LMWHs to macrophages is associated with limited hepatic clearance, and decreased binding to platelets reduces the likelihood that they will cause heparin-induced thrombocytopenia.[15] Compared with unfractionated heparin, LMWHs have a half-life that is 2 to 4 times longer, bioavailability is greater, and a more predictable anticoagulant effect is achieved in humans.[15-17]

Pharmacokinetic studies in healthy horses [18,19] and dogs[20,21] have revealed that LMWHs are well tolerated, with minimal effects on **activated partial thromboplastin time (aPTT)** and no bleeding events. In a preliminary pharmacokinetic study evaluating the effects of 2 doses of LMWH in a small number of cats, minimal effects on coagulation times at a dose of 100 U/kg (45.5 U/lb) were reported.[a] Long-term studies of LMWH use in humans have confirmed that LMWHs can be administered for periods of up to 10 years with minimal bleeding complications[22] and without laboratory monitoring.[17]

Although widely used in humans, LMWH use in cats has been limited[1,6] and there are no published reports of its extended use in cats, to our knowledge. Because LMWHs need to be injected SC on a daily or twice-daily basis, ongoing administration by the owner is required. In humans, LMWHs are advantageous because they do not require routine coagulation testing. Antifactor Xa activity may be used to determine the level of antithrombotic activity after LMWH administration. In humans, the targeted therapeutic range of antifactor Xa activity is 0.35 U/mL to 0.70 U/mL.[23] The preliminary pharmacokinetic study[a] in 4 cats revealed the achievement of therapeutic concentrations of antifactor Xa activity at a dose of 100 U/kg.

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Several forms of LMWHs with varying pharmacokinetic and pharmacodynamic properties (ie, dalteparin[b], enoxaparin, and tinzaparin) are available for use in the United States. The purpose of the study reported here was to investigate the ease and duration of administration, complications, and frequency of aortic thromboembolism in cats treated with dalteparin.

Criteria for Selection of Cases

All cats that received dalteparin were identified retrospectively by searching the pharmacy database at the Foster Hospital for Small Animals at Tufts University School of Veterinary Medicine.

Procedures

The medical records of eligible cats were reviewed, and information was collected by use of a standardized data sheet. Information recorded included signalment, results of the cardiovascular examination, medications, concurrent diseases, occurrence of aortic thromboembolism, presence of **congestive heart failure (CHF)**, outcome (lived, died, or euthanatized), and the dose and frequency of dalteparin administration. Owners who administered dalteparin were contacted by telephone to determine the duration of dalteparin administration, difficulties associated with dalteparin administration, reasons for discontinuing administration of dalteparin, and any medical problems or complications that occurred during the period of dalteparin administration.

For cats with cardiomyopathy for which dalteparin was administered by the owner as a preventative for aortic thromboembolism, the frequency of aortic thromboembolism after dalteparin administration was tabulated and the time until aortic thromboembolism was calculated.

Statistical analyses—Data are reported as mean ± SD or median and range. Data that were not normally distributed were logarithmically transformed prior to analysis. Categoric data were compared by use of χ^2 analysis. Continuous data were compared by use of independent *t* tests. Commercial statistical software was used for analysis.[c] Values of $P < 0.05$ were considered significant.

Results

Sixty-one cats were identified as having had a prescription filled for dalteparin between November 1999 and February 2003. In 4 cats, however, the medication was never administered. In the remaining 57 cats, mean age at the time of starting dalteparin treatment was 9.36 ± 3.8 years. Forty-two cats were male (40 castrated), and 15 were female (all spayed). The most common breed was domestic shorthair (n = 38). Other breeds represented included domestic longhair (n = 9), Maine Coon (3), Siamese or Siamese cross (3), Manx (1), Scottish Fold (1), Norwegian Forest Cat (1), and Persian (1). The most frequent clinical indication for starting dalteparin administration was cardiac disease with accompanying aortic thromboembolism or left atrial enlargement (n = 52). Other indications included portal vein thrombosis (n = 2), heartworm disease (1), postadrenalectomy prevention of pulmonary thromboembolism (1), and cerebral thromboembolic disease (1). Median duration of dalteparin administration for these 57 cats was 84 days (range, 1 to 1,224 days), and median dose was 99 U/kg (45 U/lb) with a range of 41 to 220 U/kg (18.6 to 100 U/lb). Ten cats received dalteparin only during hospitalization. Five of these cats died during hospitalization, dalteparin was not dispensed at the time of hospital discharge in 3 cats, and dalteparin was dispensed but not administered by the owner in 2 cats. Thus, 47 received dalteparin on a continued basis after discharge.

Of the 47 cats that received dalteparin on an ongoing basis, none received regular coagulation monitoring. Measurement of **prothrombin time (PT)** and aPTT was performed in 15 cats. All PTs were within the reference range. Activated partial thromboplastin time was measured before dalteparin administration in 9 cats and was prolonged in 3 cats. Activated partial thromboplastin time was measured after dalteparin administration in 7 cats and was prolonged in 1 cat. In that cat, aPTT was within reference range before receiving dalteparin (82 seconds; reference range, 70 to 120 seconds) and was prolonged 7 days after receiving dalteparin (28.7 seconds; reference range, 10 to 25 seconds). During dalteparin administration, 4 cats had documented bleeding events and 1 had a possible bleeding event. Dalteparin was judged to be a contributing factor to the bleeding by the attending veterinarian in only 1 cat, and the drug was continued at the same dose in the remaining cats. In the first cat, in the region of the abdomen that had recently been clipped for abdominal ultrasound examination, bruising was noted by the owner 24 hours after dalteparin administration began. The cat had also received 314 units of unfractionated heparin/kg (142.7 U/lb) SC every 6 hours for 3 days immediately prior to initiation of dalteparin administration and streptokinase (90,000 units during 1 hour and 45,000 units during 3 hours) 4 days before initiation of dalteparin administration. Dalteparin was thought by the attending veterinarian to have played a role in the bruising, and the daily dose was reduced from 94 U/kg (42.7 U/lb) to 47 U/kg (21.4 U/lb). Two cats had hematuria, which occurred once in 1 cat and periodically in the other. An aPTT was within reference range at the time hematuria was noted in the cat with periodic hematuria. Dalteparin administration was continued in both cats. The fourth cat had chronic renal failure, and the owner described minor gum bleeding close to the time of death attributable to renal failure. A fifth cat with a possible bleeding event was described by the owner as having sudden onset of blindness, weakness, and trouble walking shortly before euthanasia. In this cat, aortic thromboembolism had been detected previously and recurrent aortic thromboembolism and bleeding into the CNS were considered as differential diagnoses; however, a necropsy was not performed.

Of the 47 cats that received dalteparin on an ongoing basis at home, 43 had cardiomyopathy. Of these 43 cats, 22 had hypertrophic cardiomyopathy, 19 had unclassified or restrictive cardiomyopathy, and 2 had dilated cardiomyopathy diagnosed on the basis of the

echocardiogram and clinical evaluation performed by the attending board-certified veterinary cardiologist. Twenty of the 43 cats with cardiomyopathy had 23 episodes of aortic thromboembolism prior to initiation of dalteparin treatment. Of these 20 cats with prior aortic thromboembolism, 13 had CHF prior to receiving dalteparin. In these 13 cats, median left atrial size from the standard M-mode view at the level of the aorta and left atrium was 1.96 cm (range, 0.85 to 2.30 cm). A discrete (n = 2) or possible (3) thrombus was observed in the left atrium during echocardiography in these 20 cats.

Although 20 of the 43 cats with cardiomyopathy had aortic thromboembolism prior to receiving dalteparin, 23 cats had no prior aortic thromboembolism before receiving dalteparin. The exact indication for starting dalteparin administration could not be reliably determined from the medical record; however, in most instances, possible risk factors for aortic thromboembolism were present and presumably lead to initiation of the drug administration. Characteristics of these 23 cats that suggested an increased risk of future aortic thromboembolism included the presence of CHF, echocardiographic evidence of intracardiac thrombus, or enlarged left atrium. Seventeen of 23 had CHF before receiving dalteparin, 2 of 23 had a discrete thrombus, and 2 of 23 had a possible thrombus in the left atrium. The median left atrial size for these 23 cats was 1.93 cm (range, 1.45 to 2.86 cm).

Median dose of dalteparin for the 43 cats with cardiomyopathy that received owner-administered dalteparin was 98.8 U/kg (44.9 U/lb) with a range of 47 to 220 U/kg. The frequency of dalteparin administration for these cats was once (n = 24) or twice (18) daily. Frequency could not be determined from the record or the owner interview in 1 cat. No owners reported difficulty in administering dalteparin injections. When asked about difficulties with dalteparin administration, 5 owners indicated that injections were easier than orally administering medications. Median duration of dalteparin treatment was 172 days (range, 3 to 1,223 days). The reasons for discontinuing dalteparin treatment included death (n = 27), cost of the dalteparin (2), end of the prescribed course of treatment (1), and discontinuation of administration of all medications for reasons unrelated to cost (1). Eight cats were still receiving dalteparin at the end of the study, and 4 cats were lost to follow-up.

Twenty-four cats also received aspirin during dalteparin administration. Aspirin doses were variable and included administration frequencies of 2 times/wk (n = 5), 3 times/wk (10), every third day (8), and every other day (1). Median dosage of aspirin was 3.3 mg/kg/day (1.5 mg/lb/d) with a range of 0.2 to 5.8 mg/kg/d (0.09 to 2.6 mg/lb/d).

Eight cats had documented or possible aortic thromboembolism while receiving dalteparin. One cat had its first episode of aortic thromboembolism 78 days after initiation of dalteparin administration. Five cats had recurrence of aortic thromboembolism at 4, 83, 173, 325, and 487 days after dalteparin administration began. Clinical signs that could have been consistent with recurrence were noted in 2 cats. In the first cat, an episode of transient hind limb weakness was noted 66 days after dalteparin administration began; the cat was walking normally within a few hours. The second cat had CNS signs described previously with possible bleeding complications or aortic thromboembolism 1,017 days after dalteparin administration began. Cats with an episode of aortic thromboembolism prior to starting dalteparin administration (7/20) were more likely than cats without prior aortic thromboembolism (1/23) to develop the disease during treatment ($P = 0.03$). There was no significant difference ($P = 0.49$) in documented occurrence of aortic thromboembolism during dalteparin administration between cats receiving aspirin (4/24) and cats not receiving aspirin (2/19).

For the 43 cats with cardiomyopathy that received owner-administered dalteparin, median duration until an aortic thromboembolism occurred, death, or the end of the study was 171 days (range, 3 to 1,223 days), and this duration was not different between cats with or without aortic thromboembolism before receiving dalteparin (172 vs 152 days, respectively; $P = 0.31$). Eleven cats were alive at the end of the study, although dalteparin administration had been discontinued by the owner in 3 cats. Two cats were lost to follow-up. Causes of death in the remaining 30 cats included euthanasia (n = 8) or death (4) attributable to CHF, sudden death (6), euthanasia because of aortic thromboembolism (4), euthanasia (2) or death (4) for noncardiac systemic disease, and death because of unknown cause (2). Median survival for the 43 cats that received owner-administered dalteparin was 190 days (range, 3 to 1,223 days; **Figure 1**). Median survival for the 20 cats that had aortic thromboembolism before starting dalteparin administration was 194 days (range, 3 to 1,223 days).

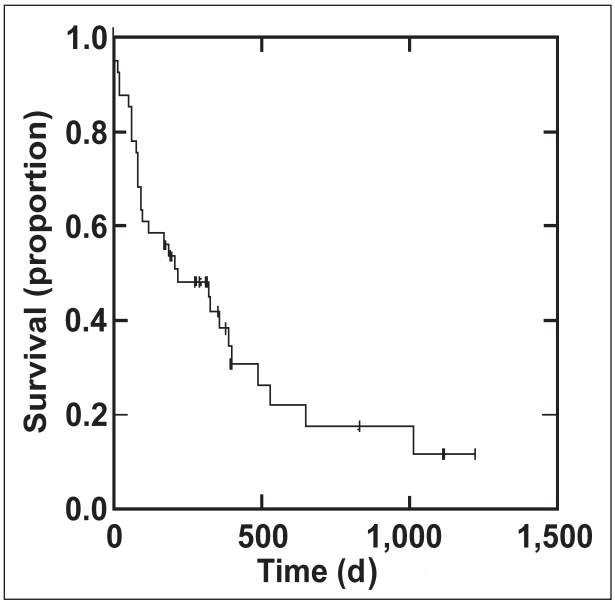

Figure 1—Kaplan-Meier survival curve for 43 cats with cardiomyopathy, after initiation of SC administration of dalteparin by their owner. The vertical marks on the curve represent cats that were censored (eg, the 11 cats that were alive at the end of the study).

Discussion

Experimental pharmacokinetic and pharmacodynamic studies[19,20] in dogs and horses have revealed that LMWHs are well tolerated and cause minimal changes in coagulation measurements with no effects on platelets or CBC values. In the retrospective study reported here, the frequency of documented bleeding events in cats treated with dalteparin was 9% and in 1 cat, dalteparin dose was reduced because of bleeding, although fatal hemorrhage was not detected in any cat. It has been reported that the frequency of fatal hemorrhage in cats treated with long-term warfarin as an antithrombotic is 11%.[3]

In our study, dalteparin was easily administered by owners and well tolerated in cats with cardiac disease. Although the median duration of dalteparin administration was 171 days, 9 cats received dalteparin for more than a year, 2 cats were treated for more than 2 years, and 1 cat was treated for more than 3 years. In human trials of LMWHs, coagulation measurement generally is not performed. For the small number of cats in which PT and aPTT were measured during owner administration of dalteparin, no coagulation times were prolonged by > 25%, compared with the reference range. On the basis of the results of our study and the recommendations in humans, routine coagulation testing in cats receiving dalteparin does not appear to be required. Bleeding complications were infrequent, and it was difficult, in this retrospective study, to determine whether bleeding was related to dalteparin administration. The dalteparin dose was reduced in only 1 cat with clinical evidence of bleeding, and in this instance, the prior administration of high-dose unfractionated heparin and streptokinase may have contributed to the bleeding. In 1 of the cats with a bleeding event (minor gum bleeding), chronic renal failure was also evident. Bleeding complications associated with LMWH administration have been reported in humans with renal insufficiency, and in a recent pharmacokinetic study, decreased antifactor Xa clearance and significantly increased half-life of LMWH with repeated doses in human patients with severe (but not mild or moderate) renal failure were reported.[24,25] These observations were attributed to the primarily renal route of elimination of LMWHs in humans. The authors of the human study suggested that dose adjustment, antifactor Xa activity measurement, or both may be recommended when LMWHs are used in human patients with severe renal failure.

The half-life of dalteparin has been reported as mean ± SD 228 ± 40 minutes in humans,[16] mean ± SEM 45 ± 2 minutes in pigs,[26] and mean ± SD 123 ± 53 minutes in dogs.[27] Results of human clinical trials indicate that both once-daily and twice-daily injections of LMWH are as effective as unfractionated heparin in preventing venous thromboembolism.[28] A recent human trial of 6 months' duration revealed that a once daily injection of dalteparin was more effective than a coumarin derivative in preventing recurrent venous thromboembolism.[29] In horses and dogs, a dalteparin dose of 50 U/kg (22.7 U/lb) was too low to achieve the targeted range for antifactor Xa activity.[18,20] A preliminary pharmacokinetic study[a] revealed that activity of antifactor Xa that was considered therapeutic in other species was achieved in 4 cats at 4 hours after SC injection of dalteparin at a dose of 100 U/kg; however a dose of 200 U/kg (91 U/lb) led to marked prolongation of aPTT. Despite the short half-life of dalteparin relative to most drugs that are administered once per day, it is unclear how long antifactor Xa activity must be in the accepted therapeutic range to achieve effective anticoagulation. Results of studies[15,30] in humans indicate that for certain conditions, once-per-day treatment with LMWH is as effective as or associated with fewer bleeding complications than twice-per-day administration. In our retrospective study, we did not find a significant difference in occurrence of aortic thromboembolism in cats that received 1 injection/d, compared with cats with 2 injections/d. Two owners discontinued dalteparin use because of its high cost, but high cost of the medication was mentioned by a number of owners during the follow-up telephone interview. During the study period, mean cost to the client for twice per day dalteparin administration for a 5-kg (11-lb) cat was $240/mo. The cost savings of once-per-day administration of dalteparin may explain the large number of cats in which the drug was used once per day in our study. Future studies to investigate the half-life of dalteparin in cats and its relationship to the optimal dose frequency (once or twice per day) are needed.

Estimates of incidence of aortic thromboembolism in cats with hypertrophic cardiomyopathy range from 33% to 50%.[1,2] In the study group reported here, in which 51% of cats had hypertrophic cardiomyopathy and 49% had other forms of cardiomyopathy, 6 of 43 (14%) cats had documented aortic thromboembolism after dalteparin administration was begun. Only 1 cat had its first aortic thromboembolism during dalteparin administration. On the basis of prior reports of cats that have had an aortic thromboembolism episode, from 25% to 75% may be expected to have another episode.[1,3-6] In our study, 5 of 20 (25%) cats with at least 1 previous episode of aortic thromboembolism had another while receiving dalteparin. Further prospective studies are required to determine whether dalteparin administration can reduce the frequency of aortic thromboembolism in cats with cardiomyopathy.

A skewed survival pattern with many early deaths followed by the prolonged survival of some cats was detected in our study. This survival pattern has been reported in cats with cardiomyopathy.[1,4] Median survival of cats that had aortic thromboembolism before dalteparin administration was begun was 194 days. Median survival times for cats after aortic thromboembolism have been reported to be 51,[6] 61,[31] 184,[1] 254,[4] and 345 days.[3] The high recurrence rate of aortic thromboembolism in cats is often cited as an argument in support of euthanasia rather than treatment. However, of the 30 cats that died during the study, more died because of CHF or CHF-related euthanasia (n = 12) than because of aortic thromboembolism-related euthanasia (4). Results of our study are in agreement with results of Smith et al,[4] who found that CHF was the most common cause of death in cats with prior aortic thromboembolism. Death attributable to recurrence of aortic thromboembolism in that study was reported at 20%.

Dalteparin appears to be a safe, easily administered drug associated with few bleeding complications at a dose of 100 U/kg administered once or twice daily. In our study, dalteparin was only administered to cats with prior arterial thromboembolism or cats judged to be at high risk of arterial thromboembolism by the attending veterinarian. Limitations of the study preclude drawing any conclusions about the efficacy of dalteparin in reducing incidence of arterial thromboembolism, either in primary prevention or in reduction of recurrence. Before widespread use can be justified, randomized, placebo-controlled, double-blind studies with sufficiently large sample sizes are needed to prove whether dalteparin is effective in preventing arterial thromboembolism in cats with cardiomyopathy.

[a]Goodman JS, Rozanski EA, Brown DJ, et al. The effects of low-molecular weight heparin on hematologic and coagulation parameters in normal cats (abstr). *J Vet Intern Med* 1999;13:268.
[b]Fragmin (dalteparin), Pharmacia and Upjohn Co, Kalamazoo, Mich.
[c]Systat 10.0, SPSS, Chicago, Ill.

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