Pharmacokinetics of tranexamic acid in healthy dogs and assessment of its antifibrinolytic properties in canine blood

Katie E. Osekavage DVM  
Benjamin M. Brainard VMD  
Selena L. Lane DVM  
Mohammed Almoslem MS  
Robert D. Arnold PhD  
Amie Koenig DVM

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From the Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, Athens, GA 30605 (Osekavage, Brainard, Lane, Arnold, Koenig); the Department of Drug Discovery and Development, Harrison School of Pharmacy, Auburn University, Auburn, AL 36849 (Almoslem, Arnold); and the Clinical Pharmacy Department, College of Pharmacy, University of Ha’il, Ha’il, Saudi Arabia (Almoslem).

Address correspondence to Dr. Brainard (brainard@uga.edu).

OBJECTIVE
To assess pharmacokinetics of tranexamic acid (TXA) in dogs and assess antifibrinolytic properties of TXA in canine blood by use of a thromboelastography-based in vitro model of hyperfibrinolysis.

ANIMALS
6 healthy adult dogs.

PROCEDURES
Dogs received each of 4 TXA treatments (10 mg/kg, IV; 20 mg/kg, IV; approx 15 mg/kg, PO; and approx 20 mg/kg, PO) in a randomized crossover-design study. Blood samples were collected at baseline (time 0; immediately prior to drug administration) and predetermined time points afterward for pharmacokinetic analysis and pharmacodynamic (thromboelastography) analysis by use of an in vitro hyperfibrinolysis model.

RESULTS
Maximum amplitude (MA [representing maximum clot strength]) significantly increased from baseline at all time points for all treatments. The MA was lower at 360 minutes for the 10-mg/kg IV treatment than for other treatments. Percentage of clot lysis 30 minutes after MA was detected was significantly decreased from baseline at all time points for all treatments; at 360 minutes, this value was higher for the 10-mg/kg IV treatment than for other treatments and higher for the 20-mg/kg IV treatment than for the 20-mg/kg PO treatment. Maximum plasma TXA concentrations were dose dependent. At 20 mg/kg, IV, plasma TXA concentrations briefly exceeded concentrations suggested for complete inhibition of fibrinolysis. Oral drug administration resulted in a later peak antifibrinolytic effect than did IV administration.

CONCLUSIONS AND CLINICAL RELEVANCE

Hypofibrinogenemia, or accelerated blood clot breakdown, is associated with a number of disease states and can lead to morbidity and death because of uncontrolled or recurrent hemorrhage.1 Hyperfibrinolysis can develop after trauma, contributing to ACOTS. In a previous study,2 ACOTS was identified in 266 of 1,088 (24.4%) human trauma patients at the time of hospital admission and was associated with a 5-fold increase in mortality rates. Hypoperfusion, shock, and inflammation result in a hypocoagulable and hyperfibrinolytic state in the immediate posttraumatic period.3 Although ACOTS mimics disseminated intravascular coagulation, it is not a consumptive coagulopathy, and the 2 conditions are considered separate entities.4 Hyperfibrinolysis in ACOTS is partly attributable to an increase in local release of TPA by damaged endothelial cells. In addition, increased circulating concentrations of activated protein C inhibit
plasminogen activator inhibitor-1, an inhibitor of the fibrinolysis pathway. Hyperfibrinolysis has also been identified in patients following cardiopulmonary bypass and can result in increased postoperative transfusion requirements. In dogs, hyperfibrinolysis has been reported following severe trauma and development of severe, acute hemoperitoneum. In addition, a hyperfibrinolytic condition is suspected to cause postoperative bleeding in retired racing Greyhounds.

Antifibrinolytic agents such as ACA and TXA can slow fibrinolysis and reduce blood loss in patients with hyperfibrinolytic conditions. Both of these drugs are synthetic lysine analogs that reversibly bind to plasminogen, preventing plasmin binding to fibrin. Results of a large, prospective study of human patients with traumatic injuries revealed a significantly lower mortality rate for those treated with TXA, compared with patients who had no antifibrinolytic treatment. Notably, the use of an antifibrinolytic in that study did not result in an increase in the incidence of thrombotic events. Administration of TXA to human patients after cardiac surgery that includes cardiopulmonary bypass reduces hemorrhage by one-third, and this treatment also reduces postoperative bleeding after elective orthopedic procedures. To the authors’ knowledge, the use of antifibrinolytic agents has not been evaluated in dogs with hemoperitoneum or ACOTS, but these treatments may be of benefit. Perioperative administration of ACA has been shown to decrease the incidence of postoperative bleeding in retired racing Greyhounds undergoing elective limb amputations or gonadectomy.

A variety of TXA doses ranging from 10 mg/kg to 50 mg/kg administered IV have been evaluated in healthy dogs. Such investigations have attempted to evaluate the antifibrinolytic properties of TXA by use of unmodified viscoelastic coagulation testing (thromboelastography or rotational thromboelastometry), with varied results. Although useful for assessing coagulation, these tests show relatively minimal fibrinolysis in blood samples from healthy dogs, making it difficult to accurately assess the pharmacodynamic effects of antifibrinolytic agents. A recently described modified thromboelastography assay that induces an in vitro hyperfibrinolytic state has been used to assess the pharmacodynamics of ACA in blood from healthy dogs. Potency of TXA is 10 times that of ACA, and recent backordering of ACA in the United States made TXA the only available antifibrinolytic agent for a period of time. Limited dosing information and unfamiliarity with TXA in this context could potentially compromise veterinary patient care.

The objective of the study reported here was to determine the pharmacokinetic and pharmacodynamic profile of TXA in dogs following administration of a single dose by IV infusion (10 or 20 mg/kg over 10 minutes) or PO (15 or 20 mg/kg). We hypothesized that administration of TXA to healthy dogs would result in dose-dependent increases in plasma drug concentrations and antifibrinolytic effects as assessed by use of a modified thromboelastography assay. We also hypothesized that orally administered TXA would have pharmacodynamic characteristics similar to those following IV administration in healthy dogs.

Materials and Methods

Dogs

Six healthy mixed-breed sexually intact female dogs between 2 and 3 years of age with a median weight of 14.2 kg (range, 13.5 to 16.3 kg) were included in the study. The dogs were deemed healthy on the basis of results of a physical examination, CBC, serum biochemical analysis, and coagulation analysis, which included prothrombin time, activated partial thromboplastin time, and analysis by TF-activated thromboelastography. The University of Georgia Institutional Animal Care and Use Committee approved all study procedures.

Drug administration and sample collection procedures

Each dog was assigned to receive 1 dose of TXA IV (10 or 20 mg/kg) or PO (approx 15 or 20 mg/kg) in a randomized, crossover design. Randomization was performed with an internet-based program. Each dog received all treatments during the course of the study, with a 7-day washout period between treatments. Food was withheld ≥12 hours prior to TXA administration.

The IV TXA treatments were given as an infusion over 10 minutes in an effort to minimize the incidence of vomiting. One tablet size (650 mg of TXA in a 1-g tablet) was available for use; the desired dose was calculated as a percentage of the tablet, and tablets were weighed and then divided accordingly. The resulting pieces were weighed to confirm that they would deliver the desired dose, assuming equal distribution of the active ingredient throughout the tablet.

The day prior to drug administration, dogs were sedated with dexmedetomidine (5 µg/kg, IV) and a 20-gauge, 12-cm indwelling catheter was placed in a jugular vein with a modified Seldinger technique. Following placement, catheters were initially flushed with sterile saline (0.9% NaCl) solution and subsequently flushed with 0.5 mL of a 50% dextrose solution to maintain catheter patency and preclude the use of an anticoagulant flush. The following day, catheters were flushed with sterile saline solution, and 3 mL of blood was withdrawn and discarded before collection of any blood for analysis. The total volume of blood collected on each sampling day was ≤17 mL. Following sample collection, the catheter was flushed with sterile saline solution. Jugular catheters were removed after the final sample acquisition. The dogs were observed for clinical signs of adverse reactions during and after administration of the drug, and any clinical effects were recorded.

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Pharmacodynamics

Blood samples for pharmacodynamic analysis were collected at time 0 (ie, baseline immediately prior to drug administration) and at 60, 240, and 360 minutes after drug administration. Blood was transferred into tubes containing 3.2% sodium citrate solutiona to a final blood-to-citrate ratio of 9:1. Thromboelastography was performed after a standard sample rest time of 30 minutes at room temperature (22°C to 24°C) by 1 researcher (BMB), who was blinded to the administered drug dose and route. At each time-point, a TF-activated thromboelastography assayb (TF-thromboelastography, with a final TF dilutionc of 1:3,400) and a modified hyperfibrinolytic thromboelastography (TPA-thromboelastography, with a final TF dilution of 1:3,400 and a final TPA concentration of 100 U/mL) were performed as described elsewhere.c All assays were continued for 60 minutes after the MA of the clot was detected. Procoagulant variables (reaction time, α-angle, and MA) and fibrinolysis variables were calculated with proprietary software,d visually inspected for accuracy, and recorded. The fibrinolysis variables were represented as LY30 and LY60, which were each calculated as a ratio of the AUC at MA to the AUC at the specified time point. Additional thromboelastography variables measured and calculated by the software included clot formation time and shear modulus strength (calculated as [5,000 X MA]/[100 – MA]).e

Pharmacokinetics

Blood samples for pharmacokinetic analysis (1 mL) were collected into EDTA-containing blood tubesa at baseline and at 5, 10, 15, 30, 60, 120, 240, and 360 minutes after drug administration. At time points when 2 samples were required, samples were collected sequentially into separate syringes, with the sample for thromboelastography analysis collected first. The EDTA-containing samples were held on ice until centrifugation (1,500 X g for 10 minutes at room temperature), which was performed ≤ 1 hour after collection. Plasma supernatant was removed and stored at −80°C for ≤ 4 months until analysis. Samples were batch analyzed by high-performance liquid chromatography–mass spectrometry at a commercial toxicology laboratory.f

The pharmacokinetic parameters were estimated by noncompartmental analysis from the plasma drug concentration–time profile data following a 10-minute IV infusion or oral administration of TXA. Analyses were performed by an investigator using commercial software.g Parameters calculated from IV data included Cmax, tmax, AUC0–last (ie, the AUC from time 0 [drug administration] to 6 hours after administration), AUC0–∞, half-life, Vd, and CI. Parameters following oral drug administration included Cmax, tmax, AUC0–last, and AUC0–∞. The Cmax and tmax were determined by examination of the drug concentration–time profiles, and AUC values were estimated by the log-trapezoidal method and the method for extrapolating exposure.

Table I—Mean ± SD thromboelastography values for blood samples collected from 6 healthy dogs immediately before (0 minutes) and 60, 240, and 360 minutes after IV or oral administration of TXA and evaluated by use of an in vitro model of TPA-induced hyperfibrinolysis in a randomized, crossover-design study with a 1-week washout period between experiments.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference range</th>
<th>Time (min)</th>
<th>Oral administration</th>
<th>IV administration</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>15 mg/kg</td>
<td>20 mg/kg</td>
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<td>R (min)</td>
<td>1.8–2.0</td>
<td>0</td>
<td>1.88 ± 0.26</td>
<td>1.73 ± 0.23</td>
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<td>60</td>
<td>1.85 ± 0.22</td>
<td>1.62 ± 0.26</td>
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<td></td>
<td></td>
<td>240</td>
<td>1.68 ± 0.17</td>
<td>1.65 ± 0.22</td>
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<td>—</td>
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<td>360</td>
<td>1.817 ± 0.19</td>
<td>1.72 ± 0.12</td>
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<td>K (min)</td>
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<td>2.27 ± 1.40</td>
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<td>60</td>
<td>0.97 ± 0.14</td>
<td>1.10 ± 0.28</td>
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<tr>
<td></td>
<td></td>
<td>240</td>
<td>1.05 ± 0.27</td>
<td>1.15 ± 0.29</td>
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<td>360</td>
<td>1.17 ± 0.47</td>
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<td>α angle (°)</td>
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<td>74.25 ± 3.56</td>
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<td></td>
<td>360</td>
<td>73.13 ± 5.77</td>
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<td>MA (mm)</td>
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<td>51.85 ± 7.83</td>
<td>52.67 ± 6.53</td>
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<td>240</td>
<td>55.98 ± 7.74</td>
<td>54.40 ± 6.63</td>
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<tr>
<td>—</td>
<td></td>
<td>360</td>
<td>54.37 ± 7.70</td>
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<td>G (dynes/s)</td>
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<td>5,596.77 ± 1,568.80</td>
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<td>6,190.18 ± 1,712.63</td>
<td>6,181.65 ± 1,427.60</td>
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</table>

Values of P < 0.05 were considered significant.

aWithin a column, value differs significantly from the value at 0 min. bWithin a column, (nonbaseline) value differs significantly from value at 60 and 240 minutes. cWithin a column, (nonbaseline) value differs significantly from value at 60 minutes.

— = Not applicable. G = Shear modulus strength. K = Clot kinetic time (defined as the time to reach an amplitude of 20 mm). R = Reaction time.
a,b Within a row, values with different superscript letters are significantly different.

Reference

16 Unauthenticated | Downloaded 01/02/23 08:15 AM UTC
from the last measured concentration to infinity. A preliminary assessment of bioavailability was determined by use of the following equation: \( \text{Bioavailability} = \frac{\text{AUC}_{\text{last}}}{\text{dose}} \) following oral administration/(\( \text{AUC}_{\text{last}}/\text{dose} \)) following IV administration.

**Statistical analysis**

Statistical analysis was performed with commercial statistical analysis software. Data were found to be normally distributed by use of the Shapiro-Wilk test and are reported as mean ± SD. The influence of TXA dose and administration route, or time (baseline, 60 minutes, 240 minutes, or 360 minutes) in relation to dose and route, on thromboelastography variables was evaluated with 2-way repeated-measures ANOVA. Values of \( P < 0.05 \) were considered significant.

**Results**

**Adverse events**

Five dogs vomited once during IV administration of TXA at 20 mg/kg. Vomiting occurred between 6 and 10 minutes after starting the infusion. The dog that did not vomit had signs of nausea (lip licking) 8 minutes after the infusion started. For each dog that vomited, no further signs of nausea were noted after emesis. No signs of nausea or vomiting were observed for the same dogs when the drug was IV administered at 10 mg/kg or when either oral dose was given. No other adverse effects were noted.

**Pharmacodynamics**

The TF-thromboelastography results for all times and treatments were within the institutional reference ranges (data not shown). There were no significant differences in results among any TF-thromboelastography samples. When TPA-thromboelastography was performed, there was a significant (\( P < 0.05 \)) increase from the time 0 (baseline [immediately prior to drug administration]) values for \( \alpha \)-angle and MA at 60, 240, and 360 minutes after TXA administration, regardless of dose or route (Table 1). At 360 minutes, the MAs for samples collected after administration of TXA at 15 and 20 mg/kg, PO, and 20 mg/kg, IV, were significantly greater than that for samples collected after IV administration of the drug at 10 mg/kg.

The LY30 was significantly (\( P < 0.05 \)) decreased from baseline at all time points after TXA administration for all treatments (Table 2). After IV administration at 10 mg/kg, LY30 at 240 and 360 minutes were greater than that measured at 60 minutes, but were not significantly different from each other. At the 240-minute time point, LY30 for the 10-mg/kg IV treatment was significantly greater than values for
the 15- and 20-mg/kg PO treatments. At the 360-minute time point, LY30 was significantly greater for the 10-mg/kg IV treatment than the values for all other treatments; LY30 for the 20-mg/kg IV treatment was also significantly greater than that for the 20-mg/kg PO treatment at this time point. For the 15-mg/kg PO treatment, LY30 at 60 minutes was significantly greater than that at 240 minutes.

The LY60 was significantly decreased from the baseline value at all time points after TXA administration at 15 and 20 mg/kg, PO, and 20 mg/kg, IV, but was decreased only at the 60-minute time point relative to baseline after IV administration at 10 mg/kg (Table 2). For the 20-mg/kg PO treatment, LY60 at 60 minutes was significantly greater than that at 240 and 360 minutes. At 240 minutes, LY60 was significantly greater for the 10-mg/kg IV treatment than for the 20-mg/kg IV and 20-mg/kg PO treatments. At 360 minutes, LY60 for the 10-mg/kg IV treatment was significantly greater than those for the 15- and 20-mg/kg PO treatments, and LY60 for the 20-mg/kg IV treatment was significantly greater than that for 20-mg/kg PO treatment.

Pharmacokinetics

Pharmacokinetic parameters were determined after administration of each TXA treatment (Table 3). The plasma drug concentration–time profiles were characteristic for short-term IV (10-minute infusion) and oral drug administration (Figure 1). An exponential decrease in drug concentration over time was observed following IV administration. The estimated pharmacokinetic parameters, Cl, Vd, and AUC0–∞ divided by dose, were similar and suggested that TXA kinetics were linear at the IV doses tested.

Following oral administration, tmax occurred at approximately 2 hours for both doses (Figure 1). The Cmax, AUC0–last, and AUC0–∞ were each dose dependent, suggesting that at 15 and 20 mg/kg, PO, the pharmacokinetics of TXA were linear. Owing to the lack of sample collection after 6 hours, the extrapolated AUCs for TXA following oral drug administration were described as the predicted mean ± SD AUC0–last and AUC0–∞. Absolute bioavailabilities for the oral doses were not determined because the predicted exposure (ie, AUC from the time of last measured concentration to infinity) following oral administration represented 41.0 ± 13.7% and 30.7 ± 13.7% of the total AUC0–∞ for the 15- and 20-mg/kg doses, respectively. However, a preliminary estimation of the bioavailability after oral administration yielded values ranging from 92% to 117% on the basis of these data.

Discussion

In the study reported here, use of an in vitro model of hyperfibrinolysis revealed that IV and orally administered TXA reduced fibrinolysis in blood samples from healthy dogs. Significant (P < 0.05) reductions in LY30, compared with the baseline (time 0; immediately prior to drug administration) values, were found for all tested IV and oral doses at 60 through 360 minutes after drug administration. The MAs, or maximum clot strengths, at the same time points were also greater than the respective baseline values for all treatments. These data indicated that treatment with TXA can enhance clot strength and duration in patients with hyperfibrinolysis. The doses administered in this study were based on previously reported veterinary use14,15,19 and extrapolated from data for human patients.10

Although IV administration of TXA at 10 mg/kg resulted in improved maximum clot strength and reduction of clot lysis relative to baseline as measured by both LY30 and LY60 1 hour after injection, the duration of the effect did not last as long as that for other doses (20 mg/kg, IV or 15 or 20 mg/kg, PO). By 6 hours after administration of this treatment, both MA and LY30 were significantly different from those for the other treatments and were returning toward the baseline value. Within this treatment, changes in LY30 indicated a reduced antifibrinolytic effect over time. These data indicated that administration of TXA at 10 mg/kg by the IV route might be needed more frequently than the other doses and routes tested to maintain a similar antifibrinolytic effect.

Oral administration of TXA resulted in delayed but relatively prolonged antifibrinolytic effects, compared with IV administration. A significant decrement in drug effect was not detected during the observation time after administration of the 20-mg/kg oral dose, and this supported a dosing interval of 6 hours or longer to maintain a clinical effect. In humans, TXA is administered orally every 8 hours, and although
amples were not collected 8 hours after drug administration in the present study, it seems that this strategy might be appropriate for dogs as well. An alternative strategy could be to administer a loading dose IV, followed by oral drug administration to maintain prolonged antifibrinolytic effects. However, further evaluation is needed to determine the duration of the antifibrinolytic effects of TXA administered orally at intervals of 8 hours or longer.

Results of a previous study\textsuperscript{16} that involved a similar in vitro hyperfibrinolysis model indicated that a TXA concentration of 144.7 µg/mL completely inhibited fibrinolysis in canine plasma. Although dosing recommendations were not made from the results of that study,\textsuperscript{16} the 20-mg/kg IV treatment did result in plasma TXA concentrations > 150 µg/mL shortly after administration in the present study. These plasma concentrations were not maintained, although antifibrinolytic effects persisted for several hours after the \( t_{\text{max}} \). None of the other treatments investigated in this study approached the target plasma concentration derived from the earlier study, but each achieved a reduction in clot lysis from the baseline value.

The \( C_{\text{max}} \) of TXA in the present study was dose dependent. The \( C_{\text{max}} \) for both IV doses was achieved shortly after administration and decreased steadily. Despite decreasing plasma concentrations of TXA, antifibrinolytic effects were still detected up to 6 hours after administration. The \( C_{\text{max}} \) after oral administration of 15 and 20 mg of TXA/kg was identified at 144 and 120 minutes, respectively; however, more accurate estimates of \( t_{\text{max}} \) values might have been identified if sampling had been performed at more frequent intervals. The antifibrinolytic effects were more evident at 240 and 360 minutes after oral drug administration, compared with the IV doses, which had demonstrable antifibrinolytic effects at the 60-minute assay time point. Assays performed 8 hours or longer after TXA administration might have been helpful in determining the total duration of effect and evaluating the CI. In human patients, TXA is eliminated by glomerular filtration.\textsuperscript{20} To the authors’ knowledge, no studies have explicitly evaluated excretion of TXA by dogs, but it is reasonable to postulate a similar elimination profile. The CI and clinical effects of renally excreted medications can be altered in animals with renal dysfunction.

Vomiting, a known adverse effect of TXA, was observed in 5 of 6 dogs during IV infusion of the 20-mg/kg dose in the present study. The dog that did not vomit during this treatment showed signs of nausea. No vomiting or signs of nausea were noted during or after administration of the drug at other doses by either route. Although each dog vomited only once, any incidence of vomiting, especially in compromised patients, may lead to complications such as development of aspiration pneumonia. Tranexamic acid is thought to induce emesis through activation of the tachykinin neurokinin 1 receptor.\textsuperscript{21} Maropitant is an antagonist of tachykinin neurokinin 1 and is routinely used for the treatment of nausea and vomiting. It may be useful to prevent vomiting associated with TXA administration; however, this has not been evaluated in veterinary patients. Each IV dose of TXA in our study was administered as a short-term infusion in an attempt to reduce the incidence of vomiting, as previously reported adverse effects were associated with rapid IV bolus administration.\textsuperscript{15} Infusion of the drug over a longer period of time would likely alter the \( C_{\text{max}} \) of the drug, but this would not be expected to reduce the antifibrinolytic properties of the drug, as antifibrinolytic effects were still present at lower plasma drug concentrations. In adult human patients with trauma, TXA is administered IV as an initial 1-g loading dose followed by 1 g administered via continuous rate infusion over 8 hours.\textsuperscript{1} This type of administration (an approx 14-mg/kg loading dose, followed by 14 mg/kg given over 8 hours, assuming a typical human patient weight of 70 kg) was not evaluated in the present study; however, a similar approach should be evaluated to assess whether it would maintain effective plasma concentrations over a longer period of time and reduce the incidence of vomiting and signs of nausea in dogs.

The present study had several limitations. The in vitro model used does not take into account the role of the endothelium in fibrinolysis, and endogenous TPA concentrations in the circulation may be higher or lower than the concentration used in the study. In addition, endothelial-derived inhibitors of fibrinolysis such as plasminogen activator inhibitor-1 are not accounted for in this model. The tablets used for oral TXA administration were not designed to be divided (ie, tablets were not scored); therefore, distribution of the drug throughout the tablet could have varied and the administered dose might have been overestimated or underestimated. The mean blood sample collected from each dog each week of testing was 1.12 mL/kg, and thromboelastography parameters can be affected by Hct and platelet concentrations\textsuperscript{22}; however, CBCs performed after the third week of testing did not reveal any changes that would be expected to alter these parameters. Only 6 dogs were used in the study, and this small number may have limited the statistical power to detect alterations in all of the thromboelastography parameters evaluated. On the basis of the observed pharmacokinetic profile, additional samples beyond the 6-hour time point following oral administration would have allowed a more accurate estimate of bioavailability. Furthermore, all of the study dogs were healthy; thus, the pharmacokinetic and pharmacodynamic data may not apply to patients with decreased perfusion or altered Vd. The same doses of TXA may not have the same degree of inhibitory effect in such patients, particularly in the context of oral drug administration and decreased gastric perfusion. However, these preliminary data suggested that evaluation of the effects of TXA in canine patients with hyperfibrinolytic conditions is warranted.
Acknowledgments
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Footnotes
a. Akorn Inc, Lake Forest, Ill.
b. Lysteda, Ferring Pharmaceuticals Inc, Parsippany, NJ.
d. Domitor, Pfizer Inc, New York, NY.
e. Arrow Teleflex, Telford, Pa.
f. Hospira, Lake Forest, Ill.
g. BD Biosciences, Franklin Lakes, NJ.
h. TEG 5000, Haemonetics Corp, Braintree, Mass.
i. Dade Innovin in 2% Albumin, Siemens Healthcare Diagnostics, Newark, Del.
j. Genetech, South San Francisco, Calif.
m. WinNonlin Professional, version 5.2, Certara USA (formerly Pharsight Corp), St Louis, Mo.
n. Sigma Stat, Systat Inc, San Jose, Calif.

References