Efficacy and safety of tranexamic acid as an emetic in dogs

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Objective—To determine dose dependency of tranexamic acid–induced emesis and the time course of the antifibrinolytic potency of tranexamic acid in dogs.

Animals—10 Beagles.

Procedures—In a dose-escalating experiment, ascending doses of tranexamic acid (10, 20, and 30 mg/kg, IV) were administered at 5-minute intervals until vomiting was observed. In a separate single-dose experiment, ascending doses of tranexamic acid (20, 30, 40, and 50 mg/kg, IV) were administered at 1-week intervals until vomiting was observed. Time to onset of vomiting and number of vomiting episodes were measured in both experiments. In a coagulation experiment, a single 50 mg/kg bolus of tranexamic acid was administered, and blood was obtained 1 hour before and 20 minutes, 3 hours, and 24 hours after administration. Antifibrinolytic potency of tranexamic acid was evaluated by use of a modified rotational thromboelastography method.

Results—Tranexamic acid induced vomiting in a dose-dependent manner. Vomiting frequency was ≤ 2 episodes, and vomiting concluded ≤ 250 seconds after administration. Antifibrinolytic potency of tranexamic acid was significantly higher at 20 minutes following administration, but not different by 24 hours, when compared with the potency measured before administration. No adverse effects were observed in any experiment.

Conclusions and Clinical Relevance—IV administration of tranexamic acid induced emesis in a dose-dependent manner. The antifibrinolytic potency of tranexamic acid decreased in a time-dependent manner and was resolved ≤ 24 hours after administration. Further studies are warranted to investigate the emetic and other adverse effects of tranexamic acid in dogs of various breeds and ages. (*Am J Vet Res* 2014;75:1099–1103)

Dogs are frequently exposed to a number of substances that are toxic to their health, including pharmaceuticals, onions, chocolate, tobacco, and insecticides.[1] A position paper[2] in human medicine suggests that there is doubtful efficacy when emetics are used for decontamination of ingested toxic substances. On the other hand, the use of emetics is still an effective way to remove ingested substances in canine medicine.[1,3,4] Intravenous and ocular conjunctival administration of apomorphine, a stimulant of D_2 receptors, and oral administration of 3% hydrogen peroxide, an external antiseptic, have been widely used to induce vomiting in dogs[5,6] and have yielded high success rates of 94% and 90%, respectively.[7] However, the interval from IV or ocular conjunctival administration of apomorphine and oral administration of 3% hydrogen peroxide to onset of vomiting can be lengthy (14.5 and 18.6 minutes, respectively).[7] Additionally, the emetic effects last for an extended period (42 and 27 minutes, respectively).[7] Another study[8] in which apomorphine was administered IV found a median time to emesis of 1 minute. Gastric transit time is usually approximately 2 hours[3,9]; thus, induction of emesis may not be effective 2 to 3 hours after ingestion of a poison.[10] To remove a large portion of the stomach contents, emesis should be induced as soon as possible (ie, when owners suspect or have witnessed that their dog has ingested inappropriate substances). Once dogs regurgitate stomach contents, further episodes of vomiting are not necessary.

Abbreviations

CF	Clot firmness
D_2	Dopamine 2
LI	Lysis index
NK_1	Neurokinin 1

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Tranexamic acid is an antifibrinolytic drug that is widely used to control bleeding in trauma patients in veterinary as well as human medicine.[11,12,a] In addition to its hematologic effects, tranexamic acid may induce emesis after IV administration of a higher-than-usual dose.[13] Nausea and vomiting are known adverse effects for tranexamic acid.[13–15] In Japan, tranexamic acid has been used empirically to induce emesis in dogs because a pharmaceutical formulation of apomorphine was not available until 2012 and the time from administration of hydrogen peroxide to onset of vomiting was too long.[16,17] Recently, our research group found that a pathway for stimulation of NK_1 receptors, but not D_2 receptors, may play a pivotal role in tranexamic acid–induced emesis, which indicated that tranexamic acid could be an emetic that is qualitatively different from apomorphine.[18] Tranexamic acid could be a useful emetic in situations whereby it can be administered IV to a dog after ingestion of toxins. However, the appropriate dosing regimen and antifibrinolytic effects of tranexamic acid when used as an emetic have not yet been determined. Thus, the purpose of the study reported here was to examine the effects of various doses of tranexamic acid on induced emesis and the time course of the antifibrinolytic potency of tranexamic acid after IV administration to dogs.

Materials and Methods

Animals—Ten healthy adult Beagles (5 males and 5 females) were used in the study. Dogs were 3 to 11 years old with a body weight of 9 to 14 kg. Dogs were housed separately in cages; dry food was provided twice daily, and water was available ad libitum. Care and handling of the animals were performed in accordance with the Azabu University Animal Experiment Guidelines, April 2000. All experiments were approved by the Committee for Animal Experimentation at Azabu University.

Emetic potency of various doses of tranexamic acid—Two experiments on induction of vomiting were conducted: a dose-escalation experiment and a single-dose experiment. There was a 1-week interval between the 2 experiments to avoid carryover drug effects from the first experiment. One hour before administration of tranexamic acid in each experiment, dogs were allowed to consume a typical meal of dry food, moved to the experimental room, and placed into separate cages.

The dose-escalation experiment was based on the fact that dogs vomit within 5 minutes after administration of tranexamic acid.[16] Therefore, tranexamic acid (10 mg/kg, IV) was initially administered to 10 dogs. Commercially available 10% tranexamic acid solution[b] was administered by IV bolus injection through an indwelling catheter inserted in a cephalic vein. The administered volume was 0.1 to 0.5 mL/kg, dependent on dosage. If a dog did not vomit within 5 minutes after administration of the first dose, a second dose of tranexamic acid (20 mg/kg, IV) was administered. If a dog did not vomit after receiving the second dose, a third dose of tranexamic acid (30 mg/kg, IV) was administered. Total dose after the first, second, and third administrations was 10, 30, and 60 mg/kg, respectively.

After a 1-week washout period, the single-dose experiment was conducted with the same 10 dogs. Because none of the dogs vomited after receiving 10 mg of tranexamic acid/kg, IV, in the dose-escalation experiment, the initial dose for the single-dose experiment was 20 mg/kg, IV. Dogs that did not vomit after that dose were allowed a 1-week washout period and then were given a higher dose of tranexamic acid (30 mg/kg, IV). Dogs that did not vomit after that dose were allowed a 1-week washout period and then were given a higher dose of tranexamic acid (40 mg/kg, IV). Dogs that did not vomit after that dose were again allowed a 1-week washout period and then were given the highest dose of tranexamic acid (50 mg/kg, IV).

For both experiments, dogs were returned to their original cages after completion of the experimental period, and their behavior was carefully monitored for 1 hour. Dogs were monitored twice daily throughout the remainder of the study period.

Effects of tranexamic acid on recombinant tissue plasminogen activator–induced hyperfibrinolysis—After a washout period of 1 week, a third experiment was conducted in which a single bolus of tranexamic acid (50 mg/kg, IV) was administered to each of the 10 dogs. Blood samples were obtained from a jugular vein 1 hour before and 20 minutes, 3 hours, and 24 hours after tranexamic acid administration. Each blood sample was added to a blood collection tube that contained 3.2% sodium citrate.[c] Tubes were incubated at 37°C until analysis (< 2 hours after collection) to preserve original viscoelasticity.

To examine the antifibrinolytic potency of tranexamic acid, a modified rotational thromboelastography method[d] was used in accordance with the method described elsewhere,[19] with minor modifications. Alteplase[e] was dissolved in sterile saline solution to a final concentration of 400 µg/mL. Alteplase (600 ng) was added to 2.7 mL of citrated whole blood (final concentration, 220 ng of alteplase/mL of blood). Samples were incubated for 1 minute at 37°C to activate tissue plasminogen. Then, 20 µL of 0.2M $CaCl_2$[f] was added, which was followed by the addition of tissue thromboplastin (phospholipids and tissue factor)[g] to convert prothrombin to thrombin. The CF, a blood viscosity index, was then recorded. The CF typically increases initially because of activation of the coagulation system. However, CF decreases when fibrinolytic potency overcomes coagulability. The time course for CF and variables were determined (**Figure 1**). As a marker of fibrinolytic potency, LI was determined 30, 45, and 60 minutes after clotting time as follows[19–21]:

$$LI = (CF/MCF) \times 100$$

where MCF is the maximum CF.

Statistical analysis—Data were expressed as mean ± SEM. Effects of tranexamic acid on LI were analyzed by means of the Dunnett multiple comparison test. Values of $P < 0.05$ were considered significant.

Results

Animals—All dogs tolerated well the injections of tranexamic acid. No adverse effects, except for vomiting, were observed during any of the experiments.

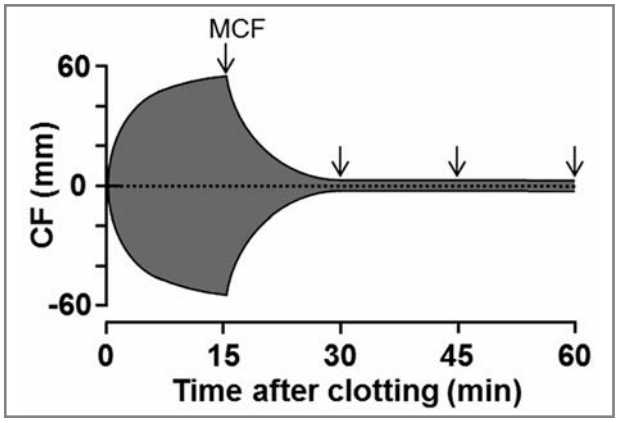

Figure 1—Schematic illustration depicting results for a rotational thromboelastometry assay that used citrated whole blood to determine recombinant tissue plasminogen activator–induced hyperfibrinolysis. The LIs at 30, 45, and 60 minutes after clotting time (arrows) were determined as markers of fibrinolytic potency. The LIs were determined as follows: LI = (CF/MCF) × 100, where MCF is the maximum CF.

Emetic potency of various doses of tranexamic acid—In the dose-escalation experiment, IV administration of tranexamic acid at a dose of 10 mg/kg did not induce vomiting in any of the dogs. When a second dose of 20 mg/kg was administered to the dogs 5 minutes after the initial administration, 5 of 10 dogs vomited within 160 seconds. When a third dose of 30 mg/kg was administered to the remaining 5 dogs, all of them vomited within 120 seconds. The time to onset of vomiting and number of episodes of vomiting were summarized (**Table 1**).

In the single-dose experiment, IV administration of tranexamic acid at a dose of 20 mg/kg induced vomiting in 1 of 10 dogs. When a dose of 30 mg/kg was administered 1 week later to the remaining 9 dogs, 3 vomited. One week later, 4 of the remaining 6 dogs vomited after administration of a dose of 40 mg/kg. Finally, tranexamic acid administered 1 week later at a dose of 50 mg/kg induced vomiting in both of the remaining dogs. The time to onset of vomiting

Table 1—Emetic profiles of escalating doses of tranexamic acid administered IV to 10 dogs.

Variable	10 mg/kg	30 mg/kg	60 mg/kg
No. of dogs that vomited/total No. of dogs that received this dose of tranexamic acid	0/10	5/10	5/5
No. of vomiting episodes per dog			
Mean ± SEM	—	1.6 ± 0.2	1.4 ± 0.2
Median (range)	—	2 (1–2)	1 (1–2)
Time to onset of first episode of vomiting (s)			
Mean ± SEM	—	120.6 ± 18.9	102.4 ± 6.1
Median (range)	—	139 (60–160)	105 (82–120)
No. of dogs that vomited twice	—	3	2
Time between first and second episodes of vomiting (s)			
Mean ± SEM	—	30.7 ± 9.7	46.5 ± 23.5
Median (range)	—	22 (20–50)	46.5 (23–70)
Time to onset of second episode of vomiting (s)			
Mean ± SEM	—	132.0 ± 20.0	156.5 ± 13.5
Median (range)	—	114 (110–172)	156.5 (143–170)

Tranexamic acid (10 mg/kg, IV) was initially administered to 10 dogs. If a dog did not vomit within 5 minutes after the first dose, a second dose of tranexamic acid (20 mg/kg, IV) was administered. If a dog did not vomit within 5 minutes after receiving the second dose, a third dose (30 mg/kg, IV) was administered. Total dose after the first, second, and third administrations was 10, 30, and 60 mg/kg, respectively.

— = Not applicable.

Table 2—Emetic effects of single doses of tranexamic acid administered IV to 10 dogs.

Variable	20 mg/kg	30 mg/kg	40 mg/kg	50 mg/kg
No. of dogs that vomited/total No. of dogs that received this dose of tranexamic acid	1/10	3/9	4/6	2/2
No. of vomiting episodes per dog				
Mean ± SEM	2	1.3 ± 0.3	1.8 ± 0.3	1.0 ± 0.0
Median (range)	—	1 (1–2)	2 (1–2)	1 (1)
Time to onset of first episode of vomiting (s)				
Mean ± SEM	120	150.7 ± 23.5	170.5 ± 27.3	180 ± 7.0
Median (range)	—	142 (115–195)	149 (135–250)	180 (173–187)
No. of dogs that vomited twice	1	1	3	0
Time between first and second episodes of vomiting (s)				
Mean ± SEM	30	48	48.3 ± 14.2	—
Median (range)	—	—	60 (20–65)	—
Time to onset of second episode of vomiting (s)				
Mean ± SEM	150	190	192.3 ± 19.7	—
Median (range)	—	—	200 (155–222)	—

There was a washout period of 1 week between successive doses; doses were administered in ascending order only to those dogs that did not vomit at a lower dose.

— = Not applicable.

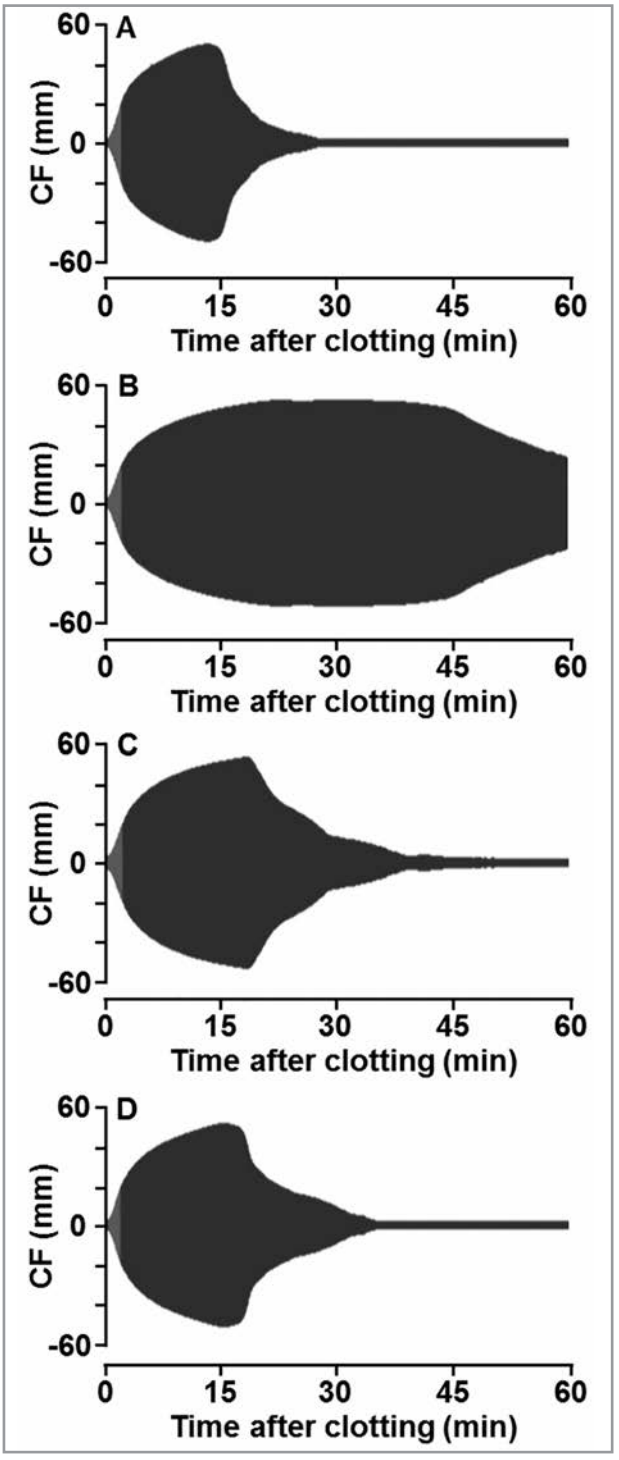

Figure 2—Representative rotational thromboelastometry tracings recorded by use of the assay for resistance to recombinant tissue plasminogen activator in blood samples collected 1 hour before (A) and 20 minutes (B), 3 hours (C), and 24 hours (D) after IV administration of tranexamic acid (50 mg/kg) to a dog.

and the number of episodes of vomiting were summarized (**Table 2**).

Effects of tranexamic acid on recombinant tissue plasminogen activator–induced hyperfibrinolysis— All 10 dogs vomited after receiving the tranexamic acid (50 mg/kg, IV). Representative rotational thromboelastometry tracings of blood samples obtained 1 hour before and 20 minutes, 3 hours, and 24 hours after recombinant tissue plasminogen activator–induced hyperfibrinolysis and administration of tranexamic acid were recorded (**Figure 2**). All of the LIs increased significantly by 20 minutes after administration of tranexamic acid, which indicated that coagulation was facilitated by tranexamic acid. Three hours after tranexamic acid administration, the LI at 45 and 60 minutes decreased to values that did not differ significantly from the corresponding values before administration of tranexamic acid. However, although LI at 30 minutes also decreased, it was still significantly higher than the corresponding value before administration of tranexamic acid. Within 24 hours after the administration of tranexamic acid, all of the LIs returned to values similar to those obtained before tranexamic acid administration (**Figure 3**).

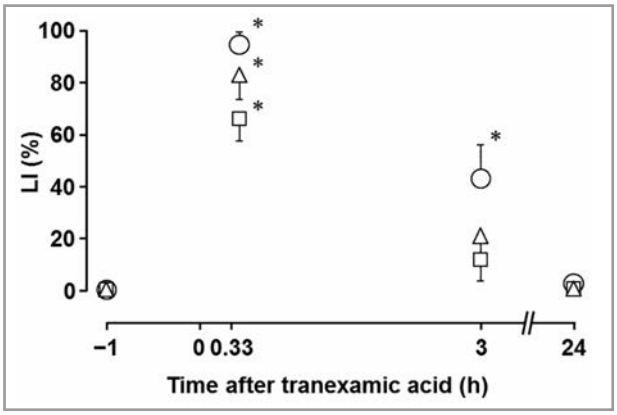

Figure 3—Time course of the mean ± SEM LI measured 30 (circles), 45 (triangles), and 60 (squares) minutes after clotting in blood samples obtained before and 20 minutes, 3 hours, and 24 hours after IV administration of tranexamic acid (50 mg/kg) to 10 dogs . Tranexamic acid was administered at time 0. *Value differs significantly (P = 0.01; Dunnett multiple comparison test) from the value for the sample collected at –1 hour.

Discussion

Findings for the single-dose experiment reported here indicated that IV administration of tranexamic acid induced emesis in a dose-dependent manner and that a 50 mg/kg dose was necessary to induce vomiting in all dogs. Lower doses of tranexamic acid (20, 30, and 40 mg/kg, IV) induced emesis, but not in all of the study dogs. Thus, a dose-escalation approach was an effective way to induce emesis when dogs did not vomit at lower doses of tranexamic acid.

The observed frequency of vomiting in the dogs did not exceed 2 episodes, even after administration of the highest dose of tranexamic acid. In addition, emesis was concluded within 250 seconds. Such a rapid and short-acting effect is an important characteristic for an emetic because emesis should be induced as soon as possible to remove ingested materials and further emesis is not necessary once the stomach contents are expelled.

Apomorphine and 3% hydrogen peroxide effectively induce emesis in dogs, and adverse effects of these emetics are considered mild and self-limiting.[7] Domperidone, a D_2-receptor antagonist, inhibits apomorphine-induced emesis, which suggests that a pathway

involving the activation of D_2 receptors might be involved in apomorphine-induced emesis.[22] Conversely, 3% hydrogen peroxide induces emesis through a vomiting reflex entailing direct irritation of the oropharynx and gastric lining.[6] Recently, our research group found that tranexamic acid induces kaolin intake in rats, which is an index of emesis in humans and dogs.[18] Aprepitant, a tachykinin NK_1-receptor antagonist, but not domperidone, decreases kaolin intake, which suggests that the activation of the pathway for tachykinin NK_1 receptors, but not D_2 receptors, may play a pivotal role in tranexamic acid–induced emesis.[18] Thus, vomiting induced by tranexamic acid may differ qualitatively from vomiting induced by apomorphine or hydrogen peroxide.

Tranexamic acid exerts antifibrinolytic action by blocking the binding of lysine to plasminogen, which plays an important role in fibrin degradation.[15] Consequently, in rotational thromboelastometry assays, recombinant tissue plasminogen activator–induced hyperfibrinolysis is counteracted by the antifibrinolytic potency of tranexamic acid. In the present study, tranexamic acid increased all of the LIs within 20 minutes after administration. However, increases in LI at 45 and 60 minutes were dramatically reversed 3 hours after tranexamic acid administration. Furthermore, within 24 hours after administration, all of the LIs returned to values similar to those before tranexamic acid administration. These results indicated that the antifibrinolytic action of tranexamic acid might begin to subside within 3 hours and be completely resolved within 24 hours after administration.

Limitations of the present study included that only Beagles were used, there was a small study population, and the ingestive material before administration of tranexamic acid was the dogs' daily food. To evaluate efficacy further, emetic profiles of tranexamic acid for dogs of various breeds, sexual statuses, and ages and after the ingestion of various materials should be evaluated in clinical studies with large populations. It is worthy of mention that an owner of a dog that ingests toxic substances should contact a house call veterinarian or bring the dog to a veterinary hospital because tranexamic acid should be administered IV through an indwelling catheter.

In the study reported here, tranexamic acid promptly induced emesis in a dose-dependent manner in dogs. Both single-dose and dose-escalating administration appeared to be feasible methods for inducing emesis with tranexamic acid. Tranexamic acid–induced antifibrinolytic potency decreased in a time-dependent manner and completely resolved within 24 hours.

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b. Transamin injection 10%, Daiichi-Sankyo Co Ltd, Tokyo, Japan.
c. 2.7-mL BD Vacutainer plastic tube, Nippon Becton Dickinson Co Ltd, Tokyo, Japan.
d. ROTEM delta, Finggal Link Co Ltd, Tokyo, Japan.
e. GRTPA injection, Mitsubishi Tanabe Pharma Corp, Saitama, Japan.
f. Star-TEM, Finggal Link Co Ltd, Tokyo, Japan.
g. EXTEM, Finggal Link Co Ltd, Tokyo, Japan.

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