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Safety and efficacy of intravenous administration for tranexamic acid-induced emesis in dogs with accidental ingestion of foreign substances

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ABSTRACT. A prospective observational study was performed in canine clinical medicine to evaluate the emetic action and adverse effects of tranexamic acid. Veterinarians treated 137 dogs with a single dose of tranexamic acid (50 mg/kg, IV) after accidental ingestion of foreign substances. If needed, a second (median, 50 mg/kg; range, 20–50 mg/kg, IV) or third dose (median, 50 mg/kg; range, 25–50 mg/kg, IV) was administered. Tranexamic acid induced emesis in 116 of 137 (84.7%) dogs. Median time to onset of emesis was 116.5 sec (range, 26–370 sec), median duration of emesis was 151.5 sec (range, 30–780 sec), and median number of emesis episodes was 2 (range, 1–8). Second and third administrations of tranexamic acid induced emesis in 64.7 and 66.7% of dogs, respectively. In total, IV administration of tranexamic acid successfully induced emesis in 129 of 137 (94.2%) dogs. Adverse effects included a tonic-clonic convulsion and hemostatic disorder in two different dogs, both of which recovered after receiving medical care. Tranexamic acid induced emesis in most dogs following a single-dose. When a single dose was not sufficient, an additional dosage effectively induced emesis. Overall, adverse effects were considered low and self-limiting.

KEY WORDS: accidental ingestion, dog, emesis, safety, tranexamic acid

Dogs are frequently exposed to various toxic materials, including chocolate, pharmaceuticals, tobacco, nuts, onions, and xylitol [13]. For the treatment of accidental ingestion of these materials, emetics are helpful to remove them from the gastrointestine and to prevent further absorption in some situation. Intravenous injection and ocular conjunctival administration of apomorphine and oral administration of 3% hydrogen peroxide are the most common methods used to induce vomiting [12, 13, 20]. Apomorphine induces emesis by directly stimulating dopamine 2 receptors in the medullary chemoreceptor zone [13, 17], whereas 3% hydrogen peroxide induces emesis through a vomiting reflex by direct stimulation of the oropharynx and stomach lining [13, 20]. Adverse effects of these emetics are generally mild and limited [13, 16]. Tranexamic acid has antifibrinolytic properties and is widely used to control bleeding in trauma patients in both veterinary and human medicine [3, 6, 11]. Nausea and vomiting are recognized as adverse effects for tranexamic acid in humans [4, 5, 22]. Moreover, a higher-than-usual dose of tranexamic acid may induce emesis after IV administration in humans [5]. Recently, our research group found that a vomiting mechanism of tranexamic acid differs qualitatively from that of apomorphine or hydrogen peroxide. Tranexamic acid induces emesis by stimulating a pathway involving tachykinin neurokinin 1 receptors, as opposed to stimulation of dopamine 2 receptors or direct stimulation of the stomach lining by apomorphine and hydrogen peroxide, respectively [9]. We also found that IV tranexamic acid induced emesis in a dose-dependent manner in both single-dose and dose-escalating administration in dogs [10]. The antifibrinolytic effect of tranexamic acid, which is its main medical application, decreased steeply and resolved completely within 24 hr in dogs [10]. Tranexamic acid-induced emesis has been applied empirically to canine patients that ingested toxic materials in Japan; however, the veterinary clinical profile of tranexamic acid as an emetic thus far, has not been systematically investigated. In the present study, the safety and emetic profiles of IV administration of tranexamic acid have been revealed in a canine clinical medicine setting.

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MATERIALS AND METHODS

Animals

Medical records from the Tokyo Jonan Regional Veterinary Medicine Promotional Association Animal Medical Center, a night-time veterinary hospital in Japan were searched for dogs accidentally ingested the materials. When owners suspected or witnessed that their dog had ingested inappropriate materials, they brought their dog to the hospital. Veterinarians used tranexamic acid for the treatment of accidental ingestion when the dog was exposed to a material with a potential risk of causing a severe clinical reaction based on the estimated amount ingested. When dogs were suspected to ingesting sharp-pointed objects, such as wire or a bamboo skewer, or large objects with a risk of occluding gastric cardia, veterinarians did not use tranexamic acid, because vomiting would induce perforation of a stomach ulcer or gastrointestinal injury. Veterinarians did not administer tranexamic acid to dogs that have already vomited several times. A depressed consciousness and underlying disorder, such as depression of laryngeal reflex, seizure, and megaesophagus were contraindications to emetic treatment. If dogs ingested epileptic agents, organic chemicals, such as kerosene and volatile agents, detergents, or strong acid and alkaline materials, tranexamic acid were not used. If such contraindications to inducing emesis existed, veterinarians used a different treatment, such as endoscopic examination or abdominal operation. Tranexamic acid was administered intravenously according to the following medical protocol: Veterinarians typically fed the dog a small meal, such as canned or paste dog food, unless the dog had eaten during the 2 hr prior to emetic administration. Veterinarians administered tranexamic acid IV to dogs through an indwelling catheter. The first dose was 50 mg/kg of 10% tranexamic acid (Daiichi-Sankyo Co., Ltd., Tokyo, Japan). When the first dose failed to induce vomiting, a second and third dose (20–50 and 25–50 mg/kg, respectively) were administered 5 to 10 min apart if the previous dose did not induce emesis. If dogs just had retching, which is called "dry vomiting", we considered that the material ingested would have already moved to intestine. Thus, veterinarians did not administer another dose and recorded it as "a dog with no vomit". If a dog did not exhibit vomiting behavior at all after administration of tranexamic acid, veterinarians judged that another emetic would induce emesis more effectively than an additional dose of tranexamic acid. Then, a 3% hydrogen peroxide solution was administered.

Data collection

Data included the following when available: signalment (breed, age, gender, body weight, anamnesis and clinical signs); information regarding materials ingested (name or type, time of ingestion); estimated amount and location of the material ingested according to an X-ray examination; what food veterinarians gave before inducing emesis; dose of tranexamic acid; number of times tranexamic acid was administered [once, twice, or thrice]; emetic profiles (time to onset of emesis episodes after IV administration of tranexamic acid [sec], duration of emesis [sec], number of emetic episodes per dog); and whether any adverse effects were observed.

Classification of materials ingested

Materials ingested were classified based on the veterinarian's interpretation of witness accounts, X-ray examinations, and findings in the vomited materials. The classification included the following: foreign substances, chocolate, other food, pharmaceuticals, tobacco, nuts, onions, grapes, refrigerant, xylitol, unknown, and rodenticide. The classification "foreign substances" included non-food items and most commonly included household items, such as sponges, cling film, buttons, gum elastic, aluminium foil, plastic goods, sanitary goods, and cosmetics. Most of the cases in the "Other food" category involved consumption of human food, such as bread, cookies, curry, sweet potato, prune, and meal. The "Clothing" category included clothing, such as cloth, stuffed toys, socks, and stockings. When a dog was suspected of ingesting an unidentified material, its case was included in the classification "Unknown".

Statistical analysis

Data were expressed as mean ± SEM, median and range according to the number of times tranexamic acid was administered [once, twice, or thrice]. Differences in age and body weight between the success and failure groups for tranexamic acid-induced emesis were analysed using Mann-Whitney's *U* test.

RESULTS

Clinical data of canine patients administered tranexamic acid for vomiting were collected in 137 dogs from 27 January 2013 to 30 October 2014. The kinds of breed and numbers of dogs were as follows: 30 Poodles (Toy); 28 Dachshunds (Miniature); 12 hybrids; 7 Chihuahuas; 6 Yorkshire Terriers; 5 Retrievers (Golden, Labrador); 4 each of Italian Greyhounds, Papillons, Border Collies, and Miniature Pinschers; 3 each of Cavalier King Charles Spaniels and Pomeranians; 2 each of Welsh Terriers, Shih Tzus, Norfolk Terriers, Pugs, Beagles, Bichon Frises, Malteses, Miniature Schnauzers, Lakeland Terriers, Japanese Shiba Inus, and French Bulldogs; and 1 each of Spaniel (American Cocker), West Highland White Terrier, Welsh Corgi, Parson Russell Terrier, and Boston Terrier.

Emetic profile of IV administration of tranexamic acid

After administration of the first dose of tranexamic acid, 116 of 137 (84.7%) dogs vomited within 370 sec. When a second dose was administered IV to 17 of the 21 dogs that did not vomit after the first administration, 11 of the 17 (64.7%) dogs vomited within

Table 1. Emetic profile of IV administration of tranexamic acid to dogs

Variable	Administration		
	1st	2nd	3rd
Dose of tranexamic acid (mg/kg, IV)			
Mean ± SEM	50 ± 0	39 ± 3	42 ± 8
Median (range)	50 (50)	50 (20–50)	50 (25–50)
No. of dogs that vomited/total No. of dogs that received tranexamic acid	116/137	11/17	2/3
No. of dogs in which materials ingested were recovered/No. of dogs that vomited	78/116	8/11	1/2
Duration of emesis (sec)			
Mean ± SEM	166 ± 8	249 ± 104	480 ± 240
Median (range)	152 (30–780)	131 (50–1,260)	480 (240–720)
No. of vomiting episodes per dog			
Mean ± SEM	2.1 ± 0.1	1.9 ± 0.3	1.7 ± 0.7
Median (range)	2 (1–8)	2 (1–4)	1 (1–3)
Time to onset of first episode of vomiting (sec)			
Mean ± SEM	124 ± 5	150 ± 38	345 ± 295
Median (range)	116.5 (26–370)	100 (50–440)	345 (50–640)
No. of dogs that vomited twice	65	7	1
Time to onset of second episode of vomiting (sec)			
Mean ± SEM	142 ± 12	198 ± 61	120
Median (range)	130 (35–780)	110 (70–493)	120 (120)
No. of dogs that vomited 3 times	39	2	1
Time to onset of third episode of vomiting (sec)			
Mean ± SEM	149 ± 8	532 ± 292	240
Median (range)	153 (40–280)	531.5 (240–823)	240 (240)
No. of dogs that vomited 4 times	15	1	—
Time to onset of fourth episode of vomiting (sec)			
Mean ± SEM	152 ± 18	1,260	—
Median (range)	130 (45–338)	1,260 (1,260)	—
No. of dogs that vomited 5 times and over	5	—	—

The details of dogs that vomited 5 times and over were not shown. —=Not applicable.

440 sec. When a third dose was administered IV to 3 of 6 the dogs that did not vomit after the second administration, 2 of the 3 (66.7%) dogs vomited at 50 and 640 sec. Results of treatment with tranexamic acid, the time to onset of vomiting, duration of emesis, and number of episodes of vomiting are summarized in Table 1.

Veterinarians did not administer additional doses of tranexamic acid to 4 dogs that did not vomit after the first administration, because 3 of the 4 dogs exhibited only retching and the other dog seemed to have almost no residual contents in its stomach because the elapsed time from ingestion to administration of tranexamic acid was over 2 hr. In addition, the veterinarians did not administer further doses to 3 dogs that did not vomit after both first and second administrations. Instead, 3% hydrogen peroxide solution (0.5 m*l*/kg, PO) was administered to 1 of the 3 dogs, and the other dogs received no further treatment as their condition was stable.

Adverse effects with IV administration of tranexamic acid

Adverse effects were observed in 2 of 137 (1.5%) dogs after the first administration of tranexamic acid. One dog (Bichon Frise, male, 11 years old, 9 kg) had a tonic-clonic convulsion. The dog received an injection of diazepam for relieving anxiety and relaxing muscles, and subsequently recovered. The other dog (Papillon, female, 8 years old, 3.26 kg) developed bleeding just after withdrew the IV catheter, and the veterinarian was able to stop the bleeding from the injection site with tape.

Differences in vomiting and non-vomiting groups

No significant differences in body weight or age were found between dogs that vomited after either the first, second, or third administration of tranexamic acid and those that did not. Data including dose, age, and body weight in vomiting and non-vomiting groups per administration of tranexamic acid are summarized in Table 2.

Materials ingested and rates of successful induction of emesis

A single-dose of tranexamic acid successfully induced emesis in all categories of ingested material. The success rate of emesis induction for each administration per category group is summarized in Table 3.

Table 2. Information in vomiting and non-vomiting groups

Variable	Administration					
	1st		2nd		3rd	
	Vomiting	Non-vomiting	Vomiting	Non-vomiting	Vomiting	Non-vomiting
No. of dogs	116	21	11	6	2	1
Dose of tranexamic acid (mg/kg, IV)						
Mean ± SEM	50 ± 0	50 ± 0	42 ± 4	35 ± 6	50 ± 0	25
Median (range)	50 (50)	50 (50)	50 (25–50)	32.5 (20–50)	50 (50)	25 (25)
Efficacy (%)	84.7	—	64.7	—	66.7	—
Age (year)						
Mean ± SEM	3.6 ± 0.3	4.6 ± 1.0	2.6 ± 1.2	7.2 ± 1.9	11.5 ± 2.5	10
Median (range)	3 (0–12)	3 (0–14)	0 (0–10)	7 (1–14)	11.5 (9–14)	10 (10)
Body weight (kg)						
Mean ± SEM	5.8 ± 0.4	6.1 ± 0.6	6.9 ± 0.9	5.2 ± 0.7	4.7 ± 0.3	3.1
Median (range)	4.5 (1.8–32.8)	5.8 (1.3–11.3)	6.2 (2.7–11.3)	5 (3.1–7.3)	4.7 (4.4–5)	3.1

Non-vomiting=Tranexamic acid did not induce vomiting in dogs. —=Not applicable.

Table 3. Materials ingested and success rates to induce emesis

Material ingested	Administration			
	1st (%)	2nd (%)	3rd (%)	Total (%)
Foreign substances	35/45 (77.8)	7/8 (87.5)	1/1 (100)	43/45 (95.6)
Chocolate	32/36 (88.9)	1/3 (33.3)	—	33/36 (91.7)
Other food	14/17 (82.4)	1/2 (50)	—	15/17 (88.2)
Clothing	12/12 (100)	—	—	12/12 (100)
Pharmaceuticals	7/9 (77.8)	1/2 (50)	1/1 (100)	9/9 (100)
Tobacco	8/8 (100)	—	—	8/8 (100)
Nuts	7/8 (87.5)	0/1 (0)	—	7/8 (87.5)
Onions	5/6 (83.3)	0/1 (0)	0/1 (0)	5/6 (83.3)
Grapes	4/5 (80)	1/1 (100)	—	5/5 (100)
Refrigerant	3/3 (100)	—	—	3/3 (100)
Xylitol	3/3 (100)	—	—	3/3 (100)
Unknown	2/2 (100)	—	—	2/2 (100)
Rodenticide	1/1 (100)	—	—	1/1 (100)
All groups	116/137 (84.7)	11/17 (64.7)	2/3 (66.7)	129/137 (94.2)

Data are expressed as number of dogs that vomited/total number of dogs that received tranexamic acid and its percentage. The case involving ingestion of more than one type of material was included in all relevant groups. 1st=A first dose (50 mg/kg, IV) of tranexamic acid was administered to 137 dogs. 2nd, 3rd=A second and third dose (20–50, 25–50 mg/kg, respectively) were administered IV to the dogs that did not vomit in the previous administration (17 dogs and 3 dogs, respectively). —=Not applicable.

DISCUSSION

The results of the present study indicate that tranexamic acid effectively induces emesis in dogs in a clinical setting. A single-dose of tranexamic acid successfully induced emesis with a high probability. For dogs that withstood the first dose, a second and third administration induced emesis. After the first administration of tranexamic acid, emesis was induced promptly, and the duration of action was short. Generally, emesis should be induced as soon as possible to remove a large portion of the stomach contents, as gastric transit time is approximately 2 hr [7, 19]. Therefore, induction of emesis may not be effective 2 to 3 hr after ingestion of a poison [1]. Once dogs regurgitate their stomach contents, further episodes of vomiting are not necessary. Taken together, the prompt and short-acting properties of tranexamic acid make it a good choice as an emetic.

Intravenous and ocular conjunctival administration of apomorphine and oral administration of 3% hydrogen peroxide have yielded high success rates of 94 and 90%, respectively [12]. The median time from IV and ocular conjunctival administration of apomorphine to onset of vomiting was 1 min and 6 min, respectively [2]. The median time from oral administration of 3% hydrogen peroxide to onset of vomiting was 10 min [12]. Therefore, tranexamic acid induces emesis in dogs as promptly as IV administration of apomorphine, and more promptly than ocular administration of apomorphine and oral administration 3% hydrogen peroxide.

We demonstrate that a second and third administration of tranexamic acid induced emesis in dogs that did not vomit after the first and second administration, suggesting that an additional dosing approach may be an effective way to recover the ingested material from the stomach. It is noted, however, the success rates of inducing emesis with a second and third administration were

less than the success rates with the first administration.

There were no differences in age and body weight between dogs in which tranexamic acid induced emesis and those in which it did not induce emesis. In addition, the success rate to induce emesis was very high in all categories of material ingested. Therefore, tranexamic acid may induce emesis in dogs with a high probability regardless of age, body weight, and kinds of material ingested. Further studies are warranted to investigate the effects of these factors on tranexamic acid-induced emesis.

In the present study, one dog developed a hemostatic disorder at the injection site. Fletcher *et al.* found that dogs are physiologically more hyperfibrinolytic than humans, which could explain the observed effect [6].

One dog that had ingested some amount of cocoa powder had a tonic-clonic convulsion after the first administration. High-dose administration of tranexamic acid increases the risk of postoperative seizures in humans [18]. Tranexamic acid postsynaptically antagonizes γ-aminobutyric acid receptors type A and glycine receptors, both of which are major central inhibitory neurotransmitters, and lead to an increased neuronal excitation *ex vivo* in mice [14, 15]. In addition, a xanthine derivative "theobromine", a main component of cocoa powder, may induce an acute seizure by itself [8, 21]. These excitatory mechanisms may be involved in the incidence of seizure in dogs treated with tranexamic acid. Further studies are warranted to investigate the proconvulsant effect of tranexamic acid in dogs.

Limitations of the present study included that the amount of the potentially toxic material recovered in the vomitus was not calculated, although veterinarians judged whether recovery of the material ingested was successful by visually comparing the amount recovered to the estimated amount ingested.

In conclusion, tranexamic acid promptly induces emesis with a high probability following single-dose administration. A dose-escalation approach also effectively induces emesis. Adverse effects of tranexamic acid are considered low and self-limiting.

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