OPEN ACCESS

PAPER

Ropinirole eye drops induce vomiting effectively in dogs: a randomised, double-blind, placebo-controlled clinical study

Minna Suokko,[1] Lasse Saloranta,[1] Terttu Lamminen,[1] Tarmo Laine,[1] Jonathan Elliott[2]

Abstract

There is a need for an effective and safe emetic agent that dog owners could easily administer to their dogs following veterinary advice in cases of potential poisoning. As a response to this need, a randomised, double-blind, multi-site, clinical field study was performed to assess the efficacy, safety and usability of ropinirole eye drops to induce vomiting in dogs. Ropinirole (target dose 3.75 mg/m^2) was applied to eyes of 100 dogs, and 32 dogs received placebo. The drug was administered by the dog owner at a veterinary clinic under the supervision of a veterinarian and led to vomition in 95% of the ropinirole-treated dogs within 30 min. The median time to first vomit was 10 min (range: 3–37 min). None of the dogs receiving placebo vomited in this time period. All owners were able to administer the product and 96% of them assessed the administration to be very easy or easy, which was confirmed by the observing veterinarian. Some ocular signs were seen both with ropinirole and placebo, hyperaemia being the most common. All observed signs were transient and in most cases mild. Ropinirole eye drops provided an effective, safe and reliable means to induce emesis in dogs.

Introduction

Induction of emesis in dogs is accepted as the first line of action for initial decontamination following ingestion of potentially toxic substances or other unwanted material, unless contraindicated. Contraindications for emesis induction include situations when the animal is depressed neurologically or the material ingested is corrosive or volatile.[1] Vomiting can be induced by a number of chemicals acting centrally and/or peripherally to trigger the vomiting response.[2] For drugs the most direct and rapid way to initiate the vomiting response is via stimulating the chemoreceptor trigger zone (CTZ) in the brain stem. The CTZ is outside the blood–brain barrier and is rich in dopamine D2-type receptors.[3 4] Drugs that activate D2-type receptors in CTZ are potent emetogens in several species, including dogs.[5–7]

Apomorphine is commonly used by veterinarians to induce emesis in dogs, but it is not licensed for animal use in the USA and is licensed only for administration by parenteral injection in Europe. Apomorphine induces vomiting by stimulating dopamine receptors in the CTZ. It is a non-selective dopamine receptor agonist that activates not only various dopamine receptor subtypes but also other classes of receptors activated by structurally related amine neurotransmitters, including a number of 5-hydroxytryptamine receptors and alpha-adrenoceptor subtypes.[8] Apomorphine also stimulates μ-opioid receptors. As a consequence of the non-selectivity, the drug can have a number of side effects and at high doses inhibit vomiting through its opioid effects.[9] This means that if vomiting does not occur after the first apomorphine injection, the repeated dosing is not likely to succeed. The side effects of apomorphine include prolonged vomiting, tachycardia and lethargy.[10 11]

Dog owners commonly use various substances such as hydrogen peroxide, table salt, ipecac syrup and liquid dishwashing detergent to induce emesis in their dog. The home remedies have limitations

Veterinary Record (2019) doi:10.1136/ vetrec-2018-104953

[1]Department of Research and Development, Orion Pharma Orion Corporation, Espoo, Finland
[2]Department of Comparative Biomedical Sciences, Royal Veterinary College, University of London, London, UK

E-mail for correspondence: Dr Minna Suokko; minna.suokko@orionpharma.com

Provenance and peer review Not commissioned; externally peer reviewed.

Received March 22, 2018
Revised June 17, 2019
Accepted July 29, 2019

including difficulty in administration, inappropriate dosing, lack of consistent efficacy and undesirable side effects.[1 11 12] Currently, there is no authorised product available that could be easily and safely administered by the owner in case of emergencies, where the risk–benefit assessment (undertaken by consultation with a veterinary professional) is in favour of inducing emesis at home. This would save valuable time, expediting gastric evacuation in a dog that has consumed a toxic substance.

Ropinirole is a full dopamine agonist with high selectivity for dopamine D2-type receptors,[13] which mediate induction of emesis very readily in the dog.[5] Therefore, ropinirole was chosen as an active ingredient for a new emetic agent for use in dogs. As ropinirole is a dopamine D2 agonist, similar side effects including tachycardia as with apomorphine are to be expected.[14] However, due to the selective pharmacology of ropinirole, the number of unwanted effects is expected to be limited and those effects can be reversed with an antidote, such as dopamine receptor antagonist metoclopramide. Furthermore, the selectivity may also allow repeated administration of ropinirole to increase the vomiting inducing effect.

Other properties for the 'ideal emetic agent' include rapid onset of effect and short duration of action and it was hypothesised that ropinirole could fulfil these criteria. A novel ocular administration route of ropinirole was chosen to allow non-invasive administration while providing a fast and reliable absorption bypassing the gastrointestinal tract. Small-scale pilot clinical and pharmacokinetic studies were undertaken to determine the appropriate dose required by this route to reliably induce emesis (data on file, Orion Pharma). In addition, standalone cardiovascular safety studies were performed to verify cardiovascular safety of ropinirole in dogs (data on file, Orion Pharma). The aim of the study described in this paper was to confirm the efficacy and safety of ropinirole to induce emesis, and the usability of the product, when trialled by owners administering the eye drops to their dogs.

Materials and methods

Study design

The randomised, double-blind, placebo-controlled, parallel-group, clinical field study was carried out over a 10-week period between October and December 2015 at six veterinary clinics in the USA. The study was conducted in compliance with the principles of Good Clinical Practice and subjected to internal ethical review at Orion Pharma. Protocol was also submitted for review to the US Food and Drug Administration (FDA) and concurrence was received prior to the study. Informed consent was obtained from the owners before enrolling their dog in the study. The welfare, treatment and care of the study animals were ensured by the investigator veterinarians.

Selection of animals

Client-owned male and female dogs of any breed and age were enrolled in this study. Dogs were recruited from the patient population of the clinic based on an earlier visit to the clinic, an owner interview and/or medical records. The owners were offered an incentive to participate in the study. To be eligible for the study, the dogs had to have a body weight of at least 1.8 kg to meet the target dose range if one drop was administered. The dogs had to be healthy or were allowed to have a mild systemic disease (status ASA I or II according to American Society of Anesthesiologists classification[15] as adopted from human medicine to veterinary patients). The exclusion criteria included dogs with confounding ophthalmic or gastrointestinal disease. Dogs were also excluded if they had received dopamine agonists or antagonists or other medications with known antiemetic properties, including antihistamines and maropitant within 1 week before the start of the study. In addition, lactating and pregnant dogs were excluded.

Treatments

The investigational veterinary product used in this study was ropinirole 30 mg/mL ophthalmic solution in a single-use blow fill sealed ampoule. The placebo ophthalmic solution was identical in appearance, and contained the same excipients but no active ingredient. The dose of ropinirole was determined based on previous studies where doses of 0.9–5.5 mg/m^2 were investigated (data on file, Orion Pharma). Based on the results of these studies, the target dose of 3.75 mg/m^2 was selected for the present clinical study.

The number of eye drops (1–8) administered was determined according to the dog's body weight. The body weight ranges were defined to match the target dose of 3.75 mg/m^2 (2.7–5.4 mg/m^2) as closely as possible. Body surface area was calculated using the following formula: body surface area=10.1 × (body weight in kg)$^{0.67}$/100.[16] Doses were administered in both eyes at one administration time and doses larger than 4 drops were divided in 2 and given 2 min apart from each other to ensure overflow did not occur.

Study assessments

The owners were requested to feed the dogs at home 1 hour (±30 min) before the treatment visit. At the treatment visit, the dog's eligibility for the study was confirmed. Each dog underwent a physical examination and blood and urine samples were taken for laboratory tests. The eligible dogs were randomised to receive either ropinirole or placebo at 3:1 ratio. Randomisation was conducted by an independent randomisation specialist using computer software before the study start. Completely randomised blocks of four dogs were stratified by centre. All owners and investigators were masked to treatment allocation. The owner administered the eye drops under the supervision

of the veterinarian. If the owner had only little or no experience of administering eye drops to dogs, they were given further instructions. Each dog was given the initial dose (of ropinirole or placebo) at 0 hour. If the dog did not vomit, an equal dose was given 20 min after the initial dose using the same ampoule. The dogs were followed in the clinic for 8±2 hours after dosing. The end-of-study visit took place 3–5 days after the treatment visit whereby the dogs were re-examined.

The dopamine antagonist, metoclopramide 0.5 mg/kg subcutaneously, was administered as an antidote based on the judgement of the veterinarian if vomiting continued for more than 1 hour or if the vomiting was considered excessive.

Efficacy and usability of the product

The primary efficacy variable was induction of vomiting within 30 min following the initial treatment administration. A treatment success was recorded if vomiting occurred within 30 min of the initial administration regardless of whether the dog received a second dose at 20 min.

Other variables recorded were time to first vomit from administration, duration of vomiting (time from first vomit to last vomit), number of vomits and form of vomited material (foam, fluid or solid). The use of metoclopramide was also recorded. The usability of the product was assessed both by the owner (a four-point categorical scale: very easy, easy, somewhat difficult or very difficult) and the observing investigator who assessed the owner's success in administering the eye drops (on a three-point categorical scale: successful, successful but with difficulties, or not successful).

Safety

Physical examination was performed before and 8 hours after dosing. Local tolerance of the eyes, cardiovascular status (by auscultation) and the presence of any other abnormal clinical signs were assessed before and 30 min, 2 hours, 4 hours and 8 hours after dosing. Laboratory variables (haematology, clinical chemistry and urinalysis) were assessed before dosing. All safety assessments were repeated at the end of study visit. Adverse events were recorded throughout the study.

Local ocular tolerance assessment included conjunctival hyperaemia, conjunctival discharge, conjunctival swelling, protrusion of the third eyelid, blepharospasm and itching. Each of the variables was scored separately on a four-point scale (none, mild, moderate or severe).

Statistics

Sample size was estimated using statistical analysis simulations. Analysis of the primary variable was repeated using 10 000 randomly generated datasets from binomial distribution expecting an average success rate of 85%. With the sample size of 90 dogs in the ropinirole treatment group, the study objective was achieved approximately in 85% of 10 000 statistical analyses yielding a 95% CI above 70%. The total planned sample size was 120 dogs, of which 25% of the dogs received placebo and so the study was powered to determine whether the success rate was significantly greater than 70%.

The primary efficacy variable, induction of vomiting within 30 min, was analysed for the ropinirole group as a single proportion analysis using a generalised linear mixed model. The proportion of responders was treated as a binomial random variable and a logit link function was applied.

The treatment group was included as a fixed effect and the study centre as a random effect in the model. Data were analysed on an intention-to-treat (ITT) basis and the number of dogs deviating from the protocol is reported. The null hypothesis for the primary efficacy variable was that less than 70% of the dogs will vomit within 30 min.

Changes in heart rate were analysed using a repeated measures analysis of a covariance model. The statistical model included treatment, time and treatment–time interaction as fixed effects, the study centre as a random effect and the baseline value as a covariate. All other variables were evaluated descriptively.

Sample size estimation and statistical analyses were performed with SAS for Windows V.9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 132 dogs were randomised, of which 100 dogs received ropinirole and 32 dogs received placebo. All randomised dogs (n=132) were included in the ITT and safety dataset.

The demographic and other baseline characteristics were comparable in the treatment groups (table 1). The age ranged from 7 months to 16 years, and the weight ranged from 1.9 to 66 kg. The dogs classified as ASA II had various types of diseases, the most common being heart murmur, arthritis and otitis externa.

Table 1 Distribution of dogs by sex, age, weight and ASA class

	Ropinirole N=100	Placebo N=32
Sex		
Female	51 (51%)	19 (59%)
Male	49 (49%)	13 (41%)
Age		
Median	6 years	5 years
Range	7 months–16 years	11 months–16 years
Weight		
Median	24 kg	21 kg
Range	1.9–66 kg	3.8–44 kg
ASA class		
I	80 (80%)	26 (81%)
II	20 (20%)	6 (19%)

ASA, American Society of Anesthesiologists Classification.

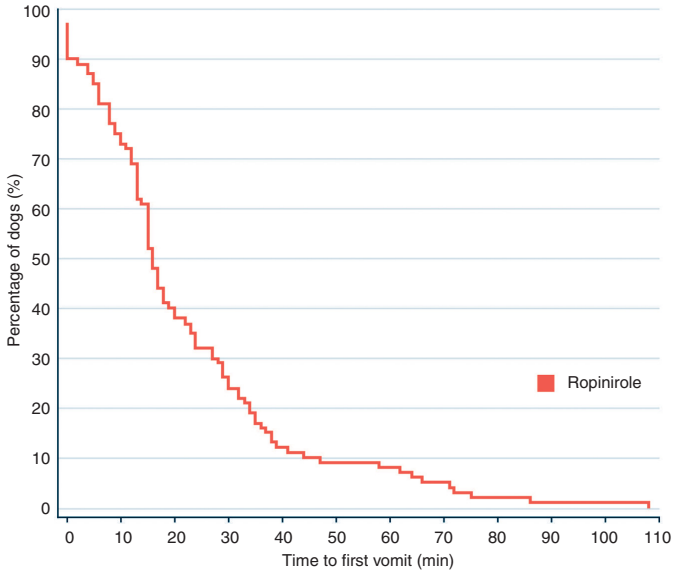

Figure 2 Duration of vomiting from first to last vomit in dogs that received ropinirole.

A wide range of breeds were represented, 40 mixed breeds and 38 purebreds of which the most common included Labrador Retriever, Golden Retriever, Shih Tzu and American Pit Bull Terrier.

The median initial and total dose of ropinirole was 3.8 (range: 2.8–5.4) mg/m^2 and 3.9 (range: 2.8–9.6) mg/m^2, respectively. The median total dose for the 13 dogs which received a second dose was 6.9 (range: 5.7–9.6) mg/m^2. The number of ropinirole drops for the initial dose varied from 1 to 8 and for the second dose from 1 to 4.

Vomiting within 30 min

In all, 95 of the 100 dogs treated with ropinirole vomited within 30 min in the ITT population. The estimate of the responder rate in the statistical analysis was 97% (95% CI: 83% to 99%). Based on the a priori power calculation, the responder rate was significantly higher than 70% as the lower 95% confidence limit exceeded 70% of the population.

The majority of dogs (87%) responded to the first dose of ropinirole, the second dose being needed in 13% (13/100) of the dogs. Out of the 13 dogs, eight dogs vomited within 30 min after the initial dose. Two more dogs vomited within 37 min.

All of the five non-responders in the ropinirole group violated the protocol with a delay in receiving the second dose. Thus, in the per protocol population, in dogs without protocol violations, all dogs (100%) vomited within 30 min. None of the dogs in the placebo group vomited within 30 min.

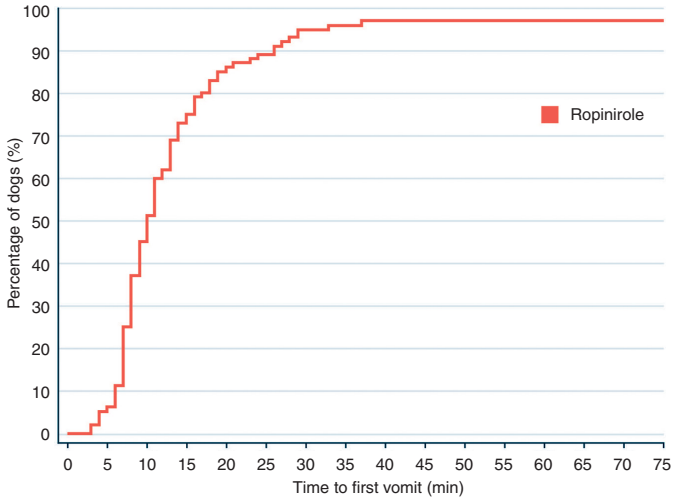

Figure 1 Time to first vomit from administration of ropinirole.

Time to first vomit

Figure 1 shows the time to first vomit for ropinirole. Half of the dogs vomited within 10 min (range: 3–37 min). There was a tendency for dogs that received a dose above the target dose to start vomiting sooner than the dogs receiving a dose below the target dose.

Other vomiting-related variables

The median duration of vomiting for ropinirole was 16 (range: 0–108) min. As shown in figure 2, for the majority (75%) of the dogs, the duration of vomiting was less than 30 min and in approximately 90% of the dogs the duration of vomiting was less than 45 min.

The median number of vomits for ropinirole was 4.0 (range 1–13). The form of vomit expelled nearly always (89%) contained solid material. Metoclopramide was given to five dogs and none of these dogs vomited again after metoclopramide had been administered; these dogs are included in figure 2. There were three dogs for which the last vomit occurred at 66–108 min but the vomits were isolated incidents with long intervals and did not require metoclopramide based on the investigator's judgement.

Usability of the product

All owners were able to administer the eye drops and 96% of them assessed the administration to be very easy or easy (figure 3A). This was confirmed by the veterinarians' assessment, which showed that 93% of the owners administered the eye drops successfully to their dog (figure 3B).

Safety

Local tolerance of the eyes to ropinirole was good. The most prevalent ocular signs in the ropinirole group were hyperaemia (51%), protrusion of the third eyelid (39%) and conjunctival discharge (35%), all of which were transient and mild or moderate. The same signs were present in the placebo group in 22%, 3% and 19% of the dogs, respectively. They were most evident at 30 min and were reduced at 2 hours and had almost completely abated by the examination performed 8 hours after the administration. Noteworthy is that ocular hyperaemia was reported in nearly 10% of the dogs prior to the treatment administration. Observations of the dogs during the treatment visit most commonly revealed lethargy (43%) and nausea (11%) in the ropinirole

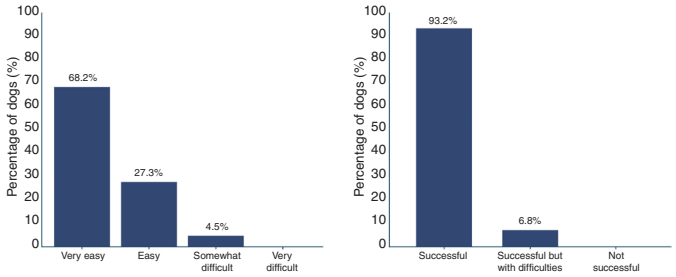

Figure 3 Usability of the product: (a) ease of administration of eye drops as assessed by owners and (b) success to administer the eye drops by the owner as assessed by veterinarians.

group 30 min after treatment administration while these signs were not reported in the placebo group.

Transient increase in heart rate lasting approximately 2 hours from dosing was noticed in the ropinirole group. After 30 min of administration of the product, the heart rate had increased by 14% (95% CI: 7% to 20%) relative to baseline heart rate, whereas following placebo administration, the proportionate change in heart rate relative to baseline was −2% (95% CI: −11 to 6%). In the ropinirole group, tachycardia was reported as an adverse event based on the investigator's clinical judgement in five dogs (median of maximum heart rate was 180 bpm, range: 160–200 bpm), while no events were reported in the placebo group. Five dogs with cardiac murmur were recruited in the study, of which four received ropinirole and one received placebo. No cardiovascular safety issues were reported in these dogs during the study. No safety concerns were raised based on the laboratory safety variables.

Discussion

The primary efficacy endpoint of the present study was vomiting within 30 min regardless of whether a second dose was required. The results clearly demonstrate that ropinirole eye drops are effective in inducing vomiting in healthy dogs, as 95% of the dogs vomited within 30 min of receiving ropinirole. Those dogs that did not respond within 30 min of the first dose did not follow the study protocol precisely in that there was some delay in administering the second dose. The present study clearly demonstrates that ropinirole has a fast onset of action because the median time to first vomit was 10 min, with a range of 3–37 min.

The sooner the dog evacuates the potentially poisonous contents of its stomach by vomiting, the lower the risk that the toxic substance will be absorbed. In cases of the most rapidly absorbed harmful substances, such as xylitol, induction of emesis is most effective within the first 30 min to 1 hour.[17] Furthermore, the time needed for the gastric contents to move into the small intestine in the dog usually has a lag phase of about 40 min following eating but there is a wide range (15–108 min), and gastric emptying also depends, among other things, on the type of food eaten.[18] Based on these published data, vomiting within 30 min was chosen as the primary efficacy endpoint in the present study as this would be effective in decontaminating dogs that have ingested harmful substances or material in the majority of cases.

The duration of vomiting period with ropinirole was short as half of the dogs vomited for less than 10 min and in nearly all dogs vomiting ended spontaneously within 40 min. Metoclopramide, the protocol-specified antidote, was considered necessary in only five dogs, which can be regarded a very low portion.

The protocol provided the option of giving a second dose to those dogs that did not vomit within 20 min of the initial dose. This was required in only 13 of the dogs treated and 8 of these subsequently vomited within the 30 min time limit. All ropinirole dogs that did not vomit within 30 min had some delay in the administration of this second dose suggesting that timely redosing may increase the efficacy of ropinirole as the delay in redosing seen in the ropinirole dogs could have explained the diminished effect. This leads to the conclusion that if a second dose is needed, it should preferably be given within 20 min after the initial dose to ensure maximal efficacy.

Overall, the product was well tolerated. Most reported side effects were mild or moderate and resolved quickly, within a few hours of treatment administration. Ropinirole solution proved to have good local eye tolerance. The signs in the eyes, associated most likely with ropinirole or the excipients, may indicate some ocular discomfort, which can be considered a disadvantage compared to parenteral administration of apomorphine. However, most of the signs in all dogs were completely resolved within 2 hours. They are suggestive of local activation of D2 receptors in the eye rather than a direct irritant effect because they resolved very quickly and have in previous studies resolved more rapidly when D2 receptor antagonists have been administered (data on file, Orion Pharma). Lethargy, which was the most commonly observed systemic sign, is considered in this context to be associated with nausea, which was another often reported finding that would be expected to be seen with any emetic as a prelude to vomiting in dogs.[2 19]

Transient tachycardia occurred in five dogs when treated with ropinirole, possibly also due to the pharmacological effect on dopamine receptors. However, vomiting itself may physiologically cause an increase in heart rate due to changes in autonomic discharge that accompany the vomiting response.[19] The number of dogs included in the present study with subclinical cardiac disease (detected by the presence of a heart murmur) was very low (only four in the ropinirole-treated group). However, none of these dogs showed adverse cardiac effects following ropinirole administration. It seems likely that short-term tachycardia caused by this drug is of little consequence to dogs with subclinical cardiac disease.

The usability of ropinirole eye drops was excellent as all owners were able to administer the product and nearly all assessed the administration to be easy or very easy. Furthermore, it is reassuring that the veterinarians assessed all owners as being able to administer the drug. An important aspect of this treatment is that in situations when the dog has ingested toxic material, the eye drop dosage form could enable owners to administer the drug to their dogs. This way valuable time would not be lost during the journey to the veterinary practice. In such emergency situations, administering the prescription product to an asymptomatic dog at home under the direction of a veterinarian, provided that no contraindications for vomiting induction are present, would expedite the decontamination process and could even save the dog's life.

There are some limitations of the present study. First, evacuation of the stomach was not measured quantitatively as the amount and form of vomit were assessed visually. Nevertheless, the number of vomiting events (median 4.0) is considered sufficient to have achieved the goal of evacuation of the stomach. In addition, the form of vomit expelled nearly always contained solid material that the dog had eaten before the treatment, which supports the fact that ropinirole induces vomiting that empties the stomach contents. Second, the study did not assess the effects of ropinirole in dogs that had ingested something harmful. This study was undertaken to assess the effect of ropinirole, when administered as eye drops by dog owners, on inducing a vomiting response in a large population of healthy dogs. The wide range of ages, weights and breeds of dogs included in the study means that the dogs can be considered representative of the target population. It would not have been ethical to run a blinded placebo controlled study involving dogs that had potentially been poisoned. Third, cardiovascular parameters measured were limited to heart rate taken by auscultation. Electrocardiography and blood pressure have been examined prior to this study in standalone cardiovascular safety studies involving laboratory dogs with no major findings, except transient increase in heart rate (data on file, Orion Pharma). Therefore, this study conducted by general practitioners was performed using the standard clinical heart rate assessment suitable to monitor the expected cardiovascular findings.

In conclusion, ropinirole, administered topically to the eye by the owner, is effective and safe in inducing vomiting in dogs with the target dose 3.75 mg/m^2 (range: 2.8–5.4 mg/m^2). The product has a fast onset of action, and the dose can be repeated within 20 min after the administration of the initial dose if the dog does not start vomiting before that. It is well tolerated with only minor and transient local discomfort to the eyes and mild, short-term tachycardia seen in a small proportion of dogs. The formulation developed proved highly practical for owners to administer successfully, despite their lack of experience in giving ocular medications. The results of this clinical study show that ropinirole eye drops are easy to use, effective and safe in inducing vomiting with a fast onset of action and a spontaneous recovery in dogs.

Acknowledgements The study was sponsored by Orion Corporation Orion Pharma. The authors thank the study team, participating investigators and dog owners. The authors also thank Stig Sundberg for editorial assistance.

Funding The study was sponsored by Orion Corporation Orion Pharma. The authors thank the study team, participating investigators and dog owners.

Competing interests MS, LS, TL and TL are employees of Orion Corporation. JE is a paid consultant of Orion Corporation.

Data availability statement All data relevant to the study are included in the article.

References

1 Peterson M. Toxicological Decontamination. In: Peterson M, Talcott P, eds. Small animal toxicology. St. Louis, Missouri: Elsevier Saunders, 2013: 73–83.
2 Elwood C, Devauchelle P, Elliott J, *et al*. Emesis in dogs: a review. *J Small Anim Pract* 2010;51:4–22.
3 Stefanini E, Clement-Cormier Y. Detection of dopamine receptors in the area postrema. *Eur J Pharmacol* 1981;74:257–60.
4 Hyde TM, Knable MB, Murray AM, *et al*. Distribution of dopamine D1-D4 receptor subtypes in human dorsal vagal complex. *Synapse* 1996;24:224–32.
5 Yoshida N, Yoshikawa T, Hosoki K, *et al*. A dopamine D3 receptor agonist, 7-OH-DPAT, causes vomiting in the dog. *Life Sci* 1995;57:PL347–50.
6 Darmani NA, Zhao W, Ahmad B, *et al*. The role of D 2 and D 3 dopamine receptors in the mediation of emesis in Cryptotis parva (the least shrew). *J Neural Transm* 1999;106:1045–61.
7 Yoshikawa T, Yoshida N, Oka M, *et al*. The broad-spectrum anti-emetic activity of AS-811$_2$, a novel dopamine D$_2$, D$_3$ and 5-HT$_3$ receptors antagonist. *Br J Pharmacol* 2001;133:253–60.
8 Ribarič S. The pharmacological properties and therapeutic use of apomorphine. *Molecules* 2012;17:5289–309.
9 Scherkl R, HASHEM A, FREY H-H, *et al*. Apomorphine-Induced emesis in the dog-routes of administration, efficacy and synergism by naloxone. *J Vet Pharmacol Ther* 1990;13:154–8.
10 Cote DD, Collins DM, Burczynski FJ, *et al*. Safety and efficacy of an ocular insert for apomorphine-induced emesis in dogs. *Am J Vet Res* 2008;69:1360–5.
11 Khan SA, Mclean MK, Slater M, *et al*. Effectiveness and adverse effects of the use of apomorphine and 3% hydrogen peroxide solution to induce emesis in dogs. *J Am Vet Med Assoc* 2012;241:1179–84.
12 Niedzwecki AH, Book BP, Lewis KM, *et al*. Effects of oral 3% hydrogen peroxide used as an emetic on the gastroduodenal mucosa of healthy dogs. *J Vet Emerg Crit Care* 2017;27:178–84.
13 Perachon S, Schwartz J-C, Sokoloff P, *et al*. Functional potencies of new antiparkinsonian drugs at recombinant human dopamine D$_1$, D$_2$ and D$_3$ receptors. *Eur J Pharmacol* 1999;366:293–300.
14 Humphrey S*Jet al*. Cardiovascular and electrocardiographic effects of the dopamine receptor agonists ropinirole, apomorphine, and PNU-142774E in conscious beagle dogs. *J Cardiovasc Pharmacol* 2006;47:337–47.
15 ASA Physical Status Classification System. American society of anesthesiologists. Available: https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system [Accessed Jun 2015].
16 Price GS, Frazier DL. Use of body surface area (BSA)-based dosages to calculate chemotherapeutic drug dose in dogs: I. Potential problems with current BSA formulae. *J Vet Intern Med* 1998;12:267–71.
17 Holowaychuk MK. Top 5 ingestations that require induction of emesis. Cliniciansbrief.com: 18-22, 2015. Available: https://www.cliniciansbrief.com/article/top-5-ingestions-require-induction-emesis
18 Schmitz S*et al*. Solid phase gastric emptying times in the dog measured by 13C-sodium-acetate breath test and 99mTechnetium radioscintigraphy. *Tierarztl Prax Ausg K Kleintiere Heimtiere* 2010;38:211–6.
19 Kenward H, Pelligand L, Savary-Bataille K, *et al*. Nausea: current knowledge of mechanisms, measurement and clinical impact. *Vet J* 2015;203:36–43.