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ORIGINAL RESEARCH

Effects of a single oral dose of gabapentin on storm phobia in dogs: A double-blind, placebo-controlled crossover trial

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Abstract

Background: Storm phobia in companion dogs is a common disorder that significantly impacts dogs' welfare. Gabapentin, the action of which is only partially understood, is widely used for its antiepileptic and analgesic properties. Only recently, the veterinary community began to use gabapentin to address phobia and anxiety in dogs. This study tested gabapentin to lower fear responses of dogs during a thunderstorm event.

Methods: Eighteen dogs suffering from storm phobia completed our double-blind, placebo-controlled crossover trial. Each dog's behaviour was evaluated twice by his owner: once under placebo, once under gabapentin. The treatment was orally administered at least 90 min before the exposure. Gabapentin was given at a dose ranging from 25 to 30 mg/kg.

Results: Our results indicate a significant reduction of the fear responses of dogs under gabapentin. The adverse effects were rare, and the most frequent amongst them was ataxia.

Conclusion: In this trial, gabapentin appears to be an efficient and safe molecule that should be considered as part of the treatment plan of storm phobia in dogs.

KEYWORDS
dogs, double-blind placebo-controlled crossover trial, gabapentin, storm phobia

BACKGROUND

Fear response to noise is a common behavioural reaction with a prevalence of up to 49% in dogs.[1] Fear is an adaptative mechanism that supposedly allows the animal to survive a possible dangerous event.

The exposure to a fearful stimulus will provoke an arousal of the sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) pathways.

The SAM pathway provides the fastest response to stress stimuli by activating the sympathetic and parasympathetic nervous systems.[2] Catecholamines (epinephrine and norepinephrine) release results in glycolysis, vasoconstriction in many networks of capillary vessels, and vasodilatation of blood vessels of the skeletal muscles and the liver. Catecholamines are positive inotropes that increase heart frequency and consequently blood pressure. These physiological changes are associated with the 'flight or fight' reactions.[3,4]

The activation of the HPA pathway increases glucocorticoids synthesis. Consequently energy reserves are mobilized, and glucogenesis, proteolysis and lipolysis are stimulated.[2,5] These physiological changes can be seen as the necessary support of the 'flight or fight' reactions.

In addition to the previous sympathetic and hormonal pathways, the amygdala plays a major role in the fear reaction by gathering information from the somatosensory and the auditory cortex (input) and by its projections to the anterior cingulate and orbitofrontal cortex (output).[6] The amygdala and the hippocampus play a central role in fear memory and the process of fear conditioning. Sensory information is sent to the basolateral region of the amygdala, where cells, in turn, send axons to the central nucleus. Efferents from the central nucleus project to the hypothalamus which will trigger an enhancement of the SAM pathways characterized by panting, salivating, shivering and escape attempts.[7]

Dogs exposed to regular, predictable and low intensity fear-inducing noises should be able to adapt to a stimulus that is not a real threat, and progressively through the process of habituation, learn not to react. Stimuli that occur unpredictably, intermittently and in high intensity, such as storms, are more likely to induce a strong reaction from the SAM and HPA pathways that may result in disproportionate reactions which are not adapted to the real level of threat of the

stimulus. Thus, in these cases, the fear reaction is not adaptive anymore, the dog is unable to quickly recover a balanced emotional state and some reactions, such as destructive behaviours and self-harming, may be even more traumatic, with severe consequences on individual's welfare. According to the literature, this non-adaptative behavioural response is called 'phobia', a term borrowed from human psychiatry and widely used in the veterinary field, particularly under the term 'noise phobia' which includes storm phobia and fireworks phobia.[8,9] Phobic reactions may have extended consequences since dogs exposed to loud noises may not recover and may show signs of behavioural disorders even weeks after the exposure.[10] For these reasons storm phobias are a real concern for the dog's wellbeing and health.

The short-term strategy to manage noise phobia by helping the dog to cope with the stressful event consists in providing the dog a place where he is able to settle down and relax.[11] The main long-term therapies consist of desensitization[12] that is exposing the dog to thunderstorm's recordings of increasing intensities, and counter conditioning that refers to pairing desirable stimuli such as food or play with recordings of thunderstorms of controlled intensity.[13] Psychotropic drugs are added in the process to either help the dog coping when exposed to the frightened noise or to support the behavioural modifications in the long term.

Recent studies have emphasized the utility of two drugs covered by a marketing authorization for noise phobia in dogs in the European Union: Sileo, Dexmedetomidine oromucosal gel[14] and Pexion, imepitoin.[15] Several other drugs are recommended in the literature to manage noise phobia[9,16,17] such as benzodiazepines, drugs targeting the γ-aminobutyric acid, type A ($GABA^A$) receptors. However, the therapeutic effects of benzodiazepines seem difficult to predict from a dog to another, and their adverse effects such as sedation and anterograde amnesia[18,19] limit their use with behavioural modifications.[20]

Different GABA-related drugs, the gabapentinoids, which includes gabapentin and pregabalin have been demonstrated to be useful for the treatment of anxiety disorders in humans such as preoperative anxiety, anxiety in breast cancer survivors and social phobia.[21]

In cats, the use of gabapentin to prevent phobic response has been evaluated by two recent double-blind, randomized, placebo-controlled studies. In the first study, 53 community cats were randomly given either a placebo, a single 50 mg or a 100 mg dose of gabapentin before their neutering. The results showed a significant reduction of the fear responses in cats that received gabapentin compared to cats that received the placebo.[22]

In the second study, 20 family cats were given once a placebo and once a single 100 mg dose of gabapentin 90 min before two separate events consisting in their transportation and veterinary examination. The cats' behaviour was evaluated by their owner, the veterinarian in charge of the examination and two board-certified veterinary behaviourists through video recordings. The results showed that owner-assessed cats' stress scores as well as veterinarian-assessed cats' compliance scores were significantly better when cats received gabapentin than when they received the placebo without serious or lasting adverse effects.[23]

In dogs, Gabapentin is a known as an anticonvulsant[24] and effective in pain management.[25–27] In a study including six dogs,[28] gabapentin was also useful during anaesthetic protocols by sparing the minimum alveolar concentration of isoflurane. The mechanism of its pharmacological effects is only partially understood. It has minimal direct effects on GABA receptors and on the $\alpha 2\delta$ subunit of N-type Ca^{2+} channels, which is the most studied target of its analgesic action.[29,30] The $\alpha 2\delta$ subunit binding inhibits the calcium flux in the cell, decreasing both monoamine and synaptic excitatory neurotransmitter like glutamate.[31] The mechanism by which the drug might enhance the GABA synthesis remains unknown.[32]

The efficacy of gabapentin in humans (then treated for epilepsy) is observed over 2 μg/ml plasma concentrations,[33] but the effective concentration in dogs remains unknown. According to the pharmacokinetic study in dogs by KuKanich and Cohen,[34] gabapentin is rapidly absorbed and eliminated. The terminal half-life is close to 3.3 h, and the administration of 10−20 mg/kg every 8 h suffices to maintain 2 μg/ml plasma concentrations in dogs.

To our knowledge, there is no placebo-controlled study that investigated the effects of gabapentin on phobia in dogs. We hypothesized that a single 25–30 mg/kg dose of gabapentin administered before a thunderstorm would reduce fear responses in dogs without significant adverse effects.

MATERIAL AND METHOD

The study was a double-blinded, placebo-controlled, cross-over trial based on two exposures, during the same winter (from November to March), to a natural thunderstorm event. Each dog received gabapentin before one exposure at a dosage that ranged from 25 to 30 mg/kg, and a placebo before the other one. Behavioural signs of fear and adverse effects were assessed by the owner during the two exposures.

All the capsules were provided by the veterinary pharmacist of the Israeli society Vetmarket Ltd. Gabapentin used in the experiment was issued from bulk powder acquired from Medisca Ltd, Canada, and dextrose was used as capsule filler in both placebo (which contained dextrose only) and capsules containing gabapentin.

Dogs' recruitment

Storm phobia is a widespread behavioural disorder in dogs living in Israel, since the country happens to have short winters punctuated by violent thunderstorms. Each year the number of consultations

for storm phobia increases significantly from November to February. Dogs from 1 to 12 years old were therefore recruited among patients of two veterinary hospitals in Tel Aviv and its suburb. The trial was explained to each owner of a dog exhibiting storm phobia.

If the owners accepted to participate, they were given an informed consent form to sign with written explanations of the trial, the possibility for them to withdraw at any time and the guaranty of confidentiality. Prior to inclusion, once the owner consent was obtained, all the dogs underwent a veterinary examination realized by the first author, including neurological and orthopaedic examination.

A dog was included in the study if and only if he was over 1 and under 12 years of age, displayed excessive, long-lasting (more than 1 min) and non-spontaneously reversible fear responses to thunderstorm event in the past, and expressed these phobic behaviours even when the owners were present.

A dog was excluded from the study if it was under 1 or over 12 years of age, was under medical treatment other than vaccines and deworming programs or presented either excessive signs of fear to other stimuli than strong noises or at least one organic or behavioural comorbidity.

At the end of the visit, an email containing the internet link allowing the owners to fill up their observations after each exposure inside the 'Thunderstorm exposure questionnaire' was sent.

The study protocol was performed in compliance with the Israeli governmental guidelines for research on animals[35]

Owners' instructions

Each owner received two envelopes named A and B with the exact same looking capsules: one envelope contained capsules of gabapentin, and the other one contained placebo capsules. The veterinarian and the owners did not know the content of the A and B caps until the end of the study. After taking their information on the weather broadcast, half of the owners were instructed to give the A caps 90 min at least before the beginning of one thunderstorm event and the B caps 90 min at least before the beginning of another separate thunderstorm event. The other half of the owners were instructed to do the other way around, that is to give first B then A caps. The choice of the A-B or B-A order was based on the enrolling order of the dogs: one out of two was alternatively instructed to start with A.

Since the half-life of gabapentin in dogs is 3.3 h,[34] the owners were asked to renew the trial with the same type of capsules if the thunderstorm did not occur within 8 h after the capsules were administrated to the dog.

The owners were invited to contact the first author during the protocol in case of difficulties or concerns related to non-expected side effects.

Thunderstorm questionnaire

The Thunderstorm questionnaire contained three parts in order to gather 3 scores per dog and per exposure: a fear score, a general owner's score and an adverse effect score.

The fear score was the sum of the results to eight questions adapted from Flint and colleagues[36] fear's and stress identification scale. The owners had to evaluate eight behavioural signs of fear according to a scale ranging from 0 (no fear) to 4 (strong fear) (Table 1). Therefore, the fear score ranged from 0 to 32.

The owner score corresponded to the owner's general feeling regarding his dog's signs of fear during the event from 0 to 4. Owners had to answer the following question: 'How afraid was your dog during the exposure from 0 to 4, zero indicating that the dog was not afraid and 4 indicating a terrorized dog'. Therefore, the owner score ranged from 0 to 4.

The adverse effects score was built on five closed-ended questions adapted from the previous studies of Pankratz and colleagues[22] and van Haaften and colleagues[23] (Table 2). The answer yes was quoted 1, and the answer no was quoted 0, therefore, the adverse effects score ranged from 0 to 5. Gabapentin is reported to have few adverse effects in dogs,[37,38] and owners were asked to report any non-expected adverse effect.

Statistical analysis

All the data were ordinal and therefore analysed with non-parametric statistical tests. Wilcoxon signed-rank tests were used for matched samples, Mann-Whitney U-tests were used for independent samples, and Spearman's correlation tests were used for secondary analyses.

Tests were performed using R statistical software (https://biostatgv.sentiweb.fr). A significance threshold of 0.05 was chosen for all the statistical analyses.

RESULTS

Sample description

Thirty-two dogs were included in the trial during two consecutive winters, but only 18 owners completed the two questionnaires. Among the other 14 dogs, one dog withdrew because of an intercurrent disease (pancreatitis) before entering the trial, and one withdrew because of a traumatic surgery. As for the other 12 other dogs, the owners only completed one questionnaire and gave no reason why they did not complete the second one.

In our final sample population of 18 dogs, 66.7% (12/18) were of mixed breed, and 33.3% (6/18) were of pure breed. All the dogs were neutered, and 55.6% (10/18) were males against 44.4% (8/18) of females. Their mean age was 7 years, (from 3 to 11 years;

TABLE 1 Fear score questionnaire

	No fear (= 0)	*Strong fear (= 4)*
1-Body Posture	*Upright/Neutral*	*Low*
2-Attempts to hide/escape/avoid the source of noise	*No attempts*	*Uncontrolled attempts*
3-Panting	*No panting*	*Strong and continuous panting*
4-Flicking tongue	*No flicking tongue*	*Strong and continuous flicking tongue*
5-Yawn	*No yawn*	*High frequency of yawns*
6-Lip licking	*No licking*	*Strong and continuous lips licking*
7-Ear position	*Neutral/Forward*	*Folded back on head*
8-Tail position	*High/NeutralOr no tail*	*Tail lowered/tucked*

TABLE 2 Adverse effects score questionnaire

	Yes	*No*
Did the dog vomit during the trial?		
Did the dog salivate during the trial?		
Did the dog suffer from ataxia (lack of equilibrium) during the trial?		
Did the dog show muscular tremors during the trial?		
Were the dog's pupils of unequal size (one large and open, one small and closed) during the trial? (Y/N) (If you haven't noticed, select "No").		

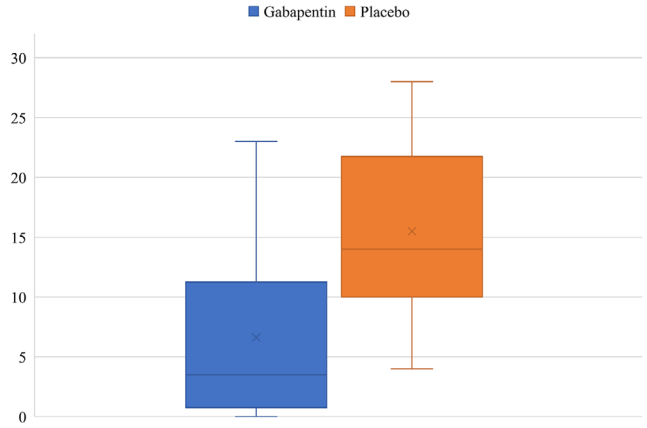

FIGURE 1 Fear score box plot

SD = 2.5), their mean weight was 21.5 kg (SD = 8.9), and the mean dosage of gabapentin administrated was 27.9 mg/kg (SD = 1.8).

Scores

Fear scores after gabapentin administration (mean = 6.61; SD = 7.55) were significantly lower (Wilcoxon, W = 163.5; $p < 0.001$) than Fear Scores after placebo administration (mean = 15.50; SD = 7.82) (Figure 1).

Delta fear scores (i.e., the fear scores under gabapentin minus the fear scores under placebo) were not significantly different between dogs that received placebo first and dogs that received gabapentin first (Mann-Whitney, U = 56.5; $p = 0.153$).

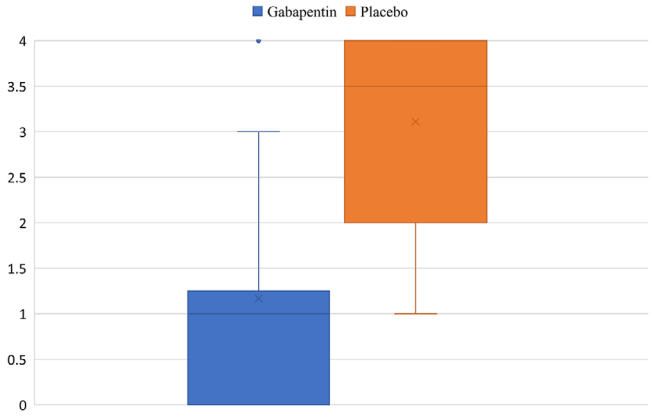

FIGURE 2 Owner score box plot

The delta fear scores of three dogs (subjects 4, 9 and 10) were negative, expressing more signs of fear under gabapentin than under placebo.

Owner scores after gabapentin administration (mean = 1.16; SD = 1.29) were significantly lower (Wilcoxon, W = 144; $p < 0.001$) than owner scores after placebo administration (mean = 3.11; SD = 1.02) (Figure 2).

Delta owner scores (i.e., the owner scores under gabapentin minus the owner scores under placebo) were not significantly different between dogs that received placebo first and dogs that received gabapentin first (Mann-Whitney, U = 60; $p = 0.073$).

The delta owner scores of two dogs (subjects 4 and 9) were negative, expressing more signs of fear under gabapentin than under placebo. The delta owner score of one dog (subject 10) was null, expressing no difference in the signs of fear under gabapentin and under placebo.

Delta owner scores and delta fear scores were positively correlated (Spearman, rs = 0.833; $p < 0.001$), demonstrating a good level of congruence between the general owner's scores and the fear scores.

Adverse effects scores after gabapentin administration (mean = 0.39; SD = 0.61) were not significantly different (Wilcoxon, W = 37; $p = 0.33$) than adverse effects scores after placebo administration (mean = 0.61; SD = 0.78) (Figure 3).

Delta Adverse Effects Scores (i.e., the adverse effects scores under gabapentin minus the adverse effects scores under placebo) were not significantly different when the dogs received placebo first or when

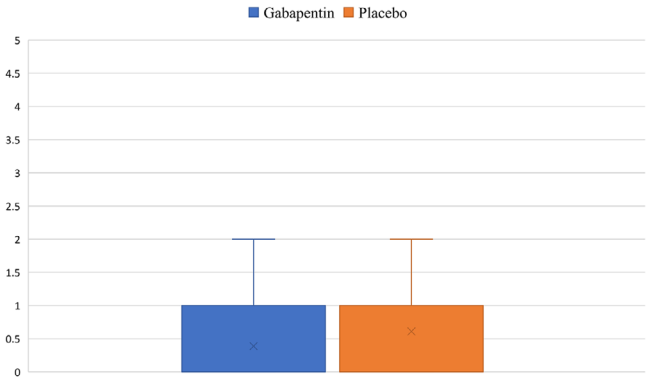

FIGURE 3 Side effects score box plot

TABLE 3 Number of dogs displaying each studied adverse effect

	Gabapentin ($n = 18$)	Placebo ($n = 18$)
Vomiting	0 (0%)	1 (5.5%)
Salivation	2 (11.1%)	3 (16.7%)
Ataxia	3 (16.7%)	1 (5.5%)
Muscular fasciculations	2 (11.1%)	4 (22.2%)
Anisocoria	0 (0%)	1 (5.5%)

they received gabapentin first (Mann-Whitney, U = 45; $p = 0.671$).

Three adverse effects were more frequently reported under placebo than under gabapentin: salivation, muscular fasciculation and anisocoria (Table 3).

Ataxia was more displayed under gabapentin, salivation and muscular fasciculations were displayed in both cases, and anisocoria and vomiting were displayed only with placebo (Table 4). The number of dogs affected by adverse effects was too small to stastitically analyse them.

Delta adverse effects scores were not correlated to gabapentin dosages (Spearman, rs = 0.212; $p = 0.397$).

DISCUSSION

The three scores, fear score, owner score and adverse effect score were designed for this study and adapted from previous experiments.[22,23,36] They are not validated and were not used in previous studies. The three scores appear to support the hypothesis that gabapentin, given at a dosage from 25 to 30 mg/kg, 90 min before exposure to a thunderstorm, significantly decreases the intensity of fear responses in the studied dog's population with minor side effects.

TABLE 4 Number of dogs displaying adverse effects according the trial phase (placebo or gabapentin)

	Always displayed	Displayed with placebo only	Displayed with gabapentin only
Vomiting	0 (0%)	1 (5.5%)	0 (0%)
Salivation	0 (0%)	3 (16.7%)	2 (11.1%)
Ataxia	0 (0%)	1 (5.5%)	3 (16.7%)
Muscular fasciculations	2 (11.1%)	3 (16.7%)	0 (0%)
Anisocoria	0 (0%)	1(5.5%)	0 (0%)

At the group level, the fear score and the owner score were significantly lower when dogs were given gabapentin than when they were given placebo, without any influence of the gabapentin dosage range used. However, three dogs among 18 (16.6%) showed more signs of fear according to their owners when they were administrated the gabapentin than when they were administered the placebo. Beside lack of efficacy, these results might be explained by two biases of our study: the impossibility to standardize the intensity of the stimulus because storms are natural phenomenon and the owners' difficulties to interpret their dog's behaviour which is a known pitfall.[39]

Future studies could avoid this bias by using video recording assessed by professionnals or by replacing human observation with computational video analysis, previously used to measure other behavioural patterns.[40] In contrast, standardizing the storm stimulus seems difficult because the sound of a storm is not easy to reproduce in laboratory: several elements that are determinant parts of the event such as wind, rain, atmospheric pressure and the home environment will be difficult to recreate. However, their variability could be addressed by repeating the experiment under a larger number of natural events.

A previous study in cats showed similar results of non-response in one individual among twenty (5%). This particular individual was known to have a history of strong phobia, and he received a dose of 16.4 mg/kg.[23] The lack of response in three dogs in this study could be explained by individual factors (i.e. it is not efficient in all dogs) or by a threshold depending on dosage that was not attained for those particular individuals.

Gabapentin administrated at a dosage of 25–30 mg/kg was well tolerated during the trial. The adverse effects score stayed low similarly to the previous studies in cats with no significant difference between gabapentin and placebo trials. By opposition to the previously mentioned studies, no sedation was reported by the owners. It is probably due to the arousal triggered by the fearful exposure to storm, and to the fact that owners did not see sedation as an adverse effect but as a benefice during the exposure to the thunderstorm.

The most reported adverse effect was ataxia, but its frequency (16.7%) is lower than the one (45%) previously observed by Platt and colleagues.[41]

Two other adverse effects reported in the present study and the one of van Haaften and colleagues in cats,[23] salivation and muscular fasciculations, could be interpreted as an expression of fear. Indeed, since these symptoms were displayed no matter the type of capsules administrated, the owners might have not been able to distinguish muscular fasciculations from

shakings, and therefore muscular fasciculations might have been fear-related signs rather than real adverse effects.

Vomiting and anisocoria were only displayed under placebo. Anisocoria could have been mistaken for pupil's dilatation, which is a major sign of fear, and the vomiting could be fear-related as well.

The duration of the side effects was not gathered in this study, but no owner mentioned side effects that exceed the effect duration of gabapentin (8 h or less)

Each dog has his own level of tolerance to noises based on its genetic background, age and early experiences.[42] After a startling exposure to an acoustic stimulus, the fear response of the dog may increase. This sensitization process[43] will produce more and more aversive experiences of fear,[44] causing a worsening of the phobia. Our results suggest that gabapentin reduces the signs of fear but do not demonstrate that gabapentin would prevent sensitization or reduce the time needed for desensitization or counter conditioning therapies. These aspects should be investigated further.

Desensitization, counterconditioning and tools like mut muffs or anti-sound cage are the main behavioural therapy leads. However, in the case of storm phobia, the intensity of the sound can be so strong and unpredictable that the conditions of the habituation process are difficult to gather.

Therefore, for all those behavioural modifications to be effective, overwhelming emotions have to be lowered. Consequently, to improve storm phobia, reducing the intensity of the fear experienced by the dog is a mandatory first step which justifies the use of medical treatments, among whom gabapentin seems to be a good choice.

CONCLUSION

Gabapentin administrated at a dosage of 25–30 mg/kg, 90 min before exposure, is efficient to reduce fear responses in the studied dog population when exposed to a thunderstorm. The adverse effects are limited to lower rates of ataxia than those reported in previous studies. Further studies are needed to confirm our results on larger samples of dogs with concomitant behavioural modification.

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