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Investigation of Neurokinin-1 Receptor Antagonism as a Novel Treatment for Chronic Bronchitis in Dogs

M. Grobman, and C. Reinero

Background: Canine chronic bronchitis (CCB) results in cough lasting ≥2 months and airway inflammation. Adverse effects include risk of secondary infection associated with lifelong corticosteroid administration and prompt investigation into alternative therapies. Neurogenic pathways mediated by tachykinins that bind neurokinin (NK) 1 receptors may induce cough and airway inflammation. Maropitant,[a] a NK-1 receptor antagonist, has been advocated for treatment of CCB based on anecdotal improvement, but without scientific evidence.

Hypothesis/Objectives: Maropitant[a] will blunt clinical signs and airway inflammation associated with CCB.

Animals: Client-owned dogs (n = 8) with cough >2 months, thoracic radiographic evidence of airway disease and sterile airway inflammation (>7% non-degenerate neutrophils, >7% eosinophils or both) on bronchoalveolar lavage (BAL) enrolled.

Methods: Maropitant[a] (2 mg/kg) administered q48h for 14 days. Study endpoints included client perception of clinical signs (surveys at baseline and 14 days, and visual analogue scale [VAS] at baseline, 7, and 14 days), and BAL % neutrophils and eosinophils (baseline and 14 days). One-way repeated measures ANOVA (VAS) and Wilcoxon-signed rank-sum tests (BAL cells, cough frequency) used with $P < .05$ considered significant.

Results: Maropitant[a] significantly decreased cough frequency ($P < .001$) and VAS scores ($P = .005$). No differences in BAL % neutrophils or % eosinophils noted with treatment ($P = .279$ and $P = .382$, respectively).

Conclusions and Clinical Importance: Preliminary results suggest that although maropitant[a] may have antitussive properties leading to perceived clinical improvement, its failure to diminish airway inflammation makes it unsuitable for treatment of CCB. Future studies could evaluate maropitant[a] as a cough suppressant for other respiratory disorders in dogs.

Key words: Cough; Maropitant; Tachykinin; TRPV1.

Canine chronic bronchitis (CCB) is a self-perpetuating, inflammatory disease of airways, characterized by cough >2 months in duration for which no other cardiac or respiratory cause can be identified. In CCB, neutrophilic inflammation, mucosal edema, and loss of ciliary epithelial cells contribute to airway narrowing, alterations in pulmonary mechanics, and ineffective mucociliary clearance. These result in architectural changes that predispose patients to potentially life-threatening respiratory complications.[1–3]

Cough is the most common presenting complaint in CCB.[2] A link between cough and airway inflammation exists through the neuro-immune system. Substance P (SP) is a neuropeptide that is widely distributed in sensory nerves of the peripheral and central nervous systems.[4,5] The action of SP and its receptor, neurokinin 1 receptor (NK1-R), have been implicated in peripheral and central sensitization of the cough reflex, and in airway inflammation by recruitment of airway leukocytes.[6–11]

In CCB, although cough is an important clinical sign to target for comfort of the affected dog and owner perception of improvement, it is more critical for treatment to address underlying inflammation. Inflammation not only perpetuates cough, but also leads to structural changes that may be permanent, leading to a decrease in lung function over time. Standard of treatment for CCB involves lifelong corticosteroid administration. However, in dogs with comorbidities including diabetes mellitus and heart disease, corticosteroids may be relatively or absolutely contraindicated. Cough suppressants alone are not adequate treatment for CCB, because they decrease clinical signs without decreasing airway inflammation, thus allowing progression of disease. NK1 antagonism has been shown to have antitussive effects in a canine model[12] with studies in other species documenting variable effects on airway inflammation.[13–15] Maropitant,[a] a NK-1 receptor antagonist, has been advocated for treatment of CCB based on anecdotal improvement, but without objective supporting evidence. It is critical to determine if perceived efficacy is

Abbreviations:

BAL	bronchoalveolar lavage
CCB	canine chronic bronchitis
NK	neurokinin
NK1-R	neurokinin 1 receptor
VAS	visual analogue scale

From the Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri, Columbia, MO (Grobman, Reinero).

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Corresponding author: C. Reinero, DVM, DACVIM (SAIM), Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri, 900 East Campus Drive, Columbia, MO 65211; e-mail: reineroc@missouri.edu.

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because of antitussive or anti-inflammatory effects, or both. We hypothesized that in pet dogs with spontaneous CCB maropitant[a] would blunt clinical signs of cough and airway inflammation.

Materials and Methods

Animals

Eight client-owned dogs presented to the University of Missouri Veterinary Medical Teaching Hospital were enrolled in this prospective clinical trial. Because of the risks inherent in anesthesia and collection of bronchoalveolar lavage (BAL) fluid, this study was designed as a non-placebo-controlled trial. Inclusion criteria included a history of cough >2 months in duration for which other bronchopulmonary or cardiac disorders causing cough had been ruled out. Enrolled dogs had radiographic evidence of airway inflammation and confirmation of sterile airway inflammation based on BAL cytology, microbial culture or both. We defined >7% non-degenerative neutrophils, or >7% eosinophils or both, as being consistent with chronic bronchitis after consideration of previously published normal BAL composition in dogs.[16,17] Exclusion criteria included dogs that were currently being treated with antibiotics or corticosteroids and dogs with comorbidities requiring treatment with antibiotics or corticosteroids. No dog received antibiotics within 2 weeks of study enrollment.

Treatment

Dogs received maropitant citrate[a] (2 mg/kg PO q48h), for 14 days. The final dose was administered within 24 hours of BAL collection.

Subjective Clinical Scoring System

Client Surveys. Client surveys were provided at enrollment and after 2 weeks of treatment with maropitant.[a] The initial cough survey was designed to collect demographic and environmental information about enrolled dogs. The survey was performed after 2 weeks and was intended to provide subjective assessment of clinical benefit after treatment with maropitant.[a] Clients were asked to quantitate the number of times their dog coughed per week in both surveys and those numbers were used for statistical comparison. To evaluate compliance, clients were asked to log missed doses and include this information as a part of the post treatment survey. The pills were counted as a further measure of compliance. Details of demographic, environmental, and clinical information are provided in Tables 1 and 2. Clients were instructed to maintain all treatments as previously prescribed during the enrollment period.

Visual Analogue Scale (VAS) Scores. A visual analogue scale (VAS) used in our laboratory for a quantitative measure of clinical signs in cats with allergic asthma was adopted to score clinical signs in dogs with CCB.[18] After training, the client performed a VAS assessment before the start of treatment, and then after 1 and 2 weeks of treatment with maropitant.[a] The VAS used a 100 mm scale to assess the range of observed clinical signs from no clinical signs (0 mm) to severe paroxysmal cough leading to respiratory distress (100 mm). The distance from 0 to the patient score was measured to provide a quantifiable VAS score and was subjected to statistical evaluation.

Collection and Analysis of Bronchoalveolar Lavage

Samples of BAL were collected using a single 20 mL aliquot of sterile saline either in a blind fashion or under endoscopic guidance. For each dog, the same technique was used for collection before and after treatment with maropitant.[a] Patients that had bronchoscopy at the time of diagnosis, again underwent bronchoscopy for follow-up to assist in sampling the same region (5/8

Table 1. A survey was completed by clients at the time of enrollment of 8 pet dogs with spontaneous chronic bronchitis. Clinical and environmental information are listed below.

Enrollment Survey	Dogs
Progression of the cough (consistent, better, worse)	
Consistent	3
Better	2
Worse	3
Did anything happen before to the start of cough?	
Recent boarding	1
Recent dog show	0
Any other new experiences	2
Recent hospitalization	0
Recent exposure to a new puppy	0
Recent exposure to any new dog	0
New smoker in the house	0
First fireplace usage	0
None	5
Where does the patient spend most of its time?	
In the home	5
Free access to entire house and garage	4
Free access to entire house only	1
In the garage only	0
In the basement	0
In own room	0
Outside the house	3
In a fenced yard	1
Roaming freely	2
In a run/crate	0
Tied in one area	0
Does anyone smoke even occasionally?	
No	6
Yes	2
If exposed to smoke, over what time period?	
Days	0
Weeks	0
Months	1
Forever	1
Nonsmoking household	6
Where do people smoke?	
Indoors	0
Outdoors	1
Everywhere	1
Nonsmoking household	6
Frequency of smoking	
Daily	0
Weekly	0
Monthly	2
Nonsmoking household	6
Has the dog been vaccinated for kennel cough?	
Yes	4
No	2
Unknown	2
Frequency of Canine Infectious Respiratory Disease Complex vaccination	
Every 6 months	0
Every year	2
Not vaccinated	2
Unknown	3
Prior to boarding	1

Table 2. A survey was completed by clients after 8 pet dogs with spontaneous chronic bronchitis received 2 weeks of treatment with maropitant. Clinical information and client perception of improvement after treatment are shown below.

Post Treatment Survey	Dogs
Since the last visit has the frequency of coughing	
Increased	0
Decreased	7
Stayed the same	1
Intensity of cough since last visit	
Increased	0
Decreased	6
Stayed the same	2
This medication trial has	
Helped dramatically	1
Helped a lot	4
Helped a little	3
Would you consider it acceptable for long term treatment?	
Yes	8

dogs). Sampling of the same area could not be confirmed in dogs that underwent blind BAL. A 200 cell differential count was performed on a Wright's-stained cytospin preparation by the Veterinary Health Center Clinical Pathology Department. The percentages of neutrophils and eosinophils were quantified and subjected to statistical evaluation. All other observed cell types also were quantified but not statistically evaluated.

Statistical Analysis

Descriptive statistics were used for the client surveys and expressed as the number of dogs displaying the parameter of interest out of 8 total. A repeated measures analysis of variance on ranks was used to evaluate differences in VAS score before treatment and after 1 and 2 weeks of treatment with maropitant.[a] Wilcoxon-signed rank-sum tests were used to evaluate the differences in number of coughs/day over the preceding 7 days (as reported on client surveys) and percentage of neutrophils and eosinophils before treatment and after 2 weeks of treatment with maropitant.[a]

Results

Animals

The 8 dogs enrolled in this study included 6 mixed breed dogs, 1 Greyhound, and 1 Chihuahua. Six were castrated males and 2 were spayed females. The median age at the onset of clinical signs reported by the owners was 5 years (range, 4 months–13 years). Median duration of clinical signs before diagnosis was 6.5 months (range, 6–18 months).

Subjective Clinical Assessment: Surveys and VAS Score

Enrollment. Clinical and environmental information was collected as part of the client enrollment survey (Table 1). Possible triggering events identified immediately before the onset of clinical signs were identified in 3 dogs and included recent boarding, oropharyngeal foreign body, and instillation of new carpet. Home environments were variable and included exclusively indoor dogs as well as dogs with free access to large outdoor properties. Twenty-five percent of clients reported that their dogs had exposure to cigarette smoke but claimed rare exposure, occurring 1–2 times a month. Vaccination history specifically for pathogens involved in canine infectious respiratory disease complex ("kennel cough") was variable. Of vaccinated dogs, frequency of vaccination and date of the most recent vaccination was known in only 50% of patients. Medications were being given to 5 dogs at the time of enrollment. In 1 dog each, these included monthly allergen-specific immunotherapy injections, diphenhydramine (25 mg PO q24h), N-acetyl cysteine (600 mg PO q12h), tramadol (50 mg PO q12h), and butorphanol tartrate (5 mg PO q12h). Verbally and with written instructions, clients were told to continue all treatments as previously prescribed during the study period. Seven of 8 dogs had received antibiotics or antitussive therapies before enrollment. These were discontinued because of lack of clinical improvement. In accordance with our inclusion criteria, no dog had received antibiotics within 2 weeks of study enrollment.

Post Treatment. Subjective assessment of clinical response was performed by clients as part of the post treatment survey (Table 2). Compliance was excellent overall with only 1 dog missing a single dose during the first week of treatment. All dogs received a dose of maropitant[a] within 24 hours of the final sample collection. All clients described a perceived clinical benefit to treatment with maropitant[a] (Table 2). Most clients described a decrease in both the severity and frequency of their dogs' coughing with 75% showing decreased cough frequency and 87.5% decreased cough severity. A significant decrease in the number of coughs/day was observed between baseline and week 2 ($P < .001$, Fig 1). Adverse effects (eg, mild decreases in appetite and activity level) were described in 1 dog, but these were not considered severe enough by the client to preclude continued treatment. Interestingly, all clients observed clinical improvement and agreed that maropitant[a] was acceptable for long term use based on a perceived benefit in their dogs' clinical condition.

Visual Analogue Score. A statistically significant decrease in the subjective assessment of clinical signs between the time of enrollment and after 2 weeks of treatment was observed (Fig 2, $P = .005$).

Bronchoalveolar Lavage. No statistically significant difference was observed in the percentage of airway neutrophils or eosinophils between the time of enrollment and after 2 weeks of treatment with maropitant[a] (Fig 3A, B; $P = .279$ and $P = .382$, respectively).

Discussion

Our pilot data showed that treatment for 2 weeks with maropitant[a] decreased subjective owner perception of clinical signs of CCB based on client surveys and VAS score. However, maropitant[a] failed to decrease objective markers of inflammation based on percentage of BAL neutrophils and eosinophils,

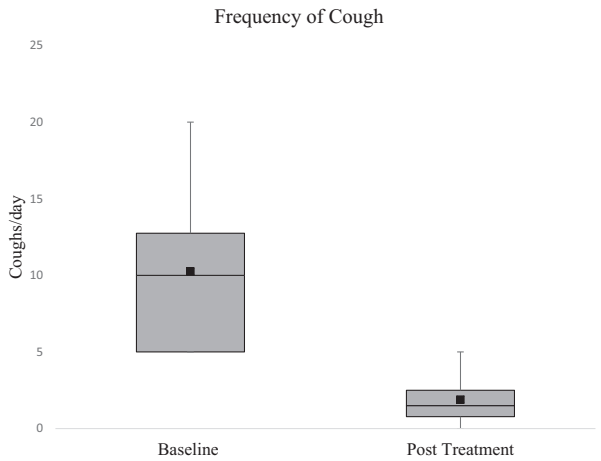

Fig 1. The owners of the dogs with chronic bronchitis were asked to complete surveys at the time of enrollment and at the completion of the study. Owners were asked to quantitate the average number of coughs per day over the preceding 7 days. The boxes represent the 25th and 75th quartiles with the horizontal line representing the median. The black circles represent the mean. The whiskers represent the range of the data. A significant reduction in the number of coughs/day was observed at 2 weeks post treatment compared with baseline values ($P < .001$). This is denoted by the asterisk above week 2.

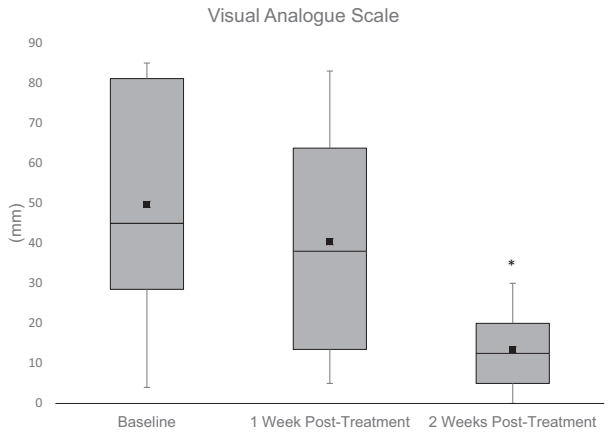

Fig 2. Eight client-owned dogs with chronic bronchitis were evaluated for severity of clinical signs using a visual analogue scale (VAS) score. The boxes represent the 25th and 75th quartiles with the horizontal line representing the median. The black squares represent the mean. The whiskers represent the range of the data. A significant reduction in client perception of clinical signs was observed between dogs at baseline and 2 weeks post treatment with maropitant based on VAS score ($P = .005$) This is denoted by the asterisk above week 2.

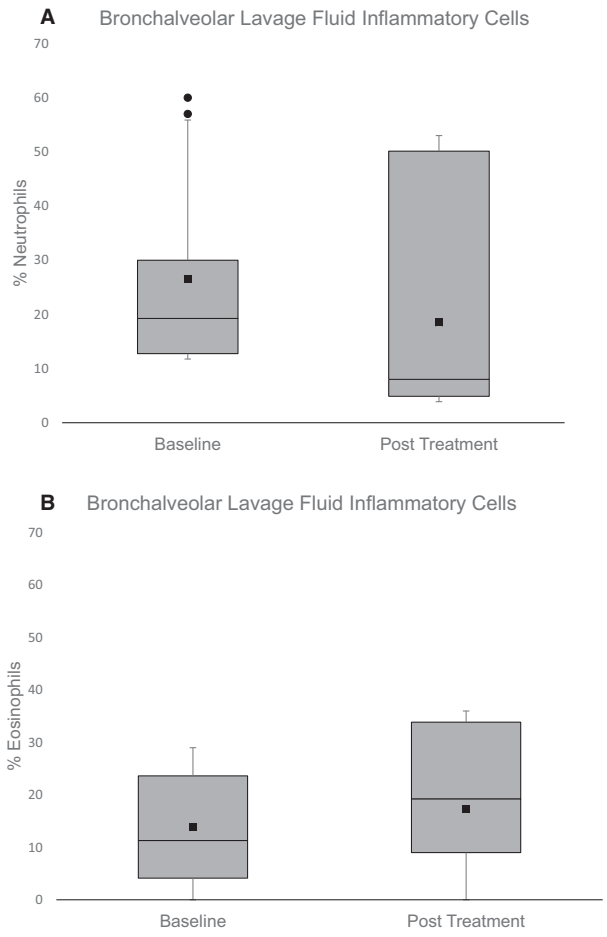

Fig 3. (**A, B**) Eight client-owned dogs with chronic bronchitis underwent bronchoalveolar lavage (BAL) collection with quantitation of airway neutrophilia and eosinophilia at enrollment and after 2 weeks treatment with maropitant. Samples of BAL were collected in a blind fashion or under endoscopic guidance. A 200 cell differential count was performed on Wright's stained cytospin preparations. Airway neutrophilia and eosinophilia is expressed as a percentage of the total cell count identified as neutrophils or eosinophils, respectively. The boxes represent the 25th and 75th quartiles with the horizontal line representing the median. The black squares represent the mean. The whiskers represent the range of the data except where outliers are present. When outliers are present, the whiskers represent 1.5 times the interquartile range (IQR). The black circles represent outliers where the percent neutrophils were found to be greater than 1.5 times IQR. The percent airway neutrophils and eosinophils were not significantly decreased after 2 weeks of treatment with maropitant ($P = .279$ and $P = .382$, respectively).

making maropitant[a] unsuitable for treatment of CCB. To the authors' knowledge, ours is the first study examining the use of maropitant[a] as a treatment for naturally occurring CB in client-owned dogs.

Maropitant[a] is a high affinity NK1 receptor antagonist that has been used extensively as an antiemetic with an excellent safety profile.[19] The antiemetic effects of maropitant citrate[a] are mediated by rapid penetration into the central nervous system and action on NK1-Rs in the brainstem, which is also the site of integration of the cough motor pattern.[20,21] Substance P has been implicated in the initiation of cough by central mechanisms and stimulation of peripheral rapidly adapting receptors secondary to edema and airway inflammation.[8,9,11,22,23] The antitussive effects of NK1-R antagonists have been shown in several animal models including dogs.[12,24] Studies examining NK1-R CP-99994 implicate both inhibition of sensory afferent

nerves as well as expiratory motor neurons affecting the frequency of cough and expiratory cough amplitudes, respectively.[21,24,25] The perceived benefit of treatment with maropitant[a] may reflect central effects of maropitant[a] on the NK1-Rs of the cough center, or a marked placebo effect. A placebo effect has been documented in 35–70% of human patients with a wide range of disorders.[26] In this study, 100% of dogs had a clinical benefit from treatment with maropitant, which would exceed that which would be expected from placebo alone. In addition, a significant decrease in VAS score with maropitant[a] was not seen after 1 week of treatment, a time before that in which steady state was achieved (ie, 8 days or 4 doses)[19]; significance was achieved only after 2 weeks of treatment. Apparent clinical remission as part of a waxing and waning clinical course also should be considered as a potential explanation for the potential antitussive effects of maropitant.[a] Many chronic airway diseases are characterized by exacerbations punctuated by periods of clinical improvement or quiescence. However, these improvements occur in the face of persistent airway inflammation. This observation highlights the fact that clinical signs should not be used as a surrogate marker for the resolution of airway inflammation. Although having a placebo-controlled clinical trial would have helped determine the magnitude of the placebo effect and transient clinical improvement in the dogs of this study, because of the risks associated with anesthesia and BAL collection, a placebo group would have been difficult to justify ethically.

Peripheral actions of NK1-R are thought to cause vasodilatation, increase vascular permeability and activate airway leukocytes resulting in inflammation and activation of airway sensory afferents.[5,10] Studies investigating the anti-inflammatory effects of NK1-R antagonists have produced variable results.[13,14,27] In our study, maropitant[a] had no significant impact on airway inflammation in CCB after 2 weeks of treatment. There are several reasons why NK1-R antagonism may have been ineffective in ameliorating inflammation associated with CCB. Because inflammation is dependent on multiple redundant pathways, blockade of NK1-R alone may be insufficient to prevent leukocyte influx and inflammation.[28] Alternatively, rapid NK1-R internalization after binding with SP may lead to desensitization of cells to SP-mediated signaling resulting in a lack of response to NK1-R blockade.[29] Depletion of SP secondary to chronic inflammation also may result in decreased response to NK1-R antagonism. Neuropeptide depletion secondary to inflammation has been documented for vasoactive intestinal polypeptide in asthmatic compared to healthy humans.[30–32]

The dosage of maropitant[a] selected for this study (2 mg/kg) is the labeled dosage recommended for extended treatment based on revised labeling of maropitant citrate[a] by the US Food and Drug Administration. Every other day dosing was selected to decrease risk of adverse effects that may be associated with chronic treatment. The time to reach steady-state concentrations based on pharmacokinetic studies in dogs is 4 doses.[19,33] Two weeks of treatment was selected to allow adequate time for immunomodulation to take place after reaching steady state. Corticosteroids, the gold standard of treatment in CCB, have been shown to blunt neutrophilic and eosinophilic inflammation in <2 weeks based on studies performed in asthmatic cats and humans diagnosed with asthma and chronic obstructive pulmonary disease.[34–36] It is unlikely therefore that insufficient dose, poor NK1-R affinity, or insufficient duration of treatment would explain the lack of statistically significant decrease in inflammation observed in this study. The effect of NK1 antagonism on inflammation in other animal models has been variable with no effect being documented in 2 studies using an experimental model of feline asthma.[13,27] Although 1 of the study limitations was a small sample size, given that none of the dogs had a substantial decrease in percentages of airway inflammatory cells with treatment, small sample size also was thought to be an unlikely explanation. The influence of small sample size on cough frequency and severity is unknown and warrants further investigation.

Anecdotally, maropitant[a] has been suggested to be beneficial for the treatment of CCB. Although placebo-controlled studies are necessary, the results of our study offer a possible explanation for the perceived improvement in clinical signs, namely, a possible antitussive effect of maropitant.[a] In CCB however, ameliorating self-perpetuating airway inflammation should be the primary goal of treatment. Suppressing clinical signs of cough without addressing the underlying inflammation has the potential to lead to a progressive decline in lung function and serious complications. The lack of significant decrease in airway inflammation based on the percentages of airway neutrophils, or eosinophils or both after 2 weeks of treatment makes maropitant[a] inappropriate for the treatment of CCB. Because dogs develop other types of respiratory disease that may warrant antitussive treatment to break the cough cycle (eg, tracheal collapse), placebo-controlled studies are indicated to determine if maropitant[a] could serve as a cough suppressant in these disorders.

Footnote

[a] CERENIA®, Zoetis, Florham Park, NJ

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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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