Effect of neurokinin-1 receptor antagonism on airflow limitation and airway inflammation in experimentally asthmatic cats

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Introduction

- Feline allergic asthma is a chronic lower airway disorder characterized by eosinophilic airway inflammation, airway hyperresponsiveness (AHR), and airway remodeling. Tachykinins have been implicated in the pathogenesis of asthma and are released by both nervous and immune cells in the lungs. Tachykinins bind to neurokinin 1 (NK1), NK2 and NK3 receptors. NK1 receptors are localized to the lungs and induce neurogenic inflammation of the airways.
- Treatment for feline asthma includes the use of bronchodilators and corticosteroids; however, these drugs are not always completely effective. Moreover, chronic use of corticosteroids can cause serious side effects and in some cases, like in patients with cardiac disease, may be contraindicated. Due to the ineffectiveness and safety concerns associated with corticosteroids there remains a need for novel treatment options.
- This study will investigate the efficacy of maropitant (Cerenia), an NK1 receptor antagonist, in an experimental feline asthma model. It has been shown in both mouse models and spontaneous human asthma that similar NK1 receptor antagonists can reduce inflammation and bronchospasm but this has not yet been proven in cats.

Hypothesis

- Oral administration of maropitant, an NK-1 receptor antagonist, but not placebo will decrease respiratory clinical signs, airflow limitation and airway eosinophilia after allergen challenge in an experimental feline asthma model.

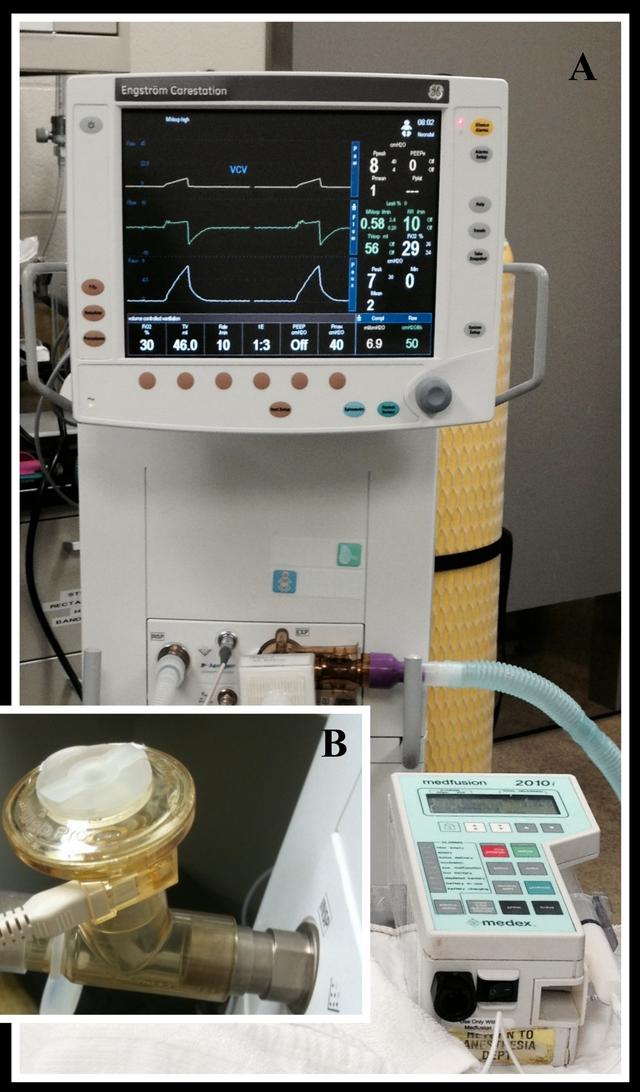

Fig. 1 (A) Pulmonary mechanics were measured using the GE Engstrom Carestation ventilator in neonatal mode. Anesthesia was induced and maintained with propofol. To standardize resistance contributions from endotracheal tubes (ETT), all cats were intubated with 4 mm internal diameter, 14 cm long cuffed ETT. Airway pressure, flow, and volume were measured continuously and airway resistance (Raw) calculated. (B) Sterile saline was delivered for 30 seconds through an Aeroneb solo in-line nebulizer followed by 4 min of baseline data collection. For bronchoprovocation, 30 second aerosols of methacholine (doubling doses from 0.0625-32 ug/ml) were followed by 4 min of data collection per dose. The study was terminated when the Raw reached 200% of the baseline (saline) value (EC200Raw).

Acknowledgements

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Study Design

- Cats (n=6) were induced to have asthma using bermuda grass allergen (BGA). After induction of the asthma, a chronic asthmatic phenotype was maintained by once weekly to twice monthly aerosols of BGA. Cats were subsequently enrolled in a prospective, placebo-controlled crossover design study. Cats randomly received either maropitant (2 mg/kg) or placebo every other day for 4 weeks. After a 6 week washout period, subjects crossed-over to the alternate treatment.
- Pulmonary mechanics were measured using the GE Engstrom Carestation ventilator (Fig. 1). Cats were initially mechanically ventilated using a tidal volume of 10 ml/kg, at 10 breaths/ min, 40% oxygen, and with a positive end-expiratory pressure of 2 cm H2O to prevent anesthesia-induced atelectasis. Airway pressure, flow, and volume were measured continuously and airway resistance (Raw) was calculated. Sterile saline was delivered for 30 seconds through an Aeroneb solo in-line nebulizer followed by 4 minutes of baseline data collection. Then thirty second aerosols of methacholine where given followed by 4 minutes of data collection per dose. The aerosol challenges ended when the Raw reached 200% of the baseline (saline) value (EC200Raw).

Methods

- **VAS-** Airflow limitation was evaluated following allergen challenge using a visual analog scale (VAS) clinical scoring system. One individual rated the observed clinical signs on a 100 mm scale, ranging from 0 mm, which represents no clinical signs, to 100 mm which represents extreme respiratory distress.
- **EC200Raw-** Airway hyperresponsiveness was determined with ventilator-acquired pulmonary mechanics using methacholine as a bronchoprovocant. AHR is expressed as the concentration of methacholine at which cats attained a 200% increase in Raw from baseline (EC200Raw).
- **Airway Eosinophilia -** Bronchoalveolar lavage fluid was collected blindly using a red rubber tube advanced through the endotracheal tube after pulmonary mechanics were recorded. A differential count to provide the % eosinophils was performed on a Wright's stained cytospin (Fig. 2).
- **Statistical Analysis -** The difference in VAS score, EC200Raw, and airway eosinophilia between placebo and maropitant treatment was tested using a Wilcoxon Signed Rank Sum Test with $p<0.05$ considered significant.

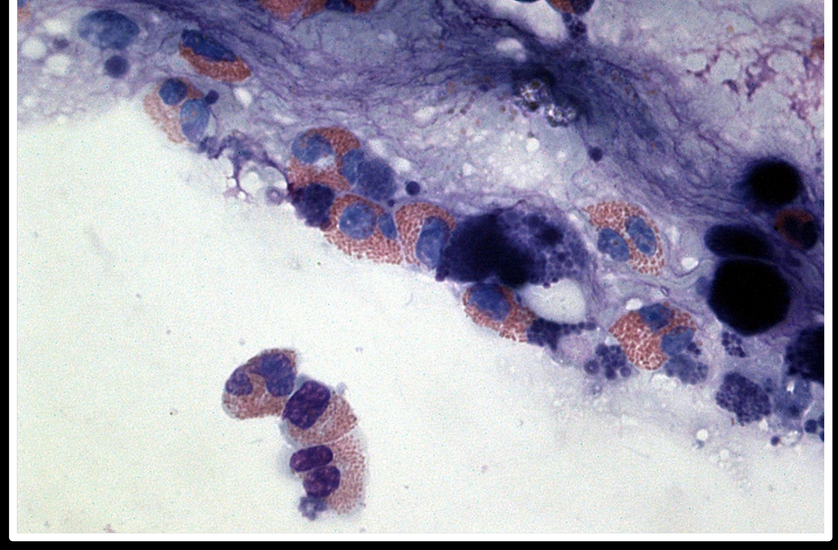
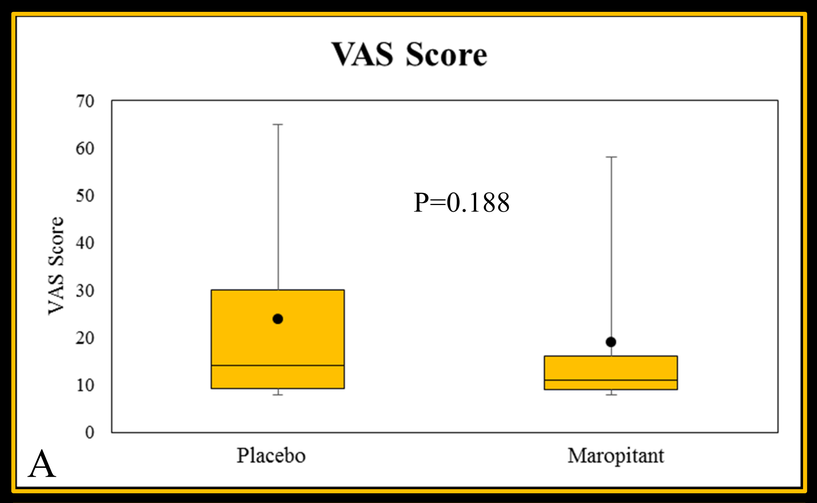
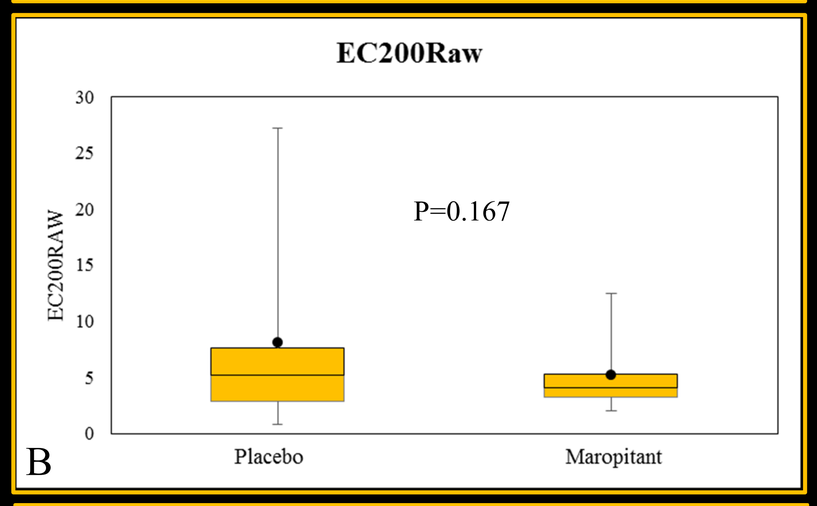


Fig. 2 Airway inflammation is one of the hallmark features of allergic asthma. Cytology of bronchoalveolar lavage fluid from an asthmatic cat shows the presence of eosinophils.

Results

- Administration of maropitant at 2mg/kg over 4 weeks failed to improve airflow limitation or eosinophilic airway inflammation in a feline asthma model (Fig. 2). Compared to placebo, chronic administration of maropitant showed no significant difference in VAS scoring (P = 0.188), EC200Raw (P=0.167) or airway eosinophilia (P=0.688) (Fig. 3).





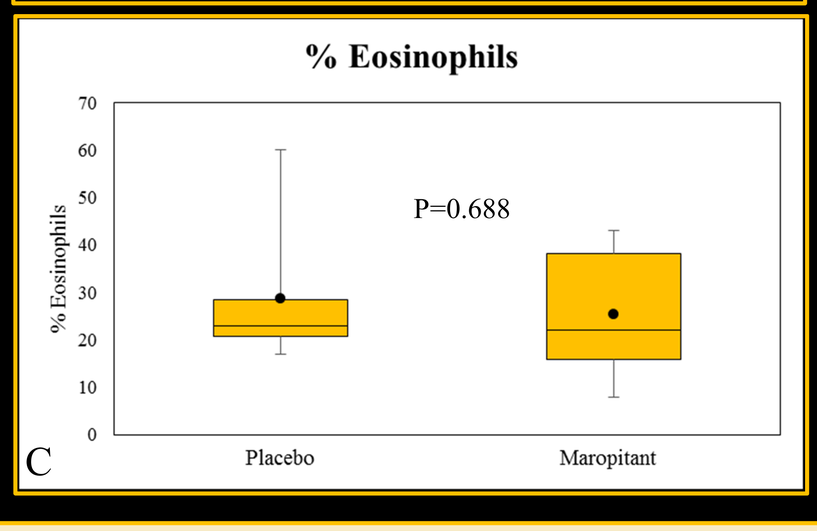


Fig 3. (A) VAS score, representing severity of clinical signs assessed after allergen aerosol challenge, was not significantly different between treatment groups. (B) Airway hyperresponsiveness, measured by ventilator-acquired pulmonary mechanics in response to bronchoprovocation with methacholine and expressed as EC200Raw, was not significantly different between treatment groups. (C) Percent of eosinophils in bronchoalveolar lavage fluid was not significantly different between treatment groups.

Discussion

- Contrary to our hypothesis, oral administration of maropitant failed to decrease respiratory clinical signs, airflow limitation or airway eosinophilia after allergen challenge in an experimental feline asthma model. Previous work in mouse and human models found that NK receptor antagonism was able to blunt airway inflammation and bronchospasm; however, this was not proven true in cats. Interestingly, previous studies primarily examined combined NK1/NK2 receptor antagonism. NK1 receptors alone may only play a small role in the complex pathogenesis of feline asthma. In future studies, combined NK1/NK2 receptor antagonism could be evaluated for efficacy at blunting airway limitation and inflammation in a feline model.
- Our results are clinically relevant as maropitant is currently being anecdotally used by some clinicians to treat asthma with no scientific evidence that it is effective. Based on the results of this study, maropitant as monotherapy can not be recommend to treat feline asthma. In the future, other mechanisms of asthma pathogenesis should be explored as potential therapeutic targets.

Conclusion

- Chronic administration of maropitant was ineffective at blunting clinical signs, AHR and airway eosinophilia in an experimental feline asthma model. Therefore, chronic administration of maropitant cannot be recommend as a novel treatment option for feline allergic asthma.