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.

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.

Results

• Administration of maropitant at 2mg/kg over 4 weeks failed to improve airflow limitation or blunting 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).

Discussion

• Contrary to our hypothesis, oral administration of maropitant failed to decrease respiratory clinical signs, airflow limitation or airway eosinophilia after allergen challenge, was not significantly different between treatment groups. (A) 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. (B) Percent of eosinophils in bronchoalveolar lavage fluid was not significantly different between treatment groups. (C) Airway eosinophilia (P=0.688) (Fig. 3).

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.

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