Theophylline formulation inhibits oxidative damage activation and may ameliorate OVA-Induced Allergic Airway Inflammation in Mouse Balb/c Model

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Abstract **1238690**

A

Abstract Body

Purpose. Asthma, a global public health issue, seriously affects the life quality of children. Theophylline, a phosphodiesterase inhibitor, is a drug that has been employed in treating respiratory diseases. Objective: Resolve the limitation in the use of theophylline in children is the lack of good pharmaceutical formulation. **Methods**. We studied the protective effects of a novel theophylline formulation on asthma induced, particularly the action on airway inflammation and on the modulation of select oxidative stress biomarkers in a standard experimental asthma model, using ovalbumin sensitized Balb/c mice. Mice was decapited after the latest administration of the treatment and their cerebrum were immediately dissected and submerged in a solution of NaCl 0.9% and maintained at 4°C. Besides, blood samples were obtained and used to asses the levels of hemoglobin and triglycerides. Each brain and lunge was homogenized in 3ml of tris-HCl 0.05M pH 7.2 and used to assay lipoperoxidation and Glutathion levels determination using previously validated methods. **Results.** The theophylline significantly inhibited Ova-induced mucus production and inflammatory response, and considerably impaired Ova-induced generation of reactive oxygen species. Besides, histological changes revealed lesions of lung cells in experimental animals treated with ovalbumin. The above results suggest that the theophylline oral formulation relieves asthmatic airway inflammation. **Conclusion**. We believe that this involves oxidative stress-responsive lipid peroxidation pathway; thus, highlighting its potential as a useful therapeutic agent in the management asthmatic children.

Introduction

Theophylline is a common drug employed in the treatment of wheezing, shortness of breath and asthma induced chest tightness, chronic bronchitis, emphysema and other lung diseases. It has effects on the Central nervous system by stimulating the respiratory center. Currently, the limitation in the use of theophylline in children is the lack of good pharmaceutical formulation. **Objective:** This has led to the development of oral theophylline solution (drops), in a concentration of 1mg / ml with adequate excipients that permit the correct dosage for pediatric patients, and their biological evaluation as anti-inflammatory agents.

Methods

B

Preformulation studies (Farmacopea; 2013):

Characterization of the active ingredient, Appearance, Particle size, True density, Identification of the active ingredient, Identity essay, Melting point, Thin Layer Chromatography (TLC), Stability of the active ingredient, Drug-Excipient compatibility tests

Formulation Studies (Alok et al; 2010):

Figure A. Dynamic viscosity, sedimentation volume, pH, flavor, suspension time, and Rheogram were measured using viscous (viscos), conservation (conserv) and sweetener (edulco) of novel oral theophylline drops (1mg/ml), by lineal model with simplex lattice experimental design.

A basic *in vivo* experimental study was performed with novel theophylline solution using 100 Balb / c mice comprised of 50 male and 50 female animals. The animals were divided in five groups of 20 mice each consisting of 10 males and 10 females. The animal groups were treated as follows: group I, healthy mice with administration of intranasal isotonic saline solution (control); group II, sick animals without theophylline treatment; group III, sick mice in treatment with oral theophylline solution (2mg / ml); group IV, sick animals in treatment with intravenous theophylline solution (20mg / ml) and group V, healthy animals with administration of intraperitoneal isotonic saline solution (control). After one week of adaptation in laboratory conditions, the animals of groups II, III and IV were sensitized with two doses of 100 µg of ovalbumin (OVA), intraperitoneally administered on days 0 and 14 without the presence of adjuvants. Thereafter, nine intranasal doses of 500 µg OVA were given to each of the mice in these groups on days 14, 27, 28, 29, 47, 61, 73, 74 and 75. Mice was decapited after the latest administration of the treatment and their cerebrum were immediately dissected and submerged in a solution of NaCl 0.9% and maintained at 4°C. Besides, blood samples were obtained and used to asses the levels of hemoglobin and triglycerides. Each brain and lunge was homogenized

D

Main Results

Figure A. Formulation studies

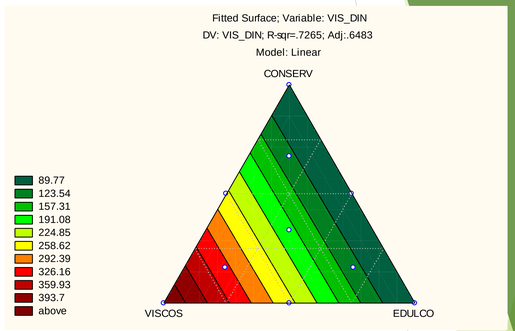
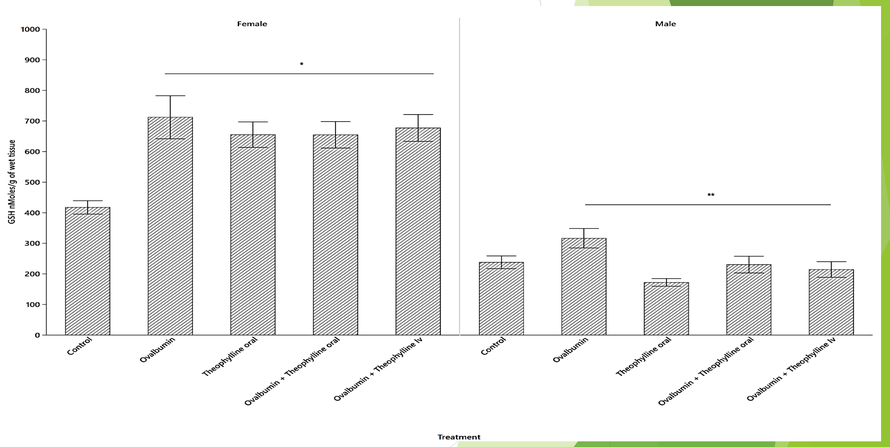


Figure 1. *In Vivo* Pharmacological Evaluation of GSH levels in the brain (Mean ± SE) in females and males in the groups treated with oral or intravenous ovalbumin and theophylline.



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Discussion

In asthma, airway remodeling is affected when there is an imbalance between oxidative stress and antioxidant defense system. Redox regulation is part of various cellular processes and a good example of this is in the immune response. In fact, protection against inflammatory damage is provided by specific redox proteins and particular enzyme activities. Nevertheless, it is reported that inflammation induced by asthma is not only restricted to the lung, but also may affect many remote organs and cause damages in them. An increase of GSH and decrease of lipoperoxidation concentration were observed in the lung and brain of the male animals treated with oral ovalbumin + theophylline.

Conclusion