Effects of Theophylline Compared with Prednisolone on Late Phase Airway Leukocyte Infiltration in Guinea Pigs

R. W.		Gristwood
J.		Llupia
A. G.		Fernández
P.		Berga

Department of Pharmacology, Laboratorios Almirall, Barcelona, Spain

Abstract

The effects of prednisolone, theophylline or salbutamol treatment were studied on leukocyte numbers in bronchoalveolar lavage (BAL) fluid taken 72 h after ovalbumin challenge in sensitized guinea pigs. Ovalbumin challenge resulted in an approximate 3-fold increase in the number of eosinophils in BAL fluid. This increase was significantly reduced by oral administration of prednisolone (59% inhibition with 10mg/ kg $\times$ 2) theophylline (56% with 50 mg/kg $\times$ 2) but not by salbutamol (10 mg/kg $\times$ 2). A comparison with the bronchodilator potency of the above drugs indicated that in guinea pigs salbutamol appears relatively selective as a bronchodilator, prednisolone is selective as an inhibitor of eosinophilia whilst theophylline displays a balance of both activities.

Correspondence to: Dr. J. Llupia, Department of Pharmacology, Laboratorios Almirall, Cardoner 68-74, E-08024 Barcelona (Spain)

Introduction

The clinical treatment of asthma includes the use of bronchodilators, such as salbutamol and/or anti-inflammatory agents, such as corticosteroids. In recent years the role of inflammation in asthma has been emphasized and the use of bronchodilators alone criticized on the grounds that they do not treat the underlying cause of the disease (i.e. inflammation).

Theophylline, widely used in asthma treatment, was originally thought to act predominantly via bronchodilatation; however, recently there have been claims for an additional anti-inflammatory component of its antiasthma actions [1].

In order to study this possibility further we have compared the effects of theophylline with the corti-costeroid prednisolone on late phase airway leukocyte infiltration in a conscious guinea pig model of

asthma [2]. We have also compared this activity of prednisolone, theophylline as well as salbutamol with their respective bronchodilator activities in anaesthetized guinea pigs.

Methods

Bronchodilatation

Male Dunkin-Hartley guinea pigs (400-500 g) were maintained with free access to water but without food for 18 h. Drugs under study were then given orally 1 h before the animals were anaesthetized with urethane (1.4 g/kg, i.p.). In order to measure spontaneous respiratory flow and rate, a specially designed animal mask piece was used [3] connected to a pressure transducer. A jugular vein was cannulated to permit the administration of histamine (2 μ g/kg, i.v. bolus) in order to induce bronchoconstriction. Histamine responses in drug-treated animals (oral administration) were compared to those in untreated control animals. ED50 values for drugs were calculated (doses causing 50% inhibition of bronchoconstriction).

Table 1. Comparison between bronchodilator and leukocyte infiltration inhibitory potencies of prednisolone, theophylline and salbutamol in guinea pigs

Predni- solone	Theo- phylline	Salbuta- mol
Bronchodilatation		
ED50mg/kg, p.o. (n = 5)	inactive at 40	35 7
Leukocyte infiltration		
ED50mg/kg, p.o. (×2)(n=7)	7	40 > IO

Leukocyte Infiltration

Male guinea pigs (450–500 g) were sensitized by the administration of aerosolized (Devilbiss 35B nebulizer) ovalbumin (0.5 w/v in 0.9% saline) on two occasions separated by 7 days. On day 14, animals were challenged by aerosolized ovalbumin under the cover of mepyramine (10mg/kg, i.p.). Drug treatments, or vehicle, were given orally at both 2 h before and 6 h after challenge. Bronchoalveolar lavage (BAL) was performed 72 h after challenge with 2 × 4 ml volumes of sterile saline. Numbers of eosinophils, neutrophils, lymphocytes and macrophages were evaluated. Total cell counts were performed using a Bürker Turk haemocytometer and differential counts carried out on cytocentrifuged preparations (Cytospin II) stained using staining foils (Sangodiff, Merck).

Results

In untreated animals, ovalbumin challenge was associated with a significant increase in the number of eosinophils in the BAL fluid ($8.3 \pm 1.3 \times 10^5$ cells saline challenge, $2.1 \pm 0.3 \times 10^6$ cells ovalbumin challenge, n = 7). Significant changes in other cell numbers were not observed in these experiments.

Prednisolone or theophylline treatment significantly inhibited the eosinophilia resulting from ovalbumin challenge whereas salbutamol had no significant effect at doses up to 10mg/kg × 2. Doses causing 50% inhibition (ED50 values) of the increase in eosinophil numbers are shown in table 1. Table 1 also compares the bronchodilator and leukocyte infiltration inhibitory potencies of the drugs.

Conclusions

Our results show that theophylline, like prednisolone, can significantly inhibit late phase eosinophil infiltration into the lungs of ovalbumin sensitized-challenged guinea pigs. Accepting that lung inflammation in asthma is related to the infiltration of leukocytes including eosinophils [2, 4], our data support the concept that the antiasthmatic activity of theophylline includes an anti-inflammatory component. At an effective bronchodilator dose (10mg/kg), salbutamol failed to significantly inhibit eosinophil influx. This result is in agreement with previously reported data for salbutamol in guinea pigs [5]. We can, therefore, conclude that in our tests salbutamol appears relatively selective as a bronchodilator, prednisolone is selective as an anti-inflammatory agent whilst theophylline displays a balance of both anti-inflammatory and bronchodilator activities.

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