J. Pharm. Pharmacol. 1998, 50 (Supplement): 71

© 1998 J. Pharm. Pharmacol.

The effect of salbutamol on early and late asthmatic responses, bronchial hyperreactivity and airway leukocyte infiltration in guinea-pigs

LIZA SPRUNTULIS AND KENNETH J. BROADLEY

Pharmacology Department, Welsh School of Pharmacy, Cardiff University, CF1 3XF

Sensitized guinea pigs have long been used as a model of bronchial asthma, as they can exhibit early and late asthmatic responses, airway eosinophilia and increased airway reactivity following exposure to antigen (Danahay & Broadley, 1997). Many studies have investigated the effect of β_2-agonists on the inflammatory events and hyperreactivity associated with an asthmatic reaction. The effect of salbutamol administered at various time points relative to antigen exposure has previously been demonstrated; Sanjar et al (1990) showed that treatment with salbutamol daily for 5 days pre-antigen exposure was ineffective against airway hyperreactivity. Matsumoto et al (1994) showed that administering salbutamol 4 hours post-antigen challenge did not affect late phase development. No investigations, however, appear to have been made into its effect when administered directly before antigen exposure and this was the aim of the present study.

Male Dunkin-Hartley guinea pigs (250-300g) were sensitized to ovalbumen by i.p. injection and were used fourteen days later. Airway function was recorded in conscious guinea pigs by whole body plethysmography and specific airway conductance (sGaw) measured using methodology developed in these laboratories (Danahay & Broadley, 1997). The sensitized guinea pigs (n=6) were given salbutamol 1mg/kg i.p. half an hour before antigen exposure (ovalbumen 100μg/ml in normal saline) for one hour. Airway function was monitored at intervals for 10 hours post-challenge. A control group (n=6) of sensitized animals was given saline 1ml/kg half an hour before ovalbumen exposure and were monitored in the same way. Airway hyperreactivity in both groups was investigated by nose-only inhalation of histamine 1mM for 20 seconds, 24 hours before and after antigen challenge. Bronchoalveolar lavage was performed to determine cellular infiltration at approximately 24 hours after exposure to ovalbumen.

Ovalbumen challenge produced an immediate early phase bronchoconstriction which was revealed as a 60.0% ±10.2 fall in conductance. This resolved to baseline by 5 hours and was followed by a late phase bronchoconstiction (20.8%±4.5 reduction in sGaw) between 6 and 10 hours. Salbutamol inhibited the early phase, the peak reduction in sGaw (16.2%±6.3) being significantly less than controls ($P<0.05$). The late phase was not inhibited by salbutamol (16.0%± 5.6 reduction in sGaw). Histamine inhalation before antigen challenge in the control group produced no significant bronchoconstriction, but 24 hours after the antigen inhalation, there was a significant bronchoconstriction (28.0%±10.3 reduction in sGaw) indicating the development of airway hyperreactivity. After salbutamol treatment, there was no hyperreactivity to histamine, the reduction in sGaw before (11.9% ±8.2) and after (15.3%±2.7) antigen not differing significantly ($P>0.05$). Bronchoalveolar lavage revealed an increase in total cells (4.3± 0.3 $(x10^6)ml^{-1}$), eosinophils (1.8±0.2 $(x10^6)ml^{-1}$) and macrophages (2.4± 0.2 $(x10^6)ml^{-1}$) in the antigen-challenged sensitized animals compared to a saline-challenged group of animals (1.9±0.2 $(x10^6)$, 0.2±0.0 $(x10^6)$ and 1.7±0.2 $(x10^6)$ ml^{-1}) respectively. This indicated the presence of airway inflammation. Salbutamol pretreatment **increased** the total cell numbers (7.4±1.0 $(x10^6)ml^{-1}$ ($P<0.05$)), macrophages (3.7±0.3 $(x10^6)ml^{-1}$ ($P<0.05$)) and eosinophils (3.4±0.8 $(x10^6)ml^{-1}$, non-significant, ($P<0.10$)).

These results show that the β_2-adrenoceptor agonist, salbutamol, inhibits the early phase bronchoconstriction presumably because of its immediate bronchodilator action. The late phase is not inhibited because the bronchodilator action will have declined by 7 hours. This result indicates that the late phase is not dependent on the appearance of an early phase. The suprising result was the increase in cell infiltration in the salbutamol treated animals. A possible reason for this is the bronchodilator effect of salbutamol permitting entry of the inhaled antigen into the lungs and a correspondingly larger inflammatory response. The hyperreactivity to histamine, however, was inhibited rather than enhanced, indicating a possible lack of relationship between influx of inflammatory cells and hyperreactivity.

Danahay H & Broadley KJ (1997) Br. J. Pharmacol., 120: 289-297

Matsumoto T, Ashida Y & Tsukuda R (1994) J. Pharmacol. Exp. Ther., 269 (3): 1236-1244

Sanjar S, Aoki K, Boubekeur S, Chapman ID, Smith D, Kings MA & Morley J (1990) Br. J Pharmacol., 99: 267-272