ELSEVIER

European Journal of Pharmacology 347 (1998) 253–255

ejp

Short communication

Antitussive effect of moguisteine on allergic coughs in the guinea pig

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Received 5 February 1998; revised 23 February 1998; accepted 27 February 1998

Abstract

The effect of moguisteine, a novel peripherally acting non-narcotic antitussive drug, on allergic coughs was examined in guinea pigs. Male Hartley guinea pigs were actively sensitized to ovalbumin. The number of coughs elicited over 5 min following a 2-min exposure to ovalbumin was counted. Exposure of sensitized guinea pigs to 0.5% ovalbumin aerosol induced 22.0 ± 3.2 coughs/5 min. Moguisteine at doses of 30 and 56 mg/kg, p.o., dose-dependently and significantly suppressed the number of allergic coughs. Dihydrocodeine at doses of 30 and 56 mg/kg, p.o., dose-dependently but not significantly reduced the number of allergic coughs. These results suggest that moguisteine may be of a therapeutic benefit in reducing allergic coughs. © 1998 Elsevier Science B.V.

Keywords: Cough reflex; Moguisteine; Non-narcotic antitussive drug; Allergic cough

1. Introduction

Moguisteine ((*R*,*S*)-2-(2-methoxyphenoxy)-methyl-3-ethoxycarbonyl-acetyl-1,3-thiazolidine), a non-opioid compound, was first synthesized by Gallico et al. (1994), who reported that it was an effective antitussive agent under several common experimental cough conditions. Moguisteine was shown to be as active as codeine to reduce coughs induced in guinea pigs by chemical irritants such as citric acid and capsaicin, or by mechanical or electrical stimulation of the trachea. Naloxone, an opioid antagonist, abolished the antitussive effect of codeine, but not that of moguisteine. Furthermore, while intracerebral administration (i.c.v.) of moguisteine had no effect on electrically induced coughs, i.c.v. codeine and dextromethorphan were dose-dependently effective under the same experimental conditions. Based on these results, Gallico et al. (1994) suggested that the site of action of moguisteine is peripheral. Recently, Gallico et al. (1996) also reported that moguisteine reduced tobacco smoke-induced bronchial hyperreactivity. Furthermore, moguisteine abolished eosinophil recruitment in bronchoalveolar lavage fluid, prevented sloughing of the epithelium and significantly reduced airway microvascular leakage induced by tobacco smoke. Based on these results, the authors suggested that moguisteine has interesting inhibitory effects on the airway-inflammation process, in addition to its antitussive properties. Recently, we demonstrated that moguisteine dose-dependently inhibited the enhancement of capsaicin-induced coughs associated with angiotensin converting enzyme inhibitor (Kamei and Morita, 1996).

Cough variant asthma, which is characterized as a persistent, non-productive cough with little or no wheezing and dyspnea, is an occult form of asthma in which the only sign or symptom is a chronic cough (Corrao et al., 1979; McFadden, 1975). Indeed, a chronic persistent cough can be the sole manifestation of bronchial asthma. However, few studies have investigated the pharmacology of coughs in allergic animals (e.g., Bolser et al., 1995). In the present study, we examined the antitussive effect of moguisteine on coughs in actively sensitized guinea pigs that were exposed to antigen aerosols.

2. Materials and methods

2.1. Animals

Male Hartley guinea pigs (Tokyo Animal Laboratory, Tokyo, Japan) weighing about 300 g at the beginning of the experiments were used. The animals were housed in groups of four per cage under a 12-h light–dark cycle with

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food and water available ad libitum. This study was carried out in accordance with the Declaration of Helsinki and/or with the guide for the care and use of laboratory animals as adopted by the committee on care and use of laboratory animals of Hoshi University, which is accredited by the Ministry of Education, Science, Sports and Culture.

2.2. Sensitization of guinea pigs

Guinea pigs were actively sensitized to ovalbumin. The animals were injected s.c. with 0.5 ml of ovalbumin (200 mg) and aluminum hydroxide (200 mg). In addition, animals also received 0.3 ml (i.p.) of 10×10^{10} heat-killed pertussis organisms at the same time as ovalbumin injection. The same dose of ovalbumin, aluminum hydroxide and heat-killed pertussis organisms were given 2 weeks later. The experiments were conducted 1 week after administration of the booster. Sham-sensitized animals did not receive ovalbumin. At the end of the experiment, antisera were collected, and reagin-like immunoglobulin titers were determined by 72-h homologous passive cutaneous anaphylaxis. The titer of antisera of immunized guinea pigs was above 2000.

2.3. Antitussive assay

The cough reflex was induced as previously described (Kamei et al., 1989; Kamei and Kasuya, 1992). Briefly, animals were exposed to a nebulized solution of ovalbumin (0.5%) under conscious and identical conditions using a body plethysmograph. Ovalbumin was dissolved in 0.9% saline solution. The animals were exposed for 2 min to ovalbumin 60 min after p.o. administration of antitussive drugs. The coughs elicited over 5 min following a 2-min exposure to ovalbumin were counted. The coughs were counted only after exposure to ovalbumin.

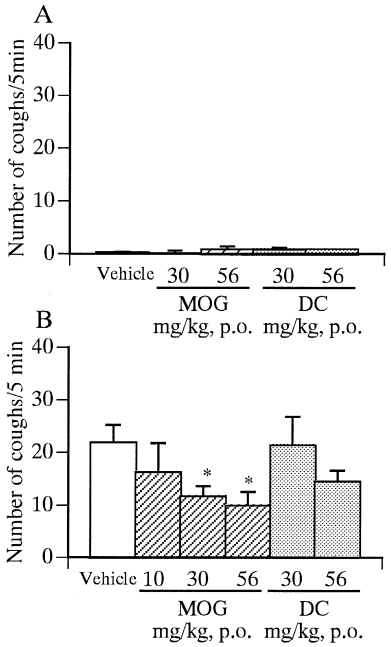

Fig. 1. Effects of moguisteine (MOG) and dihydrocodeine (DC) on ovalbumin-induced cough in sham-sensitized (A) and sensitized (B) guinea pigs. The animals were exposed to ovalbumin 60 min after p.o. administration of antitussive drugs. Each column represents the mean with S.E. ($n = 6$–7) of the number of coughs elicited over 5 min following a 2-min exposure to ovalbumin. $* P < 0.05$ vs. the respective vehicle-treated value (open column).

2.4. Drugs

Moguisteine ((*R*,*S*)-2-(2-methoxyphenoxy)-methyl-3-ethoxycarbonyl-acetyl-1,3-thiazolidine) was generously supplied by Boehringer Mannheim Italia. Dihydrocodeine hydrochloride was purchased from Sankyo, Tokyo, Japan. Moguisteine was suspended in 0.5% sodium carboxymethyl cellulose. Dihydrocodeine was dissolved in saline. Antitussive drugs and their vehicle were given p.o. using the feeding probe.

2.5. Statistics

Data are expressed as the means ± S.E. The statistical significance of differences was assessed with the Mann–Whitney *U*-test to evaluate the antitussive effect. A level of probability of 0.05 or less was considered significant.

3. Results

In vehicle-treated sensitized guinea pigs, exposure to 0.5% ovalbumin aerosol induced 22.0 ± 3.2 coughs/5 min. Sham-sensitized animals exhibited negligible coughing in response to 0.5% ovalbumin (0.3 ± 0.2 coughs/5 min) (Fig. 1A).

Moguisteine, at doses of 10, 30 and 56 mg/kg, p.o., dose-dependently reduced the number of allergic coughs when it was administered 60 min before the ovalbumin challenge (Fig. 1B). Significant reduction was observed at doses of 30 and 56 mg/kg. On the other hand, treatment with dihydrocodeine (30 mg/kg, p.o.) had no significant effect on the number of allergic coughs (Fig. 1B). While dihydrocodeine (56 mg/kg, p.o.) reduced the number of allergic coughs, this effect was not statistically significant. Treatment with either moguisteine or dihydrocodeine had no effect on the very small number of coughs in sham-sensitized animals.

4. Discussion

In the present study, we found that moguisteine was an effective antitussive agent to reduce allergen-induced coughs in sensitized guinea-pigs. In humans, Koh et al. (1993) observed that airway hyperreactivity in patients with cough variant asthma was not significantly different

from that in classic asthma. Doan et al. (1992) reported that prednisone was useful in a diagnostic–therapeutic trial for cough variant asthma. In this regard, they suggested that since inflammation is a major factor in the pathogenesis of asthma, a short course of prednisone may reverse the inflammation of the bronchi (Doan et al., 1992). Gallico et al. (1996) reported that moguisteine reduced airway inflammation, which is characterized by bronchial hyperreactivity induced by a variety of stimuli, such as exposure to cigarette smoke, infusion of platelet activating factor or inhalation of an allergen. This anti-inflammatory effect of moguisteine was observed at doses within the range effective against experimental coughs (Gallico et al., 1994). Therefore, it seems likely that the inhibitory effect of moguisteine on allergic coughs and the anti-inflammatory effect of moguisteine are somehow related. Morikawa et al. (1997) suggested that the antitussive action of moguisteine is mediated at least in part by a decrease in the excitatory response of the airway rapidly adapting receptors to tussive stimuli. Riccio et al. (1996) reported that antigen can stimulate rapidly adapting receptors in antigen-sensitized guinea pigs. It is possible that inhibition of the airway rapidly adapting receptors may also account for the antitussive effect of moguisteine on allergic coughs.

The antitussive efficacy of moguisteine against allergic coughs was greater than that of dihydrocodeine. This finding is not consistent with the observation of Bolser et al. (1995). They showed that allergic coughs in actively sensitized guinea pigs can be inhibited by 30 mg/kg of codeine. Furthermore, they reported that both allergic and capsaicin-induced coughs were inhibited with equal efficacy and potency by codeine. We previously demonstrated that moguisteine is an effective antitussive agent that is as active as dihydrocodeine to reduce capsaicin-induced coughs in guinea-pigs (Kamei et al., 1989). The reason for this difference in the effect of an opioid antitussive on allergic cough should be clarified. Bolser et al. used a single injection of antigen for sensitization, but we boosted the antigen 2 weeks after the first antigen injection. The titer of antisera of immunized guinea pigs used in this study was above 2000. The immune response in sensitized guinea pigs in our study may have been higher than that in the study by Bolser et al. (1995). Indeed, the numbers of allergen-induced coughs in the present study were relatively greater than those obtained by Bolser et al. (1995). Thus, the difference in the efficacy of opioid antitussives on allergic coughs in this study and that in Bolser et al. (1995) may be related to the degree of sensitization. As mentioned above, we suggested that the antitussive action of moguisteine on allergic coughs is mediated at least in part by a decrease in the excitatory response of the airway rapidly adapting receptors to tussive stimuli. The airway rapidly adapting receptors are thought to play an essential part in responses to irritant-induced coughing and bronchoconstriction (Forsberg et al., 1988). Thus, the relatively slight effect of dihydrocodeine on allergic coughs relative to that of moguisteine may also be due to the difference in the efficacy of these drugs on the airway rapidly adapting receptors.

In conclusion, moguisteine is more effective to reduce allergen-induced coughs in sensitized animals than is dihydrocodeine. Furthermore, the present results provide a basis for the potential use of moguisteine for treating cough variant asthma.

Acknowledgements

We are grateful to Dr. Ceserani (Boehringer Mannheim Italia) for the gift of moguisteine.

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