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Effects of mometasone furoate on a rat allergic rhinitis model

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Abstract

The present study was undertaken to clarify the effects of mometasone on nasal symptoms induced by repeated intranasal application of antigen in sensitized rats in comparison with that of chlorpheniramine. Rats received mometasone intranasally or chlorpheniramine orally 1 h before a topical antigen challenge for 7 days. Mometasone caused a decrease in the instances of nasal rubbing and an inhibition of this response was observed during the treatment period. Almost identical findings were observed with chlorpheniramine. This response was inhibited, even after the interruption of mometasone treatment, while such an effect was not observed with chlorpheniramine. On day 36, the changes in sensitivity to histamine were investigated. Unlike chlorpheniramine, hypersensitivity to histamine was significantly reduced in the mometasone-treated group. The passive cutaneous anaphylaxis titers were elevated and reached a maximum 8 days after the start of the topical antigen challenge. The passive cutaneous anaphylaxis titer in the mometasone-treated group was significantly lower than that in the control group. The results indicated that mometasone is effective in allergic rhinitis, not only during the period of application, but also after the interruption of application.

Keywords: Experimental allergic rhinitis; Sensitivity of histamine; Passive cutaneous anaphylaxis titer; Mometasone; Chlorpheniramine

1. Introduction

It is well known that intranasal corticosteroids, including mometasone, are more effective than a placebo in relieving symptoms in patients with seasonal allergic rhinitis, without severe side effects (Hebert et al., 1996; Meltzer et al., 1998). Although a considerable number of publications have appeared of clinical trials, little work has been done using animal models of allergic rhinitis. We have reported that the topical application of mometasone (0.001%–0.1%) is effective in experimental allergic rhinitis in rats (Kamei et al., 1995). In addition, it was also found that mometasone (0.02%) significantly inhibited the increase in antigen-induced nasal rubbing even 6 h after topical application, indicating that the drug has a long-lasting effect (Sugimoto et al., 2000a). However, these findings were obtained by single application of mometasone. It is well known that anti-allergic drugs, including corticosteroids are used repeatedly and chronically. Therefore, the present study was undertaken to clarify the effect of repeated topical application of mometasone on nasal symptoms by a daily antigen challenge in sensitized rats, in comparison with that of chlorpheniramine. The changes in nasal symptoms after interruption of drug administration were also investigated. In the rat allergic rhinitis model used in this study, nasal rubbing and sneezing are stably induced as symptoms by antigen challenge. We have already investigated the suppressive effects of several antihistamines and glucocorticoids on nasal rubbing and sneezing in the same model (Sugimoto et al., 2000a,b), and reproducible suppression of symptoms was clearly observed. We therefore evaluated the effect of mometasone on allergic rhinitis using nasal rubbing as the endpoint for evaluation in this study.

2. Materials and methods

2.1. Animals

Six-week-old male Wistar strain rats were obtained from Nippon SLC, Shizuoka, Japan. The animals were housed in an air-conditioned room, maintained at 24±2 °C, with a humidity

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of 55%±15%. The rats were given a standard laboratory rodent food (Oriental Yeast, Tokyo, Japan) and water ad libitum. Rats were 6 weeks old at the start of the experiments.

2.2. Reagents

The following reagents were obtained from the sources shown in parentheses: egg albumin (Grade VII, Sigma, St. Louis, MO, USA), aluminum hydroxide gel (LSL, Tokyo, Japan), *d*-chlorpheniramine maleate (chlorpheniramine, Sigma), Evans blue (Wako Pure Chemical Industries, Osaka, Japan) and histamine dihydrochloride (histamine, Sigma). The following drugs were kindly provided by the companies indicated; *Bordetella pertussis* inactive microorganisms suspension (*B. pertussis*, Kitasato Institute Research Center for Biologicals, Saitama, Japan) and mometasone furoate (mometasone, Schering-Plough K.K., Osaka, Japan). Egg albumin was dissolved in physiological saline.

2.3. Sensitization

Rats were systemically sensitized by injection of 0.6 ml of physiological saline containing egg albumin (1 mg), aluminum hydroxide gel (2 mg) and 1×10^{10} *B. pertussis* into the four foot pads on the first day. Five days later, a booster was administered by the subcutaneous injection of 1 ml of physiological saline containing egg albumin (0.5 mg) in 10 sites on the back. Then, local sensitization was performed every day from day 14 to day 35 by dripping the egg albumin dissolved in physiological saline (1 mg/ml, 10 μl per each nostril) into the bilateral nasal cavities using a micropipette.

2.4. Evaluation of antigen-induced nasal symptoms in sensitized rats

After dripping 10 μl of egg albumin dissolved in physiological saline solution (1 mg/ml) into the bilateral nasal cavities, the instances of nasal rubbing were counted for 30 min.

2.5. Effects of test drugs on antigen-induced nasal symptoms in sensitized rats

In this study, the rats received the test drugs from day 21 to day 27 after the first sensitization. Mometasone suspension, for clinical use, was administered topically at a volume of 10 μl into the bilateral nasal cavities by micropipette 1 h before the nasal antigen challenge. Chlorpheniramine was administered orally at a dose of 3 mg/kg, 1 h before the nasal antigen challenge.

2.6. Evaluation of histamine-induced nasal hypersensitivity in sensitized rats

To evaluate hypersensitivity after interruption of the drugs, histamine dissolved in physiological saline (1 μmol/ml, 10 μl per nostril) was administered intranasally to rats on day 36, and the instances of nasal rubbing were counted for 30 min.

2.7. Measurement of anti-egg albumin IgE antibody titers

0.5 ml of blood was drawn from the tail vein after the evaluation of nasal symptoms on day 18, 21, 28 and 35, and the sera were separated. A two-fold serial dilution of the sera with physiological saline was then conducted, and the IgE antibody titers against egg albumin were assessed by the passive cutaneous anaphylaxis method.

2.8. Statistical analysis

All data are presented as means±S.E.M. Statistical analysis was performed using Student's *t*-test, Dunnett's and Steel's test. A probability value of less than 0.05 was considered significant.

3. Results

Fig. 1 shows the effects of the chronic administration of mometasone and chlorpheniramine on the nasal rubbing induced by the repeated topical application of antigen in sensitized rats. Mometasone (0.05% solution) caused a significant reduction in the instances of nasal rubbing during the period of application (from day 22 to day 27). The inhibition of this response lasted for 7 days after the interruption of mometasone treatment. That is, a significant effect was also observed from day 28 to day 34. Chlorpheniramine was also

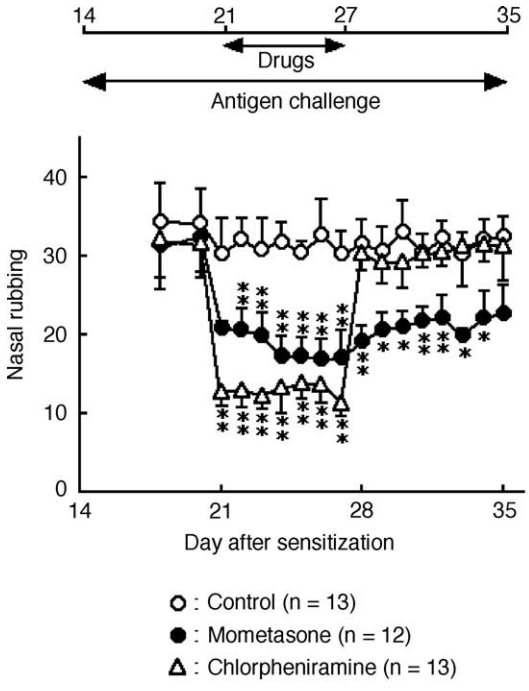

Fig. 1. Effects of chronic administration of mometasone and chlorpheniramine on nasal rubbing induced by repeated topical application of antigen in sensitized rats. Each point and vertical bar represents the means±S.E.M. Mometasone was administered topically and chlorpheniramine was administered orally 1 h before daily nasal antigen challenge, and the number of nasal rubbing was counted for 30 min. *, **: Significantly different from control group with $P<0.05$ and $P<0.01$, respectively (Dunnett's test).