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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

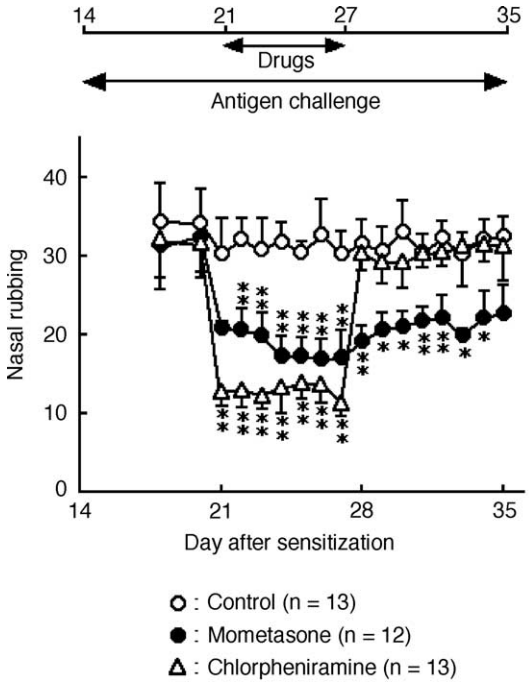

Fig. 1. Effects of chronic administration of mometasone and chlorpheniramine on nasal rubbing induced by repeated topical application of antigen in sensitized rats. Each point and vertical bar represents the means±S.E.M. Mometasone was administered topically and chlorpheniramine was administered orally 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).

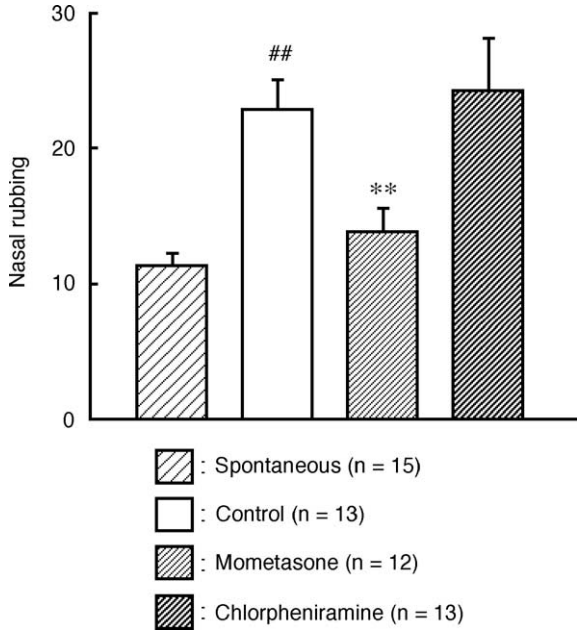

Fig. 2. Nasal hypersensitivity against histamine in the mometasone- or chlorpheniramine-treated group. On day 36, 9 days after the interruption of drug treatments, histamine (1 μmol/ml, 10 μl) was applied topically and the instances of nasal rubbing were counted for 30 min. Each column and vertical bar represents the means ± S.E.M. ##: Significantly different from spontaneous group with $P<0.01$ (Student's t-test). **: Significantly different from control group with $P<0.01$ (Student's t-test).

effective during the period of administration (from day 21 to day 27). However, no significant inhibition was observed after the interruption of the drug. The changes in the sensitivity to histamine were investigated after chronic administration of mometasone and chlorpheniramine. On day 36, histamine (1 μmol/ml, 10 μl) was applied topically and the instances of nasal rubbing were counted. As shown in Fig. 2, the instances of nasal rubbing in the control group (daily topical application of antigen in sensitized rats) were significantly increased compared with the spontaneous group (nonsensitized rats). Significant inhibition of the nasal response was observed in the mometasone-treated group, whereas no significant changes were observed in the chlorpheniramine-treated group. Fig. 3 shows the passive cutaneous anaphylaxis titers in sensitized rats over a period of 35 days following immunization. High passive cutaneous anaphylaxis titers were observed with topical application for 8 days (on day 21), and this high titer was reduced by consecutive local sensitization. The passive cutaneous anaphylaxis titers in the mometasone-treated group were significantly low compared with the control group. In contrast to the mometasone group, the passive cutaneous anaphylaxis titers observed in the chlorpheniramine-treated group were almost identical to that of the control group.

4. Discussion

In the present study, repeated application of mometasone was observed to be effective against the increase in nasal symptoms induced by the daily topical application of antigen in sensitized rats. The same results were obtained with the repeated oral administration of chlorpheniramine. As shown in the present study, chlorpheniramine is more potent than mometasone in the inhibition of nasal rubbing. It seems likely that this difference of potency was due to the difference in the administration route or the dose used in the study. The dose of chlorpheniramine selected for this study was 3 mg/kg administered orally which provides maximum suppressive effects in this model (Sugimoto et al., 2000b). For mometasone, the available clinical preparation (0.05%) was used and administered to the nasal cavity at a volume of 10 μl which is the maximum suitable volume for application to rat nostrils. In a previous study, the number of nasal rubbings decreased from 30 to 12 per 30 min in the control group when 10 μl of 0.1% mometasone was administered as a single dose (Sugimoto et al., 2000a). This effect is nearly identical to the inhibitory effect of chlorpheniramine on day 21 in the present study. It is therefore possible that the concentration of mometasone used in the present study was sub-maximal. In addition, mometasone also caused a significant effect after the interruption of the drugs, different from chlorpheniramine. Mometasone has been reported in a clinical study to be effective in inhibiting perennial allergic rhinitis for one week after the end of treatment (Schenkel, 2003). As for the mechanism for this finding, the functional disorders of inflammatory cells, including mast cells, may have occurred due to the chronic administration of corticosteroids. For instance, Holm et al. (1999) reported that significant decreases in the numbers of Langerhans' cells of the epithelium, $CD3^+$, $CD4^+$, $CD8^+$ cells, mast cells, and eosinophils were observed with long-term topical nasal corticosteroid therapy in humans. Jacobson et al. (1999) also found that fluticasone, a corticosteroid, inhibited seasonal increases in epithelial eosinophils and epithelial infiltration by mast cells in patients. Almost identical findings were also reported by Johnson (1995) in rats.

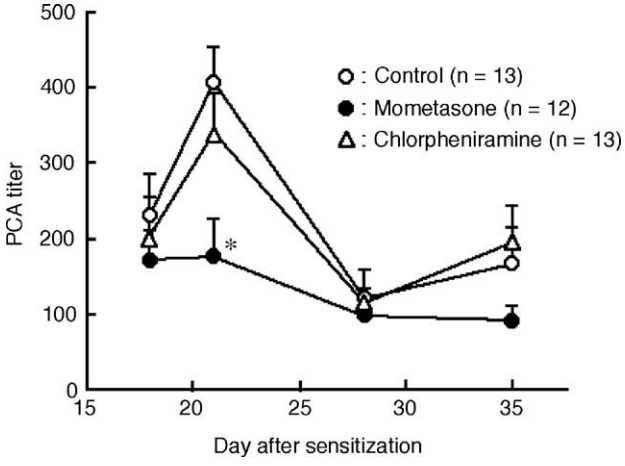

Fig. 3. Changes in passive cutaneous anaphylaxis titers in the mometasone- or chlorpheniramine-treated group in sensitized rats over a period of 35 days following immunization. Each point and vertical bar represents the means ± S.E.M. *: Significantly different from control group with $P<0.05$ (Steel's test).

Non-specific nasal hypersensitivity is a characteristic of patients with allergic rhinitis (Asakura et al., 1984). In the present study, hypersensitivity to histamine was observed in rats when nasal rubbing was used as an index of allergic symptoms, and protective effect was observed with repeated application of mometasone. Narita et al. (1998) also reported that multiple administration of fluticasone gradually reduced histamine hypersensitivity in a guinea pig model of allergic rhinitis. Even in humans, de Graaf-in't Veld et al. (1995) found that fluticasone significantly decreased the histamine-induced nasal hyperreactivity in patients with house dust-mite allergy.

Passive cutaneous anaphylaxis titers in the control group were increased and reached a maximum 8 days after the start of the topical antigen challenge. The passive cutaneous anaphylaxis titer was significantly reduced by the repeated application of mometasone, indicating that mometasone inhibits IgE antibody production in this rhinitis model. In allergic rhinitis, the nasal cavity is the site directly exposed to allergen, and immune cells are also known to be present in the nasal cavity. It seems likely that mometasone is effective in suppressing antibody production by directly affecting nasal immune cells, such as antigen presenting cells and antigen specific T cells. In addition, it has been reported that there is almost no detectable systemic availability with intranasal application of mometasone (Szefler, 2001). Holm et al. (1999) found that a decrease in these immune cells was observed in the nasal epithelium of patients with perennial allergic rhinitis who were receiving long-term administration with a topical steroid. From these results, it seems likely that a decrease in immune cells in the nasal cavity is partly involved in the suppression effect of mometasone on antibody production. In addition, whereas chlorpheniramine inhibits nasal symptoms by direct anti-histamine activity, mometasone possesses immunosuppressive effect besides direct allergy reaction inhibitory effect which is thought to result in sustained inhibitory effect on nasal symptoms and IgE production even after the end of dosing.

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