The Effect of KW-4679, an Antiallergic Drug, on Experimental Allergic Rhinitis in Guinea Pigs: Effects on Nasal Blockage

Toshihiko Kaise¹, Kenji Ohmori¹, Yasuo Sakakura² and Kotaro Ukai²

¹Department of Pharmacology, Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411, Japan
²Department of Otorhinolaryngology, Mie University School of Medicine, 2-174 Edobashi, Tsu, Mie 514, Japan

Received August 2, 1995 Accepted October 2, 1995

ABSTRACT—We investigated the effect of KW-4679 (Z-11-(dimethylaminopropyliden)-6,11-dihydrodibenzoxepin-2-acetic acid hydrochloride), an antiallergic agent, on the nasal blockage induced by antigen challenge into the nostrils of actively sensitized guinea pigs. The change of the nasal cavity volume caused by nasal mucosal swelling after antigen challenge was measured by acoustic rhinometry. Oral administration of KW-4679 (0.01 - 10 mg/kg) significantly inhibited the decrease in the nasal cavity volume at 10 min, 30 min and 6 hr after antigen challenge. Ketotifen (1 - 10 mg/kg, p.o.) also inhibited the decrease in the nasal cavity volume after antigen challenge. These results indicate that KW-4679 may be useful for the treatment of allergic rhinitis.

Keywords: KW-4679, Experimental allergic rhinitis (guinea pig), Nasal blockage

KW-4679, Z-11-(dimethylaminopropyliden)-6,11-dihydrodibenzoxepin-2-acetic acid hydrochloride, is a new antiallergic agent developed for the treatment of allergic diseases (1). In vitro, KW-4679 has been shown to inhibit the release and action of histamine, the release of peptide leukotrienes, and the production of platelet activating factor (PAF) and leukotriene B₄ (T. Ikemura et al., unpublished data). Furthermore, it was found that KW-4679 reduced the tachykininergic contraction of guinea pig smooth muscle evoked by electrical field stimulation (2). Oral administration of KW-4679 inhibited homologous passive cutaneous anaphylaxis (PCA) in rats and IgE-mediated anaphylactic bronchoconstriction in guinea pigs. These inhibitory effects of KW-4679 persisted for 12 hr (3). KW-4679 also inhibited antigen-induced late asthmatic response and eosinophil infiltration into bronchoalveolar lavage fluid in actively sensitized guinea pigs (4). These results suggest that KW-4679 is a potent antiallergic agent with a long duration of action.

Allergic rhinitis is a typical allergic disease that presents nasal irritation, sneezing, rhinorrhoea and nasal blockage. We previously found that oral administration of KW-4679 inhibited the sneeze responses and increase of vascular permeability in the nasal mucosa after antigen challenge in sensitized guinea pigs (T. Kaise et al., unpublished data). In the present study, we investigated the effects of KW-4679 on the nasal blockage induced by antigen challenge into the nostrils of actively sensitized guinea pigs.

KW-4679 was synthesized at the Pharmaceutical Research Laboratories (Kyowa Hakko Kogyo, Shizuoka). Ketotifen fumarate was purchased from Sigma Chemicals (St. Louis, MO, USA). The drugs were dissolved in distilled water for oral administration. Reagents used were Ascaris suum allergenic extract (Funakoshi, Tokyo), 2,4-dinitrobenzenesulfonic acid sodium salt and urethane (Tokyo Kasei, Tokyo). Ascaris suum allergenic extract was coupled with dinitrophenyl (DNP-Ascaris) by the method of Eisen et al. (5).

Active sensitization was performed as previously described by Ishida et al. (6). Male Hartley guinea pigs (5-week-old; Japan SLC, Shizuoka) were actively sensitized by intraperitoneal injection of DNP-Ascaris (3.12 µg protein) and alum (1 mg) 4 times at 2-week intervals and were boosted by inhalation of DNP-Ascaris (15.6 µg protein/ml saline, for 3 min) beginning 1 week after the fourth injection and repeated every day for 5 days. The sensitized animals were used at least 10 days after the final intranasal sensitization. Immediately after the experiments, blood was obtained from guinea pigs by cardiac puncture. The mean antibody titer in the sera was 200 as estimated by 8-day homologous PCA. The antisera were inactivated by heating at 56°C for 2 hr, indicating that these sera mainly contained IgE antibody.
Sensitized guinea pigs were anesthetized with urethane (1.2 g/kg, i.p.). The nasal volume was measured by acoustic rhinometry (GJ Elektronik, Skanderborg, Denmark). The details of the acoustic reflection technique have been reported elsewhere (7, 8). In rhinometry, the method involves measurements of acoustic reflections from the nasal cavity of a sound pulse created by a spark in a sound tube connected with the nasal cavity via a nosepiece. The results are presented as a curve describing the cross-sectional area of the nasal cavity as a function of the distance from the nostrils. From this curve, the nasal cavity volume between the nostril and 2 cm into the nasal cavity was calculated with a computer (IBM PS/2 N 33SX) for each measurement. The nasal patency of each animal was evaluated by the sum of the volume of the left and right nasal cavities. Changes in volume after the nasal challenge are expressed as the percentage changes from the pre-challenge values. The antigen challenge was performed by instilling 20 μl of the solution (DNP-Ascaris, 1.8 mg protein/ml in saline) into bilateral nostrils. Nasal volume was measured at 10 min, 30 min and 6 hr after the antigen challenge.

KW-4679 and ketotifen were administered orally 1 hr before the antigen challenge. In the control group, the vehicle was given instead of the drugs. Data are shown as the mean value ± standard error. Wilcoxon’s signed rank test was used to analyze differences between the pre- and the post-challenge volumes in the control. Steel’s multiple range test was used for analysis of the percentage changes among the control and drug-treated groups at each time; that is, at 10 min, 30 min and 6 hr after the antigen challenge. A value of P less than 5% was considered significant. ID₅₀ values were calculated by linear regression analysis.

Figure 1 shows the time course of % volume changes of the nasal cavity after antigen challenge or saline instillation in actively sensitized guinea pigs. The basal volumes of the nasal cavity were 140.5 ± 2.2 μl in the antigen-challenged group and 126.6 ± 2.5 μl in the saline-instilled group, respectively. In the antigen-challenged group, significant decreases in the nasal cavity volume of 20.7%, 17.6% and 24.4% occurred at 10 min, 30 min and 6 hr after the antigen challenge, respectively. On the other hand, in the saline-instilled group, the nasal cavity volume did not change at all at 10 min and 30 min after saline instillation. At 6 hr after saline instillation, a significant decrease in the volume of 7.8% (P < 0.05) occurred, but the decrease was much smaller than that of the antigen-challenged group.

Oral administration of KW-4679 significantly inhibited the decrease in the nasal cavity volume at 10 min after the antigen challenge at a dose of 0.1 mg/kg or higher. KW-4679 also dose-dependently inhibited the decrease in the nasal cavity volume at 30 min and 6 hr after the antigen challenge. At 6 hr after the antigen challenge, significant inhibition was observed at 1 mg/kg or higher (Fig. 2).
Oral administration of ketotifen significantly inhibited the decrease in the nasal cavity volume at 10 and 30 min after the antigen challenge at 10 mg/kg and at 1 mg/kg, respectively. Ketotifen at a dose of 1 mg/kg or higher showed about 40% inhibition of the decrease of the nasal cavity volume at 6 hr after the antigen challenge, but the inhibition was not significant (Fig. 3).

ID₅₀ values of KW-4679 and ketotifen for the decrease of the nasal cavity volume at 30 min after the antigen challenge were 0.23 mg/kg and 0.86 mg/kg, respectively.

The present study demonstrates that swelling and thus nasal blockage developed throughout the nasal mucosa following the antigen challenge and that nasal blockage occurred at 6 hr as well as immediately after the antigen challenge in actively sensitized guinea pigs. In the saline-instilled group, the nasal cavity volume significantly decreased from the pre-challenge value at 6 hr after saline instillation, but the decrease was much smaller than that of the antigen-challenged group. Therefore, the decrease of the nasal cavity volume at 6 hr after the antigen challenge was considered to be specific for antigen-antibody reactions. It is reported that the late-phase response in the nose associated with nasal swelling occur in men at several hours after the antigen challenge (9). The nasal blockage observed at 6 hr after the antigen challenge in guinea pigs may correspond to the late phase response in the human nose, although there is a possibility that the immediate response that occurred at 10 and 30 min after the antigen challenge may have lasted for 6 hr.

KW-4679 at a dose of 0.1 mg/kg or higher inhibited the decrease of the nasal cavity volume after the antigen challenge. Ketotifen also inhibited the decrease of the nasal cavity volume after the antigen challenge at a dose of 1 mg/kg or higher. The ID₅₀ value of KW-4679 for the decrease of nasal cavity volume at 30 min after the antigen challenge was lower than that of ketotifen. KW-4679 inhibited the decrease of the nasal cavity volume at 6 hr after the antigen challenge, but ketotifen did not. These results suggest that the inhibitory effect of KW-4679 on nasal blockage in our model was more potent than that of ketotifen.

It has been reported that histamine (10), peptide leukotrienes (10) and PAF (11) play important roles in causing nasal mucosal swelling and thus nasal blockage. It is also reported that capsaicin sensitive sensory nerve reflexes were related to nasal blockage (12). It has been shown that KW-4679 inhibits the release and the action of histamine, the release of peptide leukotrienes, the production of PAF and leukotriene B₄, and the release of neuropeptides (2). Accordingly, the efficacy of KW-4679 on nasal blockage is likely to be based on these actions; that is, inhibitory actions on the release of histamine, peptide leukotrienes and neuropeptides, and on the production of PAF as well as based on the antagonistic actions on histamine. Furthermore, it is reported that KW-4679 inhibited the nasal glandular secretion that is one of the causes of nasal blockage by an inhibitory action on the increase of intracellular Ca²⁺ concentration induced by acetylcholine in the isolated acini of guinea pig nasal glands (13). More detailed studies such as measurements of mediators in nasal secretions will be required to ascertain the precise mechanism of action of KW-4679 on nasal blockage.

Ketotifen has been shown to inhibit the release and the action of histamine (14) and the release of neuropeptides (15). These actions may be involved in the effectiveness of ketotifen on nasal blockage.

In conclusion, KW-4679 given orally inhibited the nasal mucosal swelling and thus the nasal blockage caused by antigen-antibody reactions. Therefore, KW-4679 may be useful for the treatment of allergic rhinitis.

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