European Journal of Pharmacology 602 (2009) 138–142

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Pulmonary, Gastrointestinal and Urogenital Pharmacology

Effect of TA-270, a novel quinolinone derivative, on antigen-induced nasal blockage in a guinea pig model of allergic rhinitis

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ARTICLE INFO

Article history:
Received 22 October 2008
Accepted 3 November 2008
Available online 9 November 2008

Keywords:
TA-270 [4-hydroxy-1-methyl-3-octyloxy-7-sinapinoylamino-2(1H)-quinolinone]
Peroxynitrite
Nasal blockage
Allergic rhinitis
Cedar pollen
Leukotriene D4

ABSTRACT

TA-270 (4-hydroxy-1-methyl-3-octyloxy-7-sinapinoylamino-2(1H)-quinolinone) is a novel quinolinone derivative that has been demonstrated to possess an anti-oxidative activity against peroxynitrite, a potent oxidant, that is generated by the reaction of nitric oxide with superoxide anions. The current study describes the inhibitory effect of TA-270 on the biphasic nasal blockage induced by repeated antigen challenge in an allergic rhinitis guinea pig model. In the present in vitro study, TA-270 potently inhibited the oxidative reaction induced by peroxynitrite (IC_{50}=79 nM). In addition, TA-270 (0.3–30 mg/kg, p.o.) dose-dependently inhibited peroxynitrite (3 mM, 10 μl/nostril)-induced nasal blockage in guinea pigs. In the antigen-induced allergic rhinitis model, TA-270 (0.3, 3, and 30 mg/kg, p.o.) given 1 h before the antigen challenge suppressed early phase nasal blockage by 36%, 42%, and 63%, respectively. Furthermore, TA-270 (0.3, 3, and 30 mg/kg, p.o.) showed a relatively strong suppression of late phase nasal blockage (39%, 62%, and 72%, respectively). The late phase nasal blockage was significantly inhibited (61%) even when TA-270 (30 mg/kg, p.o.) was administered 18 h before the antigen challenge. In conclusion, TA-270 improved antigen-induced nasal blockage, probably through its peroxynitrite scavenging action, and the effect was sustained for at least 18 h. Thus, TA-270 would be expected to relieve nasal blockage in allergic rhinitis patients.

1. Introduction

Patients with allergic rhinitis have serum IgE antibody against specific allergens included in pollens of trees, grasses or weeds, and their characteristic symptoms of the condition are nasal blockage, sneezing, and rhinorrhea (Naclerio, 1991). Nasal blockage is considered to be the most serious problem for patients suffering from allergic rhinitis. When a specific allergen is applied to the nasal cavities of allergic rhinitis patients, over 90% show an immediate nasal blockage response, sneezing and rhinorrhea. In addition, approximately 50% develop a late phase reaction, with the predominant symptom of nasal blockage (Ilipoulos et al., 1990; Pelikan 1978). The nasal mucosa contains venous sinusoids, and an increase in blood flow into the sinusoids produces a rapid reduction in the volume of the nasal airway. Thus, it is strongly suggested that nasal blockage is mainly induced by dilation of the blood vessels in the sinusoids (Eccles, 1995).

Nitric oxide (NO) is known as a powerful vasodilator that modulates systemic vascular tone (Rees et al., 1989). We have demonstrated that a non-selective NO synthase inhibitor, N^{ω}-nitro-L-arginine methyl ester (L-NAME), strongly suppresses both early and late phase nasal blockages (Imai et al., 2001). In addition to its direct vasodilatative action, NO rapidly reacts with superoxide anions, which are released from inflammatory cells such as neutrophils (Salman-Tabcheh et al., 1995; McCall et al., 1989; Carreras et al., 1994; Sutherland et al., 1993; Weiss, 1989), macrophages (Avron and Gallily, 1995; Rodenas et al., 1995), eosinophils (Pincus et al., 1982; Nabe et al., 1998a; Hashimoto et al., 2003) and endothelial cells (Szabo et al., 1995; Kooy and Poyall, 1994), and this results in the formation of peroxynitrite, a highly proinflammatory molecule. It has been reported that the levels of nitrotyrosine that are formed after peroxynitrite attacks tyrosine residues are markedly elevated in the nasal mucosa of patients with perennial allergic rhinitis, but are absent in nonallergic patients (Sato et al., 1998). Furthermore, we reported that the intranasal instillation of peroxynitrite induced nasal blockage in guinea pigs (Mizutani et al., 2008). Taken together, these findings suggest that peroxynitrite may be a novel target in the development of new drugs for allergic rhinitis.

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doi:10.1016/j.ejphar.2008.11.006

TA-270 (4-hydroxy-1-methyl-3-octyloxy-7-sinapinoylamino-2 (1H)-quinolinone), a novel quinolinone derivative, was designed as an antioxidant to scavenge reactive oxygen species. TA-270 has been demonstrated to possess an anti-oxidative activity against the potent oxidant peroxynitrite. Furthermore, it has been reported that TA-270 improved biphasic asthmatic responses and hyperresponsiveness in a guinea pig model of allergic asthma, and its inhibitory effect was markedly stronger than that of a cysteinyl leukotriene antagonist (Aoki et al., 2000). Based on these results, TA-270 is currently being developed for clinical use as an anti-asthmatic drug.

In the present study, in order to assess the potential value of TA-270 as a therapeutic agent for allergic rhinitis, we evaluated the effect of TA-270 on allergic biphasic nasal blockage in an experimental allergic rhinitis model.

2. Material and method

2.1. Animals

Male std: Hartley guinea pigs (3–5 weeks of age) were purchased from Japan SLC (Hamamatsu, Japan). The animals were housed under controlled temperature (24±1 °C) and humidity (55±5%) and were given access to food and water ad libitum.

All of the experimental procedures were approved by the Experimental Animal Research Committee at Kyoto Pharmaceutical University.

2.2. Reagents

TA-270 and pranlukast were synthesized by DIC Corporation (Chiba, Japan). Japanese cedar pollen (*Cryptomeria japonica*) was harvested in Gifu and Shiga prefectures in 1998. Peroxynitrite and 3-(4-morpholinyl) sydnonimine hydrochloride (SIN-1) were obtained from Dojindo Laboratory (Kumamoto, Japan).

Peroxynitrite (3 mM) was diluted in phosphate buffered saline (PBS) 1 min before the intranasal instillation. For the negative control, decomposed peroxynitrite was prepared by leaving the solution at room temperature for more than 1 month in sterile conditions.

$Al(OH)_3$ gel was prepared using 0.25 N NaOH and 0.25 N $Al_2(SO_4)_3$, as described previously (Nabe et al., 1997a).

The cedar pollen extract used for sensitization was prepared as described previously (Nabe et al., 1998b). Briefly, pollen was suspended in PBS at 100 mg/ml and kept at 4 °C for 18 h with mild stirring. The suspension was then centrifuged (1700 ×g, 15 min), and the supernatant was stored at −80 °C until it was used as the sensitization antigen.

2.3. Scavenging effect of TA-270 on peroxynitrite-mediated dihydrorhodamine (DHR)-123 oxidation

The scavenging effect of TA-270 on peroxynitrite-mediated DHR-123 oxidation was assessed as follows: TA-270 (6.3–800 nM) was added to 0.1 M phosphate buffer solution (pH 7.4) containing 5 μM DHR-123 solution in a final volume of 2994 μL. The mixture was subjected to fluorescence measurement (excitation wavelength/absorption wavelength=500 nm/536 nm). Six μl of 5 mM SIN-1 solution (a peroxynitrite generator) were then added 4 min after the measurement, and the fluorescence was measured for 8 min. Changes in the rate of oxidation in each group were calculated based on the change before and after adding SIN-1.

2.4. Measurement of nasal blockage

sRaw was measured by a two-chambered, double-flow plethysmograph system in accordance with the method of Pennock et al. (1979). In brief, an animal was placed with its neck extending through the partition of a two-chambered box, and after airflow detection using sensors attached to both the front and rear chambers, sRaw was measured with a Data analyzer Pulmos-I (M.I.P.S., Osaka). The change in sRaw was expressed as the % increase from the pre-challenge baseline value (before).

2.5. Effect of TA-270 on peroxynitrite-induced nasal blockage

To induce sRaw elevation by peroxynitrite, peroxynitrite (3 mM, 10 μl/nostril) was intranasally instilled into normal guinea pigs as reported previously (Mizutani et al., 2008). sRaw was measured 10 min after the instillation. It has been reported that instillation of peroxynitrite causes a swift elevation of sRaw that peaks at 10 min and then decreases at 20 min.

TA-270 (0.3–30 mg/kg) or pranlukast (100 mg/kg) was orally administered 1 h before the peroxynitrite instillation.

2.6. Sensitization and challenge with cedar pollen

The animals were sensitized with Japanese cedar pollen according to the method described by Nabe et al. (1998b). Briefly, the animals were sensitized by intranasal instillation of cedar pollen extracts adsorbed onto $Al(OH)_3$ gel at a concentration of 0.3 μg protein/0.3 mg $Al(OH)_3$/3 μl/nostril twice daily for 7 days. Then, the sensitized animals were bilaterally intranasally challenged once a week by inhalation of cedar pollen using a hand-made inhalation apparatus, which allowed quantitative inhalation of pollen at a dose of 1.8 mg/nostril (Nabe et al., 1997b).

2.7. Effect of TA-270 on the biphasic nasal blockage induced by pollen inhalation challenge

TA-270 (0.3, 3 and 30 mg/kg) or pranlukast (30 mg/kg) was orally administered 1 h before the 6th antigen challenge in this allergic rhinitis model. Furthermore, in order to investigate whether the effect of TA-270 on the biphasic nasal blockage was sustained after an oral administration, TA-270 (30 mg/kg) was administered 1, 18, or 24 h before the 10th antigen challenge.

2.8. Effect of TA-270 on the nasal blockage induced by leukotriene D_4 (LTD_4) instillation

Nasal responsiveness tests described previously (Mizutani et al., 2001) were performed according to the following procedure: Two doses of LTD_4 (10^{-8} and 10^{-6} M, 10 μl/nostril) were consecutively instilled at a 20-min interval into the bilateral nostrils of the sensitized guinea pigs 2 days after the 15th antigen challenge. sRaw was measured 10 min after the respective instillations. TA-270 (30 mg/kg) was orally administered 1 h before the LTD_4 (10^{-8} M) instillation.

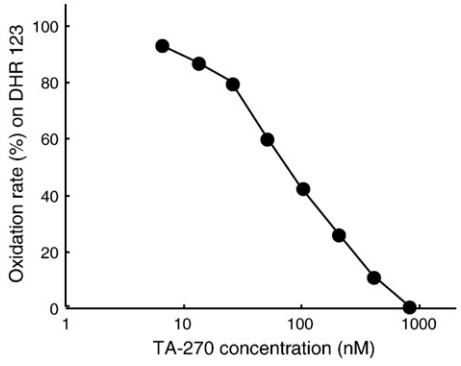

Fig. 1. Effect of TA-270 on the oxidation of DHR123 by the peroxynitrite generator SIN-1. DHR: dihydrorhodamine, SIN-1: 3-(4-Morpholinyl) sydnonimine hydrochloride.

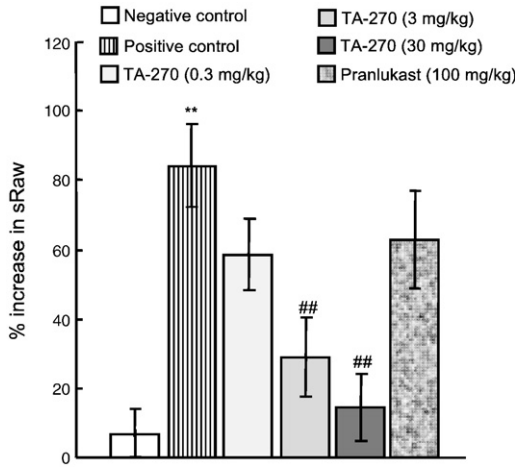

Fig. 2. Effect of TA-270 on the nasal blockage induced by peroxynitrite in guinea pigs. Each column represents the mean±S.E. of 9 animals. **P<0.01: significantly different from the negative control group. ##P<0.01: significantly different from the positive control. Specific airway resistance: sRaw, negative control: decomposed peroxynitrite-treated, positive control: peroxynitrite (3 mM)-treated.

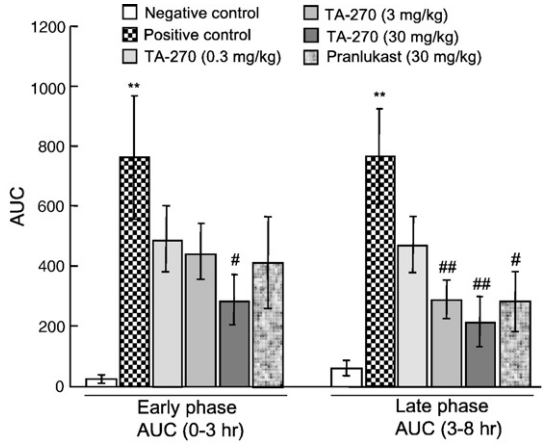

Fig. 4. Effect of TA-270 on the early and late phase nasal blockage induced by the 6th inhalation challenge with Japanese cedar pollen in sensitized guinea pigs. Early and late phase increases in sRaw were determined by calculating the area under the curve (AUC) for the change in sRaw from 0 (before) to 3 h and from 3 to 8 h, respectively, after the pollen inhalation challenge. TA-270 or pranlukast was orally administered 1 h before the 6th antigen challenge. Each column represents the mean±S.E. of 12 animals. **P<0.01: significantly different from the negative control group. #P<0.05 and ##P<0.01: significantly different from the positive control. Negative control: nonsensitized-challenged, positive control: sensitized-challenged.

2.9. Statistical analyses

Statistical analysis was performed using one-way analysis of variance. If a significant difference was detected, the individual group difference was analyzed using Bonferroni's multiple comparison test. A probability value of P<0.05 was considered to indicate statistical significance.

3. Results

3.1. Peroxynitrite scavenging activity of TA-270

TA-270 inhibited the in vitro oxidation caused by peroxynitrite formed by SIN-1 in a concentration-dependent manner (Fig. 1). The IC_{50} value of TA-270 was 79 nM (41.4 ng/ml).

Fig. 2 shows the effect of TA-270 on the nasal blockage induced by the intranasal instillation of peroxynitrite in guinea pigs. TA-270 (0.3–30 mg/kg) inhibited the nasal blockage in a dose-dependent fashion, and statistical significance was observed in the 3 and 30 mg/kg-treated groups. On the other hand, pranlukast (100 mg/kg) hardly influenced the peroxynitrite-induced nasal blockage.

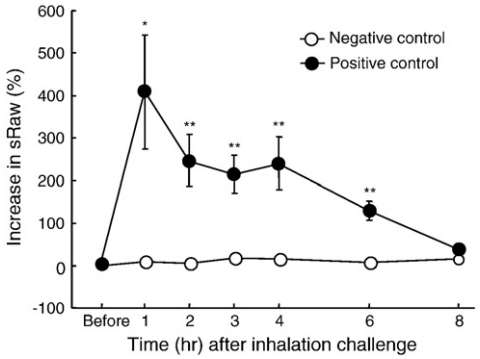

Fig. 3. Time-course change in sRaw after the 6th inhalation challenge with Japanese cedar pollen in sensitized guinea pigs. Each point represents the mean±S.E. of 12 animals. *P<0.05 and **P<0.01: significantly different from the negative control group. Specific airway resistance: sRaw, negative control: nonsensitized-challenged, positive control: sensitized-challenged.

3.2. Effect of TA-270 on antigen-induced biphasic nasal blockage

As shown in Fig. 3, consistent with our previous studies, a biphasic elevation of sRaw peaking at 1 and 4 h was observed after the antigen challenge in the sensitized-challenged guinea pigs (positive control). However, when non-sensitized guinea pigs were forced to inhale the pollen, no alterations in sRaw were seen (negative control). Oral administration of TA-270 at 0.3, 3, and 30 mg/kg 1 h before the antigen challenge inhibited late phase nasal blockage by 39%, 62%, and 72%, respectively, as estimated by $AUC_{3-8\ h}$, and the effects at 3 and 30 mg/kg were statistically significant (Fig. 4). Early phase nasal blockage was also suppressed by TA-270 at 0.3, 3, and 30 mg/kg by 36%, 42%, and 63%, respectively, as estimated by $AUC_{0-3\ h}$, and significant inhibition was seen at 30 mg/kg (Fig. 4). On the other hand, pranlukast (30 mg/

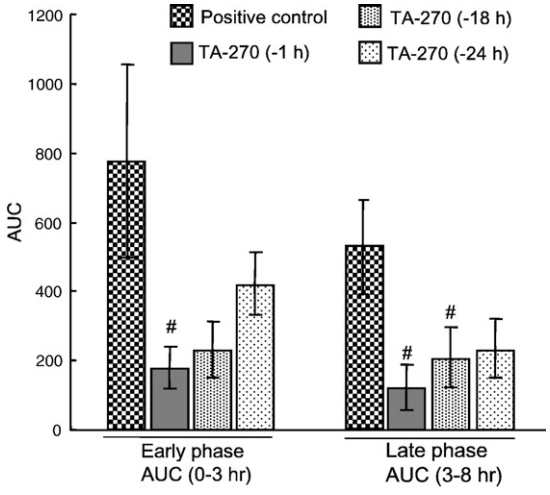

Fig. 5. Long-lasting ameliorative effect of TA-270 on the biphasic nasal blockage induced by the 10th inhalation challenge with Japanese cedar pollen in sensitized guinea pigs. Early and late phase increases in sRaw were determined by calculating the area under the curve (AUC) for the change in sRaw from 0 (before) to 3 h and from 3 to 8 h, respectively, after the pollen inhalation challenge. TA-270 (30 mg/kg) was orally administered 1, 18 or 24 h before the 10th inhalation challenge. Each column represents the mean±S.E. of 8 animals. #P<0.05: significantly different from the positive control. Positive control: sensitized-challenged.

Table 1
Effect of TA-270 on leukotriene (LT) D_4-induced nasal blockage, assessed 2 days after the 15th antigen challenge in sensitized guinea pigs

	% increase in sRaw to LTD_4	
	10^{-8} M	10^{-6} M
Positive control	22.16±4.99	34.07±5.69
TA-270 (30 mg/kg)	9.39±7.02	9.81±3.76[a]

Data represent the mean±SEM of 6 animals. [a]$P<0.05$ compared with the positive control. sRaw: specific airway resistance, positive control: sensitized-challenged.

kg) also inhibited the early and late phase nasal blockage by 47% and 63%, respectively, and the inhibition of the late phase response was statistically significant (Fig. 4). However, the magnitude of inhibition of late phase nasal blockage induced by 30 mg/kg pranlukast was weaker than that of 30 mg/kg TA-270.

3.3. Long-lasting ameliorative effect of TA-270 on biphasic nasal blockage

In order to investigate how long the ameliorative effect of TA-270 on biphasic nasal blockage is sustained after oral administration, TA-270 (30 mg/kg) was administered 1, 18, or 24 h before the antigen challenge. One h-pre-treatment with TA-270 inhibited both early and late phase nasal blockage by approximately 80%. When administered 18 or 24 h before the challenge, the inhibition tended to be weakened, but the suppression of the late response by the 18 h-pre-treatment was still statistically significant (Fig. 5).

3.4. Effect of TA-270 on LTD_4-induced nasal blockage

Table 1 shows the effect of TA-270 (30 mg/kg) on the nasal blockage induced by LTD_4 instillation. In the sensitized guinea pigs, a dose-dependent nasal blockage was observed at 10^{-8} and 10^{-6} M LTD_4 2 days after the 15th antigen challenge. TA-270 significantly inhibited the nasal blockage induced by LTD_4 in the sensitized animals.

4. Discussion

The present in vitro study further indicated that TA-270 has a potent anti-oxidant effect against peroxynitrite at nanomolar concentrations. In the in vivo study, TA-270 was also suggested to possess peroxynitrite-scavenging activity because it markedly suppressed peroxynitrite-induced nasal blockage. More interestingly, TA-270 clearly inhibited the cedar pollen antigen-induced biphasic nasal blockage in a dose-dependent manner, and the degree of suppression induced by TA-270 (30 mg/kg) was greater than that of pranlukast (30 mg/kg), a $CysLT_1$ receptor antagonist that has been demonstrated to effectively relieve nasal blockage in patients suffering from allergic rhinitis (Numata et al., 1999; Riccioni et al., 2007). Collectively, these results strongly suggest that TA-270 would be useful as a therapeutic drug for allergic rhinitis.

The late phase nasal blockage in this model was potently suppressed not only by pranlukast (Mizutani et al., 2001) but also by L-NAME, a peroxynitrite scavenger, ebselen and a xanthin oxidase inhibitor, allopurinol (Imai et al., 2001; Mizutani et al., 2008). Furthermore, the nasal blockage induced by the instillation of LTD_4 was also inhibited by L-NAME, ebselen, and allopurinol (Mizutani et al., 2008). These results suggest that NO reacted with the superoxide anions, that were produced by the LTD_4 stimulation or progressively produced after the antigen challenge in the nasal mucosa, and was lead to the formation of peroxynitrite. Taken together, peroxynitrite could be an important mediator in the formation of late phase nasal blockage. These findings suggest that the inhibitory effect of TA-270 on late phase nasal blockage is explained by its peroxynitrite scavenging action, which is produced via the activation of $CysLT_1$. This hypothesis was further confirmed by the finding that TA-270 significantly inhibited the LTD_4-induced nasal blockage in the sensitized guinea pigs.

Also, when TA-270 was orally administered 18 h before an antigen challenge, the late phase nasal blockage was significantly suppressed. Thus, the ameliorating effect of TA-270 was sustained for at least 18 h. However, because TA-270 is easily glucuronized (unpublished data), its plasma concentration after oral administration was not sufficiently maintained for 18 h in guinea pigs: the plasma concentration of free TA-270 after an oral administration of 30 mg/kg peaked at 1 h and gradually declined until 10 h. Nevertheless, in our preliminary study, when the concentration of TA-270 in the airway epithelial lining fluid (ELF) was measured by the urea dilution method (Rennard et al., 1986), free TA-270 in ELF at 24 h after an oral administration (30 mg/kg) was maintained at a sufficient concentration for scavenging peroxynitrite (unpublished data). These results suggest that the glucronized TA-270 was converted to free TA-270 by glucronidases in the lungs of guinea pigs. Therefore, we speculated that the conversion of glucronized TA-270 to free TA-270 occurs in the nasal mucosa.

TA-270 (30 mg/kg) showed a significant inhibitory effect on early phase nasal blockage, and the degree of the suppression was greater than that of pranlukast. We have reported that early phase nasal blockage induced by antigen challenge was inhibited by L-NAME but not by ebselen, indicating that NO but not peroxynitrite was responsible for the induction of the early phase response (Mizutani et al., 2008). Therefore, the inhibitory effect of TA-270 on early phase nasal blockage might be due to its NO radical scavenging action, because NO radicals are also scavenged by TA-270 with an IC_{50} value of 1.3 μM (unpublished data). However, this is not sufficient to explain the inhibitory mechanism of TA-270 against early phase nasal blockage, because the IC_{50} value of TA-270 against NO radicals is relatively higher than that of its peroxynitrite scavenging action. We may need to elucidate other mechanisms through which TA-270 acts to relieve early phase nasal blockage than its action on NO radicals.

In conclusion, TA-270 improved antigen-induced nasal blockage, probably through its peroxynitrite scavenging action. Thus, TA-270 is expected to be a strong reliever of nasal blockage in allergic rhinitis patients.

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