The Influence of 5-Lipoxygenase Inhibition in Allergic Rhinitis

P.H.	Peter H.	Howarth
K.		Harrison
L.		Lau

University Medicine, Southampton General Hospital, Southampton, UK

Key Words

Allergic rhinitis
5-lipoxygenase inhibition
Leukotrienes

Correspondence to: Dr. Peter H. Howarth, University Medicine, Southampton General Hospital, Southampton SO9 4XY (UK)

Introduction

Leukotrienes (LTs) are considered to be involved in the genesis of the symptoms which characterise allergic rhinitis [1]. Elevated levels of immunoreactive leukotriene (LT)C₄ and LTD₄ have been reported in nasal lavage fluid from patients with perennial and seasonal allergic rhinitis. In acute provoked disease, nasal lavage studies reveal an increase in luminal levels of LTB₄, LTC₄, LTD₄ and LTE₄ within 10 min of nasal allergen challenge and further increments in both LTB₄ and LTC₄ are reported during the late-phase nasal response to allergen challenge. These increments are allergen directed, as no changes in LTC₄ levels in nasal lavage can be identified following nasal challenge with saline, methacholine or bradykinin.

The relevance of these mediator changes to symptom generation has been suggested from nasal insufflation studies. Both LTC₄ and LTD₄ can induce an immediate and sustained increase in nasal airway resistance in the absence of any effect on nasal itch or sneezing. These findings indicate a vascular, rather than a neural effect of topically administered LT within the nose. Consistent with this, in addition to its effects on the state of engorgement of the venous sinusoids, changes in nasal mucosal blood flow are also described with LTD₄.

To confirm the relevance of these nasal studies involving LTs to allergic rhinitis, we have investigated the influence of a novel N-hydroxyurea 5-lipoxygenase inhibitor, N-[3-[5-(4-fluorophenoxy)-2-furanyl]-1-methyl-2-propynyl]-N-hydroxyurea (A-78773), on the acute nasal response to allergen challenge.

Subjects and Methods

Thirteen seasonal grass-pollen-sensitive male rhinitis subjects (mean age 39.2 years, range 24-56) participated in the study, which had a two-phase, double-blind randomised crossover design in which subjects received oral A-78773 or matched placebo as paired medication, outside the pollen season when the subjects were asymptomatic and on no medication. Each phase consisted of two nasal challenges, separated by a minimum interval of 7 days, with a single application into each nostril of a predetermined individually titrated concentration to allergen administered as an aqueous extract. All challenges were performed at the same time of day for each subject and

the concentration of allergen selected to produce an approximately 200% increase in nasal airways resistance (NAR). Medication was administered 5 h prior to each challenge, with a 400-mg dose of A-78773 selected for study.

Results

In this acute-challenge model, A-78773 attenuated the allergen-induced changes in NAR ($p < 0.02$), as objectively monitored by active posterior rhinomanometry, and over the 40-min period of observation reduced the weighed recovery

© 1995 S.KargerAG, Basel 1018-2438/95/1073-0423 \$8.00/0

of anterior nasal secretions ($p < 0.03$), in the absence of an effect in nasal itch or sneeze. Nasal lavage studies also revealed an inhibitory effect of A-78773 administration on allergen-induced plasma protein extravasation. Ex vivo studies in whole blood confirmed the efficacy of A-78773 as a 5-lipoxygenase inhibitor.

Discussion

These findings identify the efficacy within the nose of 5-lipoxygenase inhibition with A-78773, when administered as a single 400-mg dose, and indicate the relevance of LT release to allergen-induced nasal obstruction, rhinor-rhoea and plasma protein leakage. These objective findings extend the one previous subjective report that 5-lipoxyge-nase inhibition limited allergen-induced nasal congestion [2] and encourage the further assessment of therapies which modify LT synthesis in naturally occurring allergic rhinitis.

References

- Howarth PH: Lipid mediators and allergic rhinitis; in Robinson C (ed): Lipid Mediators in Allergic Disease of the Respiratory Tract. Boca Raton, CRC, 1994, pp 117-128.
- Knapp HR: Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. N Engl JMed 1990;327:1745-1747.