

Early and late onset asthmatic responses following lysine-aspirin inhalation in aspirin-sensitive asthmatic patients

H. S. PARK

Department of Internal Medicine, National Medical Center, Seoul, Korea

Summary

Inhalation of aerosolized lysine-aspirin (L-ASA) has been described as an alternative diagnostic method in aspirin-sensitive asthma. To further understand the pathogenetic mechanism of aspirin-sensitive asthma, we performed L-ASA (Inyesprin[®]) bronchoprovocation test (BPT) in 51 asthmatic patients (45 non-atopic and six atopic asthma). Twenty-six patients showed significant bronchoconstriction after the inhalation of L-ASA. Bronchoprovocation test produced immediate asthmatic responses in 13 cases as well as dual asthmatic responses in four cases, whose late onset asthmatic response was noted at 4–7 h after L-ASA inhalation. We conclude that L-ASA bronchoprovocation might be a useful method for the diagnosis and investigation of aspirin-sensitive asthma. However, L-ASA inhalation can also induce late onset asthmatic responses.

Clinical and Experimental Allergy, Vol. 25, pp. 38–40. Submitted 23 December 1993; revised 28 April 1994; accepted 27 May 1994.

Introduction

Aspirin (ASA) and NSAIDs can induce bronchoconstriction in 10–20% of adult asthmatic patients [1,2]. In asthmatics with associated rhinosinusitis, or polyps or both, the proportion is as high as 30–40%, even without a history of ASA-induced respiratory reaction [3,4]. The mechanism of L-ASA-induced bronchoconstriction is not clear. Recently, several investigators [5–7] reported an alternative method to challenge the airway by L-ASA, but they did not show the presence of a late asthmatic reaction.

In this study, we report four cases of aspirin-sensitive asthma who all showed a late onset asthmatic response as well as an immediate response following lysine-aspirin inhalation.

Methods

Subjects

Fifty-one subjects, aged between 23 and 72 years, participated in this study. Twenty-six showed positive responses on L-ASA BPT and four had dual asthmatic

responses. The clinical characteristics of four patients who showed a dual asthmatic response were shown in Table 1. Atopy was defined on the basis that they showed more than 2+ skin-prick test reactions to two or more common inhalant allergens such as *Derмато-phagoides farinae*, alder, oak, rye grass, mugwort, ragweed, *Aspergillus* spp. (Bencard Allergy Service, Brentford, Middlesex, UK). Most of them were treated with theophylline, β_2 agonists and/or corticosteroids. No subject was investigated within 4 weeks of an upper respiratory tract infection or an exacerbation of asthma. All the subjects gave their written informed consent approved by the National Medical Center, Seoul, Korea.

Methacholine bronchial challenge test

Airway hyperresponsiveness to methacholine was determined by a method described previously [8]. An aerosol of 0.9% NaCl, followed by serial doubling concentrations of methacholine (0.075–25 mg/ml), was inhaled. FEV₁ was measured 5 min after each inhalation until the FEV₁ had fallen by 20% from the post saline value. Airway hyperresponsiveness was considered present if a patient demonstrated more than a 20% decrease in FEV₁ after inhalation of any concentration (0.075–25 mg/ml).

Correspondence: H. S. Park, Department of Internal Medicine, National Medical Center, Jung-ku Eulgiro 6-ka, Seoul, Korea.

Table 1. Clinical characteristics of patients who experienced dual asthmatic responses following lysine-aspirin inhalation

Patient	Sex	Age (years)	History of adverse reaction	Atopy	Rhinosinusitis	Methacholine PC20 (mg/ml)
N.Y.	F	28	+	-	+	ND
K.J.	F	55	-	+	+	25
L.K.	F	41	+	-	+	ND
L.B.	M	28	-	-	-	2.5

F. Female. M. Male. +. Present. -. Absent. ND. Not done.

Atopy was defined as a reactor that showed larger than 2+ response to more than two common inhalant allergens on skin-prick test.

of methacholine. The PC20 value was obtained from the dose-response curve.

L-ASA bronchoprovocation test

L-ASA BPT was performed according to the method modified from those described previously [5-7]. Pulmonary function was measured with a spirometer (chest), the FEV₁ and maximum mid-expiratory flow (MMEF), before and during provocation. All medication, including theophylline, bronchodilators and steroids, were stopped 24 h before the procedure. The test solutions were delivered by a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, Penn., USA) and connected to a compressed air source (5 l/min). Normal saline was inhaled as

a placebo solution. The patients were asked to breathe the nebulized aerosol up to their vital capacity, 10 times. L-ASA (Laboratorios Andromata S.A., Madrid, Spain), as a powder containing 1800 mg of L-ASA with 200 mg of glycine, was made up freshly on each challenge day with 10 ml of normal saline to produce a L-ASA solution containing 180 mg/ml. The challenges with placebo were performed seven days before the L-ASA BPT. If there was less than a 10% fluctuation of FEV₁ with placebo inhalation, L-ASA BPT from 11.25 up to 180 mg/ml was performed to determine the provocative dose of L-ASA which induced more than a 20% fall of FEV₁. All provocations were carried out at the same time of day. The FEV₁ and MMEF were measured frequently during the first hour, and then hourly for 8 h.

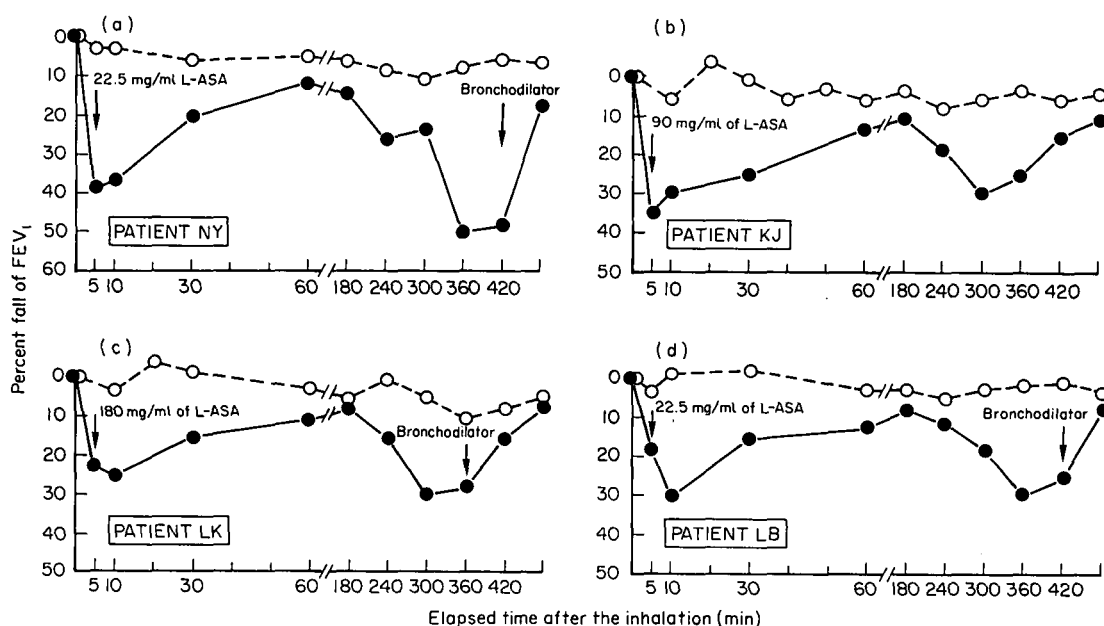


Fig. 1. The results of bronchoprovocation test with lysine aspirin (L-ASA) in four patients who showed a dual asthmatic response. ○—○, Placebo challenge. ●—●, L-ASA challenge. (a) Patient N.Y. (b) Patient K.J. (c) Patient L.K. (d) Patient L.B.

Results

Bronchoprovocation results

Among 51 patients, 26 showed positive responses on L-ASA bronchoprovocation test, 13 showed an isolated immediate asthmatic response and four showed an immediate and late onset asthmatic response. Figure 1 shows the results of bronchoprovocation test with placebo and L-ASA in four patients who had a dual asthmatic response. Changes of FEV₁ were less than 10% following placebo inhalation. L-ASA inhalation could significantly induce bronchoconstriction within 10 min, with recovery after 1 h. Late onset asthmatic responses were noted at 4–7 h. The provocative dose of L-ASA ranged from 22.5 to 180 mg/ml, as shown in Fig. 1. The PD₂₀ value of L-ASA was 16 mg/ml for patient N.Y., 74 mg/ml for patient K.J., 174 mg/ml for L.K. and 18 mg/ml for patient L.B.

Discussion

For adult asthmatics who reported a prior history of an ASA-induced respiratory reaction, the prevalence of ASA sensitivity during oral ASA challenges ranged from 66 to 97% [2,3,9]. Our previous study [10] revealed that 36.1% of intrinsic asthmatic patients showed positive responses on oral aspirin provocation.

The definitive diagnostic test for respiratory sensitivity has been the oral provocation with ASA and NSAIDs. L-ASA inhalation has become an alternative diagnostic test to detect ASA sensitivity in asthmatic patients. Phillips *et al.* [6] reported that L-ASA did not induce a late asthmatic reaction. In the present study, however, late onset asthmatic reactions were noted after the inhalation of L-ASA. As we monitored the changes in FEV₁ following the placebo inhalation, it is likely that these were true late phase asthmatic reactions, and not diurnal variations. It suggests that we should observe at least for seven hours whether a late onset asthmatic response follows after L-ASA inhalation.

The mechanisms of ASA-induced bronchoconstriction have been partly clarified. It is widely accepted that ASA and NSAIDs block the cyclo-oxygenase pathway and therefore the arachidonate substrates may be preferentially diverted down the 5-lipoxygenase pathway. 5-lipoxygenase products can mediate chemotaxis (leukotriene B₄) and are potent bronchoconstrictors and secretagogues [11,12]. An IgE or other possible immune mechanism is an unlikely mechanism [7]. Dual asthmatic reactions observed in this study are commonly noted in atopic asthmatic patients, but, in the present study, none of them gave a positive response on skin-prick testing with L-ASA. The degree of airway hyperresponsiveness and medication taken before the study, whether steroid or

sodium cromoglycate, is not different between immediate responders and late onset responders. Slader *et al.* [13] observed the recruitment of mast cells, lymphocytes and eosinophils in BAL studies following L-ASA inhalation in aspirin-sensitive asthmatic patients. The possibility of the immunological mechanism in the development of late onset asthmatic responses in this study seems very low. Cellular infiltrations noted in the BAL study might be involved in the development of late onset asthmatic responses. Further investigations are need to clarify these mechanisms.

In conclusion, L-ASA inhalation can induce early and late onset bronchoconstrictions in aspirin-sensitive asthmatic patients.

References

- McDonald JR, Mathison DA, Stevenson DD. Aspirin intolerance, detection by oral challenge. *J Allergy Clin Immunol* 1972; 50:198–207.
- Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patient. *J Allergy Clin Immunol* 1979; 64:500–6.
- Delaney JC. The diagnosis of aspirin idiosyncrasy by analgesic challenge. *Clin Allergy* 1976; 6:177–81.
- Weber RW, Hoffman M, Raine D. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. *J Allergy Clin Immunol* 1979; 64:32–7.
- Dahlen B, Zetterstrom O. Comparison on bronchial and per oral provocation with aspirin in aspirin-sensitive asthmatics. *Eur Respir J* 1990; 3:527–34.
- Phillips GD, Foord R, Holgate ST. Inhaled lysine-aspirin as a bronchoprovocation procedure in aspirin-sensitive asthma: its repeatability, absence of a late-phase reaction and the role of histamine. *J Allergy Clin Immunol* 1989; 84:232–41.
- Melillo G, Padovano A, Cocco G, Masi C. Dosimeter inhalation test with lysine acetylsalicylate for the detection of aspirin-induced asthma. *Ann Allergy* 1993; 71:61–5.
- Chai H, Farr RS, Froelich LA *et al.* Standardization of bronchial inhalation challenge procedure. *J Allergy Clin Immunol* 1975; 56:323–7.
- Pleskow WW, Stevenson DD, Mathison DA. Aspirin-sensitive rhinosinusitis/asthma: spectrum of adverse reactions to aspirin. *J Allergy Clin Immunol* 1983; 71:574–9.
- Hong SP, Park HS, Lee MK, Hong CS. Oral provocation tests with aspirin and food additives in asthmatic patients. *Yonsei Med J* 1989; 30:339–45.
- Stevenson DD, Lewis R. Proposed mechanisms of aspirin sensitivity reactions. *J Allergy Clin Immunol* 1987; 80:788–90.
- Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin like drugs. *Nature* 1971; 231:232–5.
- Slader K, Dworski R, Soja J *et al.* Eicosanoid levels in bronchoalveolar lavage fluid in aspirin induced asthma patients after placebo and lysine aspirin inhalation. *Am Rev Respir Dis* 1993; 147:A555.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.