Eur Respir J, 1995, 8, 619–623
DOI: 10.1183/09031936.95.08040619
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European Respiratory Journal
ISSN 0903 - 1936

Inhibitory effect of terfenadine, a selective H_1 histamine antagonist, on alcoholic beverage-induced bronchoconstriction in asthmatic patients

S. Myou*, M. Fujimura**, K. Nishi*, T. Ohka*, T. Matsuda**

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ABSTRACT: We wanted to evaluate the effect of terfenadine, a selective H_1-receptor antagonist, on alcoholic beverage-induced bronchoconstriction.

Eight patients with alcohol-induced asthma received terfenadine (60 mg, twice on the test day) or placebo, with the last dosing 2 h before the test in a double-blind, randomized, cross-over manner. On two separate study days, each subject drank the same brand and volume of alcoholic beverage (beer or Japanese saké), and bronchoconstriction was assessed as change in peak expiratory flow (PEF) over 120 min postchallenge. Inhalation challenges were performed with the same alcoholic beverage with which they had been orally challenged.

The mean (SEM) percentage fall in PEF 15, 30, 45, 60, 90 and 120 min after the oral alcohol challenge was significantly reduced from 12.0 (3.1), 17.0 (1.7), 15.8 (2.3), 15.2 (3.4), 16.6 (4.8) and 14.7 (5.2) %, to 2.6 (1.8), 2.1 (1.6), 3.9 (1.2), 5.7 (2.2), 6.5 (2.6), 5.1 (1.6) %, respectively, by terfenadine. No significant bronchoconstriction was observed after the inhalation challenge.

We conclude that the release of histamine makes a major contribution to alcoholic beverage-induced bronchoconstriction in Japanese asthmatic patients, and that histamine H_1 antagonists may be effective in preventing alcoholic beverage-induced bronchoconstriction.

Eur Respir J., 1995, 8, 619–623.

*Division of Respiratory Medicine, Ishikawa Prefectural Central Hospital, Kanazawa, Japan. **The Third Dept of Internal Medicine, Kanazawa University School of Medicine, Kanazawa, Japan.

Correspondence: S. Myou
The Third Dept of Internal Medicine
Kanazawa University School of Medicine
13-1 Takara-machi
Kanazawa 920
Japan

Keywords: Alcohol
asthma
histamine
terfenadine

Received: June 21 1994
Accepted after revision January 1 1995

Nearly half of Japanese patients with asthma show bronchoconstriction after drinking alcohol [1], which is called alcohol-induced asthma. In Caucasians, it appears that alcohol is not a bronchoconstrictor. For example, AYRES and CLARK [2], following response to a questionnaire, reported that alcohol caused improvement of asthmatic symptoms in 32.1% of patients and exacerbation in 23.2%. They also reported that ethanol when swallowed quickly caused an acute bronchoconstriction followed by bronchodilation in patients with asthma, and hypothesized that irritant receptors in the upper air passages are responsible for the acute bronchoconstriction [3].

Ethanol is oxidized to acetaldehyde, which in turn is oxidized to acetate mainly by aldehyde dehydrogenase (ALDH), which consists of two main isozymes with low and high Km (Michaelis-Menten constant: the substrate concentration at which an enzyme-catalysed reaction proceeds at one half its maximum velocity) aldehyde. About half of Japanese, but not Caucasians, lack the low Km enzyme (ALDH 2), and show an elevation of serum acetaldehyde concentration due to their inability to metabolize acetaldehyde quickly and effectively [4]. It has been reported that ALDH 2 activity is a major determining factor of asthmatic exacerbations after drinking pure ethanol or alcoholic beverages in Japanese asthmatics, and that changes in specific airway conductance (sGaw) are closely related to blood acetaldehyde levels [5].

In addition to acetaldehyde, histamine concentrations also increase during ethanol-induced bronchoconstriction [1]. In previous studies [6–8], we have reported that inhaled acetaldehyde provokes bronchoconstriction indirectly *via* histamine release both in guinea-pigs [6] and asthmatics [7], and that acetaldehyde causes bronchial hyperresponsiveness by mechanisms other than histamine release in asthmatics [8]. Furthermore, GONG *et al.* [9] reported the case of an Asian with asthmatic alcohol-induced bronchoconstriction, in whom cyproheptadine, atropine, acetylsalicylic acid, and chlorpheniramine had a partial inhibitory effect on the alcohol-induced bronchoconstriction. WATANABE *et al.* [10] also reported that cyproheptadine, a histamine H_1-receptor antagonist, had a partial inhibitory effect on the alcohol-induced bronchoconstriction. Despite the partial inhibition of bronchoconstriction by H_1-receptor antagonists, it remains unclear whether histamine is a dominant mediator in alcohol-induced bronchoconstriction. Larger doses of antihistamine could not be given because of the central

nervous system side-effects observed with conventional antihistamines [11]. Terfenadine is a potent H_1-receptor antagonist, and as it does not cross the blood/brain barrier it is devoid of major central nervous system side-effects [12].

We therefore performed this study to evaluate the role of histamine in alcohol-induced bronchoconstriction using terfenadine, in order to assess the usefulness of H_1-receptor antagonist for clinical management of alcohol-induced asthma.

Methods

Subjects

Eight male asthmatic patients with a mean (SEM) age of 41 (5) yrs participated in this study (table 1). All were lifelong nonsmokers and had not suffered respiratory tract infection for at least 8 weeks prior to the study. Each patient, suffering from asthma attacks occurring after drinking all forms of alcoholic beverages, satisfied the American Thoracic Society definition of asthma [13]. This study was carried out when their symptoms were mild and stable, whilst they were taking an aerosol β_2-agonist, oral theophylline, and/or inhalation of beclomethasone. Informed consent was obtained from all subjects. This study was approved by the Ethics Committee of our hospital.

Baseline pulmonary function and bronchial responsiveness

Two weeks before Study 1, baseline forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured using a spirometer (Chestac 55, Chest Ltd, Nagoya, Japan). The subjects wore a noseclip and were in the standing position. Bronchial responsiveness was then evaluated by methacholine challenge as described previously [7]. Briefly, methacholine chloride was dissolved in physiological saline solution to make concentrations of 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10 and 20 mg·ml^{-1}. Saline (placebo) or methacholine were inhaled for 2 min by mouth tidal breathing, wearing a noseclip, from a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, PA, USA) operated by compressed air at 5 l·min^{-1}. The nebulizer output was 0.14 ml·min^{-1}. The best of three FEV_1 manoeuvres measured immediately after each solution was used to construct the dose-response curve, the end-point being a fall of 20% or more in FEV_1 from the postsaline baseline value. The provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}-MCh) was interpolated from the dose-response curve. In our laboratory, values of PC_{20}-MCh above 10 mg·ml^{-1} are considered to be within normal range [14]. All medication was stopped at 1 p.m. on the previous day to allow a wash-out period of 24 h. The pulmonary function test was then carried out at 1 p.m.

Study 1 (effect of terfenadine on alcoholic beverage-induced bronchoconstriction)

Oral challenge with alcoholic beverage. The highest of three measurements of peak expiratory flow (PEF) using a mini-Wright peak flow meter (Clement Clarke International Ltd) was taken as the baseline value before alcohol testing. Before the study, subjects drank beer or saké within 5 min to determine a volume of the alcoholic beverage to be challenged in each subject. The minimum volume of beer or saké causing more than 15% decrease in PEF was recorded (table 1). On each study day, each subject drank the same brand and volume of the alcoholic beverage within 5 min. Each time of 15, 30, 45, 60 or 120 min after drinking the alcoholic beverage, PEF was measured three times and the best of three attempts was recorded. The subjects had nothing but the alcoholic beverage during the test period.

Effect of terfenadine. Effect of terfenadine on alcoholic beverage-induced bronchoconstriction was evaluated in a double-blind, randomized, placebo-controlled, crossover fashion. Oral challenge with alcoholic beverage

Table 1. – Subject characteristics

Sub No.	Age yrs	FVC % pred	FEV_1 % pred	FEV_1/FVC %	PC_{20}-Mch mg·ml^{-1}	Oral challenge ml	Amount of ethanol g†	Treatment
1	65	110	105	75.4	0.50	S 270	35	Sa, Th
2	51	94	86	74.0	0.33	B 633	28.5	Sa, Th
3	31	111	87	73.9	0.11	B 700	31.5	Sa
4	39	106	102	75.6	0.36	S 360	46.5	Sa
5	42	130	116	72.9	0.74	S 360	46.5	Sa
6	42	111	91	72.5	0.30	B 700	31.5	Sa, Be (400 µg), Th
7	28	115	87	70.2	1.08	B 700	31.5	Sa, Be (200 µg), Th
8	27	127	91	67.8	0.18	B 1000	45	Sa
Mean	41	113.0	95.6	72.8	0.36*		37.0	
SEM	5	4.0	3.8	0.9	1.3**		2.7	

Sub: subject; PC_{20}-Mch: the provocation concentration of methacholine producing a 20% fall in FEV_1; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; S: saké; B: beer; Sa: salbutamol *via* metered-dose inhaler; Be: beclomethasone *via* metered-dose inhaler (daily inhaled dose); Th: oral theophylline; *: geometric mean; **: geometric standard error of the mean. †: calculated from the content (by percentage) indicated by the marker.

was performed on two occasions, separated by at least 4 days. Terfenadine was given orally, at a dose of 60 mg twice a day at 8 and 4 p.m. on the test day. Placebo was administered by the same procedure as terfenadine. All medication except for the pretreatment with terfenadine or placebo was stopped at 6 p.m. on the previous day, to allow a wash-out period of 24 h. The oral alcohol challenge test was then carried out at 6 p.m. All subjects refrained from drinking any alcoholic beverages for at least 4 days before Study 1, and they ate nothing after 12 noon on the study day. All patients were interviewed, and a diary was used to record a history of alcohol consumption, asthmatic symptoms, and therapy received for each patient.

Study 2 (inhalation challenge with alcoholic beverage)

In order to investigate whether ethanol or other substances contained in alcoholic beverage provoked bronchoconstriction, inhalation challenge with alcoholic beverage was performed 2 weeks after completion of Study 1. All medication was stopped at 1 p.m. on the previous day, to allow a wash-out period of 24 h. The inhaled alcohol challenge test was then carried out at 1 p.m.

Each subject inhaled the same brand of alcoholic beverage with which they had been orally challenged. The alcoholic beverage was not diluted and was inhaled for 6 min by mouth tidal breathing, wearing a noseclip, from a DeVilbiss 646 nebulizer (DeVilbiss Co, Somerset, PA, USA) operated by compressed air at 5 $l \cdot min^{-1}$. The nebulizer output was 0.14 $ml \cdot min^{-1}$. It was, therefore, calculated that about 0.84 ml of the alcoholic beverage was inhaled at the mouth. Measurements of PEF were repeated prior to, immediately after, and 30 and 60 min after the inhalation. The best PEF value of three attempts was recorded each time.

Data analysis

The analysis of PEF of two-period (terfenadine and placebo) repeated measurements cross-over design was compared using analysis of variance (ANOVA) [15]. Student's paired t-test was used for differences between baseline PEF before inhalation of alcoholic beverage and the lowest value after the inhalation. Significance was based on a 95% confidence level ($p<0.05$) and all measurements were expressed as mean±SEM.

Results

Study 1 (oral challenge with alcoholic beverage and effect of terfenadine)

The mean baseline PEF value before alcohol challenge following placebo and terfenadine was 554±27 and 565±22 $l \cdot min^{-1}$, respectively. There was no significant difference between these results. Time course of mean percentage decrease in PEF following each treatment is shown in figure 1. The mean percentage fall in PEF after 15, 30, 45, 60, 90 and 120 min postcompletion of the oral challenge were significantly (p=0.014, ANOVA) reduced from 12.0±3.1, 17.0±1.7, 15.8±2.3, 15.2±3.4, 16.6±4.8

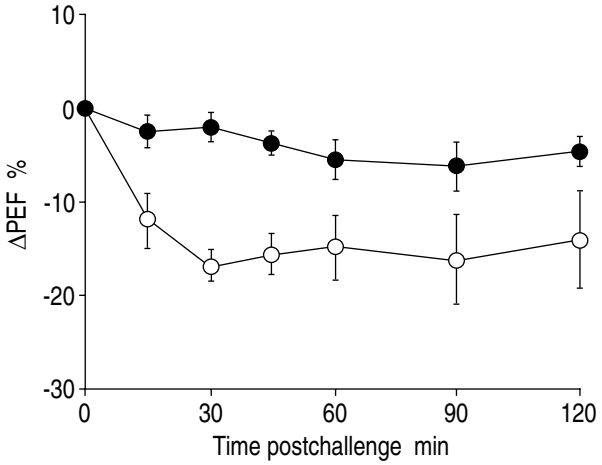

Fig. 1. – Time course of alcoholic beverage-induced bronchoconstriction, expressed as mean percentage changes (±SEM) in peak expiratory rate (ΔPEF) after oral challenge with alcoholic beverage (beer or saké) over 120 min, following the oral administration of placebo (—○—) or terfenadine (—●—). Alcohol-induced bronchoconstriction was significantly (p=0.014) prevented by terfenadine.

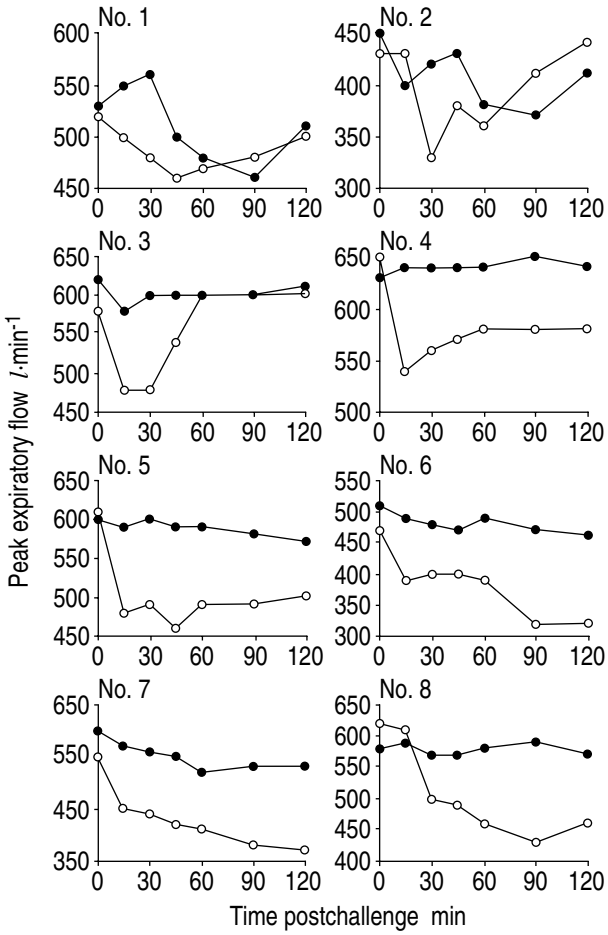

Fig. 2. – Time course of alcoholic beverage-induced bronchoconstriction for each subject following placebo (—○—) or terfenadine (—●—) treatment.

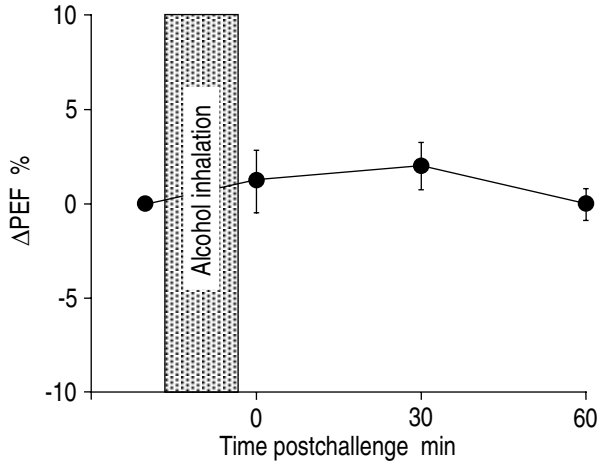

Fig. 3. – Effect of aerosolized administration of alcoholic beverage on airway calibre expressed as mean percentage changes (±SEM) in peak expiratory rate (ΔPEF).

and 14.7±5.2%, to 2.6±1.8, 2.1±1.6, 3.9±1.2, 5.7±2.2, 6.5±2.6, 5.1±1.6%, respectively, by terfenadine. The time course for individual subjects is shown in figure 2. Almost total inhibition of the fall in PEF by terfenadine was observed in six of the eight patients, although no inhibitory effect was observed from 60 to 120 min after the challenge in two patients.

Study 2 (inhalation challenge with alcoholic beverage)

Mean percentage changes in PEF after inhalation of the alcohol beverage are shown in figure 3. PEF before inhalation of alcoholic beverage, and the lowest value after the inhalation was 562±22 and 556±20 *l*, respectively. No significant change in PEF was observed between pre- and postinhalation of alcoholic beverage.

Discussion

In this study, we demonstrated that terfenadine, a selective histamine H_1-receptor antagonist, blocked alcoholic beverage-induced bronchoconstriction in 6 out of 8 asthmatic patients in a significant way. Furthermore, inhaled alcoholic beverages did not affect airway calibre, although any irritant or early allergic response may not be completely detected.

As baseline, PEF did not differ between terfenadine and placebo treatment, changes in baseline airway calibre [16] can, therefore, be ruled out as an explanation for the protective effect of terfenadine. Terfenadine is a highly potent and selective histamine H_1 receptor antagonist [12]. Terfenadine has a blocking effect on histamine-induced bronchoconstriction, whilst terfenadine failed to protect the airway against the constrictor effect of inhaled methacholine [17, 18]. RAFFERTY and HOLGATE [17] demonstrated that 60, 120 and 180 mg of terfenadine displaced the histamine-induced bronchoconstriction curve in a parallel fashion to the right in asthmatic subjects by factors of 14.8, 22.9, and 34.3%, expressed as a concentration ratio (histamine concentrations producing a 20% fall in FEV_1 (PC20-Hist) after terfenadine/PC20-Hist after placebo). They reported that the effect of terfenadine, 180 mg, is approximately 12, 7 and 2 times more potent than orally administered chlorpheniramine 8 mg [19], clemastine 1 mg [20], or astemizole 10 mg [21]. In addition to terfenadine's lack of anticholinergic, antiserotonin, or antiadrenergic properties [11], it is likely that the inhibitory effect of this drug is a result of its direct antagonism of histamine.

WATANABE *et al.* [10] demonstrated that cyproheptadine partially inhibited the fall in FEV_1 after oral ethanol challenge in six asthmatic patients. The main reason for the partial inhibition may be that cyproheptadine can not be administered at doses sufficient to antagonize histamine because its action on the central nervous system is a limiting factor. The second reason may be that the authors administered a single dose of 8 mg about 1 h before the ethanol challenge, whereas the peak plasma level of cyproheptadine is observed 6–9 h [22] after single oral dosing. On the other hand, peak plasma levels of terfenadine and carboxylic acid derivative, a metabolite of terfenadine and an effective H_1 receptor antagonist, are observed 1–2 h after single oral dosing [23, 24], and a histamine wheal study suggested that the effect on wheal area is observed from 2 h, and that maximal H_1 blockade occurred at 4 h [24].

It was reported that atropine and acetylsalicylic acid also have a partial inhibitory effect on oral ethanol-induced bronchoconstriction [9], and that ethanol can stimulate production of prostaglandins of both E and F series [25]. In addition, our study shows that terfenadine had no inhibitory effect on alcoholic beverage-induced bronchoconstriction 60–120 min after the alcohol challenge in two subjects. This suggests that another mechanisms may be concerned with alcohol-induced bronchoconstriction.

In this study, it is unclear that the bronchoconstriction is produced by ethanol, congeners, or metabolites of ethanol. Although clinical asthma, based on history, does not always concur with the inhalation reactions, bronchial sensitivity to allergen depends on the degree of nonspecific bronchial responsiveness [26, 27]. Considering our subjects' bronchial hyperresponsiveness (table 1), it is likely that alcoholic beverage is an indirect challenge, and that metabolites of alcoholic beverage, such as acetaldehyde, are thought to produce bronchoconstriction. Indeed, acetaldehyde causes dose-dependent histamine release from leucocytes of asthmatics *in vitro* [1]. We [7] also reported that inhaled acetaldehyde causes bronchoconstriction *via* release of histamine in asthmatic airways. It is unclear why the maximum fall appears to be within 15 min in three of the subjects and 90–120 min in three others. Since the peak acetaldehyde values from breath for Chinese were observed 10–40 min after ethanol ingestion [28], it is thought to be not inconsistent that a large response was seen by 30 min in half of the patients in this study, even if alcohol produces an indirect challenge *via* acetaldehyde formation.

This phenomenon, in which an antihistamine minimally effective for asthma in general is very effective in this particular type of asthma, is extremely interesting,

from academic as well as practical perspectives. Usually, many patients with alcohol-induced asthma restrict their alcohol intake on their own initiative to avoid exacerbation of asthmatic symptoms. To evade the cause of this phenomenon, we should recommend total abstinence from alcohol as the ideal method of prophylaxis. However, alcohol often plays an important part of various personal and professional events and activities. The administration of terfenadine before alcohol ingestion is effective for preventing asthmatic symptoms and improving the patient's quality of life.

In conclusion, histamine is a dominant mediator in alcoholic beverage-induced bronchoconstriction, and terfenadine may be of value in the clinical management of alcoholic beverage-induced bronchoconstriction.

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