

Short communication

Effect of ethanol on airway caliber and nonspecific bronchial responsiveness in patients with alcohol-induced asthma

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No study has investigated the effects of ethanol on bronchial responsiveness in patients with alcohol-induced asthma, although acetaldehyde, which is a metabolite of ethanol and is thought to be a main factor in alcohol-induced asthma, causes both bronchoconstriction and bronchial hyperresponsiveness. The purpose of this study was to investigate the direct action of ethanol on the airway in patients with alcohol-induced asthma. First, we investigated the bronchial response to inhalation of ascending doses (5, 10, and 20%) of ethanol in nine patients with alcohol-induced asthma. Then, the bronchial responsiveness to methacholine was measured in 14 patients who were pretreated with saline or 20% ethanol in a double-blind, randomized, placebo-controlled, crossover fashion. Ascending doses of inhaled ethanol caused no significant changes in FEV₁. The methacholine concentrations producing a 20% fall in FEV₁ (PC₂₀-MCh) after 20% ethanol (0.769 mg/ml, GSEM 1.514) were significantly ($P=0.0357$) higher than those after saline (0.493 mg/ml, GSEM 1.368). This indicates that ethanol has a reducing effect on nonspecific bronchial responsiveness in patients with alcohol-induced asthma; this paper is the first report on the effects of ethanol on bronchial responsiveness.

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Exacerbation of asthmatic symptoms after drinking alcoholic beverages, which is called alcohol-induced asthma, has been observed among 50% of Japanese asthmatic patients (1). Blood acetaldehyde, a metabolite of ethanol, and histamine concentrations increase in asthmatics during ethanol-induced bronchoconstriction (1). We recently reported that inhaled acetaldehyde causes bronchoconstriction indirectly via histamine release in asthmatics (2), as well as bronchial hyperresponsiveness to methacholine by mechanisms other than histamine release (3) in the asthmatic airway with and without alcohol-induced bronchoconstriction. These findings suggest that acetaldehyde, rather than ethanol, plays an important role in alcohol-induced asthma.

In Caucasians, alcohol in itself is a bronchoconstrictor as well as a bronchodilator, when given either by the oral or the inhaled route (4–7). For example, oral (4) or intravenous (5) administration

of ethanol is considered to be therapeutically beneficial for patients during severe asthmatic attack. In contrast, other studies have demonstrated that inhaled (6, 7) or oral (6) ethanol causes bronchoconstriction. The cause of the high rate of alcohol-induced asthma in Japanese as compared to Caucasian asthma patients is believed to be the lack of aldehyde dehydrogenase (ALDH) in nearly half Japanese population.

On the other hand, the effect of intravenous or inhaled administration of ethanol is unclear in asthmatic patients with oral ethanol-induced bronchoconstriction. Furthermore, no study has investigated the effect of ethanol on bronchial responsiveness in asthmatic subjects including Caucasoids. Therefore, we performed this study to examine the direct effect of ethanol on the airway caliber and the nonspecific bronchial responsiveness to methacholine in patients with alcohol-induced

asthma. It has been reported that acetaldehyde, a rapidly formed metabolite of ethanol, induces bronchoconstriction (2) and bronchial hyperresponsiveness to methacholine (3). Moreover, ethanol itself may act on the central nervous system and the cardiovascular system. In this study, we chose aerosol administration of ethanol in order to assess the direct effect of ethanol on the airway, excluding the effects of acetaldehyde and the systemic effects of ethanol.

Material and methods

Subjects

Asthmatic patients with alcohol-induced bronchoconstriction participated in this study. Each patient, suffering from asthma attacks occurring after drinking any kind of alcoholic beverage, satisfied the American Thoracic Society's definition of asthma. All had never smoked and had not experienced any respiratory tract infection for at least 8 weeks prior to the study or chronic cardiac, hepatic, or renal insufficiency. The determination of atopic type was based on positive results of specific IgE testing (radioallergosorbent test) for common aeroallergens such as house-dust mite, Japanese cedar, ragweed, cat fur, and dog hair. Six of nine patients in study 1 and 8/14 in study 2 were atopic.

This study was carried out when their symptoms were mild and stable while they were receiving aerosol β_2 -stimulant (salbutamol) and/or orally administered theophylline. They had not received steroid therapy for at least 8 weeks. All medication was stopped at 1:00 pm on the previous day to allow a washout time of 22 h. This study was then started at 11:00 am. Informed consent was obtained from all subjects. This study was approved by the ethics committee of our hospital.

Study 1 (effect of inhaled ethanol on airway caliber and pilot study for study 2)

Nine patients participated in study 1. Ethanol was dissolved in physiologic saline to make concentrations of 5, 10, and 20 v/v%. Saline and ethanol solutions were inhaled from a nebulizer (DeVilbiss 646, DeVilbiss Co, Somerset, PA, USA) operated by compressed air at 5 l/min. The nebulizer output was 0.14 ml/min. The saline solution was inhaled first for 2 min by mouth tidal breathing while the subject wore a noseclip, and FEV₁ (Chestac 55, Chest Ltd, Nagoya, Japan) was measured. Ethanol was inhaled for 2 min, and this was followed immediately by measurements of FEV₁. Increasing concentrations of ethanol were inhaled in order to measure the dose-response curves. FEV₁ was meas-

ured three times, and the best FEV₁ value of three attempts was recorded each time.

Study 2 (effect of inhaled ethanol on nonspecific bronchial responsiveness)

Fourteen patients participated in study 2. This study was performed on 2 days separated by 2 weeks in a double-blind, randomized, placebo-controlled, crossover fashion. Saline placebo or 20 %v/v ethanol dissolved in saline was inhaled from a nebulizer (DeVilbiss 646) operated by compressed air at 5 l/min. Each solution was inhaled for 4 min by tidal breathing with a noseclip through the nebulizer, and this was followed immediately by measurements of FEV₁. Then bronchial responsiveness was measured.

Nonspecific bronchial responsiveness was evaluated by methacholine challenge, as we have previously (2, 3) described. Methacholine chloride was dissolved in physiologic 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. Saline and methacholine solutions were inhaled from a nebulizer (DeVilbiss 646) operated by compressed air at 5 l/min. Saline solution was inhaled first for 2 min, and FEV₁ (Chestac 55) was measured. Methacholine was inhaled for 2 min, and this was followed immediately by measurements of FEV₁. Increasing concentrations of methacholine were inhaled until a fall of 20% or more in FEV₁ from the value after saline inhalation and before the first inhalation of methacholine. These values were plotted on semi-logarithmic graph paper, and the methacholine concentration producing a 20% fall in FEV₁ (PC₂₀-MCh) was determined. FEV₁ was measured three times, and the best FEV₁ value of three attempts was recorded each time.

Data analysis

FEV₁ data were expressed as mean $\pm$ SEM. FEV₁ values after saline and each concentration of ethanol were compared using the repeated measures analysis of variance (ANOVA). PC₂₀-MCh values were logarithmically transformed for analysis and reported as the geometric mean (GSEM). Student's paired *t*-test was used for differences in baseline FEV₁, percent change in FEV₁ induced by ethanol or saline, and PC₂₀-MCh between 2 test days. A value of *P* < 0.05 was accepted as statistically significant.

Results

Study 1 (effect of inhaled ethanol on airway caliber and pilot study for study 2)

The baseline value of FEV₁ before saline inhalation was 2.36 ± 0.29 l. No significant change in FEV₁

was caused by inhalation of 5–20% of ethanol. None of the subjects had a more than 10% fall in FEV₁.

Study 2 (effect of inhaled ethanol on nonspecific bronchial responsiveness)

There were no significant differences in the FEV₁ at baseline (saline: 2.43 ± 0.18 l, ethanol: 2.45 ± 0.23 l) or percent change after inhalation (saline: $-0.9 \pm 1.2\%$, ethanol: $-2.3 \pm 1.6\%$). However, inhalation of 20% ethanol caused a more than 10% decrease in FEV₁ in two of the 14 subjects in whom a more than 10% fall in FEV₁ was not observed in study 1. The geometric mean (GSEM) PC₂₀-MCh value significantly ($P=0.0357$) increased from 0.493 (1.368) mg/ml after saline to 0.769 (1.514) mg/ml after ethanol (a change of 0.64 (0.27) doubling doses). When the two subjects were excluded, the geometric mean (GSEM) PC₂₀-MCh value significantly ($P=0.013$) increased from 0.518 (1.442) mg/ml after saline placebo to 0.920 (1.589) mg/ml after 20% ethanol (0.83 (0.28) doubling doses) (Fig. 1).

Discussion

In this study, we investigated the airway response to inhaled ethanol in patients with alcohol-induced asthma. The results of the present study showed that 5–20% ethanol did not alter the airway caliber,

and that 20% ethanol caused a decrease in the nonspecific bronchial responsiveness to methacholine.

Ayres & Clark (5) investigated the effect of intravenous infusions of 2, 4, and 8% (v/v in saline) ethanol on airflow in five asthmatics, and demonstrated that specific airways conductance (*sGaw*) showed a sustained rise of 32.8% with 8% ethanol, a rise which was not seen at lower doses. Ayres et al. (4) also reported that 60% ethanol, when the drink was taken slowly, resulted in significant bronchodilation in 4/5 patients with asthma. In contrast, Zellweger (7) and Gong et al. (6) demonstrated that inhaled administration of 30 and 40% ethanol, respectively, causes bronchoconstriction, measured as *sGaw*. In the present study, 20% ethanol caused bronchoconstriction in only two patients in study 2. This is thought to be a nonspecific phenomenon since a concentration-dependent decrease in FEV₁ was not observed in the same subjects in study 1. Indeed, Ayres et al. (4) demonstrated that an immediate fall in *sGaw* was observed after the drinking of 60% ethanol as quickly as possible but not slowly, and speculated that ethanol may stimulate irritant receptors in the upper air passage. Moreover, Zellweger (7) and Gong et al. (6) evaluated the bronchoconstrictive effect of ethanol by inhalation of one concentration (30 or 40%) of ethanol, which is higher than that in this study. Furthermore, *sGaw* is a more sensitive measure of small changes in airflow than FEV₁. This may reflect our finding that ethanol does not alter the airway caliber.

The mechanisms that reduce the effect of ethanol on bronchial hyperresponsiveness are unclear. It has been reported that ethanol and three other alcohols (propanol, butanol, and propylene glycol) inhibit both the contractile response to ovalbumin and ovalbumin-induced mediator release in sensitized guinea pigs (8). Tamaoki et al. (9) reported that benzyl alcohol relaxes airway smooth muscle, probably through the decrease in intracellular Ca²⁺ release by inhibiting agonist-mediated phosphatidylinositol turnover *in vitro*. Since ethanol penetrates membranes and cells rapidly (10), ethanol could also interfere with the mobility of Ca²⁺, both on membranes and intercellularly, like benzyl alcohol (9). Indeed, several reports (11, 12) in which ⁴⁵Ca and isolated arteries and veins were used, have indicated that ethanol can inhibit membrane-bound calcium by 30–40%; total exchangeable calcium is also attenuated. At the moment, it is impossible to suggest which mechanisms may cause the reducing effect of ethanol on bronchial responsiveness.

The present study has the following weak points. In the first place, studies 1 and 2 were not performed in the same subjects. Secondly, study 1 was not

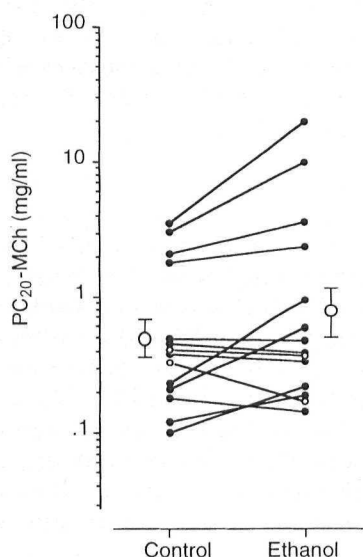


Fig. 1. Reducing effect of inhalation of 20% ethanol on PC₂₀-MCh (provocative concentration of methacholine producing 20% fall in FEV₁) in 14 patients with alcohol-induced asthma. Closed circles: preinhalation of 20% ethanol did not induce more than 10% fall in FEV₁; open circles: preinhalation of ethanol induced more than 10% fall in FEV₁. There was significant ($P=0.0357$) difference between ethanol and control.

blinded. Thirdly, methacholine challenge was performed only after, not before, inhalation of ethanol or placebo. Fourthly, asthmatic patients without alcohol-induced asthma were not examined. It is necessary to investigate the effect of ethanol on bronchial responsiveness in asthmatic patients without alcohol-induced asthma, such as Caucasians, and to compare the changes in methacholine responsiveness by ethanol or placebo between the two groups. Fifthly, inhaled ethanol has a sweet taste, but none of the patients noticed ethanol. The design of this study, strictly speaking, may be single-blind. However, since there were no changes in FEV₁ after inhalation between saline and 20% ethanol, this taste seems to have had no serious effect on the results of PC₂₀.

Ijiri (13) reported that the blood ethanol and acetaldehyde level in the Japanese facial flushing group increased and reached the maximal levels of 0.47 µg/ml and 3.02 µg/ml, respectively, after intake of 200 ml sake (Japanese alcoholic drink) (approximately 0.30–0.61 g ethanol/kg body weight). The concentration of inhaled ethanol in this study was approximately 340 times higher than the blood level reported by Ijiri (13). We (3) recently reported that 0.8 mg/ml acetaldehyde, a level 265 times higher than the blood level, induces bronchial hyperresponsiveness. This suggests that in view of the blood concentration the capacity of ethanol to alter bronchial responsiveness is the same as that of acetaldehyde.

These results indicate that inhaled ethanol decreases nonspecific bronchial hyperresponsiveness, and that even in alcohol-induced asthma, inhaled ethanol, when used as a solvent in anti-asthma drugs, does not lead to airway narrowing in most subjects.

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