

chodilator, and dopamine, the anaphylactic symptoms were resolved, BP returned to normal, and FEV₁ was 2.47 l (80% of predicted). One month later, he had experienced same anaphylactic symptoms 30 min after taking medications including one tablet (150 mg) of ranitidine (Ponaltin®; Daehwa Pharm., Seoul, Korea). These two episodes of anaphylaxis were presumed to be caused by ranitidine ingestion.

A total serum IgE was 2330 IU/ml. Skin prick test with common aeroallergens showed negative response. Skin prick tests with ranitidine (Urantac®; Whanin Pharm., Seoul, Korea) were positive (mean wheal diameter of 2, 6, and 8 mm for 0.25, 2.5, and 25 mg/ml, respectively; 5 mm for histamine positive control). Three unexposed healthy control subjects exhibited no reactions. Skin prick tests with other H₂-receptor antagonists, including cimetidine (Tagma®; Samsung Pharm., Seoul, Korea) and famotidine (Gaster®; Dong-A Pharm., Seoul, Korea), were negative. After written informed consent was obtained, a single-blind, placebo-controlled oral challenge test with ranitidine, cimetidine, and famotidine was performed in the patient until a therapeutic dose was reached or an adverse reaction appeared. The oral challenge test resulted in the reappearance of symptoms 7 min after the administration of 100 mg of ranitidine (Zantac®). Cimetidine (Himetin®; Ildong Pharm., Seoul, Korea) and famotidine (Gaster®) were well tolerated.

To determine ranitidine-specific serum IgE, ELISA was performed. Ranitidine-HSA conjugate was prepared in our laboratory according to a method described previously (3), and were used to detect specific IgE in serum using ELISA. Eleven nonatopic healthy subjects with no history of exposure, who had negative skin prick tests to ranitidine, were enrolled as controls. The final absorbance value of the patient was determined from the subtraction of the HSA-coated value from that of the ranitidine-HSA-coated value. The positive cut-off value for specific IgE (0.06) was determined using the mean + 2 SD of the absorbance values of controls. The patient had high specific IgE level

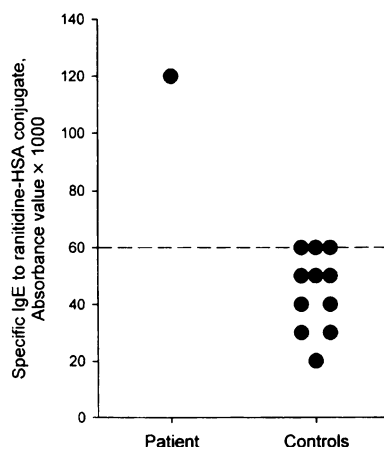


Figure 1. Serum specific IgE levels to ranitidine-HSA conjugate determined by using ELISA in our patient and 11 unexposed nonatopic controls. Dotted line indicates the cut-off value for positive specific IgE bindings, which was determined as mean + 2 SD of absorbance values of controls.

to ranitidine-HSA conjugate (0.12, Fig. 1).

This is the first report to succeed in detecting serum specific IgE reacting to ranitidine, as previous evidences of the presence of specific IgE antibodies were indirect and derived from positive skin tests (1, 2, 4) and leukocyte histamine release test (4) with ranitidine. This case suggests that ranitidine could induce the IgE-mediated anaphylaxis based on positive skin prick test, high serum specific IgE antibody, and immediate response to oral challenge test. It was unlikely that there was cross-reactivity between ranitidine and cimetidine or famotidine based on negative oral challenge tests in our case, which is consistent with the findings by Lazaro et al. (1) and Morisset et al. (4). A diagnostic method based on skin tests and specific IgE determination could be proposed in case of ranitidine-induced anaphylaxis.

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Is ethanol-induced bronchospasm an inflammation-driven event?

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Key words: asthma; ethanol; inhalant steroids; TRPV1.

Ethanol is used as a co-solvent in the preparation of new pressurized metered dose inhalers to enhance the solubility of the principal agents (beclomethasone, flunisolide, formoterol) in hydrofluoroalkane propellents.

We recently reported that the ethanol content in inhalant corticosteroid (ICS) formulations can induce bronchospasm (1). This result is consistent with those yielded by animal models, which demonstrate that ethanol is able to induce bronchospasm via stimulation of sensory airway nerves by a transient receptor potential vanilloid-1 (TRPV1) activation

Topical anti-inflammatory therapy can reverse ethanol-induced bronchospasm.

(2). Moreover, the authors suggest that inflammatory mediators can sensitize or upregulate these receptors (2).

To verify whether anti-inflammatory therapy prevented ethanol-induced TRPV1 activation, a relatively high dose of ICS formulation (fluticasone dry powder 500 mg once a day) was administered to a 31-year-old Caucasian patient with mild allergic asthma for 3 months.

The consumption of alcohol had never caused the patient's asthma to worsen but bronchospasm was triggered by the inhalation of an ICS formulation containing ethanol.

A bronchial challenge test using two puffs of extrafine beclomethasone aerosol containing alcohol (Clenilexx autohaler 100 mcg; Chiesi, Parma, Italy) was performed before and after treatment.

Before both challenges, fractional exhaled nitric oxide (FeNO) (Ecomedics CLD 88 sp; Duernten, Switzerland) was evaluated.

Respiratory function before each challenge was normal and reproducible (before therapy FVC = 5.65 l, 109% predicted, FEV₁ = 4.43 l, 108% predicted; after therapy FVC = 6.04 l, 116% predicted, FEV₁ = 4.71 l, 115% predicted). Anti-inflammatory therapy produced a significant fall in FeNO from 61.0 to 16.8 p.p.b and the resolution of ethanol-induced bronchospasm (Fig. 1).

Our findings suggest that the improvement of bronchial inflammation, as confirmed by the decrease in FeNO, reverses ethanol-induced bronchospasm.

Consistent with the results coming from guinea-pig's airways (2), our data seem to confirm the role of inflammatory

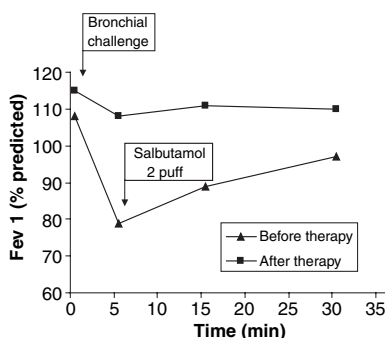


Figure 1. Effects of bronchial challenge on the response of FEV₁ before and after 3 months of therapy (fluticasone 500 mg once a day).

mediators in upregulating the reactivity of TRPV1.

In humans, capsaicin is currently considered a TRPV1 agonist but its bronchoconstrictor effect is difficult to evaluate due to the simultaneous stimulation of severe cough interfering with the measurement of bronchial function (3, 4).

Ethanol triggers bronchoconstriction without cough and this effect seems related to the degree of inflammation. Therefore this observation could signify a step toward the potential use of ethanol as a further tool in the evaluation of bronchial reactivity specifically orientated to study the neurogenic inflammation induced by TRPV1 stimulation.

Obviously this speculation is questionable as the data were obtained for a single patient and were not placebo controlled.

In conclusion, topical anti-inflammatory therapy seems to reverse ethanol-induced bronchospasm.

Further studies will be necessary to confirm this suggestion and in particular

to determine both the provocation dose and the potential collocation of this bronchial challenge with respect to present broncho-stimulation agents (methacolin, adenosin, etc.).

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