

Ethanol metabolite acetic acid as causative agent for type-I hypersensitivity-like reactions to alcoholic beverages

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Summary

Background Adverse reactions to alcoholic beverages are common and more frequently mediated by immunological mechanisms than previously thought.

Objective To elucidate relevant allergens in this context we studied patients with an informative medical history.

Methods This report describes a comprehensive allergological approach in a patient exhibiting type-I hypersensitivity-like reactions towards beverages and medication containing alcohol, and salad dressings with acetic acid.

Results The ethanol metabolite acetic acid was found to yield positive prick test results in concentrations not eliciting reactions in healthy and atopic controls.

Conclusion Among other ethanol metabolites, acetic acid is a potential allergen in the context of hypersensitivity towards alcoholic beverages.

Keywords: ethanol, metabolism, acetic acid, hypersensitivity, angioedema

Clinical and Experimental Allergy, Vol. 26, pp. 1089–1091. Submitted 4 December 1995; revised 19 March 1996; accepted 24 April 1996.

Introduction

Reactions to alcoholic beverages are frequent and highly variable regarding the spectrum of symptoms. According to recent investigations, immunologic pathomechanisms seem to be involved more often than previously thought [1], although elucidation of the relevant allergen can be very difficult. Among the candidates are ethanol and its metabolites, and also food additives like preservatives and dyes, or — in the case of beer — cereals.

We report on a patient suffering from conjunctivitis, angioedema, dyspnoea and urticarial rashes within minutes after ingestion of alcoholic beverages, for which the ethanol metabolite acetic acid was demonstrated to be the causative agent.

Case report

Since 1988 this 68-year-old Caucasian female patient suffered numerous episodes of conjunctivitis, swelling of the tongue and lips, dyspnoea and an urticarial rash. These symptoms occurred 5 to 15 min after ingestion of

even minor amounts of beer, wine or other alcoholic beverages. More recently she observed similar signs when taking medication containing ethanol (Sinupret^R liquid) or after eating salads with dressings containing acetic acid. All symptoms resolved spontaneously within several hours. Other than this the patient did not recall any further allergic reactions; she has a negative history for atopy.

Clinical investigation revealed a white dermographism, the patient's serum IgE was elevated to 327 U/ml (normal: <150 U/ml). A standardized skin prick test (Bencard, Worthing, UK) was negative for several seasonal and perennial inhalative allergens and nutritives, specifically meat, fish, crustaceans, fruits, vegetables and nuts. Moreover, prick tests of relevant cereals (malt, barley, rice, rye, wheat) as well as hop and brewer's yeast, along with food preservatives (sodium salicylate 5%, hydroxybenzoic acid 1%; both diluted in distilled water and in pharmaceutical quality) and tartrazine were negative; so were similar tests with several brands of beer and red and white wine (all of them tested in native form). To test whether ethanol or its metabolites might be the relevant allergens, the respective prick tests were performed. Ethanol, as well as acetaldehyde, yielded negative results, whereas acetic

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Table 1. Outcome of the allergologic tests focusing on potential allergens in alcoholic beverages. Prick tests were carried out according to the EAACI guidelines. Test solutions for brewer's yeast and cereals were purchased from Bencard (Worthing, UK); alcoholic beverages were tested in native form; all other substances were diluted in distilled water. Oral challenge was done with the substances moulded into gelatine capsules; in the case of ethanol a 0.96% solution was prepared by dilution in a 5% glucose solution (Glukose 5 Braun^R, Melsungen)

Mode	Substance	Result
Skin prick	Preservatives*	Neg.
	Tartrazine	Neg.
	Brewer's yeast	Neg.
	Cereals	Neg.
	Ethanol 96%	Neg.
	Ethanol 9.6%	Neg.
	Acetaldehyde 100%	Neg.
	Acetic acid 9.6%	++
	Acetic acid 1.2%	+
	Acetic acid 0.6%	Neg.
	Beer	Neg.
	Light beer	Neg.
	White wine	Neg.
	Red wine	Neg.
Oral challenge	Preservatives†	Neg.
	Tartrazine‡	Neg.
	Ethanol 0.96%	Pos.§

* Including sodium salicylate 5% and hydroxybenzoic acid 1%.

† Including 500 mg sodium salicylate and 500 mg hydroxybenzoic acid.

‡ 100 mg tartrazine.

§ Conjunctivitis, swelling of lips and tongue, dyspnoea, urticarial rash.

acid diluted in 0.9% NaCl was positive in concentrations ranging from 9.6% to 1.2%. To exclude the possibility of an irritative effect the respective concentrations were tested in five healthy volunteers along with five atopic patients. None of these controls exhibited a positive reaction. All prick tests were carried out and interpreted according to the EAACI guidelines [2]. RAST analyses were performed for IgE- and IgG-antibodies directed against acetic acid (Dr H. Schwertner, ITMC, Marburg/Germany) but yielded negative results. Oral challenge with food preservatives (500 mg sodium salicylate, 500 mg hydroxybenzoic acid) and 100 mg tartrazine did not result in any reactions. In contrast, 5 min after ingestion of 1 ml 96% ethanol in 9 ml of a 5% glucose solution the patient developed conjunctivitis, swelling of the lips and tongue, dyspnoea and an urticarial rash. All symptoms resolved spontaneously within 30 min.

Discussion

The patient described here developed symptoms of type I hypersensitivity within minutes after ingestion of ethanol. This clinical condition, observed during oral challenge, resembled the one described by the patient after consumption of alcoholic beverages, medication in liquid form, and salads with certain dressings. The ethanol metabolite acetic acid is likely to be the causative agent of these symptoms, as demonstrated by further skin prick tests with acetic acid in non-irritative concentrations being the sole substance yielding positive test reactions. Failure to demonstrate IgE- or IgG-antibodies directed towards acetic acid is not too surprising given the small size of this molecule and the problems arising with regard to linkage.

Also from a clinical point of view acetic acid is a likely candidate as the allergen in this patient. Ethanol, which is present in the beverages and medication triggering the patient's symptoms, gets metabolized into acetic acid within minutes after consumption [3]. Moreover, this metabolite is already abundant in wine (up to 1.2 g/L are tolerable according to German food law) and the relevant salad dressings. Considering the different agents causing the patient's symptoms, both exogenous acetic acid already present in wine and salad dressings, as well as endogenous acetic acid produced during digestion, seem to contribute to the type-I reaction.

Adverse reactions to food are common and can be classified into toxic and non-toxic reactions; the latter are further divided based on their pathogenetic mechanism into immune-mediated and non-immune-mediated reactions [4]. Among non-toxic reactions to food, those caused by alcoholic beverages more often fall into the category of non-immune-mediated intolerance rather than true food allergy; the latter can be of type I as well as type IV [1]. In cases of allergic reactions the repertoire of potential allergens ranges from ethanol itself [1,5,6] to cereals [7,8] and metabolites of ethanol, particularly acetaldehyde and acetic acid [9]. Impurities or food additives such as preservatives or dyes have also to be considered [10,11]. The exact determination of the relevant allergen is often very difficult [12].

Compared to hypersensitivity to ethanol, allergic reactions to its metabolites are rare and the patient reported here is one of only a few cases where an allergic reaction to acetic acid has been established as very likely, although not formally proven [9]. Due to its size acetic acid itself is unlikely to function directly as an antigen. A role as hapten seems to be more feasible in the explanation for allergic reactions to this substance.

To summarize, we report here on a patient showing type-I hypersensitivity-like reactions following ingestion

of alcoholic beverages, medication containing ethanol, and salad dressings with acetic acid. Based on the patient's history, as well as the results of our allergological tests, acetic acid is the likely causative agent for these reactions. This report underlines the necessity to keep acetic acid in mind as a potential allergen in the context of hypersensitivity towards alcoholic beverages.

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