

No correlation between wine intolerance and histamine content of wine

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Background: Histamine is thought to be the main cause of adverse reactions to wines.

Objective: The purpose of this study was to test the hypothesis that the level of histamine in wine affects the tolerance to wine in 16 subjects with wine intolerance.

Methods: We performed a study to examine the effects of wine histamine content in 16 adults with wine intolerance. Each subject underwent 2 double-blind provocation tests with wine: 1 with a wine poor in histamine (0.4 mg/L), and 1 with a wine rich in histamine (13.8 mg/L). Blood was collected for histamine and methylhistamine RIAs at 0, 10, 30, and 45 minutes after ingestion of the wine. Methylhistamine and methylimidazolacetic acid (gas chromatography and mass spectrometry) were measured in urine 5 hours before and 5 hours after ingestion.

Results: No significant differences in the occurrence of adverse reactions were noted after ingestion of either of the wines (McNemar test). At 10 minutes, a significant increase was observed in plasma histamine with histamine-poor wine. No significant changes (Wilcoxon test) were observed in the methylhistamine and methylimidazolacetic acid levels after ingestion of either histamine-poor or histamine-rich wine.

Conclusion: This study demonstrates that there is no correlation between the histamine content of wine and wine intolerance. The increase of plasma histamine levels at 10 minutes with histamine-poor wine suggested the role of a histamine-releasing substance. The role of acetaldehyde is discussed. (*J Allergy Clin Immunol* 2001;107:375-8.)

Key words: Adverse food reactions, histamine, wine, biogenic amines, double-blind food challenge test

The histamine content of certain foods, especially fish of the scombroid family, has been incriminated in food intoxication reactions.¹ Histamine is present in the cytoplasmic granules of normal mast cells and is involved in the mechanism of immediate hypersensitivity when liberated from

Abbreviations used

MH: Methylhistamine

MIAA: Methylimidazolacetic acid

these cells in the course of an IgE antibody-dependent reaction. Some individuals appear to be abnormally sensitive to histamine absorbed from foods through the intestinal tract, and they may have a pseudoallergic food reaction.²⁻⁴ Some people report that they have adverse reactions when they drink wine.⁵ The frequency of wine intolerance is estimated at 0.2% in the French population.⁶ The symptoms most often reported by these individuals are flushing of the face, headache, nasal congestion, and/or respiratory distress.⁷⁻⁹ In addition, wine is frequently cited as a triggering factor by persons who have migraine headaches.^{10,11} Biogenic amines in wine, principally histamine,¹² are considered to be the main cause of these adverse effects.⁹ It has been postulated that the histamine contained in certain wines can cross the intestinal barrier and increase the plasma histamine level.¹³ Up to the present time, there have been few studies relating the histamine content of wine to the induction of an adverse reaction,¹³⁻¹⁵ and the probability of biogenic amines present in wine altering histamine metabolism has not been tested. Previously, we demonstrated that wine histamine content did not affect the tolerance of wine in healthy subjects.¹⁶

The aims of this study were to test the hypothesis that the level of histamine and other biogenic amines in wine would affect the tolerance to wine in 16 subjects with wine intolerance and to analyze the metabolism of histamine after ingestion of wine. The effects of 2 types of wine were compared: one of the test wines contained a low amount of histamine (0.4 mg/L), and the other had a high level of histamine (13.8 mg/L).

METHODS

Selection of the test wines

Two samples of wines (pinot noir), one containing a low amount of histamine (0.4 mg/L) (wine A) and the other naturally containing a high level of histamine (13.8 mg/L) (wine B), were selected. The degree of alcohol in the test wines was 13.3% vol/vol. The amount of sulfites was 90 mg/L for wine A and 65 mg/L for wine B. The concentration of biogenic amines, as determined by HPLC, is shown in Table I. As usually observed, the level of other biogenic amines varies with the histamine level.^{12,17}

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TABLE I. Concentration of biogenic amines in wine A and wine B determined by HPLC

Biogenic amines	Wine A (mg/L)	Wine B (mg/L)
Histamine	0.4	13.8
Tyramine	2.4	9.0
Putrescine	12.1	61.0
Methylamine	0.1	0.6
Ethylamine	1.1	3.1
Phenylethylamine	0.6	0.9
Isoamylamine	0.5	1.8
Cadaverine	0.5	0.6

TABLE II. Clinical symptoms after ingestion of wine A and wine B

Symptom	Wine A	Wine B
Increased heart rate (≥ 8 bpm)	7	3
Decreased blood pressure (≥ 10 mm/Hg in systolic and diastolic pressure)	7	4
Facial flushing	5	5
Urticaria	1	2
Headache	3	2
Gastrointestinal symptoms (nausea, epigastralgia)	2	4

TABLE III. Urinary MH and MIAA before and after wine A and wine B

	Wine A		Wine B	
	Before	After	Before	After
MH ($\mu\text{mol/mol}$ creatinine)	166 $\pm$ 82	194 $\pm$ 113	137 $\pm$ 78	149 $\pm$ 73
MIAA (mmol/mol creatinine)	8.3 $\pm$ 12	2.9 $\pm$ 2.6	3.4 $\pm$ 4.7	4.1 $\pm$ 3.3

Selection of the patients

Sixteen adults were selected in our department of internal medicine, allergology, and clinical immunology. They had chronic urticaria and reported wine intolerance. Eleven women and 5 men (aged 43 ± 13 years) were included in this study. Intolerance to sulfites was excluded on the history, restricting the clinical manifestations to wines and not to other sulfite-containing foods. None of the patients had asthma.^{18,19}

A previously published double-blind study with a histamine-rich wine versus a histamine-free wine in 8 healthy subjects demonstrated that histamine content did not influence the tolerance of wine in 8 healthy subjects. None of the subjects had an adverse reaction, and no significant changes were observed in the histamine and metabolite levels after ingestion of either histamine-free or histamine-rich wine.¹⁶

Protocol

Each subject underwent 2 blind provocation tests with wine: 1 with the wine poor in histamine, and 1 with the wine rich in histamine. The subjects drank 190 mL of wine at 12:30 PM after a 5-hour fast. Breakfast was taken at 7:30 AM and consisted of a cup of black coffee with a piece of bread and butter. At 1:30 PM they ate a lunch low in histamine, which consisted of a green salad, potatoes, a hamburger, cream cheese, and water. The subjects were closely monitored throughout the afternoon. Test A and test B were separated by at least 1 day for all subjects.

Assay of histamine and methylhistamine

Blood samples were obtained from each subject immediately before drinking the test wines (baseline) and at 10, 30, and 45 minutes after ingestion for measurement of plasma histamine and methylhistamine (MH) concentrations. Urine was collected 5 hours before and again 5 hours after ingestion of the wines for MH and methylimidazolacetic acid (MIAA) assay. Plasma histamine levels were determined by a radioimmunologic method (Immunotech, Marseille, France).²⁰ MH was also assayed with a radioimmunologic method (Pharmacia, Uppsala, Sweden).²¹ MIAA was measured by gas chromatography and mass spectrometry.²²

Statistical analysis

Comparisons between test groups A and B were made with the McNemar test for clinical symptoms and the nonparametric Wilcoxon test for biologic values (histamine, MH, MIAA). The level of significance was set at 5%. The analyses were made with the BMPD program.²³

RESULTS

Adverse reactions were noted after ingestion of each wine (Table II). Symptoms of wine intolerance occurred for 14 subjects who drank histamine-rich wine and for 15 subjects who drank histamine-poor wine. Symptoms consisted of slight cardiovascular changes occurring during the first half hour. Facial flushing occurred early during the first 15 minutes. Urticaria and/or headache appeared during a time varying from 1 to 5 hours after ingestion of wine. Gastrointestinal symptoms were represented mainly by nausea occurring between 5 minutes and 2 hours after the ingestion of wine. No respiratory symptoms or changes in expiratory peak flow were noted. Comparison of symptoms occurring after ingestion of each wine did not reveal any significant difference (McNemar test).

The baseline level of plasma histamine was not statistically different (nonparametric Wilcoxon test): 4.95 ± 1.00 nm/L for wine A and 6.45 ± 1.99 nm/L for wine B. At 10 minutes an increase in plasma histamine was noted with histamine-poor wine (Fig 1). At this time, the plasma level of histamine was significantly higher after the challenge test with histamine-poor wine A (6.36 ± 1.30 nm/L) than with histamine-rich wine B (3.43 ± 0.58 nm/L) ($P < .05$).

The baseline plasma level of MH before ingestion of the 2 wines was not statistically different: 5.32 ± 0.61 nm/L for wine A and 5.28 ± 0.76 nm/L for wine B. There was no significant difference in the kinetics of the plasma MH concentration after the ingestion of histamine-poor wine and histamine-rich wine (Fig 2). The plasma level of MH remained stable after ingestion of each wine.

Urinary MH and MIAA levels remained stable. There was no significant change when we compared their levels before and 5 hours after ingestion of each wine (Table III).

DISCUSSION

The intestines have effective defense mechanisms that prevent the absorption of ingested histamine.²⁴ A normal

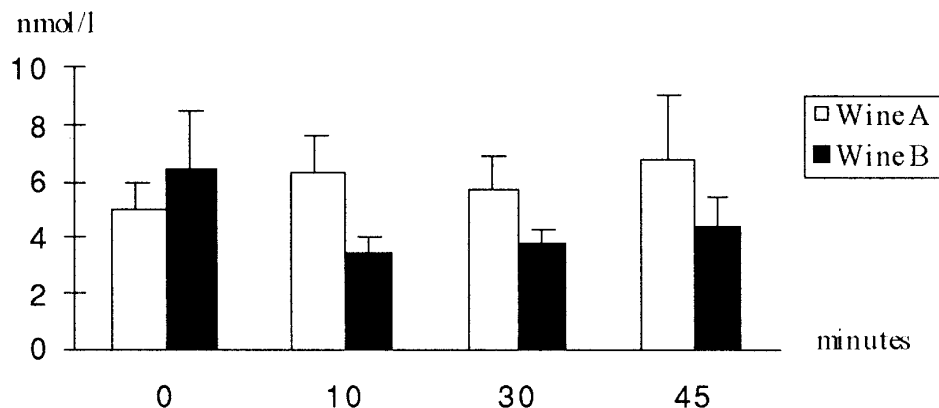


FIG 1. Variation of plasma histamine during double-blind challenge test with wine poor in histamine (wine A) and wine rich in histamine (wine B).

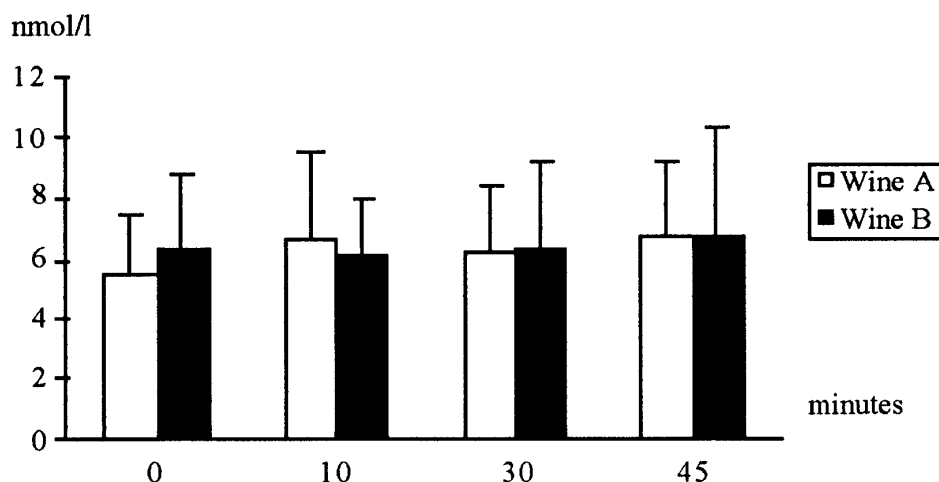


FIG 2. Variation of plasma MH during double-blind challenge test with wine poor in histamine (wine A) and wine rich in histamine (wine B).

individual can tolerate 120 mg of histamine taken orally, whereas as little as 7 μ g of histamine given intravenously is sufficient to induce symptoms.^{25,26} The initial barriers opposing the absorption of histamine are mechanical and include the intestinal mucin layer and the closely linked epithelial cells. A second barrier is formed by intestinal enzymes, especially diamine oxidase, localized mainly in enterocytes and MH transferase.²⁷ Other biogenic amines that are likewise present in wine (tyramine, putrescine, and cadaverine) might favor the passage of histamine from the intestines into the systemic circulation by competing for binding sites in intestinal mucins or interfering with the catabolism of histamine by saturating the activity of diamine oxidase.

This double-blind study reveals that wine intolerance is not related to wine histamine content. The histamine content of wine seems insufficient to explain the occurrence of wine intolerance. It might be explained by differences in the quantity of other substances in the wines

studied, for example, other biogenic amines that could interfere with the histamine metabolism. However, histamine-rich wine also has a higher content of putrescine and other biogenic amines. This leads us to conclude that the biogenic amine content of wines does not explain the occurrence of adverse reactions with either wine. Moreover, with regard to the hypothesis of an exclusive role for ingested biogenic amines, it is surprising to note that certain fermented cheeses contain amounts of histamine that are very much greater than those found in wines, whereas signs typical of intolerance to histamine have rarely been reported after ingestion of cheeses.²⁸

The clinical findings and the results of this study argue in favor of the participation of a substance other than histamine or biogenic amines in the generation of adverse reactions to wines. The increase of plasma histamine at 10 minutes with histamine-poor wine could be explained by the presence in wine of a histamine-releasing substance. Wine is a complex product. Numerous substances might

be incriminated in wine intolerance. However, the role of acetaldehyde in wine intolerance was suggested in a study by Shimoda et al.²⁹ They showed that the ingestion of ethanol by persons with asthma is followed by an increase in the blood acetaldehyde and plasma histamine levels, and this increase is significantly higher in responders to the ethanol challenge with a decrease in FEV₁ greater than 20% than in nonresponders. Mizoi et al.³⁰ noted the same relationship between facial flushing and blood acetaldehyde levels after alcohol intake. Acetaldehyde has been shown to be a histamine releaser in subjects who are deficient in alcohol dehydrogenase.⁸ Acetaldehyde was found to induce histamine release in a volume-dependent manner.²⁹ Nonetheless, acetaldehyde dehydrogenase activity must be evaluated in subjects intolerant to wine but so also must the acetaldehyde content of wine. The variability of the acetaldehyde content of wines might explain why intolerant subjects react only with certain wines with quite similar alcohol contents.

In conclusion, this study does not argue in favor of the sole role of histamine in the induction of adverse reactions to wines. Further studies are needed to identify the relevant substances responsible for wine intolerance and to clearly define the way they act. The role of other histamine-releasing substances, such as acetaldehyde, in wine has to be studied.³¹

REFERENCES

- Morrow JD, Margolies GR, Rowland J, Roberts LJ. Evidence that histamine is the causative toxin of scombroid-fish poisoning. *N Engl J Med* 1991;324:716-20.
- Kanny G, Moneret-Vautrin DA, Schohn H, Feldman L, Mallie JP, Gueant JL. Abnormalities in histamine pharmacodynamics in chronic urticaria. *Clin Exp Allergy* 1993;23:1015-20.
- Kanny G, Grignon G, Dauca M, Guedenet JC, Moneret-Vautrin DA. Ultrastructural changes in the duodenal mucosa induced by ingested histamine in patients with chronic urticaria. *Allergy* 1996;51:935-9.
- Hermann K, Hertenberg B, Ring J. Measurement and characterization of histamine and methylhistamine in human urine under histamine-rich and histamine-poor diets. *Int Arch Allergy Immunol* 1993;101:13-9.
- Kanny G, Bauza T, Frémont S, Blaise A, Cabanis JC, Nicolas JP, et al. Les intolérances aux vins. Un modèle d'étude des fausses allergies alimentaires. *Rev Fr Allergol* 1997;37:381-6.
- Moneret-Vautrin DA, Kanny G, Thevenin F. A population study of food allergy in France: a survey concerning 33,110 individuals [abstract]. *J Allergy Clin Immunol* 1998;101:S87.
- Lowenberg DW, Ough CS, Lepkovsky S, Furuta FF. The effect of ethanol and wine on the plasma histamine level of chickens and man. *American Journal of Enology and Viticulture* 1981;32:128-31.
- Harada S, Agarwal DP. Aldehyde dehydrogenase deficiency as cause of facial flushing reaction to alcohol in Japanese. *Lancet* 1981;2:982.
- Bauza T, Kanny G, Blaise A, Teissedre PL, Daumas F, Moneret-Vautrin DA, et al. Les amines biogènes des vins: métabolisme et toxicité. *Bulletin de l'Office International de la Vigne et du Vin* 1995;767-8:42-67.
- Larmande P, Ligeard P, Maillot F, Belin C. Le déclenchement alimentaire des crises de migraine. *Méd Nutr* 1993;29:263-7.
- Littlewood JT, Glover V, Davies PTG, Gibb C, Sandler M, Rose FC. Red wine as a cause of migraine. *Lancet* 1988;1:558-9.
- Zee JA, Simard RE, L'Heureux L, Tremblay J. Biogenic amines in wines. *Am J Enol Vitic* 1983;34:6-9.
- Jarish R, Pirker C, Möslinger T, Götz M. The role of histamine in wine intolerance [abstract]. *J Allergy Clin Immunol* 1992;89:197.
- Wantke F, Götz M, Jarish R. The red wine provocation test intolerance to histamine as a model for food intolerance. *Allergy Proc* 1994;15:27-32.
- Wantke F, Goetz M, Jarisch R. The wine test: a simple method to verify intolerance to histamine as a model of food intolerance. *Allergologie* 1992;15:55-6.
- Kanny G, Bauza T, Frémont S, Guillemin F, Blaise A, Daumas F, et al. Histamine content does not influence the tolerance of wine in normal subjects. *Allerg Immunol (Paris)* 1999;31:45-8.
- Bauza T, Blaise A, Teissedre PL, Mestres JP, Cabanis JC. Teneurs en amines biogènes et facteurs de leurs variations dans les vins de côtes du Rhône, de la vallée du Rhône et de Provence. *Sci Aliments* 1995;15:367-80.
- Maria Y, Vaillant P, Delorme N, Moneret-Vautrin DA. Les accidents graves liés aux métabisulfites. *Rev Med Interne* 1989;10:36-40.
- Simon RA, Green L, Stevenson DD. The incidence of ingested metabisulfite sensitivity in an asthmatic population. *J Allergy Clin Immunol* 1982;69:A103.
- Morel A, Delaage M. Immunoanalysis of histamine through a novel chemical derivatization. *J Allergy Clin Immunol* 1988;92:646-54.
- Stephan V, Zimmerman A, Kuhr J, Urbanek R. Determination of *N*-methylhistamine in urine as an indicator of histamine release in immediate allergic reactions. *Clin Immunol* 1990;86:862-8.
- Khandelwal JK, Hough LB, Pazhenchevsky B, Morrisshow AM, Green JP. Presence and measurement of methylimidazoleacetic acids in brain and body fluids. *J Biol Chem* 1982;257:12815-9.
- BMDP. Statistical software 7.0. Los Angeles: John Wiley & Sons: Los Angeles; 1992.
- Neugebauer E, Lorenz W. Histamine in health and disease. *Behring Inst Mitt* 1981;68:102-33.
- Moneret-Vautrin DA. Biogenic amines. In: Somogyi JC, Müller HR, Ockhuisen T, editors. Food allergy and food intolerance. Basel, Switzerland: Bibl Nutr Dieta; 1991. p. 61-71.
- Mordelet-Dambrin, Parrot JL. Action de l'histamine introduite par voie buccale ou formée dans le tube digestif. *Méd Nutr* 1970;6:59-73.
- Hesterberg R, Sattler J, Lorenz W, Stahlknecht CD, Barth H, Crombach M, et al. Histamine content, diamine oxidase activity and histamine methyltransferase activity in human tissues: fact or fiction? *Agents Action* 1984;14:325-34.
- Chambers TL, Starvskiewicz WF. Fluorometric determination of histamine in cheese. *J Assoc Anal Chem* 1978;61:1092-7.
- Shimoda T, Kohno S, Takao A, Fujiwara C, Matsuse H, Sakai H, Watanabe T, et al. Investigation of the mechanism of alcohol-induced bronchial asthma. *J Allergy Clin Immunol* 1996;97:74-84.
- Mizoi Y, Ijiri I, Tatsuno Y, Kijima T, Fujiwara S, Adachi J. Relationship between facial flushing and blood acetaldehyde levels after alcohol intake. *Pharmacol Biochem Behav* 1979;10:303-11.
- Takao A, Shimoda T, Kohno S, Asai S, Harda S. Correlation between alcohol-induced asthma and acetaldehyde dehydrogenase-2 genotype. *J Allergy Clin Immunol* 1998;101:576-80.