The Red Wine Provocation Test: Intolerance to Histamine as a Model for Food Intolerance

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ABSTRACT

Sneezing, flush, headache, diarrhea, skin itch, and shortness of breath are symptoms occurring in patients intolerant to wine after drinking one glass of red wine. The role of histamine in wine intolerance was evaluated by a red wine provocation test in 28 patients with a history of wine intolerance and in 10 controls with good tolerance of wine. Patients were challenged with 125 ml red wine (equivalent to 50 μg histamine); blood samples were drawn before and after 15 and 30 minutes. Plasma histamine was assessed by a radioimmunoassay. Lung function tests were performed before and after the wine test. Twenty-two of twenty-eight patients had symptoms showing significantly higher plasma histamine levels 30 minutes after wine challenge ($p < .01$) compared with asymptomatic controls. Basal histamine levels of patients were higher ($p < .05$) than in controls. A slight asthmatic attack as well as a 30% decrease of FEF 25 was seen in 2/22 patients. Terfenadine premedication significantly eliminated symptoms in 10/12 patients ($p < .05$) in a subsequent wine test. Histamine assessment was done in 52 wines (red, white, and champagne) and in 17 beers by radioimmunoassay. Histamine levels ranged from 3–120 μg/l in white wines; 15–670 μg/l in champagnes; 60–3800 μg/l in red wines; and 21–305 μg/l in beers. Histamine is causing wine intolerance. Patients intolerant to wine seem to have diminished histamine degradation probably based on a deficiency of diamine oxidase. (Allergy Proc 15:27–32, 1994)

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Histamine is one of the most potent biological substances occurring in foods. Histamine affects the cardiovascular system by vasodilatation causing hypotension to cardiovascular shock and severe headache and induces vomiting and diarrhea as known in scombroidosis.[1]

In everyday life histamine occurs in cheese, fish, sausage, vegetables, and alcoholic beverages. Primarily in red wine, which often contains up to 10 mg of histamine per liter[2,3], a high incidence of intolerance reactions has been reported,[4] but the relevance of histamine has never been truly considered.

Adverse effects to red wine are found within a population showing negative allergy tests to food although reporting adverse reactions to histamine-rich food (e.g., fish, cheese).[5–9] Some patients show symptoms such as sneezing, flush, headache, diarrhea, or even shortness of breath after drinking red wine, although most white wines are tolerated well.

Histamine, ingested with various food, is catabolized by enteral diamine oxidase.[10] A deficiency of diamine oxidase may cause impaired histamine degradation as well as enhanced histamine uptake leading to increase in plasma histamine and typical symptoms in patients.[11]

The aim of the present study was to assess the role of histamine in wine intolerance as well as to establish a method to evaluate intolerance to histamine.

PATIENTS AND METHODS

Patients

Twenty-eight patients (22 female, 6 male; mean 40.4 years, range 19–63 years) with suspected wine in-

tolerance reporting symptoms such as sneezing, flush, headache, itching of the skin, or diarrhea were tested. Skin-prick testing (ALK, Copenhagen, Denmark) and specific IgE (Auto CAP System, Pharmacia, Uppsala, Sweden) to food allergens were done throughout, but were negative.[13] Four patients were atopics. Two of them showed allergy to animal epithelias, one had birch and hazel pollen allergic rhinitis, and one had atopic dermatitis. Total IgE level was 99 kU/l mean (range: 4–1000 kU/l). No medication (i.e., terfenadine) was allowed within 7 days before the wine test.

Ten healthy volunteers (5 female, 5 male; mean: 35.1 years, range: 20–68 years) with negative skin-prick test (ALK, Copenhagen, Denmark) and negative case history to food allergens served as controls.

The test was performed in fasting probands during the morning hours (8:30 a.m.-11:30 a.m.).

Test Substance

One particular Austrian red wine was used in testing throughout. The histamine content was 400 ± 10 μg/l; the sulfite content was 75 mg/l total SO_2 (30 mg/l free SO_2).

Test Procedure

After baseline lung function test (Jaeger Pneumoscope®, Würzburg, Germany) to evaluate FEV 1, FEF 50 and FEF 25 blood was drawn to evaluate basal histamine levels. In order to provide security for the probands, patients showing FEV 1 below 70% were excluded from testing. Within 10 minutes each patient had to drink 125 ml of red wine (equivalent to 50 μg histamine, wine temperature: 20°C). Fifteen and 30 minutes after the start of the test second and third blood samples were taken, respectively. Five minutes after the third blood sample, a second lung function test was done.

Each blood sample was taken without tourniquet separately from the cubital vein using a needle with a diameter of 1.2 mm. In histamine free EDTA tubes (EDTA K_3 0.054 ml, 0.34 M) 3 ml blood was collected and immediately stored in ice water (4°C). Blood was centrifuged for 10 minutes at 2500 rpm and 4°C. Five hundred μl supernatant of each sample was put in polypropylene tubes and stored at −30°C.

Antihistamine Premedication

Twelve patients (9 female, 3 male; mean 47.3 years, range 22–63 years) showing symptoms in their first wine test repeated the test with antihistamine premedication. Each patient took one tablet of terfenadine 60 mg 2 hours before wine intake. The same test procedure was performed.

Symptom Score

Symptoms in patients were assessed at 15 and 30 minutes.

Objective symptoms:

flush:

- \+ redness of face
- ++ redness of face and feeling of warmth
- +++ massive redness of face and feeling of heat

sneezing

flow of tears

lung function:

a decrease of FEV 1 by more than 20% or a decrease of FEF 50 or FEF 25 by more than 30% were scored as symptom.

Subjective symptoms:

itching

headache

weariness:

- \+ slight
- ++ severe
- +++ somnolence

To prevent scoring possible alcohol induced flush or weariness as reaction to histamine these two symptoms were not scored in their mildest category of severity (+).

Histamine Assessment in Plasma

Histamine assessment was done in double assay using a radioimmunoassay (Immunotech Kit #1302; Marseille, France).[10]

Histamine Assessment in Wine and Beer

Fifty-two different, mainly Austrian wines [red wines (n = 19), including an Italian Chianti and a French Bordeaux), white wines (n = 22), rosé wines (n = 3), dessert wines (n = 3), champagne (n = 1; France), and sparkling wines (n = 4)] as well as 17 different, mainly Austrian beers [wheat beers (n = 2), draught beers (n = 11; including American Budweiser, Czechoslovakian Budweiser and Chinese Tsingtao) and beers free of alcohol (n = 4)] were assessed.

Wines and beers were filtered and CO_2 was extracted by shaking a 5 ml sample 30 minutes at room temperature. One milliliter wine was mixed with NaOH O.1 N to obtain pH 7, measured by indicator sticks (Neutralit® pH 5–10, Merck, Darmstadt). To reach the sensitivity range of the radioimmunoassay (0.02–10 ng histamine/ml at pH 6.0–8.0),[13] the samples had to be diluted with distilled water. For white wines, sparkling wines, and beers the standard solution was diluted 1:9 and consecutively diluted 1:1 twice, for red wines, dessert wines and champagne the standard solution was diluted 1:49 and consecutively diluted 1:1 three times.

Histamine assessment was done in double assay using a radioimmunoassay (Immunotech Kit #1302; Marseille, France).[13]

To assess the accuracy of the histamine radioimmunoassay for wine, a series of three identical white wine samples was additionally assessed in two different laboratories by two slightly modified HPLC methods using fluorimetric detection after derivatization with orthophtal dialdehyde. Histamine (histamine hydrochloride, Merck, Darmstadt) was added to wine sample two (+0.1 mg/l) and wine sample 3 (+0.26 mg/l); wine sample one did not contain additional histamine.

Statistical Analysis

Statistical analysis was carried out using the matched t-test and pooled t-test to compare histamine levels of patients and controls and the sign test to compare the results of antihistamine premedication.

RESULTS

Wine Provocation Test

Twenty-two of twenty-eight patients with suspected wine intolerance reacted positively in the wine test, 6/28 did not react. (Table I) Ten of ten controls remained symptomfree.

Basal histamine levels in the symptomatic patient group were significantly ($p < .05$) higher compared to controls. Thirty minutes after wine challenge, plasma histamine levels in patients showing symptoms were significantly higher ($p < .01$) compared to controls. (Fig. 1)

In patients showing symptoms, mean plasma histamine increased continuously from 0.20 ± 0.10 ng/ml basal level to a maximum level of 0.25 ± 0.15 ng/ml at 30 minutes. However changes in plasma histamine did not reach statistical significance. In contrast controls showed a slight increase in plasma histamine at 15 minutes followed by a decrease to basal level at 30 minutes. (Fig. 1 and Table I)

Terfenadine premedication significantly eliminated symptoms in 10/12 patients ($p < .05$) in a second wine test. (Fig. 2 and Table II)

One female patient had a slight asthma attack 10 minutes after the end of her wine test, which improved after fenoterol hydrobromide and ipratropiumbromide. One female patient showed a decrease in FEF 25 of more than 30% after the wine test, which could be eliminated by terfenadine premedication in a second wine test.

Except for two patients, no changes in the lung function tests were observed after drinking red wine, neither in patients nor in controls. (Table III)

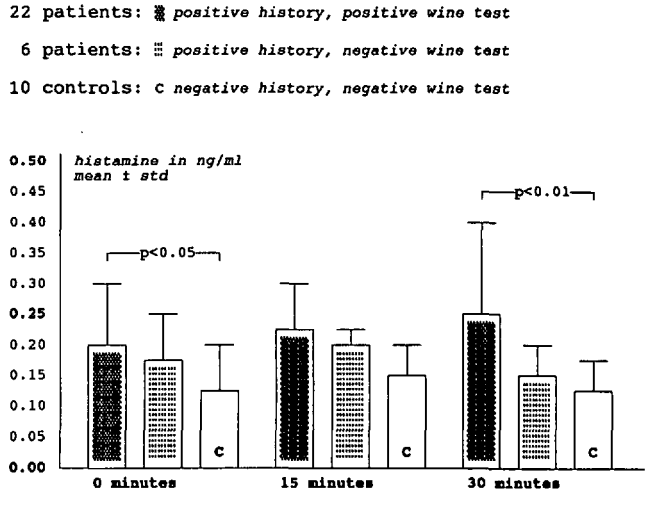
Histamine Content in Wine and Beer

The recovery rate of low amounts of histamine added to wine samples was found to be 70%/81% for

TABLE I

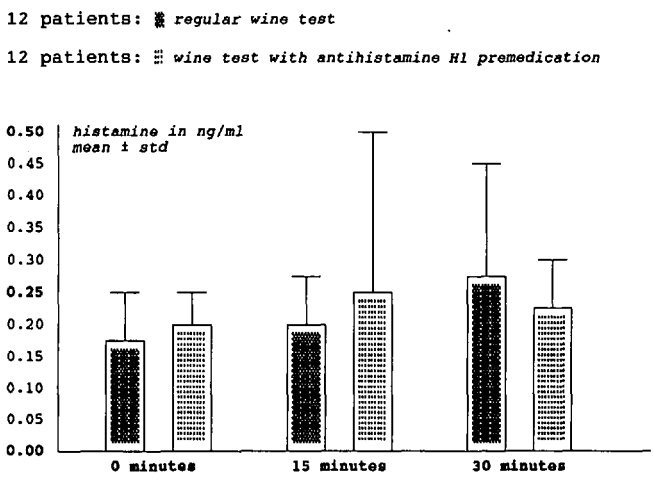
Symptoms in 28 Patients with a History of Wine Intolerance

Positive Wine Test 22 Patients	15 Min 1+	15 Min 2+	15 Min 3+	30 Min 1+	30 Min 2+	30 Min 3+
Objective findings.						
Flush	6	9	3	8	8	4
Sneezing	3			4		
Flow of tears	2			1		
Subjective symptoms.						
Itching	8			7		
Headache	4			5		
Weariness	9	1	1	7	2	1
Additional findings.						
Asthma				1		
Decrease of FEF 25 >30%				1		
Diarrhea				1		
Additional symptoms.						
Palatial swelling	1			1		
Negative Wine Test 6 patients	**15 Min 1+**	**15 Min 2+**	**15 Min 3+**	**30 Min 1+**	**30 Min 2+**	**30 Min 3+**
Objective findings.						
Flush	1			1		
Subjective symptoms.						
Weariness	2			2		



WINE TEST	0 minutes	15 minutes	30 minutes
patients ▩	0.20 ± 0.10 ng/ml	0.22 ± 0.09 ng/ml	0.25 ± 0.15 ng/ml
range	0.06 - 0.42 ng/ml	0.04 - 0.41 ng/ml	0.08 - 0.78 ng/ml
patients ⁞⁞	0.18 ± 0.08 ng/ml	0.18 ± 0.04 ng/ml	0.16 ± 0.04 ng/ml
range	0.05 - 0.27 ng/ml	0.12 - 0.24 ng/ml	0.10 - 0.22 ng/ml
controls C	0.12 ± 0.07 ng/ml	0.15 ± 0.05 ng/ml	0.12 ± 0.05 ng/ml
range	0.01 - 0.23 ng/ml	0.08 - 0.22 ng/ml	0.04 - 0.18 ng/ml

Figure 1. *Plasma histamine levels before and after red wine provocation.*



WINE TEST	0 minutes	15 minutes	30 minutes
regular ▩	0.17 ± 0.08 ng/ml	0.19 ± 0.08 ng/ml	0.27 ± 0.19 ng/ml
range	0.06 - 0.36 ng/ml	0.04 - 0.38 ng/ml	0.08 - 0.78 ng/ml
H1 blocker ⁞⁞⁞	0.20 ± 0.06 ng/ml	0.26 ± 0.21 ng/ml	0.22 ± 0.09 ng/ml
range	0.13 - 0.31 ng/ml	0.08 - 0.85 ng/ml	0.10 - 0.43 ng/ml

Figure 2. Red wine provocation after antihistamine premedication.

HPLC method (laboratory in Germany), 90%/92% for HPLC method (laboratory in Switzerland) and 103%/99% for the radioimmunoassay used in our laboratory.

Results of Wine Assessment (Table IV)

DISCUSSION

Primarily women report symptoms such as sneezing, flush, headache, itching, and even shortness of breath immediately after drinking a glass of red wine. These symptoms are also reported after drinking beer or after ingestion of food rich in histamine,[7-9] but allergy tests to food allergens are almost always negative.[7-12] The histamine content in wines and beers as shown by us and in food varies considerably.[2,3] Histamine in wine is an indicator for hygienic wine making, because histamine is believed to be produced by bacteria during the catabolism of malic acid to lactic acid.[14] Histamine producing bacteria have their growth opti-

TABLE II

Red Wine Provocation after Antihistamine Premedication: 10/12 Patients Remain Symptom-free ($p < .05$)

Wine Test	Regular Test			+H1 Blocker Premedication		
15 minutes	1+	2+	3+	1+	2+	3+
Objective Findings.						
Flush	2	4	1	4		
Sneezing	1					
Flow of tears	2					
Subjective Symptoms.						
Itching	4					
Headache	1					
Weariness	3					
30 minutes	**1+**	**2+**	**3+**	**1+**	**2+**	**3+**
Objective Findings.						
Flush	3	4	1	2		
Sneezing	2					
Flow of tears	1					
Subjective Symptoms.						
Headache	2					
Itching	5					
Weariness	4	1				
Additional Findings.						
Decrease of FEF 25 >30%	1					
Diarrhea	1					

TABLE III

FEV 1, FEF 50, and FEF 25 Before and After Red Wine Provocation

Lung Function Test	Before Provocation	After Provocation
Symptomatic patients (n = 22)		
FEV 1	91% ± 11%	90% ± 12%
FEF 50	86% ± 21%	84% ± 19%
FEF 25	78% ± 20%	77% ± 23%
Asymptomatic patients (n = 6)		
FEV 1	87% ± 6%	87% ± 5%
FEF 50	84% ± 28%	89% ± 30%
FEF 25	87% ± 14%	73% ± 19%
Controls (n = 10)		
FEV 1	93% ± 13%	96% ± 14%
FEF 50	103% ± 33%	100% ± 31%
FEF 25	83% ± 21%	84% ± 19%

TABLE IV

Histamine Content in Wine and Beer

Histamine in Red Wine	
Maximum	3800 μg/l
Mean (n = 19)	1010 μg/l
Minimum	60 μg/l
Bordeaux France	2200 μg/l
Chianti Italy	1930 μg/l
Histamine in Champagne	
Pommery (n = 1) France	670 μg/l
Histamine in Dessert Wine	
Maximum	400 μg/l
Mean (n = 3)	280 μg/l
Minimum	80 μg/l
Histamine in Wheat Beer	
Maximum	305 μg/l
Mean (n = 2)	211 μg/l
Minimum	117 μg/l
Histamine in Sparkling Wine	
Maximum	78 μg/l
Mean (n = 4)	46 μg/l
Minimum	15 μg/l
Histamine in Rosé Wine	
Maximum	61 μg/l
Mean (n = 3)	40 μg/l
Minimum	15 μg/l
Histamine in White Wine	
Maximum	120 μg/l
Mean (n = 22)	37 μg/l
Minimum	3 μg/l
Histamine in Beer	
Maximum	52 μg/l
Mean (n = 11)	32 μg/l
Minimum	21 μg/l
Budweiser USA	28 μg/l
Budweiser CSFR	26 μg/l
Tsingtao China	21 μg/l
Histamine in Beer Free of Alcohol	
Maximum	38 μg/l
Mean (n = 4)	26 μg/l
Minimum	15 μg/l

mum at pH ≥3.60, therefore white wines having low pH levels contain almost no histamine.

Among the multitude of substances occurring in wine[4] sulfite[4,15] and histamine[7–9,16] are established to cause wine intolerance and red wine asthma.[15] Only a few reports exist on allergic reactions to alcohol and wine itself,[15,17,18] indicating mainly non-allergic intolerance reactions.

Sulfite is considered to cause red wine intolerance,[4,15] although red wine contains much less sulfite than does white wine. The mean sulfite levels of Austrian wines are 75 mg/l SO_2 for red wine and 100 mg/l SO_2 for white wine. Our patients however did not report white wine intolerance. Sulfite is capable of elevating plasma histamine levels in patients with recurrent anaphylaxis and mastocytosis.[19] Atopics show sulfite-induced red wine intolerance mainly during the pollen season, but the same patients tolerate wine outside the pollen season.[15] Sulfite causes symptoms only during a period of enhanced histamine sensitivity, therefore histamine may be involved in the pathomechanism of sulfite hypersensitivity.

Orally ingested histamine is catabolized by enteral diaminoxidase the main enzyme metabolizing histamine in the gut.[10,11] Diamine oxidase is inhibited competitively by alcohol and biogenic amines such as tyramin also occurring in wine.[11] Inhibition of diamine oxidase increases enteral histamine uptake leading to enhanced plasma histamine levels and additional inhibition of N-methyltransferase by histamine metabolites.[11] Women have lower levels of diamine oxidase than do men, possibly explaining the high incidence of wine intolerance in women.[20]

Our data indicate enteral histamine uptake in both patients and controls already after drinking 125 ml red wine containing only 50 μg histamine. In patients showing symptoms after challenge we could observe a continuous increase in plasma histamine reaching a mean elevation of 0.05 ng/ml histamine above baseline level. Despite the small mean increase in plasma histamine, symptoms were observed making it likely that our patients reacted even to small changes in blood histamine. However, the significantly higher basal histamine levels in patients may already indicate their tendency for histamine intolerance.

According to the relatively low amount of histamine in our wine used for provocation, changes in plasma histamine seem to be of clinical relevance as a good correlation of increase in plasma histamine and symptoms was observed in five patients showing the strongest symptoms such as asthma, sneezing, and itching. In addition, most patients reported that symptoms caused by our red wine challenge were quite weak compared to symptoms experienced after drinking other red wines.

In contrast, controls and patients who did not react in the test showed a slight increase in plasma histamine at 15 minutes with a decrease to basal level at 30 minutes. This decrease indicates effective activity of histamine degrading enzymes. The remarkable difference in patients is observed in histamine degradation which does not take place within 30 minutes indicating a lack of enzymatic activity.

Plasma histamine levels may even rise after 30 minutes and cause late onset of symptoms such as diarrhea.

Enteral histamine uptake does not induce histamine release from mast cells.[1,21]

Levels and activity of diamine oxidase seem to be the key to wine intolerance. In patients intolerant to wine we assume a diminished histamine degradation based on a deficiency of diamine oxidase. Inhibition of already reduced levels of diamine oxidase would cause enhanced enteral histamine uptake and symptoms in these sensitive patients even after oral ingestion of small amounts of histamine, which are well tolerated by healthy persons.

Enteral diamine oxidase as first barrier against oral histamine is of main importance for the effective histamine catabolism. Experimental inhibition of diamine oxidase and food challenge with commercially available cheese and wine in pigs induced anaphylactic reactions in each animal and death in one-fifth of the pigs.[11] Inhibition of diamine oxidase additionally impairs the histamine catabolism of N-methyltransferase by histamine metabolites.[11] A first slight evidence for reduced diamine oxidase levels has already been observed in atopics and patients suffering from recurrent urticaria.[22,23]

Although this is an open study, symptoms of wine intolerance could be significantly eliminated in patients pretreated with terfenadine strongly suggesting evidence that histamine is causing wine intolerance.

The wine test thus may be a method to verify intolerance to histamine and may be useful for diagnosing patients with food intolerance.

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