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Wine and Headache

Key Words

Histamine intolerance
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Histamine in wine

Abstract

Headache can be induced by histamine in wine in patients suffering from histamine intolerance, a disease characterized by impaired histamine degradation based on reduced diamine oxidase activity or a lack of the enzyme. Diamine oxidase is localized in the jejunal mucosa and is the most important enzyme metabolising histamine. It is competitively inhibited by alcohol and numerous drugs. In preliminary investigations, assessment of diamine oxidase levels gave decreased activity (0.03 nKat/l) in patients with histamine intolerance compared to healthy controls (0.07 nKat/l). In pregnancy, diamine oxidase levels are known to be about 500-fold elevated, giving mean levels of 25.0 nKat/l. Other biogenic amines such as phenylethylamine or serotonin may be causative for wine/food-induced headache. In experimental models, headache has been induced by histamine infusion as well as red wine provocation. Histamine-induced headache is a vascular headache likely to be caused by nitric oxide which probably represents a key molecule in vascular headaches. A histamine-free diet is the treatment of choice for patients with histamine intolerance and chronic headache. To start treatment, an antihistamine (H1 blocker) for 14 days as well as a histamine-free diet for at least 4 weeks are recommended. Clinical improvement to the diet as well as in vitro tests for plasma histamine and diamine oxidase in the serum as well as vitamin B₆ levels have to confirm the diagnosis. As supportive treatment, a vitamin B₆ (pyridoxal phosphate) substitution appears useful in histamine-intolerant patients as pyridoxal phosphate seems to be crucial for diamine oxidase activity. Histamine intolerance, based on reduced diamine oxidase activity or a lack in the enzyme is causative for wine/food-induced chronic headache. According to the localization of diamine oxidase in the jejunal mucosa, histamine intolerance is primarily a disease of intestinal origin. A histamine-free diet is the treatment of choice in histamine-intolerant patients suffering from chronic headache. In addition, it is also important to avoid diamine-oxidase-blocking drugs and alcohol which act as inhibitors of diamine oxidase. As avoidance of histamine-rich food is a simple, inexpensive and harmless treatment, histamine-containing food such as cheese and alcoholic beverages should be labeled.

Introduction

Headache is a multifactorial symptom causing numerous consultations at the general practitioner and prescriptions of medication. Subsequently, patients are checked at neuro-

logists, orthopedists and radiologists. However, the often negative results of expensive diagnostic procedures such as computed tomography or magnetic resonance tomography must not indicate that the otherwise healthy patient has no somatic substrate for his/her headache. As histamine is

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Table 1. Histamine in Austrian red wine, rosé wine, white wine, sparkling wine and champagne and dessert wine: histamine assessment was done by radioimmunoassay (Immunotech, France)

Histamine in red wine		Histamine in white wine		Histamine in sparkling wine and champagne	
Cuvée 1989	3,776 µg/l	Riesling 1989	120 µg/l	Pommery, France	670 µg/l
Cuvée 1989	3,418 µg/l	Pinot gris 1990	92 µg/l	MM Sekt	78 µg/l
Cuvée 1989	2,873 µg/l	Pinot gris-Grauburger 1990	70 µg/l	Henkel Brut	62 µg/l
Bordeaux Superieur 1989, France	2,197 µg/l	Langenloiser 1986	67 µg/l	Hochriegl Alte Reserve	28 µg/l
Chianti 1989, Italy	1,929 µg/l	Pinot blanc 1990	66 µg/l	Schlumberger Sparkling	15 µg/l
Zweigelt 1990	1,170 µg/l	Pinot cuvée 1990	65 µg/l	Histamine in dessert wine	
Blauer Portugieser 1990	596 µg/l	Riesling 1988	55 µg/l	Auslese 1990	
St. Laurent trocken 1990	568 µg/l	Chardonnay 1988	42 µg/l	(Welschriesling/Pinot gris)	400 µg/l
Veratina Cuvée 1990	445 µg/l	Weissburgunder Spätlese 1985	35 µg/l	Bccrenauslese 1989	360 µg/l
Zweigelt Kabinett 1990	413 µg/l	Riesling 1989	31 µg/l	Weissburgunder 1989	80 µg/l
Blauer Zweigelt 1989	406 µg/l	Welschriesling 1990	28 µg/l		
Blauer Zweigelt 1989	375 µg/l	Rheinriesling 1989	28 µg/l		
Zweigelt 1991	281 µg/l	Gewürztraminer 1988	22 µg/l		
Zweigelt Exklusiv 1990	251 µg/l	Kremser Goldberg 1988	17 µg/l		
Goldeck 1988	133 µg/l	Grüner Veltliner 1987	11 µg/l		
Cabernet Merlot 1988	110 µg/l	Welschriesling 1991	10 µg/l		
Pinot Noir 1987	101 µg/l	Messwein 1991	10 µg/l		
Cuvée 1987	92 µg/l	Grüner Veltliner 1989	9 µg/l		
St. Laurent 1988	60 µg/l	Welschriesling 1990	9 µg/l		
		Grüner Veltliner 1988	8 µg/l		
		Langenloiser 1988	7 µg/l		
			3 µg/l		
Histamine in rosé wine					
Rosé 1988	61 µg/l				
Rosé 1990	45 µg/l				
Schilcher 1989	15 µg/l				

Table 2. Histamine in beer and beer free of alcohol: histamine assessment was done by radioimmunoassay (Immunotech, France)

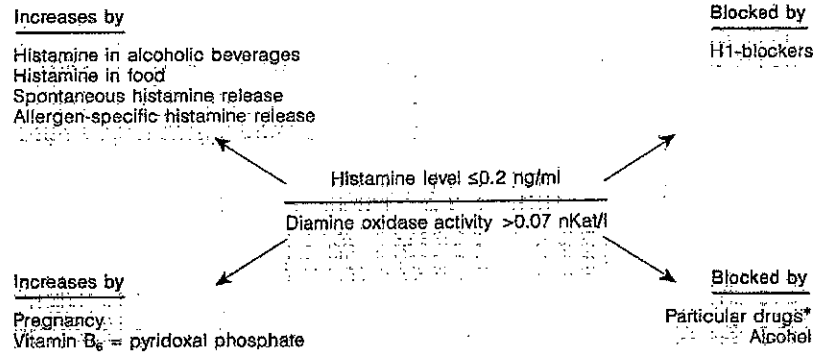
Histamine in beer	
Wheat beer	305 µg/l
Wheat beer dark	117 µg/l
Ottakringer Goldfassl	52 µg/l
Schladminger	41 µg/l
Puntigamer	35 µg/l
Gösser Märzen	34 µg/l
Zipfer Märzen	33 µg/l
Kapsreiter Landbier	33 µg/l
Budweiser, USA	28 µg/l
Budweiser, CSFR	26 µg/l
Egger leicht	25 µg/l
Schwechater	24 µg/l
Tsingtao, China	21 µg/l
Histamine in alcohol-free beer	
Schlossgold	38 µg/l
Birell	26 µg/l
Clausthaler	24 µg/l
Ottakringer Null Komma Josef	15 µg/l

quite often the cause of headache and diagnosis and treatment is nowadays easy, histamine as a cause for headache should be considered first.

Drinking red wine is a common cause of headache, not only after consuming too high quantities of alcohol. Red wine is known to contain ingredients such as flavonoids and tannins as well as biogenic amines such as tyramine, putrescine and especially histamine. Red wine usually contains up to 20- to 200-fold more histamine than white wine. In previous studies, histamine assessment was done in 52 different wines (red wine, white wine and champagne) and 17 beers by radioimmunoassay. Histamine levels obtained ranged from 3 to 120 µg/l in white wines, 21 to 305 µg/l in beer, 15 to 670 µg/l in sparkling wines and champagnes and 60 to 3,800 µg/l in red wines [1] (tables 1, 2). In our laboratory, the highest histamine content found in red wine was 13,000 µg histamine per liter.

A connection between drinking wine and the occurrence of headache has been observed and reported [2-7]. As consumption of red wine is repeatedly accused of inducing headache, histamine in wine may account as a cause for headache.

Fig. 1. Interaction between plasma histamine levels, diamine oxidase activity and external influences. *c.g.: Dihydralazine, isoniazide, clavulanic acid, promethazine, verapamil, metoclopramide and ambroxol hydrochloride [12, 13, 19].



Histamine in Wine and Food as a cause for headaches

Histamine in wine can induce headache in patients suffering from histamine intolerance, a disease characterized by impaired histamine degradation based on reduced diamine oxidase activity or a lack of the enzyme [1, 6, 7; unpubl. results]. Diamine oxidase is localized in the jejunal mucosa [8–11] and is the most important enzyme metabolising histamine [9, 12–14].

Patients with intolerance to histamine present with headache and facial flush after drinking red wine or ingestion of food rich in histamine such as cheese, pickled cabbage, tuna or mackerel, tomatoes or hard cured sausages. Other symptoms, however, such as rhinopathia, bronchial asthma [double-blind, placebo-controlled histamine challenge, unpubl. data], gastric and bowel disorders, diarrhea as well as urticaria [6, 7] may also be caused by histamine intolerance. As histamine acts as a vasodilator these patients typically are hypotonic, some of them report cardiac arrhythmias which may be associated with ingestion of histamine-containing wine or food [16, 17]. Patients suffering from histamine intolerance may show all the symptoms mentioned above (up to now this was found in only one female) or some or only a single symptom [6, 7].

Histamine intolerance can also occur in allergic patients representing an aggravation of the disease [6, 7, 14, 15]. Headache in type I allergic patients is a strong indicator for a possible histamine intolerance.

The suspect diagnosis of histamine intolerance can be found by carefully doing a case history in most patients.

Mechanisms

In order to investigate the biologic action of ingested histamine we performed an oral histamine challenge using red wine as a medium, shortly called 'the wine test' [1]. Patients reporting chronic headache were selected for this test but also patients showing allergy-like symptoms such as sneezing, flush, skin itch, diarrhea or shortness of breath. Patients had to drink red wine and changes in plasma histamine as well as symptoms were assessed. In patients showing headache after drinking red wine, plasma histamine did not decrease to the basal level after 30 min as observed in controls, but showed an increase. In order to prove the genesis of histamine, symptoms of wine intolerance could be significantly eliminated by H1-blocker premedication. In the wine test we observed significantly higher basal histamine levels in patients experiencing symptoms after drinking wine which may already indicate their tendency to histamine intolerance [1]. According to recent findings in our patients, we suggest a basal histamine level exceeding 0.2 ng/ml to be elevated and indicating histamine intolerance (fig. 1). Histamine-induced headache on the basis of food intolerance is not an IgE-mediated disease as skin prick testing and specific IgE to food allergens are typically negative [1, 6, 7].

Orally ingested histamine is catabolized by enteral diamine oxidase the main enzyme metabolising histamine in the gut [8–13]. Diamine oxidase is found in the liver, kidney as well as in blood in neutrophils and eosinophils. However, diamine oxidase is not found in the brain. Diamine oxidase is inhibited competitively by alcohol and biogenic amines such as tyramine or putrescine also occurring in wine [1, 9, 10]. Inhibition of diamine oxidase increases enteral histamine uptake leading to enhanced plasma histamine levels and additional inhibition of N-methyltransferase, the sec-

ond enzyme degrading histamine, by histamine metabolites [8–10, 12, 13]. Enteral histamine uptake does not induce histamine release from mast cells [18]. Alcohol and drugs are also remarkable inhibitors of diamine oxidase. To date, 94 drugs are known inhibitors of diamine oxidase such as dihydralazine, isoniazide, clavulanic acid, promethazine, verapamil, metoclopramide and ambroxol hydrochloride [12, 13, 19] (table 3). Patient under long-term medication with these drugs seem to be prone to histamine-induced headache and should therefore be put on a histamine-free diet and on H1 blockers [6, 7] (table 3). In addition, women have lower levels of diamine oxidase than men, possibly explaining the high incidence of red wine-induced headache in women [1, 6, 7]. Children have lower diamine oxidase levels than adults.

In preliminary investigations, serum diamine oxidase levels using the ^{14}C -putrescine method [20] gave decreased activity (0.03 nKat/l) in patients suspected of having histamine intolerance compared to healthy controls (0.07 nKat/l). In pregnancy, diamine oxidase is known to be elevated by about 500-fold compared to the nonpregnant status [21, 22]. Diamine oxidase is produced by the placenta. In our preliminary investigations serum diamine oxidase activity levels gave a mean of 25.0 nKat/l for pregnant women. In women with food-associated headache, we observed remissions occurring in pregnancy with recurrences some weeks after delivery. As remission of symptoms is associated to the presence of the diamine-oxidase-producing placenta, this finding gives strong evidence for the genesis of histamine [6, 7].

Even in healthy persons massive amounts of ingested histamine cause symptoms such as severe headache and flush, as is known in scombroid intoxication [23]. Symptoms occurring 10–30 min after eating histamine-poisoned food can be reduced by antihistamines [23]. The occurrence of headache and allergy-like symptoms in scombroid intoxication clearly demonstrates the importance of the equilibrium of histamine and histamine degradation by diamine oxidase.

Not only histamine in wine [24] causes headache but also other biogenic amines such as phenylethylamine [25–29] or serotonin [30, 31] may be causative for wine/food-induced headache [32]. In experimental models, headache has been induced by histamine infusion [33] in 24/25 patients suffering from migraine. In 13/25 patients a severe attack was induced while in 9/25 a moderate and in 2/25 a mild attack was seen. Symptoms could be eliminated by H1 blockers. Littlewood et al. [28] investigated the influence of drinking red wine versus vodka on patients suffering from migraine. In 10/11 migraineurs he could induce an attack and concluded that red wine contains a substance inducing headache which is neither alcohol nor tyramine. In scom-

Table 3. Drugs acting as inhibitors of diamine oxidase [12, 13, 19]

Ambroxol hydrochloride
Clavulanic acid
Dihydralazine
Isoniazide
Metoclopramide
Promethazine
Verapamil

broid intoxication (histamine intoxication caused by spoiled food) headache was a major symptom which could be successfully eliminated by H1 blocker treatment [23]. This involuntary histamine challenge also affects healthy persons not suffering from histamine intolerance. Finally, in our red wine provocation test 50 μg histamine in 125 ml red wine was sufficient to induce headache in histamine-intolerant patients. Induction of headache could successfully be prevented by antihistamine premedication [1].

Histamine-induced headache is a vascular headache [34–41] according to recent findings. The underlying pathomechanism is likely to be caused by nitric oxide, which represents, according to Olesen et al. [37, 38], a key molecule in migraine and other vascular headaches. In the context of histamine-induced headache and diamine oxidase, it has to be underlined that diamine oxidase is not present in the brain.

Diagnosis, Treatment and Prevention

A histamine-free diet is the treatment of choice for patients with suspected histamine intolerance and chronic headache [6, 7]. To start treatment, we recommend giving an anti-histaminic (H1 blocker) [42] for 14 days as well as a histamine-free diet (table 4) for at least 4 weeks to support the diagnosis clinically. In vitro tests for plasma histamine and diamine oxidase in the serum as well as decreased vitamin B₆ levels are needed to confirm the diagnosis [unpubl. data].

A histamine-free diet represents a harmless diet which will not cause deficiency syndromes and therefore is also useful in children as long as they drink enough milk to prevent calcium deficiency.

As additional supportive treatment, vitamin B₆ (pyridoxal phosphate) substitution [43] appears useful in histamine-intolerant patients as pyridoxal phosphate seems to be crucial for diamine oxidase activity [43–45]. According to preliminary investigations, we hypothesize that patients with

Table 4. Histamine-free diet

Fish	
Tunny	<0.1–13,000 mg/kg
Sardine	110–1,500 mg/kg
Anchovy	176 mg/kg
Cheese	
Emmentaler	<0.1–555 mg/kg
Harzer cheese	390 mg/kg
Gouda	29.5–180 mg/kg
Stilton (Roquefort)	158 mg/kg
Tilsiter	50–60 mg/kg
Camembert	35–55 mg/kg
Cheddar	34 mg/kg
Monte Nero cheese	19 mg/kg
Hard cured sausage	
Osso collo	<0.1–318 mg/kg
Salami	<0.1–279 mg/kg
Ham of Westfal	38.2–159 mg/kg
Knappseer	94 mg/kg
Vegetables	
Pickled cabbage	6–200 mg/kg
Spinach	38 mg/kg
Tomato (Ketchup)	22 mg/kg
Wine and Beer	
Red wine	60–3,800 µg/l
White wine	3–120 µg/l
Sparkling wine/ champagne	15–78/670 µg/l
Beer	21–305 µg/l

histamine intolerance seem to have a vitamin B₆ deficiency as they show clinical improvement after pyridoxal phosphate substitution. As therapeutic dose 1 mg vitamin B₆ per kg body weight seems to be sufficient for successful supplementation.

Headache on the basis of histamine intolerance can only be prevented by strictly keeping to a histamine-free diet as well as avoidance of diamine-oxidase-blocking drugs. In addition, intake of an antihistamine (H1 blocker) about 1 h before drinking wine or eating potentially histamine-containing food may prevent the patient from getting a headache. In case of dietary errors or after forgetting this premedication, an antihistamine may induce relief from headache as observed in several of our patients.

Conclusions

According to recent findings, histamine-induced headache is of a vascular genesis. Patients with histamine intolerance suffer from headache and respond to a histamine-free diet with considerable improvement and even total remission. Histamine intolerance, based on reduced diamine oxidase activity or a lack of the enzyme is causative for wine/food-induced chronic headache. According to the localization of diamine oxidase in the jejunal mucosa, histamine intolerance is primarily a disease of intestinal origin.

A histamine-free diet is the treatment of choice in histamine-intolerant patients suffering from chronic headache and is recommended as supportive treatment in all patients suffering from chronic headaches. In addition, it is also important to avoid diamine-oxidase-blocking drugs and alcohol which act as inhibitors of diamine oxidase. As avoidance of histamine-rich food is a simple, inexpensive and harmless treatment, histamine-containing food such as cheese and alcoholic beverages should be labeled.

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