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REVIEW ARTICLE

Histamine Intolerance in Clinical Practice

Laura Maintz, Thomas Bieber, Natalija Novak

SUMMARY

Introduction: Histamine intolerance results from disequilibrium of accumulated histamine and the capacity for histamine degradation. The main enzyme for metabolism of ingested histamine is diamine oxidase (DAO). It has been proposed that DAO as a secretory protein might be responsible for scavenging extracellular histamine after mediator release. **Methods:** Search of PubMed and book extracts, combined with the authors' own experience of a histamine intolerance clinic. **Results:** Inadequate histamine degradation based on a reduced DAO activity and the consecutive excess of histamine may cause numerous symptoms in multiple organs such as diarrhoea, headache, hypotension, arrhythmias, urticaria, pruritus, flushing and even asthma after ingestion of histamine-rich food, alcohol or drugs releasing histamine or blocking DAO. The multifaceted presentation means that the condition is frequently missed. **Discussion:** In patients with the above clinical picture, with negative allergological investigations and no general medical disease, histamine intolerance should be considered. After diagnosis, patients affected by Histamine intolerance improve considerably by relatively simple therapeutic measures consisting of a histamine-free diet – if necessary – supported by antihistamines or substitution of DAO.

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Key words: histamine intolerance, histamine, diamine oxidase, food intolerance, allergy

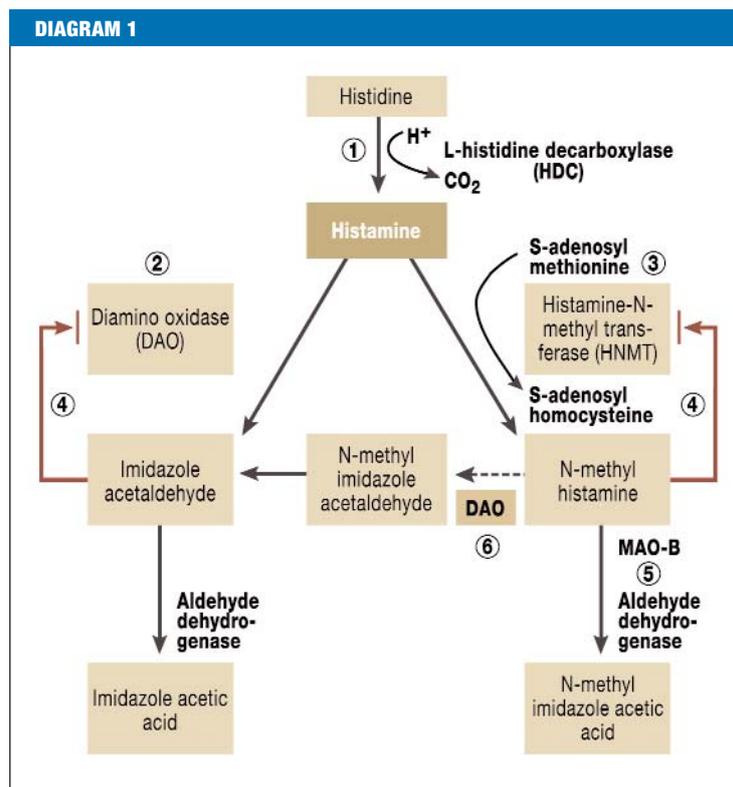
Patients frequently complain of headache, rhinitis, flushing, diarrhea, tachycardias or arrhythmias following ingestion of specific foods. Because these symptoms are reminiscent of allergy, allergy testing is usually performed. However, these tests are often negative for an IgE mediated immune response. In these cases, histamine intolerance should be considered as a possible diagnosis. Around one percent of the population is affected by this condition (1).

The following is an overview of the etiology, diagnosis and treatment of this often poorly recognized syndrome. Its recognition is important both because of the wide range of specialities to whom it may present, with its broadly ranging symptomatology, and because it is relatively easily treatable, with good effect on symptoms and therefore quality of life.

Pathogenesis

Histamine (2-[4-imidazolyl]ethylamine) was first described as an endogenous substance in 1910, and as a mediator of allergic reactions in 1932. Histamine is a biogenic amine, synthesized from the amino acid histidine by pyridoxal phosphate (Vitamin B6) containing molecule L-histidine decarboxylase (HDC). It is produced in mast cells, basophils, platelets and some neurons, where it is stored intracellularly in vesicles and released on stimulation. Histamine is a potent mediator of a number of biological reactions. In addition to mast cell degranulation, which occurs via cross linking of IgE antibody on the cell surface following binding of the allergen, histamine release can occur independently of IgE.

IgE independent release is regulated by the cyclical nucleotides cAMP and cGMP, which act as secondary messengers. Triggers such as histamine or β -adrenergic stimuli increase cAMP concentration, which inhibits mast cell degranulation via a negative feedback loop. Histamine release is increased by stimuli which reduce cAMP concentration (α -adrenergic and cholinergic), by certain cytokines which are released in inflammation, and by the binding of complement factors C5a and C3a to mast cell complement receptors. These "non-allergic" histamine liberators may be medications, foods, chemical and physical



Histamine metabolism. Histamine (1) is synthesized via the decarboxylation of histidine catalyzed by L-histidine decarboxylase, and broken down extracellularly via oxidative deamination catalyzed by diamino oxidase (DAO) (2), and intracellularly via ring methylation catalyzed by histamine-N-methyl transferase (HNMT) (3). Where enzyme activity is insufficient (reduced levels or inhibition) histamine build up can occur. Both enzymes can be inhibited by their own breakdown products via a feedback loop (4). N-methyl histamine can be oxidized by monoamino oxidase B (MAO B) (5) or by DAO (6). However, as the methylation pathway occurs in the cytosol, MAO B (5) appears to be the main pathway for N-methyl histamine breakdown in vivo.

stimuli, hypoxia, neuropeptides or enzymes such as phospholipase. Histamine intolerance is based on an imbalance between the build up and breakdown of histamine.

Histamine can be metabolized by two pathways:

- oxidative deamination via diamino oxidase (DAO) (formerly known as histaminease)
- ring methylation via histamine-N-methyl transferase (HNMT) (diagram 1).

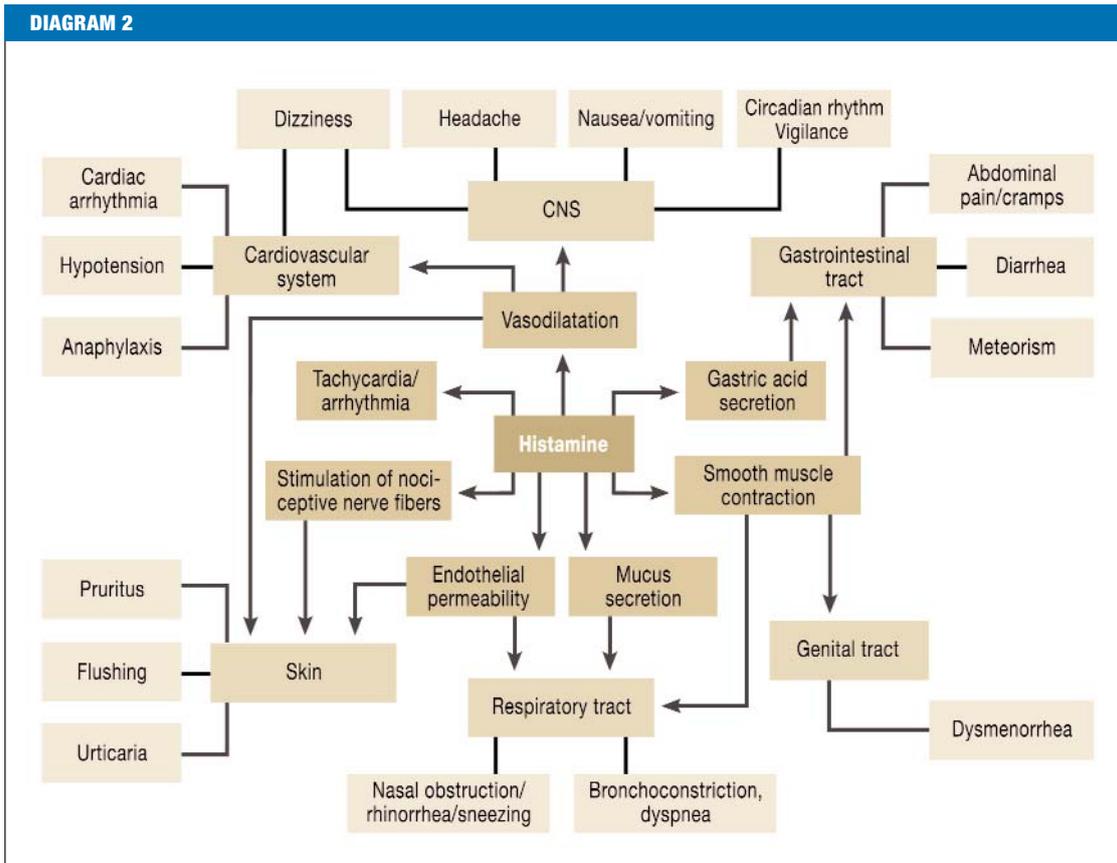
DAO is a secretory protein responsible for the breakdown of extra cellular histamine, whereas HNMT, a cytosolic protein, inactivates histamine only intracellularly, for example in the liver (2). The enzyme DAO therefore plays a key role in the breakdown of dietary histamine. Insufficient DAO activity can thus lead to the symptoms described, e.g., after ingestion of histamine rich foods, (5), alcohol (6) or histamine liberating or DAO blocking medications (7).

Various possible mechanisms have been discussed as the cause of histamine intolerance (1). The production of DAO may for example be reduced by damage to enterocytes in gastrointestinal disease (11, 21). Other biogenic amines, alcohol (18) and medications (7, 19) can also competitively inhibit the breakdown of histamine by DAO. Acquired histamine intolerance may be reversible where the cause if removed, such as the discontinuation of DAO blocking medications.

However in addition to acquired forms, interest has recently focussed on a number of potential ge-netic causes of reduced histamine breakdown in a group of associated conditions. Various DAO polymorphisms have been identified in association with inflammatory and neoplastic diseases such as food allergies, sprue, Crohn's disease, ulcerative colitis and colonic adenomas (22, 23, 24), giving rise to discussion of a partially DAO associated genetic predisposition to the development of the disease (2).

Clinical findings

Of the one percent of the population who suffer from histamine intolerance, 80 percent are middle aged women (1). The exceeding of the personal threshold for histamine tolerance leads to histamine related symptoms in a dose-response relationship. In patients with reduced DAO activity, even small amounts of histamine intake lead to symptoms, which can be manifest via the distribution of histamine receptors in multiple organs (*diagram 2*). Typical symptoms and signs of histamine intolerance include gastrointestinal symptoms, nasal obstruction or rhinorrhea, headache (8, 9), dysmenorrhea, hypotension, arrhythmias, urticaria, itch, flushing, and wheeze (1, 6).



Histamine related symptoms

Headache

Histamines can cause headache both in migraine sufferers and migraine free patients, in a dose-response relationship. Histamine induced headache is a vascular headache, caused primarily by nitric oxide (NO). Histamine can cause the release of NO from the endothelium via histamine receptor (H1R) stimulation in the large intracranial arteries, among other places.

Many migraine patients show reduced DAO activity, and affected individuals report triggering by histamine rich foods, such as wine or mature cheese, and relief, which may be complete, with a histamine free diet (9, 10). Pregnancy, which is associated with a high placental production of DAO, is associated with remission in some women who suffer from diet related headache (8).

Gastrointestinal tract

Gastrointestinal symptoms are another common symptom of histamine intolerance, and can include non specific abdominal pain, colic, flatulence and diarrhea. Raised histamine levels in association with reduced DAO activity have been reported in a number of inflammatory and neoplastic gastrointestinal diseases such as Crohn's disease (11), ulcerative

colitis, allergic enteropathy (12), food allergies (FA) (13, 14), colorectal polyps and carcinomas (15). Colonic biopsies of patients with food allergy showed an associated reduction in HNMT, combined with a reduced total histamine degradation capacity. The enzymes are unable to compensate for each other under these conditions. Mucosal damage in gastrointestinal disease can therefore lead to disturbed histamine metabolism due to reduced DAO production.

Respiratory tract

During or immediately after the intake of histamine rich food or alcohol, patients with histamine intolerance may complain of rhinorrhea, nasal obstruction or in extreme cases, asthma attacks. A reduced activity of the enzyme responsible for histamine breakdown in bronchial epithelium HNMT has also been found in asthma (16).

TABLE 1

Histamine rich foods

Food	Histamine content (mg/kg)		Recommended histamine limit (mg/kg)
Fish	Frozen	Smoked or cured	200
Mackerel	1–20	1–1 788	n.d.–210
Herring	1–4	5–121	1–479
Sardine		14–150	3–2 000
Tuna			1–402
Cheese	Histamine (mg/kg)	Tyramine (mg/kg)	No official recommendation
Gouda	10–900	10–900	
Camembert	0–1 000	0–4 000	
Cheddar	0–2 100	0–1 500	
Emmental	5–2 500	0–700	
Swisstal	4–2 500	0–700	
Parmesan	10–581	0–840	
Meat			No official recommendation
Sausage	n.d.–650	n.d.–1 237	
Salami	1–654	–	
Smoked ham	38–271	123–618	
Vegetables			
Sauerkraut	0–229	2–951	10
Spinach	30–60		
Aubergine	26		
Tomato ketchup	22		
Red wine vinegar	4 000 µg/l		
Alcohol	Histamine (mg/l)	Tyramine (mg/l)	recommended upper limit in Germany (mg/l)
White wine	n.d.–10	1–8	2
Red wine	n.d.–30	n.d.–25	2
Top fermented beer	n.d.–14	1,1–36,4	
Bottom fermented beer	n.d.–17	0,5–46,8	
Champagne	670 µg/l		

Modified from Jarisch et al. 2004 und Sarkadi L. 2005 (1, e4); n.d. = not detectable

Sex hormones

In the female genital tract, histamine is produced mainly by mast cells, endothelial and epithelial cells in the uterus and ovary. Women with histamine intolerance often suffer cyclical headache and dysmenorrhea. In addition to a contraction promoting effect, this is attributable to the fact that histamine, via the H1 receptors, increases estradiol production markedly, but progesterone production only mildly (e1). The painful uterine contractions associated with dysmenorrhea are caused by an increased production of prostaglandin F2a in the endometrium, which is promoted by estrogens and inhibited by progesterone. Histamine can therefore intensify dysmenorrhea via an increase in estrogen production. Conversely, estrogen can affect histamine activity: the cyclical rise in plasma estrogen was shown to be associated with a larger skin weal in skin prick tests (e2).

Food

Histamine, its precursor histidine and other biogenic amines are present in almost all foods in varying concentrations, however the histamine content is increased by maturation and fermentation processes (3). As many bacteria and yeasts have high L-histidine decarboxylase (HDC) activity and histidine arises during proteolytic processes, high histamine concentrations are particularly found in microbiologically produced foods such as mature cheese, sauerkraut, wine or microbially contaminated protein rich food such as fish, meat and sausage (table 1). Other biogenic amines in combination with histamines can also lead to intolerance. This can be explained both by the inhibition of DAO by these amines as well as by the promotion of histamine release in the gut.

Red wine is both histamine rich and a potent inhibitor of DAO. These characteristics account for its association with a rise in plasma histamine leading to sneezing, flushing, headache and asthma attacks. The administration of antihistamines reduces symptoms. This association was confirmed in several studies (6, 8, 10, 17, 18). However, in addition to histamine, other substances contained in wine such as sulphites and the ethanol metabolite acetaldehyde may also play a part in "wine intolerance." In addition to histamine rich foods, some foods, such as citrus fruits, act as non-specific histamine liberators of stored histamine, despite having a low histamine content themselves (box).

By contrast with IgE mediated food allergy (FA), in which symptoms follow the ingestion of even a small amount of the allergenic food, the cumulative amount of histamine is a key factor in histamine intolerance. In addition to the content in the food, which can vary according to length of storage and maturation processes, the amount consumed and the content of biogenic amines plays an important part, as does the simultaneous consumption of alcohol or DAO blocking medications.

Medications

A number of medications of differing categories can cause intolerance reactions or induce histamine intolerance via the release of histamine or the inhibition of DAO (7, 19, 20) (table 2). All medications, in particular long term treatments, should therefore be taken into account when interpreting histamine intolerance symptoms, as well as the DAO level, where appropriate.

Associated Diseases

Reduced DAO activity can be found in patients with chronic renal failure, viral hepatitis, advanced hepatic cirrhosis, and chronic urticaria – a typically histamine related illness with a reduced tolerance for endogenous histamine. In addition, a role for histamine intolerance has been discussed in relation to sea sickness. In favor of an association is the similar risk profile (women, migraine patients), the predominantly histamine rich food at sea due to preserved foods, and the therapeutic use of antihistamines.

Clinical implications

Diagnosis

The wide ranging symptoms in various organ systems requires careful history taking including any precipitating foods or medications which may influence histamine metabolism. The accompanying gastrointestinal symptoms and allergies must also be borne in mind. It cannot be assumed that all clinical findings related to histamine are attributable to the underlying

TABLE 2

The commonest histamine liberating or DAO inhibiting medications

Substance class	Active agents
Radiological contrast media	
Muscle relaxants	Pancuronium, Alcuronium, D-Tubocurarin
Narcotics	Thiopental
Analgesics	Morphine, pethidine, NSAR, ASS, metamizole
Local anesthetics	Prilocaine
Antihypotensives	Dobutamine
Antihypertensives	Verapamil, alprenolol, dihydralazine
Antiarrhythmics	Propafenon
Diuretics	Amiloride
Motility agents	Metoclopramide
Antibiotics	Cefuroxime, cefotiam, isoniazid, pentamidine, clavulanic acid, chloroquine
Mucolytics	Acetylcysteine, ambroxol
Broncholytics	Aminophylline
H2 receptor antagonists	Cimetidine
Cytostatics	Cyclophosphamide
Antidepressants	Amitriptyline

DAO, diamino oxidase

BOX

Foods with potential histamine releasing effect

- Vegetable
 - Citrus fruits
 - Papaya
 - Strawberries
 - Pineapple
 - Nuts
 - Tomato
 - Spinach
 - Chocolate
- Animal
 - Fish
 - Shellfish
 - Pork
 - Egg white
- Other
 - Additives
 - Liquorice
 - Spices

Modified from Vlieg-Boersta BJ, 2005 (e3)

pathology. Allergy testing should also be carried out, using skin prick tests and identification of specific IgE, to exclude a true food allergy. Serum tryptase should also be assayed, to exclude an occult mastocytosis.

The diagnosis of histamine intolerance is made in the presence of at least two typical symptoms (6) (table 3), improvement on a histamine free diet and antihistamines, and a reduced DAO level and/or raised histamine level. These findings should be tested using a placebo controlled histamine provocation test. The keeping of food diaries and dietary advice have proven helpful in many patients. These mechanisms allow the documentation of symptomatic improvement through compliance with a histamine reduced diet, and recurrent symptoms where there have been dietary lapses.

Where there is clinical suspicion of histamine intolerance, the activity of DAO in serum (24) or in a biopsy specimen can be ascertained, using radio extraction assays (REA) developed for the ascertainment of enzymatic DAO activity. [3H]- or C14-labelled putrescine dihydro chloride are used as a substrate. The DAO activity in plasma is normally relatively low. A heparin injection releases tissue bound DAO. Hence prior to the development of new, sensitive assays, heparin administration followed by plasma DAO measurement were the main diagnostic method. While several studies have shown a correlation between DAO activities in the intestine and in blood following heparin stimulation, no direct comparative measurements have been performed to date of blood DAO activity in blood without heparin stimulation, with tissue DAO activity. A number of studies have shown low serum DAO activity with mucosal damage of various etiologies (7, 8, 9). Since reduced serum DAO activity in symptomatic patients correlates well with histamine intolerance (1), and serum DAO does not vary significantly by time of day or with gender (20), the diagnostic blood test is for the most part used, for reasons of practicability.

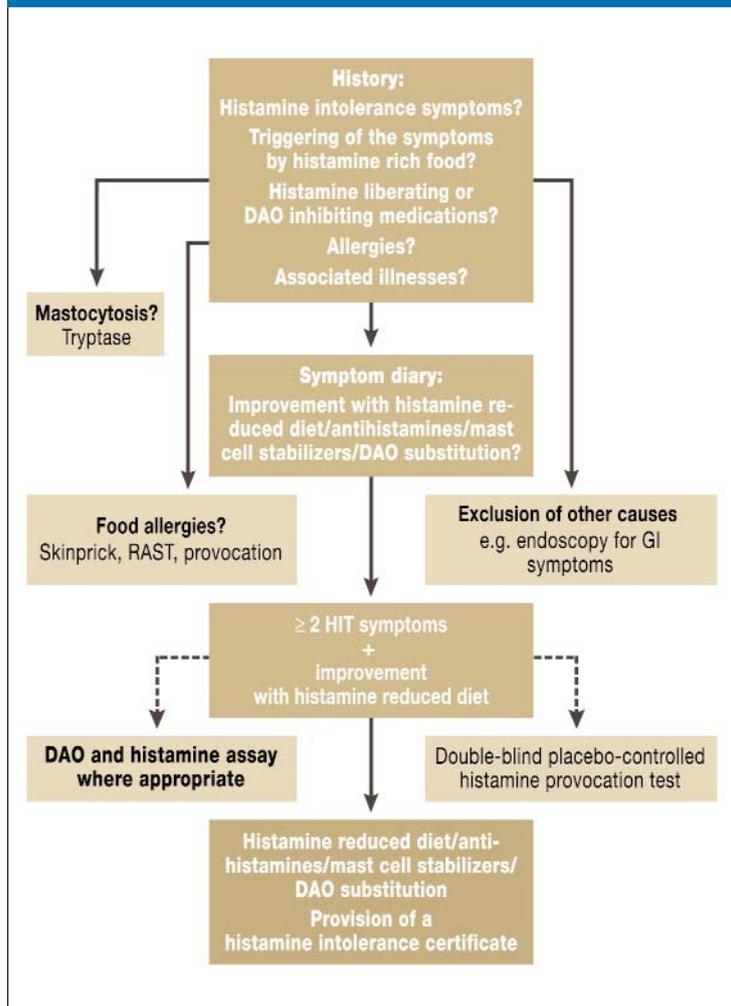
A DAO activity of < 3 U/ml is suggestive of histamine intolerance, with an activity of < 10 U/ml it is probable, whereas an activity greater than or equal to 10 U/ml makes the diagnosis unlikely (1). In some patients with an unequivocal clinical picture, however, normal DAO activities have been observed; in these patients, histamine level assay is a helpful addition to the diagnostic process. Histamine can be measured in plasma and, as its

TABLE 3

Symptoms of histamine intolerance

Organ	Symptoms
Skin	Flush Urticaria Itch
Gastrointestinal tract	Nausea/vomiting Abdominal pain Meteorism Diarrhea
Central nervous system	Headache Dizziness
Cardiovascular system	Hypotension Tachycardia Cardiac arrhythmia
Respiratory system	Nasal obstruction Rhinorrhea
Urogenital tract	Dysmenorrhea
Intolerance of histamine liberating/DAO blocking medications	
Intolerance of histamine rich food/alcohol	

DIAGRAM 3



Diagnostic flow diagram for use in suspected histamine intolerance

breakdown product, N-methyl histamine, in urine. A lack of DAO cofactors vitamin B6, copper and vitamin C can also occur. The latter supports histamine breakdown (1).

Since DAO and histamine level assays are not supported by the statutory health insurance companies in Germany and are only carried out in a small minority of laboratories, budgetary considerations reduce the use of these diagnostic tests to patients with a typical clinical picture. The gold standard of diagnosis is a double-blind placebo-controlled provocation test following a histamine reduced diet (*diagram 3*).

Treatment options

The basis of treatment is the reduction of exogenous histamine via the consistent pursuit of a histamine reduced diet. Alcohol and matured or fermented products such as mature cheese, cured meats, yeast products and spinach, tomatoes or histamine liberating foods should be avoided (10).

Prophylaxis with H1 and H2 receptor antagonists is also recommended, where histamine rich foods are unavoidable, for example while traveling. In the presence of a histamine reduced diet, antihistamines appear to confer no additional benefit (9). In individual cases of patients in whom a lack of DAO cofactors is etiological, the use of Vitamin B6 and Vitamin C has been reported (1). Mast cell stabilizers appear to improve gastrointestinal symptoms, in particular (1). Capsules have recently been developed which substitute for DAO. These have recently become freely available in Germany for use in histamine intolerance. Early placebo controlled (n = 48) and uncontrolled (n = 43) intervention studies found the active agent statistically significantly superior to placebo in improving symptoms. Further studies in this area are currently in progress (Dr. Albert Missbichler, personal communication).

Because intolerance to medications which interfere with histamine metabolism is common, these medications should be avoided if at all possible wherever they are suspected of playing a role in causing or maintaining histamine intolerance. Where their administration cannot be avoided, e.g. in studies using contrast media, or perioperatively, antihistamines should be given prophylactically. An oral dose of 40 mg prednisolone three and six hours prior to the intervention, together with an H1 and H2 antagonist an hour beforehand are recommended. The patient can be given a certificate of confirmed histamine intolerance documenting the disease and its associated risk factors and preventive measures, for use where needed.

Conflict of Interest Statement

The author's declare's that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

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Corresponding author

Dr. med. Laura Maintz
 PD Dr. med. Natalija Novak
 Klinik und Poliklinik für Dermatologie
 Rheinische-Friedrich-Wilhelms Universität Bonn
 Sigmund-Freud-Str. 25
 53105 Bonn, Germany
 Laura.Maintz@ukb.uni-bonn.de, Natalija.Novak@ukb.uni-bonn.de