

CHAPTER 7

Antihistamines in the Treatment of Urticaria

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Abstract

Most urticaria subtypes have a profound impact on patients' quality of life and performance. Effective treatment is thus required in all cases where the avoidance of eliciting factors and the elimination of underlying causes is not feasible. In nearly all subtypes histamine released by mast cells plays a predominant role. For symptomatic relief second generation nonsedating histamine H₁ receptor (H₁R)-antihistamines are, therefore, the first choice. However, double-blind controlled studies have shown that dosages required to achieve complete protection from urticaria symptoms may exceed those recommended for other diseases, e.g., allergic rhinitis. Therefore, the current guidelines suggest increasing the dosage up to fourfold, whereas alternative treatments should be reserved as add-on therapy for unresponsive patients.

Introduction

Urticaria as a disease was described as far back as Hippocrates, but the many different types and subtypes of urticaria have only been recognized and characterized during the past century. With an increasing understanding of the molecular mechanisms involved in urticaria pathogenesis, there is also growing evidence for the heterogeneity of the disease. This new knowledge calls for an individualized approach, which is especially important since the impairment of the quality of life in urticaria is often high. For example, Poon et al¹ report that chronic spontaneous urticaria patients suffer an impairment of health that is similar to that seen in patients with psoriasis or acne in a study of 170 consecutive patients attending a specialist urticaria clinic.

According to the new EAACI (European Academy of Allergology and Clinical Immunology) Dermatology Section, the EU-funded network of excellence, GA²LEN (Global Allergy and Asthma European Network), the EDF (European Dermatology Forum) and WAO (World Allergy Organization) guidelines the different urticaria subtypes can be grouped into spontaneous urticaria, which includes acute urticaria and chronic urticaria, the physical urticarias and other urticarias including contact urticaria, e.g., wheals and angioedema formation that is directly linked to the degranulation of mast cells either in superficial layers (wheals) or in deeper layers of the skin (angioedema). Because of the many different subtypes of urticaria a clear definition and classification of the disease is a prerequisite for a suitable treatment. The clinical appearance is defined as follows:

- Urticaria is characterized by the rapid appearance of wheals and/or angioedema.
- A wheal consists of three typical features:
 1. a central swelling of variable size,
 2. an associated itching or sometimes burning, and
 3. a fleeting duration of usually 1-24 hours.

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Table 1. Classification of urticaria³⁰

Type	Subtype	Definition
Spontaneous urticaria	Acute spontaneous urticaria	Spontaneous wheals and/or angioedema <6 weeks
	Chronic spontaneous urticaria	Spontaneous wheals and/or angioedema >6 weeks
Physical urticaria	Cold contact urticaria	Eliciting factor: cold objects/air/fluids/wind
	Delayed pressure urticaria	Eliciting factor: vertical pressure (wheals arising with a 3-12 h latency)
	Heat contact urticaria	Eliciting factor: localized heat
	Solar urticaria	Eliciting factor: UV and/or visible light
	Symptomatic dermographism/Urticaria factitia	Eliciting factor: mechanical shearing forces (wheals arising after 1-5 min)
	Vibratory urticaria/angioedema	Eliciting factor: vibratory forces, e.g., pneumatic hammer
Other urticaria disorders	Aquagenic urticaria	Eliciting factor: water
	Cholinergic urticaria	Elicitation by increase of body core temperature due to physical exercises, spicy food
	Contact urticaria	Elicitation by contact with urticariogenic substance
	Exercise induced anaphylaxis/urticaria	Eliciting factor: physical exercise

Angioedema is defined by:

- Sudden, pronounced swelling of the lower dermis and subcutis.
- Possible pain.
- Resolution is slower than for wheals (up to 72 hours).

Nearly all symptoms of urticaria are mediated by histamine as the major proinflammatory mast cell mediator binding to H₁R on endothelial cells and sensory nerves. However, the clinical manifestations of different urticaria subtypes vary considerably. Also, it is important to note that in one patient two or more different subtypes of urticaria can coexist. Table 1 presents a classification for clinical use.

Physical urticarias, although of a chronic nature, are grouped separately since they depend on the presence of their eliciting physical factors, whereas in acute and chronic spontaneous urticaria wheals arise spontaneously without external physical stimuli.

Another important factor in classifying urticaria is disease activity. Where physical triggers are implicated, e.g., temperature, an exact measurement of the intensity of the eliciting factor can be made. However for spontaneous urticaria, assessing disease activity is more complex. The new guidelines propose a unified scoring system that will facilitate comparison of study results from different centers. This simple scoring system is based on the assessment of key urticaria symptoms (wheals and pruritus). The self-evaluation of the last 24 hours each day by the patient has proven to be very robust and helpful since disease activity often varies during the day.

Acute Urticaria

For acute urticaria life-time prevalence ranges from 12-15%^{2,3} or even, in one study, 23.5%.⁴ In a prospective study, in a rural area of Brandenburg in Germany, a one-year incidence of 0.154% was found, which equals a life-time prevalence of 12.32% based on a life expectancy of 80 years.^{5,6} However, mild symptoms may not have been reported and the true life-time prevalence must be estimated to be rather 15-20%.

Regarding the etiology of the disease, the above-mentioned prospective study in acute urticaria showed that although 63% of the patients suspected food to be the cause, in only 1 of 109 patients was food shown to be the causing agent upon thorough investigation. This highlights that patient history, especially in acute urticaria, may be misleading.⁶ Drugs can elicit acute urticaria both as allergens (e.g., penicillin) and as pseudoallergens (e.g., NSAID). The most frequent reason for acute urticaria, however, appears to be viral infections of the upper respiratory tract.

Chronic Spontaneous Urticaria

Due to the lack of cross-sectional studies, there is no reliable data regarding the prevalence of chronic spontaneous urticaria although it is estimated to be 1%. As for acute spontaneous urticaria, Type I—allergic reactions are only rarely responsible for the development of chronic spontaneous urticaria.^{7,8} In different subsets of patients with chronic spontaneous urticaria, the role of pseudoallergic reactions against food and food additives have been repeatedly discussed in the past as well as an infectious or autoreactive etiology.

Our own results⁸ show that in those patients who improve on a diet low in pseudoallergens, 30% show a decrease of symptoms only after 10-14 days on the diet. The study included unselected chronic spontaneous urticaria patients with daily or almost daily symptoms who had not received a diagnostic work-up before. Approximately 50% of the responders did not express a total clearance of symptoms, pointing at other possible cofactors involved in the pathogenesis. These results were confirmed by Pigatto and Valsecchi⁹ who investigated a group of 202 patients with chronic spontaneous urticaria using the same diet. In this study 126 patients improved on diet, whereas 35 patients did not show any benefit from the diet and 41 patients dropped out. In both studies reactions to food additives were only seen in a minority of patients (19% and 37%, respectively). Meanwhile the relevance of naturally occurring pseudoallergens, especially aromatic compounds found in vegetables and wine, have been confirmed.¹⁰ Various studies have investigated the occurrence of anti-FcεRIα autoantibodies, which have been described to be of pathophysiological relevance in some patients with urticaria.¹¹⁻¹³ In our own study these autoantibodies were found in the same frequency as described earlier, but they could be found in both patients with idiopathic chronic spontaneous urticaria (7 of 22) and in patients with pseudoallergy against food whose symptoms cleared with elimination diet (6 of 17).¹⁴ In addition, it has been shown that these autoantibodies crosslink the IgE-receptor only if it is not occupied by IgE, which is rarely the case under physiological conditions.^{15,16} Two possible explanations for these findings are conceivable. First, the FcεRIα autoantibodies are not of pathophysiological relevance in all patients with urticaria or second, a synergism between the autoantibodies and other eliciting stimuli, e.g., food, is necessary for the appearance of clinical symptoms in some patients. Future research in this field is necessary to answer this question.

Apart from anti-IgE receptor autoantibodies, thyroid autoantibodies are also associated with chronic spontaneous urticaria,¹⁷ although the pathomechanism is unclear. Infections such as hepatitis A and B, bacterial infections, e.g., of the nasopharynx or helicobacter pylori of the gastrointestinal tract,¹⁸⁻²¹ can also trigger chronic spontaneous urticaria and should be treated appropriately.

Parasites, a rare cause of urticaria in North European countries but more frequent in other regions, should be eliminated. In the past, intestinal candidosis has been regarded as a highly important eliciting factor for chronic spontaneous urticaria,³ but recent findings fail to support a significant causative role.⁶ Nevertheless, it is recommended that massive candidosis should be treated. In general, the frequency and relevance of infectious diseases as a cause for chronic urticaria varies between different patient groups and in different regions. For example, hepatitis virus infections are a more frequent cause for chronic spontaneous urticaria in southern Europe, but a

rare cause in northern Europe. Apart from infections, also non-infectious chronic inflammatory processes such as gastritis, reflux esophagitis, inflammation of the bile duct or bile gland,^{6,22} or rarely autoimmune disorders, e.g., SLE, have been identified to cause urticaria in some patients.

Management of Urticaria Follows Basic Principles

The management of urticaria should follow the newly developed EAACI/GA²LEN/EDF/WAO-Guideline.²³ This guideline is the result of a consensus reached during a panel discussion at the 3rd International Consensus Meeting on Urticaria, *Urticaria 2008*, a joint initiative of EAACI Dermatology Section, the EU-funded network of excellence, GA²LEN, the EDF and WAO.

Although urticaria is elicited by a great diversity of factors and clinically presents in a highly variable way its treatment mainly follows the same basic principles. These are:

- Avoidance or elimination of the eliciting stimulus or underlying cause.
- Symptomatic treatment mainly targeting either reducing mast cell mediator release or reducing the effect of these mediators on the target organs.

In all cases symptomatic relief should be offered while searching for causes. Avoidance, elimination or treatment of the eliciting stimulus or cause is most desirable since it is curative, but unfortunately it is not applicable in the majority of patients as the exact eliciting stimulus is frequently unknown.

Antihistamines Play the Major Role in Urticaria Treatment

Nearly all symptoms of urticaria are mediated primarily by the actions of histamine on H₁R located on endothelial cells (the wheal) and on sensory nerves (neurogenic flare and pruritus). Thus, H₁R antagonists are of eminent importance in the treatment of urticaria. The availability of this class of therapeutics since the 1950s has made urticaria a disease that can be treated effectively with a very low adverse effect profile. The older 1st generation antihistamines have pronounced CNS and anticholinergic effects which last longer than 12 hours, whereas the antipruritic effect lasts only for 4-6 hours. Consequently, many drug interactions have been described for these sedating antihistamines, particularly with drugs affecting the central nervous system, like analgesics, hypnotics, sedatives and mood elevating drugs as well as alcohol. Also, MAO inhibitors can prolong and intensify the anticholinergic effects of these drugs. In addition, 1st generation antihistamines can interfere with REM sleeping phases and impact learning and presentation.

The development of 2nd generation antihistamines led to drugs that are non-sedating or minimally-sedating and are free of anticholinergic effects. However, two of the earlier 2nd generation drugs, astemizole and terfenadine, which were essentially pro-drugs requiring hepatic metabolism to become fully active, had cardiotoxic effects if this metabolism was blocked by concomitant administration of ketokonazole or erythromycin. These two drugs are no longer available in most countries. Further progress with regard to drug safety was achieved by the development of the new generation antihistamines fexofenadine and desloratadine, which are cytochrome P450 independent metabolites of earlier antihistamines. Levocetirizine is the active enantiomer of cetirizine, thus, where cetirizine is indicated as effective treatment, levocetirizine could also be considered.

Thus, considering their good safety profile, 2nd generation antihistamines must be considered as first line symptomatic treatment for urticaria. However, as of now well-designed randomized controlled clinical trials comparing the efficacy and safety of different non-sedating H₁R-antihistamines in chronic urticaria are largely missing. However, while single dose is sufficient in up to 50% of patients with chronic spontaneous urticaria, many patients need additional therapy. There are some studies showing the benefit of a higher dosage of antihistamines in individual patients.^{24,25} This has been verified in studies using up to fourfold higher than recommended doses of desloratadine.²⁶ Interestingly, however, Asero²⁷ reported that increasing the dose of cetirizine for chronic spontaneous urticaria threefold did not produce further efficacy in severely affected patients. Most likely the increase of dosage does not only block histamine mediated effects, but also reduces mast cell activation and has an impact on various cytokine and endothelial adhesion molecules. The highest reported accidental overdosage of antihistamine (fifty-fold the prescribed dosage of cetirizine in an 18-month-old boy) induced no adverse effects.²⁸

Further Therapeutic Possibilities Are Limited

Alternative treatments are needed for patients unresponsive to higher dosages of antihistamines. Although the mechanism remains unclear, it can be speculated that individual profiles of other mediators and histamine receptors other than the H₁R are involved. Since the side-effects of many of these substances are considerable, it may be wise to try to use them as add-on therapy only in patients unresponsive to antihistamines. Since the severity of urticaria may fluctuate and since spontaneous remission may occur at any time, it is recommended that the necessity for continued or alternative drug treatment should be re-evaluated every 3-6 months.

Modern Antihistamines Should also Be Used for Children

Many clinicians use 1st generation H₁R-antihistamines as their first choice in the treatment of children with allergies assuming that the safety profile of these drugs is better known than that of the 2nd generation nonsedating H₁R-antihistamines due to a longer life on the market. Also the use of 2nd generation H₁R-antihistamines is restricted for children less than 6 months of age, while the recommendation for the 1st generation H₁R-antihistamines is sometimes less clear as these drugs have been licensed in a period when the code of Good Clinical Practice for pharmaceutical industry was less stringent. As a consequence many doctors choose a 1st generation antihistamine, which as pointed out above have a lower safety profile compared with a 2nd generation H₁R-antihistamine. This practice must be discouraged. Thus, in children the same first line treatment and up dosing (weight adjusted) is recommended as in adults.

The same considerations in principle apply to pregnant and lactating women. So far no reports of birth defects in women having used 2nd generation antihistamines during pregnancy have been published. Although only small sample size studies are available²⁹ it must be assumed that due to the wide use of 2nd generation antihistamines in allergic rhinitis and urticaria many women have used these drugs especially in the beginning of pregnancy, at least before the pregnancy was confirmed and most likely later since a number of these drugs do not require a prescription.

Conclusion

Modern H₁R-antihistamines are the mainstay in the treatment of urticaria. However, until now it is not clear if the mode of action in increased dosages is related only to the inactivation of the H₁R-receptor response. Due to the many other anti-inflammatory properties of modern H₁R-antihistamines which are not found in antihistamines of the first generation it is more likely that the positive effects of up-dosing are based on extended modes of action.

Further research is needed to better understand this as well as the role of other histamine receptors than H₁R-receptors in the pathogenesis of urticaria.

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