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REVIEW ARTICLE

H1-Antihistamines for Allergic Diseases: Old Aged but Not Old-Fashioned Drugs

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Histamine is a chemical messenger synthesized from the amino acid histidine by L-histidine decarboxylase. It plays an important role in the system of immunoregulation and in acute and chronic allergic inflammation binding to four subtypes of receptors H1, H2, H3 and H4, described as heptahelical transmembrane molecules that activate specific G-proteins. These receptors placed on the membranes of different cellular jambs (mast cells, endothelial cells, sensory nerve fibres, bronchial smooth muscle) cause different biological actions: Vasodilatation, increased vascular permeability, itching, smooth muscle contraction, coronary spasm, sleep-wake rhythm regulation. Histamine interaction with H1-receptors potentially leads to increasing antigen-presenting cell capacity, release of histamine and other mediators from mast cells and basophils inducing cellular adhesion molecule expression and chemotaxis of eosinophils and neutrophils [1-3].

H1-antihistamines were introduced for clinical use in 1942 [4] and since then more than 45 H1-antihistamines have been available worldwide representing the largest class of medications used in the treatment of allergic diseases [2]. H1-antihistamines are functionally classified into two groups: First generation and second generation antihistamines. The older, so-called first generation H1-antihistamines, such as Chlorpheniramine, Diphenydramine, Doxepin, Hydroxyzine after oral or parenteral administration are metabolized in the liver and excreted in large part with the urines. Pharmacological action occurs after 30-60 minutes and persists for about 4-6 hours. First generation antihistamines are characterized by poor receptor selectivity and therefore correlated with side effects such as antimuscarinic, anti-alfa adrenergic and anti-serotoninergic effects [5]. Once introduced systemically they may also cause drowsiness, sedation, and somnolence as a consequence of crossing the blood-brain barrier [6]. Among first generation H1-antihistamines chlorpheniramine is, even nowadays, the most used especially for emergency treatment and prevention of severe systemic allergic reactions such as anaphylaxis due to adverse reactions to food, drugs or Hymenoptera [7]. Premedication with chlorpheniramine is also prescribed in association to systemic corticosteroids in patients with a positive history of severe allergic reactions before undergoing surgery [8].

In the 1980s newer second generation H1-antihistamines were introduced and described as non-sedating. It has been shown that second generation H1-antihistamines cross the blood-brain barrier to a significantly smaller extent than their predecessors thus decreasing H1-antihistamine concentration at the level of the central nervous system [2,9]. Recently, it has been shown that a new H1-antihistamine, bilastine, does not cross the blood brain barrier as it is a substrate for P-glycoprotein, a high molecular weight protein, increasing the safety profile of this drug [10].

Second generation H1-antihistamine administration can be oral, topical nasal, ocular and cutaneous, with a half-life of 24 hours. It has been shown that second-generation H1-antihistamines inhibit allergy induced inflammation reducing the production of proinflammatory TH2 cytokines such as IL-4 and IL-13 as well as chemokines, interfere with the recruitment

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of eosinophils in the late phase allergic reaction, down regulate the expression of membrane receptors at the level of nasal epithelial cells and of the vascular endothelium [11]. Among second generation H1-antihistamines, cetirizine, loratadine, levocetirizine, desloratadine and rupatadine can be prescribed to patients over 2 years of age, while fexofenadine, mizolastine, ebastineand bilastine can be prescribed only over 12 years of age. The most used topical H1-antihistamines are azelastine (ocular and nasal) and ketotifen (ocular) [12].

Second generation H1-antihistamines are favoured compared to those of the first generation, both in the light of their anti-allergic-anti-inflammatory activity and of their good safety profile [13]. Furthermore, these molecules have been found to be effective both in the treatment of acute allergic episodes and in long-term prophylaxis [14].

In patients with allergic rhinitis, oral second-generation H1-antihistamines prevent and relieve the itching, sneezing and rhinorrhea. Topical nasal H1-antihistamine formulations have a more rapid onset of action than oral formulations (e.g. 15 minutes for nasal azelastine vs. 150 minutes for oral desloratadine), usually improving symptoms in patients who are unresponsive to oral H1-antihistamines and in patients with vasomotor rhinitis [15,16].

In light of the pathophysiological and clinical evidence of the existence of a relationship between the upper and lower airways, the role of H1-antihistamine therapy, as an additional benefit in the control of asthma symptoms in patients with concomitant allergic rhinitis, has been discussed [17,18].

H1-antihistamines are used in patients with urticaria, decreasing itching and reducing the number, size and duration of wheals and flares. Cetirizine and levocetirizine are reported to reduce acute urticaria in young, atopic children [19,20]. In general second-generation H1-antihistamines (cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, bilastine, and rupatadine) reduce symptoms and improve quality of life in patients with chronic urticaria. In these patients, the standard once-daily dose is usually effective but it has been suggested in patients with unresponsive chronic urticaria to progressively increase the dose up to four-fold, because of their safety profiles [21,22].

Oral H1-antihistamines for the treatment of atopic dermatitis is still under discussion, as itching has a complex pathogenesis, which is not only linked to the release of histamine. It has recently been reported that the predominant component of itching in atopic dermatitis is mediated by PAR-2 receptors, present on keratinocytes and on other skin cells and activated by proteases. Furthermore, topical use of H1-antihistamines is also not indicated due to the possible risk of systemic absorption through the skin or the occurrence of contact allergy. Therefore, the use of H1-antihistamines in the management of atopic dermatitis is not recommended [23,24].

First generation H1 antihistamines are also suggested as a prolonged, life-long daily treatment for cutaneous and systemic mastocytosis in order to improve the health of these patients [25].

H1-antihistamines can also be administered in special situations such as pregnancy and breast feeding. In pregnancy there is documented evidence of safety regarding only second-generation H1-antihistamines. Cetirizine, loratadine and bilastine seem to present a higher safety profile than other second-generation antihistamines, also during breastfeeding. These drugs can be used either on demand, if symptoms occur occasionally, or for prolonged, at least 60 days, in the case of perennial rhinitis or chronic urticaria [26,27].

Topical ocular H1-antihistamines, such as ketotifen or azelastine, can be used in patients with allergic conjunctivitis, improving itching, erythema, tearing and oedema. Ophthalmic formulations have a rapid onset of action (3-15 minutes) and improve also nasal symptoms [28].

H1-antihistamines, therefore, even if they were introduced in the second half of the past century, are still considered up to date for the treatment of acute or chronic allergic reactions and for their prophylaxis [29].

Even in the third millennium the only available parenteral H1-antihistamine is chlorpheniramine, a first generation antihistamine. The current role of second generation H1-antihistamines, which have outweighed first generation ones, is of first choice for treatment of allergic reactions both, IgE and non-IgE mediated, while new possible uses of these molecules also in non-allergic diseases is to be expected based on the predominantly anti-inflammatory role targeting the immune system [30]. Further studies should also highlight the role played from antihistamines directed against other receptors, in particular on H3 and H4 receptors.

H1-antihistamines are therefore to be considered of great actuality, especially first generation ones, because of their present multiple use, high efficacy and safety standards.

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