Second-Generation Antihistamines
A Comparative Review

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Abstract

Second-generation histamine H1 receptor antagonists (antihistamines) have been developed to reduce or eliminate the sedation and anticholinergic adverse effects that occur with older H1 receptor antagonists. This article evaluates second-generation antihistamines, including acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, ketotifen, loratadine, mizolastine and terfenadine, for significant features that affect choice.

In addition to their primary mechanism of antagonising histamine at the H1 receptor, these agents may act on other mediators of the allergic reaction. However, the clinical significance of activity beyond that mediated by histamine H1 receptor antagonism has yet to be demonstrated.

Most of the agents reviewed are metabolised by the liver to active metabolites that play a significant role in their effect. Conditions that result in accumulation
of astemizole, ebastine and terfenadine may prolong the QT interval and result in torsade de pointes. The remaining agents reviewed do not appear to have this risk.

For allergic rhinitis, all agents are effective and the choice should be based on other factors. For urticaria, cetirizine and mizolastine demonstrate superior suppression of wheal and flare at the dosages recommended by the manufacturer. For atopic dermatitis, as adjunctive therapy to reduce pruritus, cetirizine, ketotifen and loratadine demonstrate efficacy. Although current evidence does not suggest a primary role for these agents in the management of asthma, it does support their use for asthmatic patients when there is coexisting allergic rhinitis, dermatitis or urticaria.

Histamine was first identified by Sir Henry Dale in 1910, and by the 1920s it was recognised as a major pathogenic mediator of allergic disorders such as rhinitis and urticaria. In 1937, the first histamine receptor antagonist was discovered by Staub and Bovet, which resulted in the latter’s receiving the Nobel Prize for physiology and medicine in 1957. From 1942 to 1981, more than 40 compounds belonging to the so-called ‘first generation’ of histamine receptor antagonists reached the market. However, these first-generation agents demonstrated CNS activity and poor receptor specificity, which resulted in marked sedation and anticholinergic effects that many patients were unwilling to tolerate.

In an effort to improve the selectivity and tolerability of H1 antagonists and to ameliorate their sedative and anticholinergic adverse effects, a new or second generation of antihistamines was developed and introduced. The term ‘second-generation antihistamine’ awaits a consensus definition. Here it is defined as an antihistamine which reached the market after 1980 and demonstrates one or more of the following properties: (i) improved H1 selectivity; (ii) absence of sedation; or (iii) antiallergic properties apart from antihistaminic activity. The first of the new second-generation antihistamines to reach the market were terfenadine and astemizole in 1981. Others that have joined the market since then include: acrivastine (worldwide), azelastine (Africa, Europe, North America), cetirizine (Europe, North America, Australasia), ebastine (Europe), emedastine (Asia, North America), fexofenadine (Europe, North America), ketotifen (Asia, Europe, Australasia), levocabastine (Africa, Europe, Indonesia, North America), loratadine (worldwide), mizolastine (Europe) and oxatomide (Africa, Asia, Europe, South America).

The purpose of this article is to review selected second-generation H1 receptor antagonists for similarities, differences and liabilities that affect the choice of drug for allergic disorders, including seasonal and perennial allergic rhinitis, chronic idiopathic and physical urticaria, atopic dermatitis and allergic asthma. The agents selected for review have met one of 3 selection criteria: (i) available as an oral agent in most countries (acrivastine, astemizole, loratadine and terfenadine); (ii) available as an oral agent in several countries and extensive studies have been published in the literature (azelastine, cetirizine and ketotifen); or (iii) available as an oral agent in some countries and showing promise for widespread use (ebastine, fexofenadine and mizolastine).

1. Mechanism of Action

At low concentrations, antihistamines are reversible competitive antagonists of histamine at H1 receptor sites. Antagonism results in decreased vascular permeability, reduction of pruritus and relaxation of smooth muscle in the respiratory and gastrointestinal tracts.

In addition to antagonising the effect of histamine, the newer second-generation agents have other actions that may contribute to their antiallergic effectiveness. They interfere with mediator release from mast cells by inhibiting either calcium ion influx across mast cell/basophil plasma mem-