

EDITORIAL

Clinical and Experimental Allergy

Comparing the new antihistamines: the role of pharmacological parameters

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Introduction

Antihistamines are widely used in the management of allergic disorders. The newer second-generation H_1 -receptor antagonists are now preferred to first-generation agents because of their lower risk of side-effects. A recent review by Tillement of the pharmacological profiles of the new antihistamines published in the May issue of *Clinical & Experimental Allergy Reviews* [1] raises some interesting points with regard to differentiation between the various second-generation agents. Pharmacological differences between H_1 antihistamines are highlighted, and it is suggested that these may translate into clinical differences when the agents are used in practice. However, although pharmacology may provide a potential guide to effectiveness and safety, it is important when comparing agents that pharmacological parameters are not examined in isolation, without considering clinical evidence.

H_1 -receptor binding

The H_1 antihistamines bind to the histamine H_1 receptor and stabilize it in the inactive conformation, shifting the basal equilibrium between the active and inactive states towards the inactive form, thus reducing the physiological effects of histamine. Because they act in an agonistic (rather than antagonistic) way to decrease the constitutive activity of the H_1 receptor, they have recently been reclassified as 'inverse agonists' [2]. However, given that the H_1 antihistamines block both the histamine (agonist)-induced and the constitutive activity of the H_1 receptor, the term 'double antagonist' may in fact be a more appropriate way of describing these agents [1]. The reduction of the constitutive activity of the H_1 receptor might

provide an explanation for clinical observations of an improvement in acute symptoms of allergic rhinitis following treatment with the antihistamine cetirizine, despite the fact that histamine is not being released into the systemic circulation [1]. However, an alternative explanation for such observations is that histamine released into the nasal mucosa is rapidly degraded before being absorbed into the blood stream [3] and that antihistamines relieve symptoms by efficient blockade of local H_1 -receptor-mediated effects.

The anti-cholinergic activity of H_1 antihistamines was of concern with first-generation agents and has been associated with xerostomia (dry mouth) and mydriasis (pupillary dilatation). Several of the newer H_1 -receptor antagonists (fexofenadine and levocetirizine) do not show significant interaction with muscarinic receptors and hence are unlikely to have unwanted anti-cholinergic effects. Conversely, desloratadine shows a relatively high-affinity for muscarinic receptors in binding assays; it has therefore been suggested that desloratadine is likely to induce muscarinic side-effects [1]. However, the affinity of desloratadine for muscarinic receptors is approximately 50 to 100-fold weaker than that for H_1 receptors. The peak plasma concentrations of desloratadine at recommended doses for antihistaminic activity are approximately 10-fold lower than the concentrations required to exert functional antimuscarinic activities [4–6]. The occurrence of muscarinic side-effects is, therefore, very unlikely. This is supported by the lack of a significant increase in anticholinergic adverse events in clinical trials with desloratadine relative to placebo [7], demonstrating the importance of considering pharmacological findings in conjunction with pharmacokinetic data and clinical evidence.

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Central nervous system and cardiovascular effects

An important differentiating factor between antihistamines is the degree of sedation that they cause. In addition

to lipophilicity and level of ionization, recent developments have shown that the central nervous system (CNS) concentrations of drugs are controlled by the P-glycoprotein (P-gp) transporter system [8, 9]. The newer antihistamines are generally non-sedating at recommended dosages, possibly as a result of active efflux of the drug from the brain by P-gp (as demonstrated in P-gp knockout mice and P-gp transfected cells) [10, 11]. In these experimental models, desloratadine showed higher P-gp-mediated efflux transport than did cetirizine. Because P-gp is only one of the numerous efflux transporters that may control the brain distribution of H₁ antihistamines, a comparison of antihistamines based on efflux transporters is far from complete. In addition, because both influx and efflux transporters are involved in the distribution of H₁-receptor antagonists in the brain, these should be investigated in conjunction with each other to gain a fuller picture. The complexity of the mechanisms involved in the regulation of the brain distribution of H₁-receptor antagonists emphasizes the need for an accurate clinical evaluation of the sedative properties of antihistamines. In contrast with the first-generation antihistamines, desloratadine, levocetirizine, and other second-generation antihistamines appear to be free from sedative effects and do not impair driving or psychomotor performance in healthy subjects [12–14]. However, the newer antihistamines may still be associated with some degree of sedation in patients with allergic diseases. For example, a large prescription-monitoring study in more than 40 000 patients showed that cetirizine carried a risk of sedation that was 3.5 times that of loratadine although both drugs are classified as second-generation antihistamines [15]. Likewise, in the large Xyzal in Persistent Rhinitis Trial, XPERT, 6.8% of patients treated with levocetirizine reported somnolence versus 1.8% of those treated with placebo [16].

Another differentiating factor between antihistamines is their cardiovascular effects. Two early second-generation H₁ antihistamines, astemizole and terfenadine, blocked the rapid component of the delayed rectifier potassium current. Thus, they had the potential for a range of cardiac effects, including prolongation of the QT interval, which can induce torsade de pointes [17]. However, it was concluded in a recent review that currently approved second-generation H₁ antihistamines, including loratadine, desloratadine, cetirizine, and fexofenadine, appear to be relatively free of cardiotoxic effects [17]. Loratadine has been reported to interact with human ether-a-go-go-related gene (HERG)-encoded cardiac K⁺ channels, at submicromolar concentrations in one study [18] and at higher concentrations in others [19, 20], although the concentrations tested in these studies have no clinical relevance. No interaction with this cardiac channel appears to have been reported with the active metabolite of loratadine, desloratadine, and cardiac safety has been demonstrated with both drugs. Indeed, in the

clinical setting, no QT-interval prolongation has been reported with either loratadine or desloratadine administered at up to nine times the recommended dose in healthy volunteers or with desloratadine administered in combination with ketoconazole or erythromycin in the clinical situation [21]. Furthermore, the alleged cardiotoxicity with loratadine in some reports is not considered a clinical issue.

Volume of distribution

Another pharmacological measure that varies between second-generation H₁ antihistamines is volume of distribution (V_D), the apparent volume in which a determined dose of a drug distributes itself in the body at equilibrium. It has been suggested that a small V_D may be associated with a lower likelihood of toxicity, because any interaction with intracellular receptors in essential organs is limited [22]. Thus, it might be expected that the low V_D of cetirizine and levocetirizine would be associated with greater safety and efficacy [1]. However, low V_D by itself is an inappropriate parameter for either safety or efficacy assessments. For example, terfenadine has a low V_D of approximately 2.5 L/kg [23] but has been associated with cardiotoxicity: elevated terfenadine levels are associated with delayed cardiac repolarization and ventricular tachyarrhythmias. Conversely, a higher V_D does not necessarily imply a greater risk of toxicity, which only occurs if tissue contains drug-activated targets involved in cellular toxicity. Desloratadine, despite a higher V_D than that of cetirizine or levocetirizine, has been shown to be safe at up to nine times the clinical dose and does not require dose reductions when administered to elderly patients [7]. Furthermore, it is the ability of a molecule to exert a pharmacological effect at the plasma concentrations reached with recommended daily doses, rather than the magnitude of its V_D , that determines its clinical efficacy. However, it is clear that V_D is one of the pharmacokinetic parameters that can affect plasma concentrations. The time required to reach sufficient plasma concentrations for an efficient blockade of H₁ receptors is related to both bioavailability and absorption. Unfortunately, data on the time required to reach therapeutic concentrations are scarce. Although cetirizine and levocetirizine appear to have some of the shortest times to maximal inhibition of histamine-induced cutaneous response, this pharmacodynamic parameter does not accurately predict the onset of efficacy in the clinical situation.

Summary

A variety of pharmacokinetic and pharmacodynamic parameters can be used to compare the second-generation H₁ antihistamines. However, the real meaning of such pharmacokinetic and pharmacodynamic differences in

the actual clinical situation is not clear. Although pharmacological parameters may provide valuable insights into the characteristics of H₁ antihistamines, they should be interpreted with caution and cannot substitute for clinical evidence. Only clinically meaningful differences in efficacy or safety in patients treated for naturally occurring disease are relevant as a means of differentiating between antihistamines. If such differences are observed, then exploring the specific pharmacological profiles of the second-generation antihistamines may be a valid means of further comparison.

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