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Antihistamines: topical vs oral administration

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Summary

The pathogenesis of allergic rhinitis is complex, involving not only histamine and mast cell-derived tryptase, but also eosinophil- and neutrophil-derived mediators, cytokines, and intercellular cell adhesion molecules (ICAM-1). It is surprising that antihistamines, which block only one component of the process, have proved so effective in the management of allergic rhinitis. Research has therefore focused on whether antihistamines have additional pharmacological activities. *In vitro* studies have shown that high concentrations of second generation antihistamines can block inflammatory mediator release from basophils and mast cells, and reduce ICAM-1 expression in epithelial cell lines. *In vivo* studies have also shown an effect on the allergen-induced inflammatory reaction; both oral and intranasal antihistamines cause a reduction in nasal symptoms and inflammatory cell influx. Oral terfenadine and cetirizine and intranasal levocabastine and azelastine have also demonstrated a lowering of ICAM-1 expression on epithelial cells. With regard to clinical efficacy, topical levocabastine (0·5 mg/mL eye drop solution and 0·5 mg/mL nasal spray) was shown to be more effective than oral terfenadine (60 mg twice daily) in relieving ocular itch ($P = 0{\cdot}02$) and reducing nasal symptoms in allergic rhinoconjunctivitis. In a further study, levocabastine eye drops were as effective and well tolerated as sodium cromoglycate in seasonal allergic rhinitis. Intranasal azelastine (0·28 mg twice daily) showed a trend for superior relief of rhinorrhoea and nasal obstruction compared with oral terfenadine (60 mg twice daily). In addition, intranasal azelastine (0·28 mg twice daily) resulted in significant reductions in sneezing, nasal obstruction, rhinorrhoea and itching in perennial rhinitis, compared with the lower efficacy of beclomethasone dipropionate (0·1 mg twice daily). As well as benefits in efficacy, topical administration is associated with improved safety. Some antihistamines, particularly those metabolized in the liver, are associated with occasional reports of severe side-effects. It is therefore logical to administer antihistamines directly to the target organ.

The pathogenesis of allergic rhinitis

The pathogenesis of allergic rhinitis is complex, involving many different cell types, inflammatory mediators, cytokines and adhesion molecules. Indeed, a recent study including 30 adults with seasonal allergic rhinitis recruited during the pollen season showed that in addition to mast cell-derived tryptase (MCT) and histamine, eosinophil cationic protein (ECP), myeloperoxidase (MPO), prostaglandin D_2 (PGD_2) and leukotriene C_4 (LTC_4) were detected in the nasal lavage fluid, indicating the involvement of eosinophils and neutrophils. Interleukin-8 (IL-8) and RANTES, and soluble-intercellular adhesion molecule (sICAM-1) were also present in nasal lavage fluid, underlining the importance of chemokines and adhesion molecules (Fig. 1).

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Mast cell- and eosinophil-derived mediators increase in nasal lavage fluid after direct allergen challenge and can be influenced further by exposure to air pollutants, such as nitrogen dioxide, which acts by priming eosinophils [1] (Fig. 2).

Epithelial cells are likely to be involved in the pathogenesis of allergic rhinitis through production of

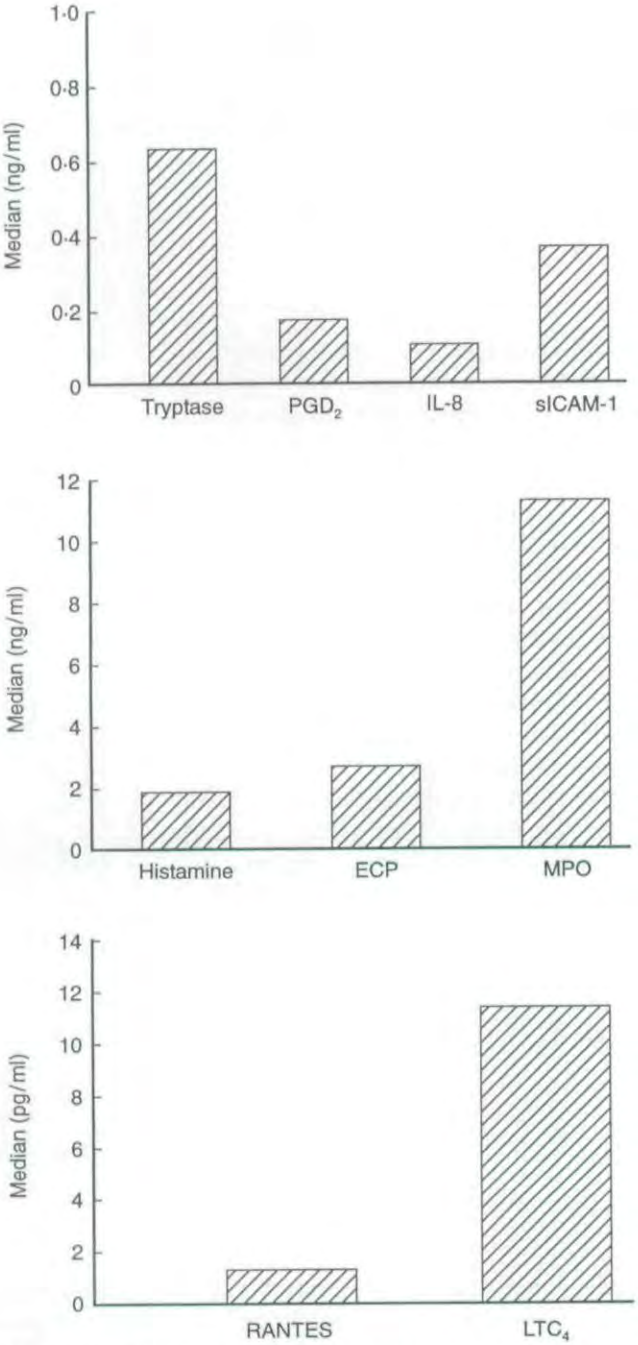

Fig. 1. The levels of inflammatory mediators, cytokines and adhesion molecules in the nasal lavage fluid of adults with seasonal allergic rhinitis during the pollen season.

cytokines which are chemoattractant for both mast cells and eosinophils. We have cultured nasal epithelial cells from biopsies of the inferior turbinates of well characterized atopic rhinitic, atopic non-rhinitic and non-atopic non-rhinitic subjects and measured the amount of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-8 and tumour necrosis factor-α (TNFα) released into the culture medium by these cells. Cell cultures from the atopic individuals released significantly greater amounts of IL-8, TNFα and GM-CSF than cell cultures from non-atopic individuals ($P < 0{\cdot}05$). Of the atopic individuals, cell cultures from those with rhinitis released the highest quantity of these cytokines. IL-8 release was the greatest and GM-CSF the least, irrespective of whether the cell cultures were derived from atopic or non-atopic subjects [2]. Importantly, the conditioned medium from atopic rhinitic patients in particular showed chemotactic activity for human eosinophils, probably due to the presence of RANTES (Fig. 3).

The actions of histamine

Histamine released from mast cells and basophils causes the symptoms of itch, pain and sneezing through stimulation of the afferent cutaneous nerve endings of the trigeminal nerve situated in the nasal epithelium. Of particular importance is the action of histamine on the subepithelial blood vessels, causing vasodilatation, hyperaemia and oedema through plasma exudation, which contribute to the symptoms of nasal blockage and rhinorrhoea. Contrary to findings from previous *in vivo* experimental work, histamine does not directly influence epithelial permeability [3]; exudation of plasma into the nasal cavity is due to extravasated fluid from postcapillary venules exerting lateral pressure on epithelial cells, causing temporary and reversible separation of the tight junctions [4,5] (Fig. 4).

Antihistamines

It is perhaps surprising, given the many mediators and cytokines involved in the pathogenesis of allergic rhinitis, that drugs such as antihistamines are so effective in the management of this disorder, since they block only one component of the process. This has led to a considerable research effort to explore other pharmacological activities of this group of drugs.

Anti-allergic and anti-inflammatory actions

In vitro *In vitro* studies have shown that high concentrations of histamine (H_1) antagonists are able to block mediator release from basophils and human mast cells. At concentrations ranging from 1 to 50 μM, loratadine blocks the release of histamine from basophils [6] and terfenadine inhibits the release of eicosanoids from mast cells and macrophages [7]. The mechanisms involved are not completely understood, though Berthon *et al.* [8] have shown that loratadine impairs the increase in

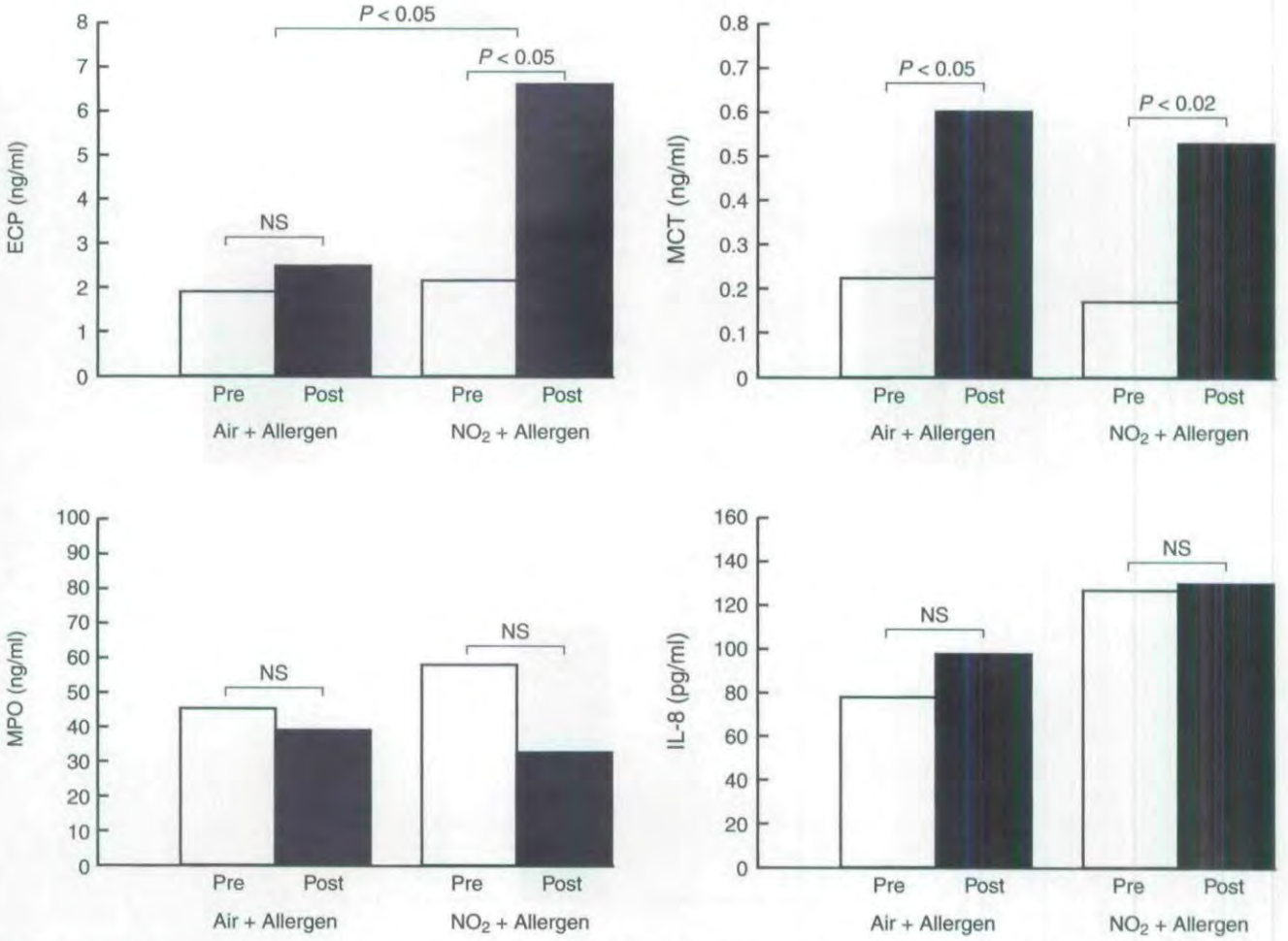

Fig. 2. The effect of 6 h pre-exposure to air or 400 ppb nitrogen dioxide (NO_2) on ECP, MCT, MPO and IL-8 concentration in the nasal lavage fluid collected 30 min after allergen challenge. From [1] with kind permission.

intracellular Ca2+ following cell activation, by decreasing the influx of extracellular Ca2+ and inhibiting the release of Ca2+ from intracellular stores. Loratadine has also been shown to inhibit the release of LTC_4 and histamine from cloned murine cells [9] and cetirizine has been shown to inhibit platelet activating factor (PAF)-induced migration of eosinophils *in vitro* and *in vivo* [10]. Azelastine inhibits both histamine release from human basophils and LTC_4/LTD_4 from neutrophils, while the stabilizing action on lung mast cells requires long preincubation [11]. Terfenadine and cetirizine are capable of reducing the *in vitro* expression of ICAM-1 on epithelial cell lines [12]. These actions are thought to be separate from the H_1 receptor blocking activity of the antihistamines.

In vivo A number of *in vivo* studies have been performed to assess the clinical effectiveness of antihistamines in inhibiting the allergen-induced inflammatory process in the nasal mucosa and the conjunctiva. In a double-blind, crossover study, Bousquet *et al.* [13] demonstrated the clinical efficacy of terfenadine (60 mg twice daily) and loratadine (10 mg once daily) on nasal allergen challenge and also showed that there was a significant reduction in the release of PGD_2 in nasal secretions in the loratadine-treated group. In addition, Ciprandi *et al.* [14,15] demonstrated that loratadine exerted a significant protective effect both on the early and late-phase allergen-induced reactions in the conjunctiva, reducing cellular infiltration.

The higher concentrations of antihistamines achievable by topical as opposed to oral administration should enhance any anti-allergic or anti-inflammatory activity possessed by these drugs. Pazdrak *et al.* [16] showed that treatment with levocabastine (0·5 mg/mL solution) caused a significant reduction in nasal symptoms and inflammatory cell influx of eosinophils and neutrophils after allergen challenge, as compared with placebo

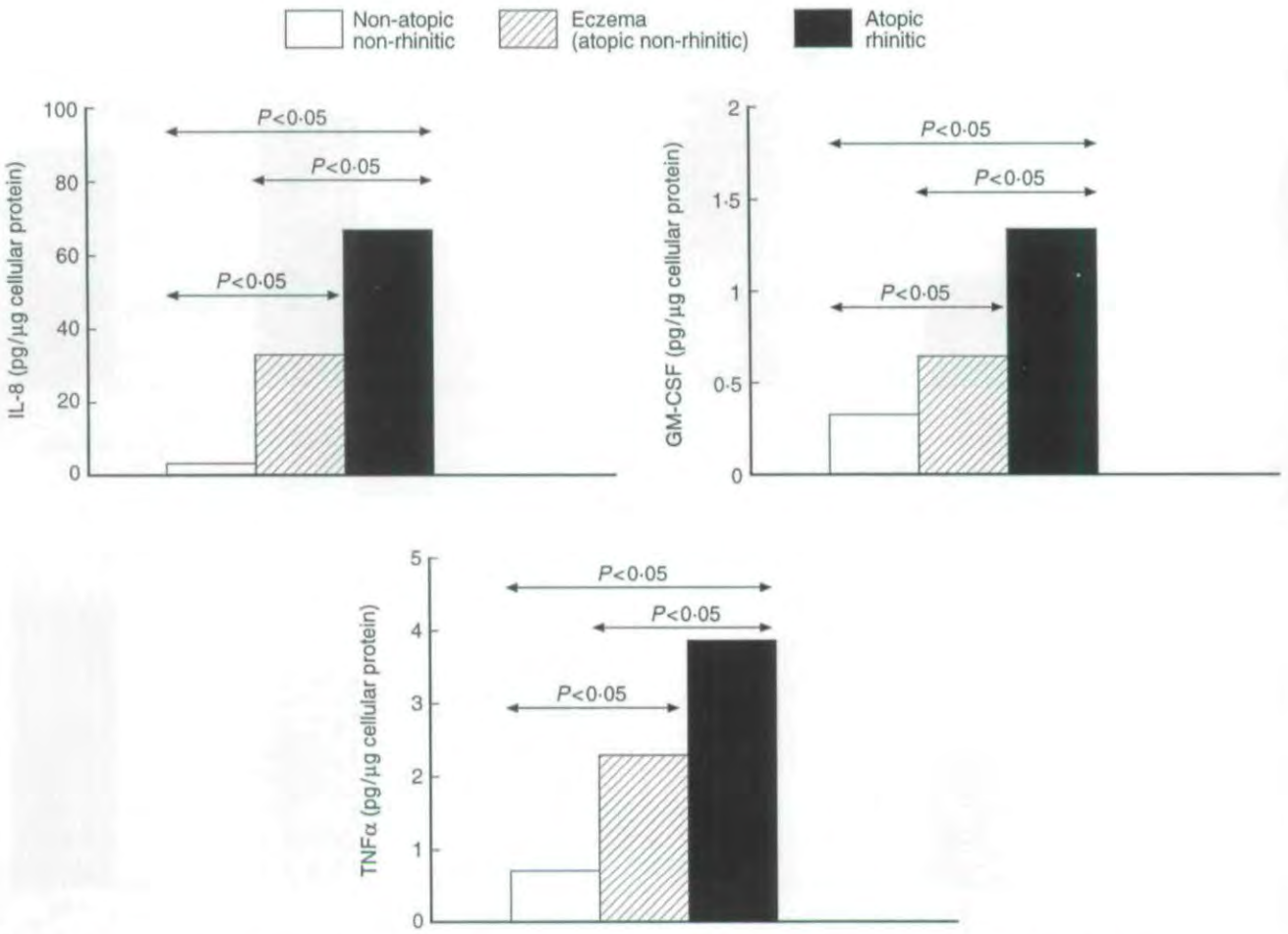

Fig. 3. Synthesis of IL-8, GM-CSF and TNFα by cultured human nasal epithelial cells. From [2] with kind permission.

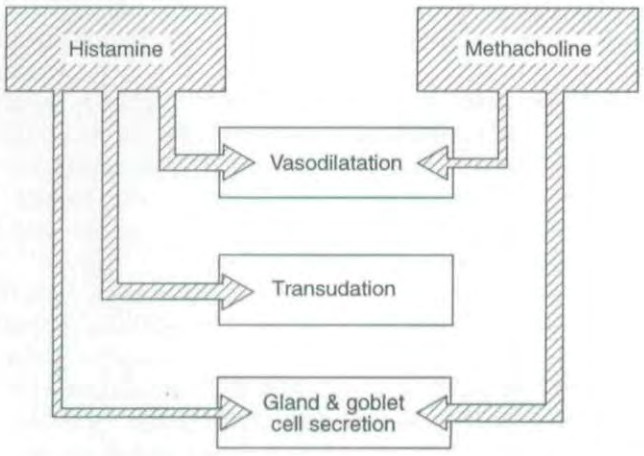

Fig. 4. The effects of histamine and methacholine on the nasal mucosa. From [5] with kind permission.

administration. Van Wauwe [17], using histamine as well as allergen provocation, showed a marked decrease in vascular permeability after the use of topical levocabastine compared with placebo.

Recently, attention has focused on the effects of both orally and topically administered antihistamines with regard to expression of the adhesion molecule ICAM-1 on epithelial cells in the conjunctiva and the nose. ICAM-1 plays a key role in the capture of inflammatory cells in the epithelium through binding with its counter-receptors, LFA-1 and Mac-1 (CD11b), on eosinophils and neutrophils. Indeed, intravenous treatment with an anti-ICAM-1 monoclonal antibody has been shown to attenuate allergen-induced airway eosinophilia and associated bronchial hyperresponsiveness in a primate model of asthma [18]. In a recent study, the effect of cetirizine (20 mg daily for 3 days) on the early and late responses induced by conjunctival allergen provocation testing was assessed in a double-blind, randomized, placebo-controlled study. Compared with placebo,

cetirizine treatment led to significantly lower symptom scores, inflammatory cell infiltration, and expression of ICAM-1 on epithelial cells after allergen provocation. In a similarly designed study, terfenadine, administered at a dose of 120 mg/day for 7 days, reduced infiltration into the nasal mucosa and expression of epithelial ICAM-1 when compared with placebo in 20 patients with allergic rhinitis studied during the pollen season [19]. The same group studied the effects of topically applied levocabastine (one drop to each eye 30 min before allergen challenge) and azelastine (one spray, 0·14 mg into each nostril 30 min before allergen challenge) in double-blind, randomized, placebo-controlled trials. Both antihistamines significantly reduced inflammatory cell infiltration and epithelial cell ICAM-1 expression compared with placebo [20,21]. However, from the published results to date, there does not appear to be any advantage of topically applied over systemic antihistamines in terms of the extent of inhibition of ICAM-1 expression, inflammatory cell infiltration, or clinical efficacy.

Onset of action

The second generation antihistamines are well absorbed when taken orally, with peak plasma concentrations being achieved within 30 min to 4 h. There is evidence that the clinical onset of action of antihistamines may be faster than is indicated by the time needed to reach maximum plasma concentration. In a recent placebo-controlled, randomized, double-blind, 1-day field study, the efficacy and onset of action of acrivastine (8 mg) were evaluated in 42 patients suffering from allergic rhinoconjunctivitis elicited by natural grass pollen exposure. The time of onset of clinical effectiveness (inhibition of nasal symptoms) using an exponential decay model was 19 min [22]. This remarkably rapid onset of clinical effectiveness parallels the speed of action of topically applied antihistamines.

Janssens and Vanden Bussche [23] found that 73% of patients reported symptom relief within 30 min of topical administration of levocabastine to the nasal mucosa. Janssens [24] also found levocabastine to be effective in the treatment of ocular symptoms, with 94% of patients experiencing symptom relief within 15 min after the first instillation of levocabastine eye drops. In our study, topical azelastine 0·28 mg applied to each nostril had a rapid (within 30 min) and long-acting (up to 10 h) inhibitory effect on allergen-induced sneezing [25].

Efficacy

Conjunctival and nasal provocation studies have been carried out in order to assess the efficacy of topical and oral preparations of antihistamines. In a randomized, double-blind, double-dummy, parallel-group study, Bahmer and Ruprecht [26] compared the safety and efficacy of topical levocabastine (0·5 mg/mL eye drop solution — one drop in each eye twice daily; and 0·5 mg/mL nasal spray solution — two sprays in each nostril twice daily) and oral terfenadine (60 mg twice daily). It was demonstrated that levocabastine was significantly more effective than terfenadine in relieving ocular itch ($P = 0·02$). The patients' symptom scores also yielded better results with levocabastine, particularly with respect to nasal symptoms. In conclusion, the authors reported that topical levocabastine was a well tolerated and effective alternative to oral terfenadine for the treatment of allergic rhinoconjunctivitis. In a double-blind, randomized study, Wihl *et al.* [27] compared levocabastine eye drops and sodium cromoglycate in seasonal allergic conjunctivitis. Levocabastine eye drops applied twice daily were as effective and well tolerated as sodium cromoglycate eye drops applied four times daily.

The efficacy and tolerability of intranasal azelastine has also been evaluated in a number of clinical trials. Gastpar *et al.* [28] compared the efficacy of intranasal azelastine (0·28 mg twice daily) with that of oral terfenadine (60 mg twice daily) in a double-blind, parallel group study in patients with perennial rhinitis. Azelastine showed a trend towards superior relief of rhinorrhoea and nasal obstruction, whereas terfenadine showed a trend towards better control of sneezing and nasal itching. However, no clinically relevant statistically significant differences between the active treatments were observed in this study. We compared azelastine nasal spray (0·28 mg twice daily) with beclomethasone dipropionate (0·1 mg twice daily) in a double-blind, randomized, parallel-group, placebo-controlled study involving 130 patients, to assess the effect of 6 weeks' treatment on the symptoms of perennial rhinitis [29]. Efficacy was assessed by patients recording the severity of the symptoms of rhinitis daily on 10 cm visual analogue scales. Analysis of the diary data showed significant reductions in sneezing, nasal obstruction, rhinorrhoea, and itching during azelastine treatment. Patients on beclomethasone dipropionate recorded a consistent reduction in rhinitis symptoms, but these reductions were significant only for sneezing on treatment day 7.

Safety

Of the second generation antihistamines, terfenadine and astemizole are the least sedative. Terfenadine has been evaluated extensively in psychomotor tests of visual and motor ability, mathematical ability, driving performance,

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