

H₁ ANTIHISTAMINES IN ALLERGIC DISEASE

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ABSTRACT

Histamine (one of the key mediators released from mast cells and basophils), plays a major role in the pathophysiology of allergic diseases, including rhinitis, urticaria, asthma and anaphylaxis. Histamine exerts its effects through its interaction with one of four distinct receptors (H₁, H₂, H₃, H₄). In allergic disease, it is the H₁ antihistamines which are of primary benefit, although H₂ antihistamines may also play a therapeutic role.

H₁ antihistamines remain first-line medications for the treatment of allergic rhinoconjunctivitis and urticaria. Second-generation antihistamines are preferred to their predecessors because of better benefit-to-risk ratios. The newer antihistamines are not only more potent, but also have anti-allergic and anti-inflammatory properties. Although they are more expensive than the traditional antihistamines, the cost is substantially offset by their superior efficacy and safety profile when used in recommended dosages.

CLASSIFICATION

H₁ antihistamines are classified into the older, or first-generation, antihistamines, and the newer, or second-generation, antihistamines. The main differences between the two generations of drugs are their propensity to cause central nervous system (CNS) side-effects. The commonly used members of these drug classes are listed in Table I. The highly lipophilic nature of the *first-generation antihistamines* allows them to penetrate well into the CNS where they induce sedation. The potential to enhance the central effects of alcohol and other CNS sedatives further limits such use. In addition, many of these drugs also have actions which reflect their poor receptor selectivity, including an atropine-like effect (anticholinergic) and blockade of both α -adrenergic and 5-hydroxytryptamine receptors (muscarinic effect) Tachyphylaxis is also a problem with the use of the older antihistamines.

Table I. Common H₁-receptor antagonists

First generation	Second generation*
Hydroxyzine	Cetirizine
Diphenhydramine	Loratadine
Chlorpheniramine	Desloratadine
Promethazine	Fexofenadine
	Levocetirizine

*Two earlier developed agents, astemizole and terfenadine, were withdrawn in 1986 because of cardiac toxicity adverse effects.

The *second-generation H₁ antihistamines* cause much reduced CNS sedation and are essentially free of this effect at doses recommended for the treatment of allergic disorders. In addition, these drugs have few or no anticholinergic or other effects. Some second-generation drugs have also been claimed to have anti-allergic and anti-inflammatory effects which may contribute to their therapeutic benefit.¹

MECHANISM OF ACTION

H₁ antihistamines are not receptor antagonists as previously thought, but are *inverse agonists*.² When neither histamine nor antihistamine is present, the active and inactive states of the H₁ receptor are in equilibrium or a balanced state. Histamine combines preferentially with the active form of the receptor to stabilise it and shift the balance towards the activated state and stimulate the cell (Fig. 1).³ Antihistamines stabilise the inactive form and shift the equilibrium in the opposite direction. Thus, the amount of histamine-induced stimulation of a cell or tissue depends on the balance between histamine and H₁ antihistamines.

Histamine effects stimulated through the H₁ receptor include pruritus, pain, vasodilatation, vascular permeability, hypotension, flushing, headache, tachycardia, bronchoconstriction, and stimulation of airway vagal afferent nerves and cough receptors as well as decreased atrioventricular-node conduction. Although most of the effects of histamine in allergic diseases are mediated by H₁ receptor stimulation, certain effects such as hypotension, tachycardia, flushing, headache, itching and nasal congestion are mediated through both H₁ and H₂ receptors.⁴

In the CNS, the effects histamine exerts through H₁ receptors include cycle of sleep and waking, food intake, thermal regulation, emotion and aggressive behaviour, locomotion, memory and learning. *First-generation H₁ antihistamines*, such as chlorphenamine, diphenhydramine, hydroxyzine and promethazine, penetrate readily into the brain, in which they occupy 50-90% of the H₁ receptors.⁵ The result is CNS sedation. In contrast, *second-generation H₁ antihistamines* penetrate the CNS poorly, as they are actively pumped out by P-glycoprotein, an organic anion transporting protein that is expressed on the luminal surfaces of vascular endothelial cells in the blood vessels that constitute the blood-brain barrier.⁶ Their propensity to occupy H₁ receptors in the CNS varies from 0% for fexofenadine to 30% for cetirizine. Thus, second-generation H₁ antihistamines are relatively free of sedating effects.

Through H₁ receptors histamine has various effects on the immune system, including the maturation of dendritic cells and modulation of the balance of helper T-cell type 1 (Th1) and Th2 towards Th1. Histamine also induces the release of pro-inflammatory cytokines² (pro-inflammatory activity). Because histamine has such effects on allergic inflammation and the immune system, treatment with H₁ antihistamines reduces the expression of pro-inflammatory cell adhesion molecules and the accumulation of inflammatory cells, such as eosinophils and neutrophils. Major clinical effects of H₁ antihistamines are seen in suppression of the early response to allergen challenge in the conjunctiva, nose, lower airway and skin.

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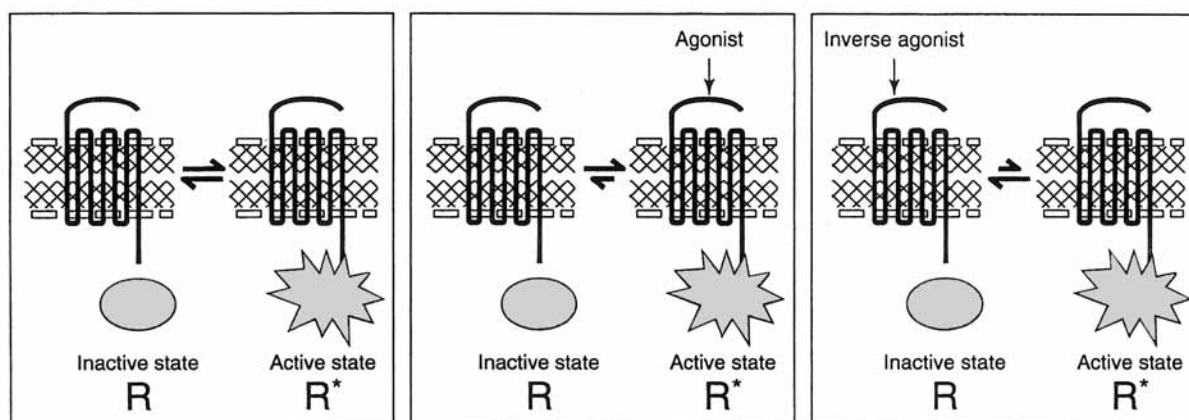


Fig. 1. Simplified two-state compartment model of the histamine H_1 -receptor. Adapted from Leurs et al.³

PHARMACOKINETIC PROPERTIES

H_1 -receptor antagonists are well absorbed from the gastrointestinal tract after oral administration. Their onset of effect occurs within 1-3 hours; their duration of action varies from several hours to 24 hours, (second-generation drugs being generally around 24 hours) (Table II).⁷ First-generation antihistamines and some of the second-generation agents are oxidatively metabolised by the hepatic cytochrome P450 system, the exceptions being levocetirizine, cetirizine, and fexofenadine.⁸ Levocetirizine and cetirizine are excreted largely unchanged in urine and fexofenadine is excreted mainly in the faeces but also the urine.⁸ Hepatic metabolism has several implications: prolongation of the serum half-life in patients with hepatic dysfunction and those receiving concomitant cytochrome P450 inhibitors, such as ketoconazole and erythromycin. Also, longer duration of action is found in elderly patients who have reduced liver function. In these patients there is a possibility of precipitating serious unwanted cardiac or CNS effects. Such adverse effects are more likely to occur with first-generation rather than second-generation antihistamines. Concomitant administration of probenecid reduces the total body and renal clearance of fexofenadine.⁹ The bioavailability of fexofenadine may be altered by simultaneous consumption of grapefruit juice (reduced rate and absorption of the drug by almost 30%)¹⁰ (However, grapefruit juice does not affect the absorption of other second-generation antihistamines. Although topical intranasal and ophthalmic H_1 antihistamines differ in their pharmacokinetics, most of the topical preparations need to be administered twice daily because of the washout from the nasal mucosa or conjunctiva.

CLINICAL USES IN ALLERGIC DISEASE

H_1 antihistamines currently constitute the largest class of medications used in the treatment of allergic disorder, allergic rhinoconjunctivitis and urticaria in particu-

lar. Formulations and dosages of the newer antihistamines are listed in Tables III and IV.

Allergic rhinoconjunctivitis

In patients with allergic rhinitis (AR) both first- and second-generation H_1 antihistamines have proven to be highly effective in relieving sneezes, itching, and nasal discharge but not nasal blockage. First-generation H_1 antihistamines have an unsatisfactory benefit-to-risk ratio in allergic rhinoconjunctivitis. In seasonal and perennial rhinitis, the evidence base for their use is small. Dosage recommendations are empirical. In seasonal AR, there is a large evidence base for the use of second-generation oral H_1 antihistamines such as cetirizine, desloratadine, fexofenadine, loratadine.¹¹⁻¹⁴ Efficacy has been well documented in hundreds of randomised, double-blind, placebo-controlled, parallel-group clinical trials involving thousands of participants. In perennial AR, the evidence base for second-generation H_1 antihistamines use is growing and the efficacy of cetirizine, desloratadine, fexofenadine, loratadine, and levocetirizine has been documented.¹⁵⁻¹⁷ Regular daily administration is associated with a significant decrease in symptoms and nasal mucosal inflammation compared with 'as needed' or 'on demand' use.¹⁸ H_1 antihistamines provide relief of allergic rhinitis comparable to that provided by intranasal cromolyn sodium 4% and are generally found to be less potent than intranasal corticosteroids in the treatment of AR symptoms. Leukotriene receptor antagonists (LRAs) may also be effective in certain patients with AR if combined with an antihistamine. In allergic conjunctivitis, the ocular symptoms induced by allergen, such as itching, tearing and reddening are reduced by administration of H_1 antihistamines either systemically or topically as eye drops such as azelastine, ketotifen, levocabastine and olopatadine. Topical application usually results in faster onset of action – within 5 minutes – than oral administration.¹⁹

Table II. Pharmacokinetics of second-generation oral H_1 antihistamines (mean \pm SD)

H_1 antihistamines (metabolite)	T_{max} (h) after a single dose	Terminal elimination half-life ($t_{1/2}$, h)	% eliminated unchanged in the urine/faeces	Duration of action (h)
Cetirizine	1.0 \pm 0.5	6.5-10	60/10	\geq 24
Loratadine	1.2 \pm 0.3	7.8 \pm 4.2	Trace	24
Desloratadine	1-3	27	0	\geq 24
Fexofenadine	2.6	14.4	12/80	24
Levocetirizine	0.8 \pm 0.5	7 \pm 1.5	86	\geq 24

Adapted from Simons et al.⁷

Table III. Formulations and dosages of second-generation oral antihistamines

Generic name	Formulation		Recommended dosage	
	Tablet	Syrup	Adult	Paediatric
Cetirizine	10 mg	5 mg/5 ml	5-10 mg od	5-10 mg od (6-11 yrs) 6 mo - 5 yr 2.5-5 mg od
Loratadine	10 mg	5 mg/5 ml	10 mg od	(6-10 yr) 10 mg or (2-9 yr) 5 mg
Desloratadine	5 mg	N/A	5 mg od	(≥12 yr) 5 mg od
Fexofenadine	60 mg, 120 mg, 180 mg	N/A	60 mg bd or 120-180 mg od	(≥12 yr) 60 mg bd or 120-180 mg od
Levocetirizine	5 mg	N/A	5 mg od	(≥6 yr) 5 mg od

Table IV. Second-generation topical antihistamines

Generic name	Formulation	Recommended dosage
Azelastine	Nasal soln 0.1%	Adult & paediatric ≥12 yr: 2 sprays/nostril bd
Ketotifen	0.025% ophthalmic soln	Adult & paediatric ≥3 yr: 1 drop/eye bd
Levocabastine	Nasal spray 50 mg/puff	Adult: 2 sprays/nostril bd – qid
Olopatadine	0.1% ophthalmic soln	Adult & paediatric >3 yr: 1 drop/eye

Acute and chronic urticaria

H₁ antihistamines are first-line medications in *acute and chronic urticaria* and very effective in providing symptomatic relief. The evidence base for the use of H₁ antihistamines in acute urticaria remains small; however, recently, in a prospective, randomised, double-blind, placebo-controlled, 24-month-long study, high-risk children given cetirizine had significantly fewer episodes of acute urticaria than did those given placebo.²⁰ Although the evidence base for the use of first-generation H₁ antihistamines in chronic urticaria also remains surprisingly small by current standards, that for second-generation H₁ antihistamines (e.g. fexofenadine) has increased considerably during the past few years.²¹⁻²³ In chronic urticaria, H₁ antihistamines should optimally be given on a regular basis to prevent hives from appearing, rather than 'as needed'.

Atopic dermatitis

In atopic dermatitis (AD), itching is one of the major symptoms and the resultant scratching usually causes worsening of the lesion. H₁ antihistamines may relieve itching and reduce scratching. Relief of itching by H₁ antihistamines is often incomplete in AD, because the itching produced by mediators other than histamine is not down-regulated. H₁ antihistamines appear to relieve itching mainly through their CNS effects and thus first-generation H₁ antihistamines (sedating) such as hydroxyzine and diphenhydramine are more effective for relief of itching in this disorder than are the second-generation H₁ antihistamines (non-sedating).²⁴ However, recent studies have shown that second-generation medications such as cetirizine and loratadine may also relieve itching in AD.²⁵⁻²⁷ In higher doses, cetirizine has been demonstrated to have a topical glucocorticoid-sparing effect in AD.

Anaphylaxis

Adrenaline is the first-line treatment in anaphylaxis. Antihistamines are considered adjunctive treatment for relief of itching, urticaria, rhinorrhoea, and other symptoms.²⁸ Because first-generation H₁ antihistamines such as chlorpheniramine, diphenhydramine, and

hydroxyzine have high aqueous solubility and are available in parenteral formulations for injection, they continue to be widely used in the treatment of anaphylaxis. Most of the second-generation H₁ antihistamines have low aqueous solubility and none is available in formulation for injection. Antihistamines also have a potential role in prevention of anaphylaxis. In anaphylaxis, many of the effects of histamine, such as vasodilation and hypotension, occur as a result of its effects at both H₁ and H₂ receptors.^{4,29} H₁ and H₂ antihistamines given concomitantly decrease the frequency and severity of these reactions, and routine prophylaxis

with these medications has been proposed.²⁹ The prophylaxis pretreatment or treatment with both an H₁ and H₂ antihistamine may be more effective than pretreatment with an H₁ antihistamine alone. Second-generation H₁ antihistamines, administered orally, prevent allergic reactions in patients receiving immunotherapy.³⁰

Asthma

In *asthma*, current evidence does not support the use of antihistamines for treatment. However, second-generation antihistamines are reported to reduce symptoms of allergic asthma in certain patients and exacerbation of asthma in adult patients with AR. The amount of improvement produced by H₁ antihistamines in asthma is modest.³¹

USE IN PREGNANCY AND LACTATION

Chlorpheniramine, one of the first-generation antihistamines, is reportedly safe in pregnancy. There is little information on the use of the new antihistamines during pregnancy although cetirizine and loratadine are considered relatively safe for use during pregnancy (FDA category B).³²⁻³⁴

H₁ antihistamines are excreted in small amounts in breast milk (<0.1% of a maternal dose). Breast-fed infants whose mothers have ingested first-generation antihistamines may experience irritability, drowsiness or respiratory depression;³⁵ no symptoms have been attributed to second-generation antihistamines to date.

ADVERSE EFFECTS

The *adverse effects* of first-generation H₁ antihistamines, mainly *on the CNS*, including drowsiness, impaired driving performance, fatigue, lassitude, and dizziness, are well documented. Other side-effects (anticholinergic) include dry mouth, urinary retention, gastrointestinal upset and appetite stimulation. Although the new-generation antihistamines are relatively free of serious CNS effects, a small number of individuals may experience sedation with these agents. *Minor side-effects* such as nausea, lightheadedness, drowsiness, headaches, agitation and dry

mouth have been reported occasionally with the new antihistamines. Weight gain (due to increased appetite) has also been reported in a few patients treated with cetirizine. *Hypersensitivity reactions*, including skin rashes and angio-oedema may also occur. In recommended dosages, the new antihistamines are generally safe. *Toxicity* associated with the new antihistamines is usually related to increased drug levels (due to over-dosage or impaired metabolism). Symptoms of over-dosage include drowsiness and agitation (especially in children).

First-generation H₁ antihistamines may cause tachycardia, supraventricular arrhythmia, and prolongation of the QT interval in a dose-dependent manner. Two second-generation antihistamines, astemizole and terfenadine, were withdrawn from the market because of their *cardiac toxic effects* (torsades de pointes and other potentially fatal ventricular arrhythmias). Cetirizine, levocetirizine fexofenadine, loratadine and desloratadine appear to be free from cardiac toxicity even at higher than recommended doses.^{36,37}

Declaration of conflict of interest

The author declares no conflict of interest.

REFERENCES

- Assanasen P, Naclerio RM. Anti-allergic, anti-inflammatory effects of H₁ antihistamines in humans. In: Simons FER, ed. *Histamine and H₁ Antihistamines in Allergic Disease*, 2nd ed. New York: Marcel Dekker, 2002: 101.
- Bakker RA, Wieland K, Timmerman H, et al. Constitutive activity of the histamine H(1) receptor reveals inverse agonism of histamine H(1)receptor antagonists. *Eur J Pharmacol* 2000; 387: R5-7.
- Leurs R, Church MK, Tagliabatella M. H₁ antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clin Exp Allergy* 2002; 32: 489-498.
- Lorenz W, Duda D, Dick W, et al. Incidence and clinical importance of perioperative histamine release: randomised study of volume loading and antihistamines after induction of anaesthesia. *Lancet* 1994; 343: 933-940.
- Tagawa M, Kano M, Okamura N, et al. Neuroimaging of histamine H₁-receptor occupancy in human brain by positron emission tomography (PET): a comparative study of ebastine, a second-generation antihistamine, and (+)-chlorpheniramine, a classical antihistamine. *Br J Clin Pharmacol* 2001; 52: 501-509.
- Chishty M, Reichel A, Siva J, et al. Affinity for the P-glycoprotein efflux pump at the blood-brain barrier may explain the lack of CNS side-effects of modern antihistamines. *J Drug Target* 2001; 9: 223-228.
- Simons FER. Antihistamines. In: Middleton E, Reed CE, Ellis EF, et al., eds. *Allergy: Principles and Practice*. St Louis: Mosby, 2006: 834-868.
- Devillier P, Roche N, Faisy C. Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine: a comparative review. *Clin Pharmacokinet* 2008; 47: 217-230.
- Liu S, Beringer PM, Hidayat L, et al. Probenecid, but not cystic fibrosis, alters the total and renal clearance of fexofenadine. *J Clin Pharmacol* 2008; 48: 957-965.
- Banfield C, Gupta S, Marino M, Lim J, Affrime M. Grapefruit juice reduces the oral bioavailability of fexofenadine but not desloratadine. *Clin Pharmacokinet* 2002; 41: 311-318.
- Van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120mg, loratadine 10mg, and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clin Exp Allergy* 2000; 30: 891-899.
- Howarth PH, Stern MA, Roi L, et al. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999; 104: 927-933.
- Leynadier F, Mees K, Arendt C, et al. Efficacy and safety of levocetirizine in seasonal allergic rhinitis. *Acta Otorhinolaryngol Belg* 2001; 55: 305-312.
- Meltzer EO, Prenner B, Nayak A, et al. Efficacy and tolerability of once-daily 5mg desloratadine, an H₁ receptor antagonist, in patients with seasonal allergic rhinitis: assessment during the spring and fall allergy seasons. *Clin Drug Invest* 2001; 21: 25.
- Ciprandi G, Cosentino C, Milanese M, et al. Fexofenadine reduces nasal congestion in perennial allergic rhinitis. *Allergy* 2001; 56: 1068-1070.
- Aaronson DW. Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma. *Ann Allergy Asthma Immunol* 1996; 76: 440-446.
- Simons FER, Prenner BM, Finn JA, for the Desloratadine Study Group. Efficacy and safety of desloratadine in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol* 2003; 111: 617-622.
- Ciprandi G, Ricca V, Passalacqua G, et al. Seasonal rhinitis and azelastine: long- or short-term treatment? *J Allergy Clin Immunol* 1997; 99: 301-307.
- Aguilar A. Comparative study of clinical efficacy and tolerance in seasonal allergic conjunctivitis management with 0.1% olopatadine hydrochloride versus 0.05% ketotifen fumarate. *Acta Ophthalmol Scand* 2000; 78(suppl 230): 52.
- Simons FER, on behalf of the ETAC Study Group. Prevention of acute urticaria in young children with atopic dermatitis. *J Allergy Clin Immunol* 2001; 107: 703-706.
- La Rosa M, Leonardi S, Marchese G, et al. Double-blind multicenter study on the efficacy and tolerability of cetirizine compared with oxatamide in chronic idiopathic urticaria in preschool children. *Ann Allergy Asthma Immunol* 2001; 87: 48.
- Paul E, Berth-Jones J, Ortonne JP, et al. Fexofenadine hydrochloride in the treatment of chronic idiopathic urticaria: a placebo-controlled, parallel-group, dose-ranging study. *J Dermatol Treat* 1998; 9: 143.
- Ring J, Hein R, Gauger A, et al. Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Int J Dermatol* 2001; 40: 72-76.
- Klein PA, Clark RA. An evidence-based review of the efficacy of antihistamines in relieving pruritus in atopic dermatitis. *Arch Dermatol* 1999; 135: 1522-1525.
- Hannuksela M, Kalimo K, Lammintausta K, et al. Dose ranging study: cetirizine in the treatment of atopic dermatitis in adults. *Ann Allergy* 1993; 70: 127-133.
- Nlageland T, Fagertun HE, Larsen S. Therapeutic effect of loratadine on pruritus in patients with atopic dermatitis: a multicrossover-designed study. *Allergy* 1994; 49: 22-26.
- Diepgen TL, on behalf of the ETAC Study Group. Long term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. *Pediatr Allergy Immunol* 2002; 13: 278-286.
- Winbery SI, Lieberman PL. Histamine and antihistamines in anaphylaxis. In: Simons FER, ed. *Histamine and H₁ Antihistamines in Allergic Disease*, 2nd ed. New York: Marcel Dekker, 2002: 287.
- Doenicke A, Moss J, Toledano A, et al. Administration of H₁ and H₂ antagonists for chemoprophylaxis: a double-blind, placebo-controlled study in healthy volunteers. *J Clin Pharmacol* 1997; 37: 140-146.
- Muller U, Hari Y, Berchtold E. Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy. *J Allergy Clin Immunol* 2001; 107: 81-86.
- Ratner PH and the Desloratadine Study Group. Desloratadine improved asthma symptoms and reduced bronchodilator use in 2 studies of patients with asthma and SAR. *Ann Allergy Asthma Immunol* 2001; 86: 109.
- Schatz M. H₁ antihistamines in pregnancy and lactation. In: Simons FER, ed. *Histamine and H₁ Antihistamines in Allergic Disease*, 2nd ed. New York: Marcel Dekker, 2002: 421.
- Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. *Am J Perinatol* 1997; 14: 119.
- Moretti ME, Caprara D, Coutinho CJ, et al. Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. *J Allergy Clin Immunol* 2003; 111: 479-483.
- Ito S. Drug therapy for breast-feeding women. *N Engl J Med* 2000; 343: 118-126.
- Yap YG, Camm AJ. Potential cardiac toxicity of H₁ antihistamines. In: Simons FER, ed. *Histamine and H₁ Antihistamines in Allergic Disease*, 2nd ed. New York: Marcel Dekker, 2002: 389.
- Craig-McFeely PM, Freemantle SL, Pearce GL, et al. Experience of fexofenadine and cardiac side effects in general practice use in England. *Pharmacoepidemiol Drug Saf* 1999; 8(suppl 2): S108.