

An overview of the novel H1-antihistamine bilastine in allergic rhinitis and urticaria

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Currently available second-generation H1-antihistamines include a wide group of drugs with a better therapeutic index (or risk–benefit ratio) than the classic antihistamines, although their properties and safety profiles may differ. Bilastine is a newly registered H1-antihistamine for the oral treatment of allergic rhinitis and urticaria, with established antihistaminic and antiallergic properties. Clinical studies in allergic rhinitis and chronic urticaria show that once-daily treatment with bilastine 20 mg is effective in managing symptoms and improving patient's quality of life, with at least comparable efficacy to other non-sedative H1-antihistamines. As far as studies in healthy volunteers, clinical assays and clinical experience can establish, bilastine's safety profile is satisfactory, since it lacks anticholinergic effects, does not impair psychomotor performance or actual driving, and appears to be entirely free from cardiovascular effects.

KEYWORDS: allergic rhinitis • antihistamine • bilastine • histamine H1-receptor antagonist • urticaria

Allergic diseases such as rhinoconjunctivitis, asthma, eczema or urticaria are among the most common chronic disorders, and their incidence in developed countries is very probably increasing [1]. Allergic rhinitis (AR) has today an estimated global prevalence of approximately 20% [1], and although it is not a life-threatening condition, symptoms can be irritating and affect the patient's quality of life, even causing sleep-disordered breathing [2] and learning difficulties [3]. AR is also considered a major risk factor for the development of asthma [1], and is very often associated with other comorbidities such as allergic conjunctivitis, chronic sinusitis or otitis media, which also deteriorate quality of life and increase the costs of the disease, both directly and indirectly [4].

Allergic rhinoconjunctivitis has traditionally been categorized into seasonal (SAR) and perennial (PAR), mainly based on the time of exposure to allergens. The Allergic Rhinitis and its Impact on Asthma (ARIA) workshop introduced a new classification for AR [5], based on duration and severity of symptoms (FIGURE 1), as well as a number of treatment guidelines, given the fact that allergic rhinoconjunctivitis is one of the top ten reasons for patients visiting their doctor [6].

Chronic urticaria (CU) is defined by the recurrent, daily appearance of wheals that last

for more than 6 weeks, and can be accompanied by angioedema. Similar to AR, the symptoms of CU are induced by the activation of mast cells and the secondary release of histamine and other inflammatory mediators. Histamine interacts with H1- and H2-receptors, increasing vasodilatation and plasma extravasation, leading to stimulation of nerve endings and the release of neuropeptides responsible for pruritus [7]. According to its possible etiology, CU is divided into three groups: physical urticarias, such as dermatographism, cholinergic or cold urticaria; autoimmune urticarias, considered to account for as much as 45% of CU cases, which are determined by the presence of IgG autoantibodies against circulating IgE or, more often, against the α subunit of the IgE high-affinity receptor (Fc ϵ R-I), which upon binding to skin mast cells would trigger degranulation [8]; and idiopathic urticarias, concerning all cases of CU of unknown cause. However, it is thought that many of the latter might also have an autoimmune origin, with the potential association of thyroid autoimmunity. As is the case with AR, CU is not considered a life-threatening disease, but is often devastating in terms of a patient's quality of life [9].

Biological effects of histamine involved in allergic reactions are related mainly to its activity

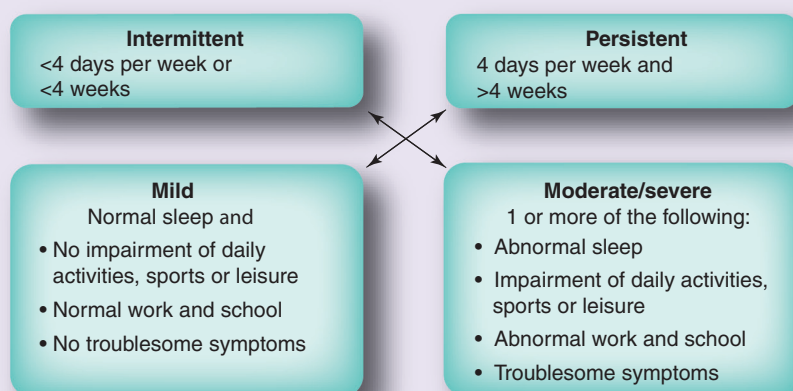


Figure 1. Allergic Rhinitis and its Impact on Asthma (ARIA) workshop classification for allergic rhinitis.

Adapted from [5].

at H1-receptors. Thus, drugs blocking the effects of histamine at H1-receptors, or H1-antihistamines, play a fundamental role in the management of AR and all kinds of urticaria. First-generation H1-antihistamines derive from the same chemical structure as cholinergic antagonists, antipsychotics and some antihypertensive agents [10], therefore they have poor receptor selectivity, causing antimuscarinic, anti- α -adrenergic, and antiserotonin effects. They also readily penetrate the blood–brain barrier (BBB), blocking histamine's role as a neurotransmitter responsible for alertness and thus cause drowsiness and somnolence [11]. Second-generation H1-antihistamines are preferred to classic antihistaminic drugs, owing to their greater selectivity for peripheral H1-receptors and their lower potential to cross the BBB, resulting in a better tolerability profile; and also owing to their better known pharmacokinetics and pharmacodynamics, allowing a single daily dose, an accurate adjustment in special situations and a better knowledge of potential interactions [12]. That is to say, second-generation H1-antihistamines show a better therapeutic index (or risk–benefit ratio) than the classic antihistamines [13].

According to the ARIA guidelines, the management of AR should include second-generation nonsedating oral H1-antihistamines. Equally, the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN) guidelines for the management of urticaria recommend nonsedating H1-receptor antagonists as the first-line treatment in all cases of AR [14], and suggest considering higher doses (up to fourfold) in nonresponding patients, before changing the therapeutic scheme – a matter based only on experts opinions, however, and one currently under discussion [15].

Overview of the market

Antihistamines are the most widely prescribed drugs for the treatment of AR and urticaria. Although from the standpoint of clinical efficacy they show little difference between them, antihistamines are actually a heterogeneous group of drugs showing different pharmacological properties and safety profiles. All second-generation antihistamines are thought to be relatively free

from significant anticholinergic effects, and cause less sedation and somnolence-related problems than the classic antihistamines, but they are not one and the same. Some second-generation antihistamines have been associated with adverse events such as weight gain, drug–drug interactions or cardiotoxicity. At the end of the past century, second-generation antihistamines terfenadine and astemizole were shown to cause ECG anomalies (QT interval prolongation) and a subsequent risk of ventricular arrhythmias (*torsades de pointes*) when administered at higher than recommended doses, or in combination with drug metabolism inhibitors such as macrolide antibiotics or ketoconazole [16]. This discovery resulted in the withdrawal of these anti-

histamines from the market in the majority of countries and led to an exhaustive investigation of cardiac safety in the development of new H1-antihistamine drugs.

In general, new drugs have demonstrated efficacy and safety in patients suffering from allergic rhinitis and urticaria. Today it is also considered essential to evaluate health-related quality of life and monitor its changes after the treatments provided. Allergic diseases, AR and urticaria in particular, are highly prevalent diseases that, despite their low or null mortality rates, very often have unfavorable effects on quality of life, with frequent sleep disruption, emotional concerns and reduced performance at work and daily activities [17].

In allergic rhinoconjunctivitis, ARIA current guidelines recommend an approach based on prevention, allergen immunotherapy and symptomatic step therapy, including intranasal corticosteroids, oral nonsedating H1-antihistamines and/or leukotriene receptor antagonists [1]. The efficacy of antihistamines in nasal obstruction in individuals with AR has been questioned. Nasal obstruction has a great impact upon patient quality of life, so this is an aspect in which these drugs should be improved. Owing to this, most patients with AR are more prone to take oral antihistamines than use nasal steroids [18]. In urticaria, oral nonsedating H1-antihistamines are also considered as the first-line therapy; however, many patients – mainly with CU – still suffer from symptoms when receiving standard treatment, so increasing the dose has to be considered before other therapies are taken into account. In addition, a definitive treatment is often lacking in AR and urticaria, accordingly, patients look for effective, safe, harmless and easy-to-take symptomatic therapies that can be taken for long periods of time and allow them to live an active life.

Introduction to bilastine

Bilastine is a new inhibitor of the histamine H1-receptor, developed by FAES Farma (Spain) and recently approved in 28 countries of the EU for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and children older than 12 years of age. It is a novel piperidinic drug that is not

structurally derived from any antihistamines currently on market, nor it is a metabolite or enantiomer of any of them. As this article describes, it is a potent and highly selective H1-antihistamine, with appropriate pharmacokinetic characteristics, no hepatic metabolism and a good-to-excellent safety profile. Studies in healthy volunteers and patients have shown that bilastine does not affect cardiac conduction, vigilance or driving ability, is free from antimuscarinic effects, and does not promote significant changes in laboratory tests, electrocardiograms or vital signs. In clinical studies, oral treatment with bilastine 20 mg once daily improved allergic rhinitis with greater efficacy than placebo and was comparable to cetirizine and desloratadine, and also was more effective than placebo and equivalent to levocetirizine in treatment of chronic urticaria; relieving symptoms, improving quality of life and controlling sleep disorder. This article reviews the published data on bilastine, its efficacy and safety in treating allergic rhinitis and urticaria, and also expresses our global impression after a short period of the drug in the European market.

Chemistry

Bilastine, or 2-[4-[2-[4-[1-(2-ethoxyethyl) benzimidazol-2-yl] piperidin-1-yl] ethyl] phenyl]-2-methylpropionic acid (FIGURE 2) is a novel molecule with a molecular weight of 463.6 daltons and a chemical structure similar to piperidinyl-benzimidazole [19]. Bilastine can be therefore classified into the same chemical group as many of the new antihistamines on the market, although it is not structurally derived, nor is it a metabolite or enantiomer of any of them, but an original molecule designed with the intent of fulfilling all the requirements of a second-generation antihistamine [20].

Pharmacodynamics

Bilastine has displayed antihistaminic and antiallergic activities in several *in vitro* and *in vivo* studies. Data from preclinical studies confirmed its high affinity and selectivity for the histamine H1-receptor over other receptors, and demonstrated antihistaminic and antiallergic properties *in vivo*.

Bilastine binds to H1-receptors of guinea pig cerebellum and to human recombinant H1-receptors with an affinity comparable to that of astemizole and diphenhydramine, and superior than that of cetirizine by threefold and fexofenadine by fivefold [21]. In different murine models, bilastine antagonizes the effects of histamine in a concentration-dependent manner, with potency similar to that of fexofenadine and between 5.5- and 10-times greater than that of cetirizine [21]. Bilastine did not inhibit muscarinic receptors, α 1- and β 2-adrenoceptors, bradykinin B1, leukotriene D4 or calcium receptors, in an *in vitro* study on a range of 30 different receptors sites; and neither bilastine, nor cetirizine or fexofenadine had any effect on H2-, H3- or H4-receptors [21]. Further *in vivo* experiments in different murine models demonstrated a dose-dependent inhibitory activity of orally administered bilastine, with long-lasting antihistaminic activity and blocking of histamine-induced bronchospasm with significantly higher activity than cetirizine [22].

In addition to histamine H1-receptor antagonism, bilastine has been shown to inhibit histamine, IL-4 and TNF- α release from human mast cells and peripheral blood granulocytes, in contrast to other H1-antihistamines such as cetirizine, which did not have any effect on TNF- α release and even enhanced the release of histamine and IL-4 from human mast cells in the same experimental study [23].

In summary, evidence from preclinical investigations draws attention to the affinity and specificity of bilastine for H1-receptors compared with other histamine receptors and other receptor subtypes. *In vivo* experimentation confirmed the antihistaminic and antiallergic activity, which was at least comparable to that of other second-generation H1-antihistamines such as cetirizine or fexofenadine.

Regarding clinical studies, a Phase I study in healthy male volunteers assessed the effect of five different bilastine single doses (2.5, 5, 10, 20 and 50 mg) on histamine-induced wheal and flare reaction over a 24-h period, compared with a single 10-mg oral dose of cetirizine [24]. The results of this research indicated that bilastine was at least as efficient as cetirizine in reducing histamine-mediated effects in healthy volunteers. Remarkably, 20 and 50 mg of bilastine reduced the wheal and flare reaction significantly more quickly than cetirizine (FIGURE 3).

Pharmacokinetics & metabolism

Pharmacokinetic properties of bilastine have been widely investigated in preclinical studies using animal models (rodents and dogs) after oral and parenteral administration. In addition, the pharmacokinetic/pharmacodynamic profile has been assessed in 14 Phase I clinical studies. Pharmacokinetic parameters of bilastine are summarized in TABLE 1.

Absorption & bioavailability

Bilastine is rapidly absorbed after oral administration in fasting conditions, reaching a mean peak plasma concentration (C_{max}) of 220 ng/ml approximately 1 h after both single and multiple dosing [24]. Absorption is reduced by a high-fat breakfast or fruit juice, so the estimated global oral bioavailability in healthy volunteers is approximately 60% [25] and has not been definitely established in patients. Bilastine has linear pharmacokinetics in the 2.5–220-mg dose range in healthy adult subjects without evidence of accumulation after 14 days of treatment. Both the C_{max} and the area under the curve (or proportion of administered bilastine that reaches systemic circulation) increased proportionally to the administered dose [25].

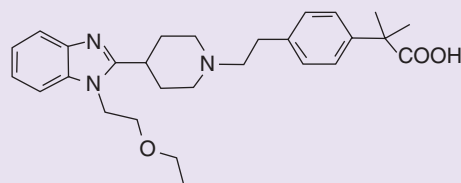


Figure 2. Bilastine.

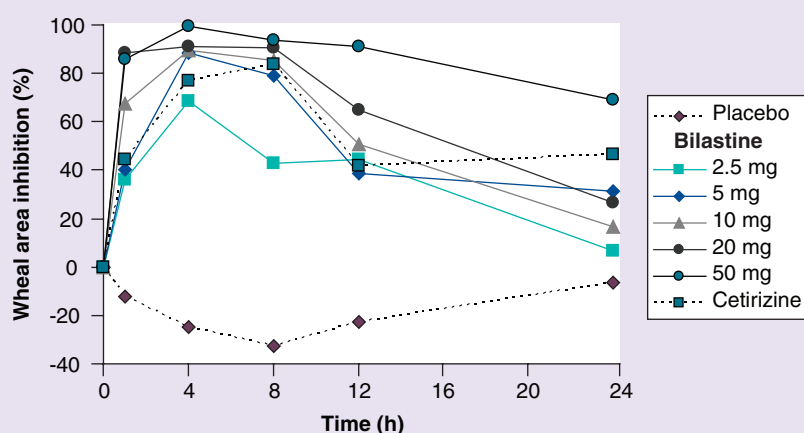


Figure 3. Inhibition of histamine-induced wheal area by cetirizine 10 mg oral dose versus different oral doses of bilastine (2.5, 5, 10, 20 and 50 mg).

Demonstrates dose–effect and time–effect relationships.

Distribution

Bilastine distribution has been characterized by two compartmental kinetics; the volume of distribution of the central compartment was 59.2 l and the peripheral compartment volume of distribution was 30.2 l. An apparent volume of distribution of 1.29 l/kg has been estimated for bilastine, as well as a terminal elimination half-life of 14.5 h and plasma protein binding of 84–90% [25].

Metabolism

Bilastine is not significantly metabolized in humans and is largely eliminated unchanged both in urine and feces – a third and two thirds of the administered dose, respectively, according to a Phase I mass-balance study with radiolabeled bilastine [26].

In cell cultures (hepatocytes and liver microsomes), bilastine is not metabolized and does not inhibit or induce the activity of cytochrome P450 isoenzymes. Bilastine has a slow elimination

with a half-life of approximately 10–14 h, which is associated with the elimination from the peripheral compartment [25]. 96% of the administered dose is eliminated within 24 h [25].

When examining the relationship between kinetics and the antihistamine effect, measured as skin wheal-and-flare surface areas for 24 h, it can be demonstrated that oral doses of 20 mg daily of bilastine achieved concentrations above the IC_{50} – that is to say, concentrations capable of inhibiting 50% of the surface areas – throughout the whole administration interval [24].

Drug interactions & food effects

Preclinical data suggest the possibility of interactions between bilastine and drugs

or food that are inhibitors or inducers of the P-glycoproteins. Coadministration of bilastine and grapefruit juice (a known P-glycoprotein-mediated drug transport activator) significantly reduced bilastine systemic exposure [27]. This interaction is due to the known effect of grapefruit flavonoids on intestinal transporter systems such as P-glycoproteins and organic anion transporting peptide (OATP) [28].

In healthy volunteers, bilastine had no effect on the pharmacokinetics of ketoconazole, a known cytochrome P450-3A4 (CYP3A4) and P-glycoprotein inhibitor. However, when bilastine was coadministered with ketoconazole 400 mg/day for 6 days, systemic exposure in steady state was increased more than two-fold, with no changes in the clearance; these data suggest an interaction on gut via P-glycoprotein and not on hepatic metabolism [29]. Other studies with erythromycin and diltiazem show similar effects [30]. Bilastine is not metabolized, so metabolic interactions are not expected. Bilastine at doses of 20 mg/day for 7 days does not significantly potentiate the depressant effects of lorazepam [30]. Other studies in young healthy volunteers showed that the administration of bilastine at the therapeutic dose of 20 mg did not potentiate the CNS depressant effects of alcohol (in contrast to hydroxyzine and cetirizine) [31].

Clinical efficacy

A total of 14 Phase I studies with single and repeated doses of bilastine, as well as interaction studies, have been completed. The safety, the tolerability and the pharmacokinetic profile of bilastine were evaluated in all the Phase I studies. Results from experimental animal models showing bilastine to be a potent H1-antihistamine have been sustained by placebo-controlled clinical trials with bilastine in allergic rhinitis and urticaria.

Phase I studies: human experience in healthy volunteers

In total, 14 Phase I studies with increasing oral doses of bilastine capsules/tablets have been conducted and completed, involving over 439 healthy volunteers, both in single administration and in

Table 1. Values of the main pharmacokinetic parameters obtained after oral administration of bilastine 20 mg in healthy volunteers.

Parameter	Value
$t_{1/2}$ (h)	14.53
Vc (l)	59.2
Vp (l)	30.2
CL (l/h)	18.1
C_{max} (ng/ml)	220
T_{max} (h)	1.29
AUC (ng/h/ml)	1104.97
Oral F (%)	61

AUC: Area under the curve; CL: Clearance; C_{max} : Maximum plasma total concentration; F: Bioavailability; $t_{1/2}$: Elimination half-life; T_{max} : Time taken to reach C_{max} ; Vc: Volume of distribution in central compartment; Vp: Volume of distribution in peripheral compartment.

repeated doses up to 14 days. In all these studies, the pharmacokinetics parameters were analyzed, and the safety and tolerability were evaluated according to clinical signs and symptoms, adverse events, and results from 12-lead ECG, blood pressure, heart rate, temperature, respiratory rate, urinalysis, hematology and blood chemistry. These parameters were evaluated before dosing and at different intervals after dosing [32].

The relationship of the bilastine dose to inhibition of skin reactivity (wheal and flare) in response to a histamine injection was investigated in a randomized, double-blind, single-dose, four-period crossover study conducted in 21 healthy male volunteers who received bilastine (2.5, 5, 10, 20 and 50 mg), cetirizine 10 mg or placebo (FIGURE 3). All doses of bilastine were equivalent or superior to cetirizine in attenuating histamine-induced wheal and flare (>50% inhibition up to 12 h). At 24 h, all bilastine doses successfully inhibited wheal by over 50%, but only the 50-mg dose was associated with a >50% inhibition of flare. In turn, cetirizine 10 mg inhibited both wheal and flare areas by over 50%. Bilastine was safe and well tolerated, with mild adverse events and no clinically significant changes in ECG or vital signs [24].

Efficacy in allergic rhinitis

Four Phase II and four Phase III controlled clinical studies have been completed with oral doses of bilastine in patients suffering from allergic rhinoconjunctivitis, either SAR or PAR, involving 3974 patients (1920 on bilastine, 998 on active comparators and 1195 on placebo). Patients were chosen worldwide and received the study treatment during 2–4 weeks, except for the environmental exposure chamber study, which was a single-dose study. A Phase III study, yet unpublished, comparing bilastine 20 mg versus cetirizine 10 mg and placebo during 4 weeks in the treatment of PAR, was followed by an open-label extension-phase to evaluate the long-term safety of bilastine 20 mg throughout 1 year [32] [FAES FARMA, SA, DATA ON FILE].

The effects of bilastine on allergen-induced nasal and ocular symptoms were evaluated in 75 young subjects with a documented allergy to grass pollen in a crossover design. The subjects were exposed to a controlled concentration of grass pollen in the Vienna Challenge Chamber, a standardized method of allergen provocation. Each of the four treatment periods included a first 6-h allergen provocation on day 1 and a new 4-h challenge 22 h after the start of the first provocation. Antihistamines (bilastine 20 mg, cetirizine 10 mg, fexofenadine 120 mg or placebo, in randomized order) were administered 2 h after the start of the first challenge. Total nasal symptom score was evaluated throughout the provocation time every 15 min. The results showed bilastine to have a similar efficacy as cetirizine and fexofenadine for nasal symptoms 1 h after administration, although fexofenadine was less effective on day 2 (22–26 h postdose) suggesting a shorter length of action (at least at the 120-mg dose) than bilastine or cetirizine [33].

These results were accordingly confirmed in two pivotal studies in patients with SAR. In a 14-day, double-blind, placebo-controlled, multicenter trial involving 721 patients in eight European countries, bilastine 20 mg once daily was significantly

more effective than placebo ($p = 0.0002$), and no different from desloratadine 5 mg, in reducing nasal and non-nasal symptoms, relieving rhinitis-associated discomfort and improving rhinoconjunctivitis quality-of-life questionnaire scores. In this study, both bilastine and desloratadine had an adverse events profile similar to that of placebo (20.6 vs 19.8 vs 18.8%) and no serious adverse events were reported [34].

In another study, a 14-day, double-blind, placebo-controlled trial involving 683 patients in 61 centers across Europe, bilastine 20 mg once daily was significantly superior to placebo ($p < 0.0001$) and analogous to cetirizine 10 mg in relieving symptoms of SAR, although bilastine treatment was associated with fewer adverse events than cetirizine (24.7 vs 36%; $p = 0.03$) and placebo (29.6%), especially less somnolence and fatigue, with significant differences in the bilastine-treated group (1.8 vs 7.5% [$p < 0.001$] and 0.4 vs 4.8% [$p = 0.02$]) [35].

Efficacy in chronic urticaria

The results obtained in a Phase I study with different doses of bilastine versus cetirizine in the inhibition of skin response (wheal and flare) to histamine [FAES FARMA, SA, DATA ON FILE] are supported by a clinical Phase III study in patients with chronic idiopathic urticaria. In a multicenter, double-blind clinical trial, 525 patients were randomized to receive bilastine 20 mg, levocetirizine 5 mg or placebo over a 28-day treatment period, and evaluation was based on patients' reflective assessment of pruritus, number of wheals and wheal maximum size according to predefined scales. Both bilastine and levocetirizine groups reported a significantly greater mean change from baseline in patient's reflective total symptom score (TSS) over 28 days than the placebo group (-4.23 and -4.63, respectively, vs -2.99; $p < 0.001$ for bilastine/levocetirizine vs placebo), while the active treatment groups were not significantly different from each other. Quality of life, assessed using the Dermatology Life Quality Index, associated discomfort and sleep disruption were also improved to a greater extent in both bilastine and levocetirizine groups, with no significant differences between them, than in placebo-treated patients. Adverse events were comparable among the three groups and no serious adverse events were reported [36].

In summary, published results indicate that bilastine 20 mg once daily is significantly superior to placebo and comparable to cetirizine 10 mg and desloratadine 5 mg in relieving symptoms of SAR. It is also comparable to levocetirizine 5 mg at improving the symptoms of chronic idiopathic urticaria. Ongoing studies are investigating the most suitable dose regimen for children in different age groups, as well as the safety and tolerability of bilastine in this pediatric population and the calculation of bilastine's oral bioavailability [FAES FARMA, SA, DATA ON FILE].

Safety & tolerability

Toxicity of bilastine was investigated in preclinical toxicology studies in mice, rats and dogs after oral and intravenous administration. No mortality was observed after oral administration of massive doses. After intravenous administration, LD₅₀ (lethal dose for 50% of animals) values were 33 and 45–75 mg/kg in mice

and rats, respectively. No signs of toxicity were observed in any organ after bilastine massive overdosing, either orally (in mice, rats and dogs), or intravenously (in rats and dogs) during 4 weeks. No effects on fertility, no teratogenic or mutagenic effects, and no apparent carcinogenic potential were seen in the studies carried out in rats, mice and rabbits [33].

In clinical research, bilastine has proven to be well tolerated, with an adverse events profile similar to that of placebo in healthy volunteers, patients with AR and with chronic idiopathic urticaria [35–37]. Although the tolerance profile of bilastine and levocetirizine or desloratadine were very similar [35,37], bilastine was markedly better tolerated than cetirizine in a clinical assay in SAR [36], with fewer adverse events in the bilastine group ($p = 0.03$). No anticholinergic adverse events were observed in the clinical trials with bilastine. No serious adverse events were reported during the research and there were no clinically significant changes in vital signs, ECG or laboratory tests. Pharmacokinetic/pharmacodynamic profiles and studies in special populations indicate that bilastine's dose adjustment is not necessary in elderly patients, or in hepatic or renal insufficiency.

Cardiovascular safety

Classical antihistamines have been used for many years but, as stated previously, it was only with the introduction of astemizole and terfenadine in the 1980s that H₁-antihistamines' potential to lengthen the cardiac QT interval in certain clinical situations was realised, leading to the appearance of ventricular arrhythmias [16]. Therefore, assessment of cardiac safety has become a key element of H₁-antihistamine development.

The main mechanism underlying an acquired QT syndrome and *torsades de pointes* arrhythmia is inhibition of the potassium channel encoded by hERG (the human 'ether-ago-go'-related gene). The concentration of bilastine required to produce a half-maximal block of the hERG potassium current (IC_{50}) in human cardiac myocytes was 6.5 μ M (1.1 μ M for cetirizine, 12.5 μ M for fexofenadine and 1.4 μ M for desloratadine in the same experiment), thus in the micromolar range [30]. Published IC_{50} values for terfenadine and astemizole are in the nanomolar range [37].

Bilastine has no effect on ventricular repolarization, as was proven in a trial conducted in 30 healthy subjects in a randomized, triple-dummy, double-blind, five-way crossover, placebo- and active comparator-controlled (moxifloxacin 400 mg) trial, with at least 7 days washout between periods. Two doses of bilastine were investigated (20 and 100 mg) as well as the 20-mg dose coadministered with 400 mg of ketoconazole. Bilastine did not produce any significant effects on QT interval at either dose on any of the measures following the dose, up to 72 h. A significant ($p < 0.05$) increase was noted, however, for bilastine plus ketoconazole treatment at 4 h. The positive control, moxifloxacin, showed significant ($p < 0.05$) increases in QTcNi (a linear individual correction of QT/RR) between 0.5 and 8 h and at 16 h (FIGURE 4). Measurement of plasma bilastine concentrations during this study revealed that the highest concentrations were achieved with the 100 mg dose of bilastine, followed by bilastine 20 mg taken with ketoconazole 400 mg. Changes observed when

bilastine was coadministered with ketoconazole were no different to the changes observed with the antifungal agent alone [38]. It can be concluded that bilastine in both single and repeated doses up to 100 mg per day, has no cardiotoxic potential, and the effects seen following dosing with bilastine plus ketoconazole are most likely due to the direct effect of ketoconazole on cardiac function [29].

CNS safety

Histamine as a neurotransmitter is implicated in many functions, such as waking–sleep cycle, attention, memory, learning or the regulation of appetite. The adverse effects of antihistamines on the CNS depend upon their capacity to cross the BBB and bind to the central H₁-receptors. This in turn depends on the lipophilicity of the drug molecule, its molecular weight and affinity for P-glycoprotein [39]. Second-generation antihistamines have been shown to cause less somnolence-related problems than the classic antihistamines, but many still penetrate the BBB to some extent, particularly when used in higher doses. It is generally accepted that piperazinic drugs (cetirizine, oxatamide or levocetirizine) are more sedative than piperidinic molecules, such as bilastine. Preclinical data show clearly that bilastine is a good substrate for P-glycoprotein which would limit its passage across the BBB into the brain. This is supported by autoradiographic evidence of negligible penetration of bilastine into rat brain when given at massive doses [40]. Bilastine has demonstrated a poor action upon the CNS, as shown by the lack of subjective drowsiness, the insignificant effects on objective psychomotor tests or real driving ability, and the lack of relevant interaction with benzodiazepines and alcohol.

A randomized, crossover study conducted in 20 healthy young subjects evaluated peripheral and central effects of a single dose and repeated drug administration for 7 consecutive days of three doses of bilastine (20, 40 and 80 mg), the first-generation antihistamine hydroxyzine 25 mg as the positive control and placebo. Compared with placebo, all treatments showed significant peripheral H₁-blocking activity by attenuating histamine-induced wheal 1–8 h after single doses ($p < 0.001$). Following repeated dosing, a significant reduction of wheal area was shown with bilastine 40 and 80 mg, and hydroxyzine in comparison to placebo and bilastine 20 mg ($p < 0.001$). Treatment effects on the CNS were assessed by means of psychomotor performance tests (evaluating motor activity, perception, attention and associative integration) and questionnaires for subjective reports on mood variables. Hydroxyzine was associated with the highest number of significant alterations in most psychomotor domains after single doses, while significant impairments decreased after repeated-dose administration. A single 80-mg bilastine dose resulted in significant impairment in associative skills, perception and attention domains, but no difference compared with placebo was seen after bilastine 40 and 20 mg. On subjective measures, hydroxyzine was associated with the greatest drowsiness and least activity [41].

A number of studies have assessed the CNS effects of bilastine in combination with other drugs known to cause sedation. In a double-blind, crossover study in healthy volunteers, bilastine 20 mg

once daily for 8 days did not increase the sedative effects of lorazepam 3 mg (as assessed by objective psychomotor testing) [31]. In a similar study, bilastine 20 mg did not affect psychomotor scores when administered with alcohol (no significant differences between alcohol plus 20 mg of bilastine in relation to alcohol alone), unlike cetirizine 10 mg or hydroxyzine 25 mg [31]. A Phase I study in healthy volunteers also investigated the effects of repeated doses of bilastine (20 and 40 mg) for 8 days on driving ability, compared with hydroxyzine 50 mg and placebo. The primary outcome was standard deviation of lateral position (SDLP), a measurement of the road tracking error in a standardized driving test, which was measured after the first and last doses. Neither dose of bilastine increased SDLP relative to placebo on both test days. Hydroxyzine significantly altered SDLP and the subjective measurements. Bilastine did not produce any driving impairment after single and repeated doses in this setting, suggesting that it can be safely used by patients who drive in doses of up to 40 mg [42].

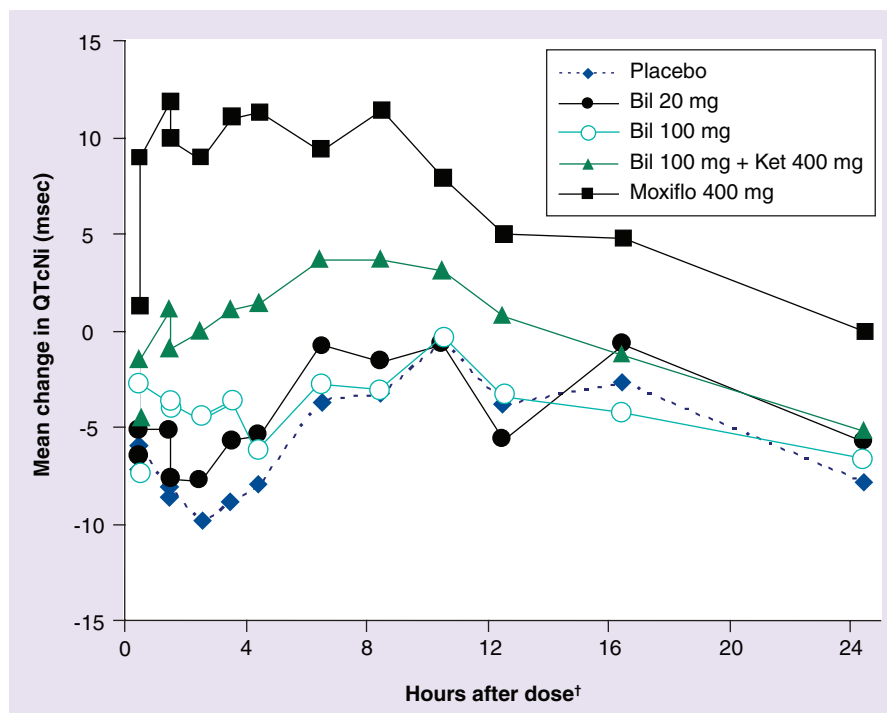


Figure 4. Electrocardiographic effects of different doses of bilastine, bilastine plus ketoconazole, moxifloxacin (positive control) and placebo in 30 healthy adults. Mean change in QTcNi from time-matched baseline versus time by treatment.

†Hours after dose is relative to dosing on day 4.

Bil: Bilastine; Ket: Ketoconazole; QTcNi: Linear individual QT/RR correction.

Regulatory affairs

Bilastine has been recently registered by FAES in 28 countries of the EU for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and children over 12 years of age. In 2007, the product was licensed to Menarini, which holds the license for the compound in 51 countries, including the EU and the Commonwealth of Independent States. Other license agreements include Yuhan Corp. for South Korea, Hikma in the Middle East and North Africa, Pfizer in Mexico, Nycomed in Brazil, and Merck Serono for India. In addition, Menarini has recently signed up several different deals to share bilastine marketing in Spain, France, Belgium, Poland and Greece.

Conclusion

Bilastine is a new inhibitor of the histamine H1-receptor, proven to be effective for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and children older than 12 years. It is highly selective, with appropriate pharmacokinetics, no hepatic metabolism and an excellent safety profile. In the settings of clinical assays and studies in healthy volunteers, bilastine, at therapeutic doses or even in an up dosing schedule, has an adverse events profile similar to placebo and does not affect cardiac conduction, alertness or driving ability.

Expert commentary

After more than a decade without innovations in the antihistamine market, bilastine appears to be a useful therapeutic tool in rhinitis and urticaria, at least as effective as other second-generation

antihistamines. Moreover, bilastine has a number of significantly different features from other antihistamines in the market, according to clinical assays and to Phase I studies in healthy volunteers. Its onset of action may be slightly faster than that of cetirizine. Bilastine's duration of action is expected to be longer than that of fexofenadine; its tolerance profile is similar to that of placebo and also very similar to that of levocetirizine or desloratadine; but patently better than that of cetirizine, overall in the CNS background. On the other hand, bilastine's oral bioavailability seems to be somewhat lower than that of other second-generation antihistamines; nonetheless, daily therapeutic doses of 20 mg achieve concentrations capable of inhibiting wheal and flare areas throughout the whole administration interval. Bilastine's lack of metabolism and elimination profile (67% by feces, 33% by urine) makes dose adjustment unnecessary in all situations.

Bilastine's initial good prospects appear to be confirmed after a short period of the drug on the market. In addition, current studies concerning its future use in children under 12 years of age are being carried out and there are good prospects for eye drop presentation.

Five-year view

Within the following years bilastine will share the oral antihistamines' market with other second-generation molecules such as desloratadine, levocetirizine and fexofenadine, in all countries where it is marketed. So far, a limited experience with the drug in the market indicates that it can be a very competitive and safe alternative.

Information resources

Further reading on bilastine is available through bibliographic references and at:

- www.faes.es/f_en.link?data=1945b2a4d0c8b402c556e81ab6f8082e

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Key issues

- Bilastine is a nonsedative H1-antihistamine newly developed for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria, in adults and children older than 12 years of age.
- Bilastine is a novel piperidinic drug not derived from any other antihistamine currently in the market.
- Bilastine is a potent, highly selective H1-antihistamine, with antiallergic/anti-inflammatory properties *in vitro*.
- Bilastine has no hepatic metabolism or interaction with CYP450 isoenzymes, and it is eliminated as an unchanged drug in the feces (67%) and urine (33%). Dose adjustment is not necessary in elderly patients, or patients with hepatic or renal insufficiency.
- Its efficacy is comparable to cetirizine and desloratadine in allergic rhinitis, and also equivalent to levocetirizine in chronic urticaria, in terms of symptom relief and quality-of-life improvement.
- Bilastine has a good-to-excellent safety profile: an adverse events profile similar to placebo; free from antimuscarinic effects; lack of effects in vital signs or cardiac conduction; and does not affect vigilance or driving ability.

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