

Bilastine as a potential treatment in allergic rhinitis

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ABSTRACT

Background: Allergic rhinitis is a very frequent disease. H_1 antihistamines have been used for treatment of allergic rhinitis for more than 5 decades. They differ in chemical structure, pharmacokinetics, pharmacodynamics, clinical efficacy and adverse effects.

Methods: We performed a detailed analysis of all available publications concerning the new H_1 -antihistamine bilastine.

Results: Bilastine, a piperidine derivative, is a novel potent H_1 antihistamine. It is at least as potent as cetirizine or fexofenadine in *in vitro* studies. In animal studies it demonstrates dose-dependent antihistaminic and antiallergic effects. In humans its metabolism is not affected by age, gender or renal function but may be affected by coadministration of P glycoprotein inhibitors. Efficacy of bilastine in therapy of allergic rhinitis patients has been documented in several large controlled clinical trials showing bilastine being at least as effective as cetirizine or desloratadine. No significant suppressive effect on central nervous system could be demonstrated when bilastine was used in the recommended doses.

Conclusion: Bilastine is a novel H_1 antihistamine with anti-allergic properties which is highly effective in the treatment of symptoms of allergic rhinitis. It has a favorable pharmacokinetic and pharmacodynamic profile and is generally well tolerated.

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Allergic rhinitis (AR) is a frequently encountered disease affecting ~10–30% of adults and up to 40% of children each year.¹ It is not a life-threatening disease, but it results in significant impairment of quality of life (QoL) and loss of productivity.^{2–5} Moreover, AR often is associated with comorbid asthma and if not managed properly may lead to other conditions, including acute/chronic sinusitis, recurrent nasal polyposis, otitis media, sleep apnea, respiratory infections, and aggravation of or predisposal to asthma.⁶

Traditionally, AR has been classified as seasonal AR (SAR) or perennial AR (PAR), dependent on the time of occurrence during the year and the nature of the major allergens triggering the symptoms. A classification of “intermittent” AR or “persistent” AR based on the duration of symptoms has been made by the Allergic Rhinitis and Its Impact on Asthma group in collaboration with the World Health Organization.⁷ The symptoms of AR are associated primarily with histamine released from mast cells.

Histamine exerts its biological effects acting on four distinct receptors referred to as H_1 – H_4 .⁸ The H_1 -receptor plays the most important role in allergic disease. It is involved in wheal and flare symptoms on injection of histamine into the skin, and in contraction of smooth muscles and increased mucous secretion in the airways. In the nose, histamine stimulates the sensory nerve endings, resulting in itching and sneezing; increases vascular permeability leading to nasal obstruction; and enhances glandular secretion causing rhinorrhea.

Because most of the allergic symptoms are elicited by action of histamine through H_1 -receptor, H_1 -antihistamines have been successfully used for years in the treatment of allergic diseases including AR.

Depending on their effect on the central nervous system (CNS) all H_1 -antihistamines have been classified as first-generation or second-generation H_1 -antihistamines (Table 1).⁷ The first-generation H_1 -antihistamines, suppress CNS function, which is clinically reflected as sedation, somnolence, and impairment of psychomotor performances. The second-generation H_1 -antihistamines, are characterized by little or no effect on CNS function at therapeutic doses.⁷ Several H_1 -antihistamines are used topically in AR patients for the treatment

Table 1 H_1 -antihistamines

First Generation	Second Generation	Topical
Chlorpheniramine	Acrivastine	Azelastine
Clemastine	Bilastine	Epinastine
Diphenhydramine	Cetirizine	Levocabastine
Doxepin	Desloratadine	Olopatadine
Hydroxyzine	Ebastine	
	Fexofenadine	
	Levocetirizine	
	Loratadine	
	Mizolastine	

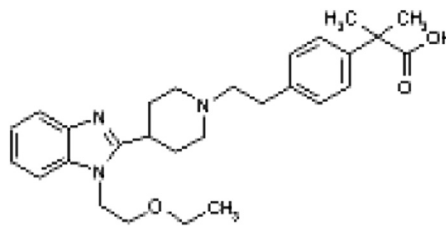


Figure 1. Chemical structure of bilastine.

of both nasal and ocular symptoms (Table 1). The second-generation H_1 -antihistamines are highly selective for H_1 -receptor and their affinities to other receptors such as cholinergic, adrenergic, or serotonergic receptors are much lower than that to H_1 -receptor. Moreover, in contrast to the first-generation H_1 -antihistamines, the second-generation H_1 -antihistamines are slowly metabolized and therefore may be administered once daily.⁷

Although H_1 -antihistamines have the same mechanism of action, they differ in terms of their chemical structure, pharmacokinetics, clinical efficacy, and potential side effects.

BILASTINE

Chemistry, Pharmacokinetics, and Pharmacodynamics of Bilastine

Bilastine, 2-[4-(2-(4-(1-(2-ethoxyethyl) 1-H-benzimidazole 2-yl) piperidine-1-yl) ethyl phenyl)-2-methyl propionic acid], is a novel, selective H_1 -antihistamine. Bilastine belongs to piperidine derivatives (Fig 1).

Bilastine is a potent and specific H_1 -antihistamine. The H_1 -receptor binding studies using guinea pig cerebellum membranes and human

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Table 2 Pharmacokinetics of bilastine in humans

Dose	Single Dose			Repeated Doses
	$C_{\max}$ (ng/mL)	$T_{\max}$ (hr)	$T_{1/2}$ (hr)	$T_{1/2}$ (hr)
10 mg	106.8 ± 52.9	1.74 ± 0.92	4.33 ± 1.24	7.76 ± 3.32
20 mg	231.8 ± 100.7	1.11 ± 0.42	4.73 ± 0.85	9.63 ± 5.25
50 mg	820.7 ± 217.5	1.24 ± 0.37	4.57 ± 1.08	9.68 ± 4.46
100 mg	1579.6 ± 382.8	1.17 ± 0.35	4.03 ± 0.96	10.2 ± 5.13

recombinant H_1 -receptors expressed in human embryonic kidney 293 cells showed that the H_1 -receptor affinity of bilastine was inferior to that of ketotifen or pyrilamine, similar to that of astemizole and diphenhydramine, and superior to that of commonly used second-generation antihistamines, cetirizine or fexofenadine.⁹ In *in vitro* H_1 -antagonistic activity studies using guinea pig ileum, bilastine exhibited, identical to cetirizine, mixed H_1 -antagonism—competitive and noncompetitive.⁹ However, it was 5.5 times more potent than cetirizine as a competitive antagonist and ~10 times more potent than cetirizine as a noncompetitive antagonist.⁹

Potency of bilastine was also shown *in vivo* using rat and guinea pig models.¹⁰ In rats, bilastine effectively reduced capillary permeability induced by intradermal histamine injection.¹⁰ After oral administration, bilastine showed dose-dependent antihistaminic activity starting at a dose 1 mg/kg, with ED_{50} of 2.45 mg/kg being equipotent to cetirizine and four times more potent than fexofenadine.¹⁰ At a dose 5 mg/kg, significantly reduced histamine-induced increase in capillary permeability, reaching $E_{\max}$ after 30 minutes with a significant reduction still observed after 16–18 hours.¹⁰ When administered intravenously, bilastine was approximately three times more potent than cetirizine, with ED_{30} of 0.083 and 0.281 mg/kg for bilastine and cetirizine, respectively.¹⁰ In an experimental model of edema induced by intradermal injections of a mast cell activator compound 48/80 in rats, bilastine was equipotent to cetirizine in reducing capillary permeability induced by 48/80.¹⁰ In guinea pigs, bilastine was at least as potent as cetirizine and approximately four times more potent than fexofenadine in reducing microvascular leakage induced by histamine and it was 11 times more potent than cetirizine in inhibiting histamine-induced bronchospasm.¹⁰ In guinea pigs after subcutaneous administration of a lethal dose of histamine or in Wistar rats after administration of a lethal dose of compound 48/80 showed that bilastine had a marked protective effect similar to that observed with cetirizine.¹⁰

Bilastine not only possesses H_1 -antihistamine activity but also exerts some antiallergic activities *in vitro* and *in vivo*. The antiallergic effects of bilastine *in vitro* were shown using immediate-type hypersensitivity Schultz–Dale reaction model in sensitized guinea pig ileum.⁹ Bilastine exhibited a potent and concentration-dependent anti-anaphylactic activity, with an IC_{50} value of 95.5 nM being three and eight times more potent than fexofenadine and cetirizine, respectively.⁹ *In vivo* bilastine was less potent than cetirizine and more potent than fexofenadine in inhibiting both active and passive cutaneous anaphylactic reactions.¹⁰ However, only bilastine was effective in inhibiting edema induced by administration of sheep red blood cells (type III allergic reaction). No antihistamine was effective in inhibiting type IV allergic reactions.¹⁰

Bilastine, but not cetirizine, both at 100 pM, seems to be effective in inhibiting anaphylactoid reactions inhibiting *in vitro* vancomycin-induced histamine release from C57 mouse mast cells.⁹

Specificity of receptor binding was shown in a series of *in vitro* experiments in which bilastine at a concentration of 100 μ M did not significantly modify the concentration–response curves induced by several agonists such as serotonin, bradykinin, leukotriene D_4 , calcium chloride, acetylcholine, noradrenaline, isoproterenol, adenosine, and dopamine in different isolated organs from rats, guinea pigs, and

rabbits.⁹ Similarly, the concentration–response curves for H_2 -agonist dimaprit and H_3 -agonist (*R*)- α -methyl histamine were not significantly modified by bilastine at concentrations 100 and 30 μ M, respectively.⁹

Pharmacokinetics Studies

Animal Studies. The absorption is fast, linear, and proportional to the administered dose.^{11,12} In rats and dogs, both area under the curve (AUC) of plasma bilastine concentration plotted against time (AUC) and maximum plasma bilastine concentration ($C_{\max}$) increased proportionally to the dose, indicating linear pharmacokinetics of the drug up to a dose of 50 mg/kg.^{11,12} Bilastine bioavailability was in the range of 25–61% and 42–69% in rats and dogs, respectively.¹¹ In Sprague–Dawley rats oral administration of radiolabeled bilastine showed a quick absorption with a $C_{\max}$ reached after 1–2 hours postdose.¹³ The majority of circulating radioactivity (83.2–94.2%) was associated with unchanged parent drug, indicating that bilastine is only partially metabolized *in vivo*.¹³ Approximately 75% of the dose was excreted in feces, 17% in bile, and 8% in the urine.¹³ In feces and urine bilastine was excreted mainly as an unchanged form, and in bile it was metabolized mainly to oxidized bilastine glucuronide conjugate.¹³ Multiple administration of bilastine has confirmed the linearity of the kinetic parameters.¹² There was no accumulation after oral repeated dose administration of bilastine over 26 weeks in mice and rats and 56 weeks in dogs using dosages up to 2000 mg/kg per day for rats and mice and up to 1000 mg/kg per day in dogs.¹² No gender or age effects on bilastine kinetics has been established.¹² In Wistar rats bilastine bioavailability mainly depends on P-glycoprotein activity and inhibition of P glycoprotein results in increase of $C_{\max}$ and AUC.¹⁴

Metabolism of bilastine has also been studied by *in vitro* incubation of bilastine with hepatic microsomes and human subjects and other species hepatocytes.¹⁵ No metabolism of bilastine in any of the species studied was established.¹⁵ Moreover, bilastine did not induce the enzymic activity of CYP450 family (CYP2B6, CYP2A6, CYP2C8, CYP2C19, CYP3A4, CYP1A2, CYP2C9, and CYP2E1).¹⁵

Human Studies

In human subjects, bilastine has linear pharmacokinetics within the 10- to 100-mg dose range administered as a single dose or as a daily dose over a period of 14 days.¹⁶ After a single administration of bilastine at a dose 10, 20, 50, or 100 mg, both AUC and $C_{\max}$ showed dose dependence and increased linearly in the range of 10–100 mg (Table 2).¹⁶ Similar pharmacokinetic results were obtained after administration of a single dose of bilastine in healthy volunteers already receiving bilastine for 2 weeks.¹⁶ The $C_{\max}$ values in patients regularly receiving bilastine tablets ranged from 99.1 ± 24.1 ng/mL to 1277.9 ± 404.9 ng/mL for a dosage of 10–100 mg/day, respectively.¹⁶ No evidence of accumulation of bilastine was established.¹⁶

Bilastine was shown to have a large volume of distribution (V_d/F): 262.7 ± 148.4 L for a dosage of 10 mg/day and 294.6 ± 153.3 L for a dosage of 100 mg/day and low clearance (Cl/F): 23.16 ± 5.82 L/hr for a dosage of 10 mg/day and 20.22 ± 3.67 L/hr for a dosage of 100 mg/day.¹⁶ The mean plasma half-life time ($T_{1/2}$) was similar after

Table 3 Randomized, double-blind, controlled studies evaluating efficacy of bilastine in treatment of allergic rhinitis

Study	Patients (n)	Duration	Comparators	Primary Outcome Measure
Ref. 23	SAR (721)	2 wk	D, 5 mg q.d.; P	Change of AUC TSS: B(−48.9%) = D(−49.5%) < P(−37.4%)
Ref. 24	SAR (681)	2 wk	C, 10 mg q.d.; P	Change of AUC TSS: B(−65.2%) = C(−71.5%) < P(−40.7%)
Ref. 25	SAR (75)	Single dose	C, 10 mg; F, 120 mg; P	AUC TSS ₀₋₄ : B(172 ± 8.1) = C(164.8 ± 8) = F(176.5 ± 8.2) < P(212.5 ± 10.2) AUC TSS ₂₂₋₂₆ : B(165.4 ± 8.7) = C(150.4 ± 8.7) < F(193.2 ± 9.9) < P(218.1 ± 10)
Ref. 26	PAR (650)	4 wk	C, 10 mg q.d.; P	AUC TSS: B = C = P AUC TSS: B = C < P*

*In a subgroup of patients in Europe and South America.

D = desloratadine; C = cetirizine; P = placebo; F = fexofenadine; SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis; AUC = area under the curve; TSS = total symptom score; q.d. = once daily.

administration of bilastine as a single dose of 10–100 mg.¹⁶ During regular daily administration of bilastine, $T_{1/2}$ values were extended.¹⁶ No significant effect of age or gender on the studied parameters has been established.¹⁷ Therefore, it is anticipated that dose adjustment in elderly patients should not be necessary.

In a study that evaluated pharmacokinetics of a single oral dose of 20 mg of bilastine in patients with renal insufficiency it was shown that renal and plasma bilastine clearance paralleled glomerular filtration rate.¹⁸ However, even in patients with severe renal insufficiency the concentration of bilastine in plasma 24 hours after administration of a single 20-mg dose was <5% of C_{max} , indicating that accumulation of bilastine because of renal insufficiency is unlikely and therefore no dose adjustment in renal insufficiency patients is necessary.¹⁸

Possible interactions between bilastine and other drugs and foods have also been studied. In 24 adult healthy volunteers who had been receiving bilastine at 20 mg/day once daily for 7 days the coadministration of ketoconazole, a known inhibitor of P glycoprotein and CYP3A4, at a dose 200 mg twice per day resulted in a greater than twofold increase in steady state systemic exposure of bilastine as evaluated by C_{max} and AUC.¹⁹ Interestingly, coadministration of bilastine with 240 mL of grapefruit juice resulted in a 33% reduction of C_{max} and 24% reduction of AUC in comparison with coadministration of bilastine with 240 mL of water.²⁰ This indicated that grapefruit juice reduces bilastine systemic exposure in a similar manner as the juice affects fexofenadine systemic exposure.

CLINICAL STUDIES

The efficacy of five different doses of bilastine at 2.5, 5, 10, 20, and 50 mg in inhibiting wheal and flare response was evaluated in a double-blind, placebo-controlled, single oral dose crossover study in 21 healthy male volunteers.²¹ All bilastine doses were comparable with or better than cetirizine (10 mg dose) from the beginning through hour 12, each causing >50% inhibition. At hour 24, only the greatest dose of bilastine inhibited wheal response >50%.²⁰ Comparison of AUC of wheal size plotted against time indicated that bilastine at a dose 20 mg was as effective as a 100-mg dose of cetirizine.²¹

The balance between the desired peripheral H_1 -antihistamine effects of bilastine and its undesired CNS effects was evaluated in a randomized, crossover, double-blind, placebo-controlled and positive standard-controlled study in 20 healthy, young volunteers.²² The peripheral and CNS effects of bilastine were compared with placebo and hydroxyzine, first-generation H_1 -antihistamine with known CNS suppressive effects.²² The antihistamine activity of bilastine was evaluated after a single dose and after 7 days of therapy including three different doses 20, 40, and 80 mg of bilastine.²² Peripheral H_1 -antihistamine activity was evaluated objectively by measuring inhibition of histamine-induced wheal area on the skin and subjectively using visual analog scale (VAS) for measuring the degree of pain, itching,

and burning.²² The CNS activity of bilastine were evaluated using the psychomotor performance test (PPT), which measured motor activity, perception, attention, and associative integration.²² Moreover, subjective reports using VAS to evaluate mood were performed (subjective reports on mood).²² Objective evaluation of the peripheral antihistamine activity indicated that bilastine was a potent H_1 -antihistamine with a rapid onset of action at all studied doses significantly superior to placebo and each dose comparably reduced the histamine-induced wheal size from 2 to 8 hours after administration.²² The magnitude of suppressive effect at 4, 6, and 8 hours after administration was comparable with that of hydroxyzine at 25 mg.²² One hour after administration, a single 20-mg dose of bilastine was less effective than 40- or 80-mg doses, but still was more effective than placebo.²² One and 2 hours after administration hydroxyzine at a dose 25 mg was less effective than any of the bilastine doses.²² Only the two higher doses of bilastine produced significant reduction of histamine-induced wheal size 24 hours after administration and the effect was comparable with that of hydroxyzine at a dose of 25 mg.²² A similar pattern of peripheral H_1 -antihistamine activity was observed after 7 days of repeated administration.²²

Both after a single and a repeated administration of bilastine at a dose of 20 mg neither objective nor subjective signs of CNS impairment were reported.²² Administration of higher bilastine doses was associated with subjective reports of sedation, but, objectively, impairments in PPT were shown only after the 80-mg dose of bilastine being still significantly less than those reported after 25 mg of hydroxyzine.²² The CNS impairment was established between 1 and 8 hours after administration of a given dose.²² No significant effects on PPT or subjective reports on mood were shown at 24 hours after the last dose in repeated dose administration for 7 days.²²

Efficacy of Bilastine in AR. Efficacy of bilastine was evaluated in SAR and PAR patients. Efficacy of bilastine in therapy of SAR was evaluated in two large, international, double-blind, placebo-controlled studies comprising >1400 patients.^{23,24} Both studies applied almost identical clinical design and efficacy and safety measures; however, only in the first study was QoL included.^{23,24} Placebo and another second-generation H_1 -antihistamine were used in both studies as control treatment options. The primary outcome measure was AUC of reflective total symptom score (TSS), which was composed of nasal symptom scores (NSSs) and nonnasal symptom scores (NNSSs) recorded by the patients from day 0 to 14. Nasal (congestion, rhinorrhea, sneezing, and itching) and nonnasal (ocular itching, burning, redness, sensation of foreign body in eye, tearing, and itching of ears and/or palate) symptoms were rated on a scale of 0–3, with 0 = no symptoms, 1 = mild symptoms occasionally present but not troublesome, 2 = moderate symptoms frequently present and annoying, and 3 = severe symptoms continuously present and interfering with work and sleep.^{23,24} Secondary outcome measures included overall assessment of discomfort due to rhinitis and the investigators' global clin-

ical impression (GCI).^{22,23} Discomfort was evaluated using VAS and GCI was assessed by the investigators based on the degree of therapeutic effect and the intensity of adverse effects. In addition, in one study rhinoconjunctivitis QoL was assessed based on seven domains: activity limitations, emotional function, eye symptoms, non-hayfever symptoms, nasal symptoms, practical problems, and sleep problems. The patients scored each item on a 7-point scale where 0 = not troubled and 6 = extremely troubled.²²

In both studies conducted in patients with SAR ($n = 1402$) the primary outcome measure AUC TSS was significantly reduced in the bilastine group to a similar extent as in the active comparator group and significantly more than in the placebo group (Table 3). The symptoms of AR improved progressively in the active treatment groups.^{23,24} Therapy with bilastine or any of the active comparators progressively reduced NSS and NNSS significantly more than placebo.^{23,24} Similarly evaluated at the day 14 patients' discomfort due to rhinitis and investigators' GCI indicated that both bilastine and the active comparators were more effective than placebo.²⁴ One study, which included also the RQLQ, showed that bilastine and desloratadine (both by 1.6 points) were significantly superior than placebo (by 1.3 points; $p < 0.005$) in improving rhinoconjunctivitis QoL.²³

Significant superiority of the active treatments over placebo were seen already from the 1st day as evaluated by instantaneous TSS recorded twice daily by treated patients.²⁴ In comparison with placebo, bilastine and cetirizine actively decreased scores for individual nasal and nonnasal symptoms after 7 days of therapy, except for ocular redness, also after 14 days of therapy.²⁴ Significantly greater decrease of NSS and NNSS from the baseline values was reported for bilastine (42.4 and 49.8%, respectively) and cetirizine (48.2 and 51.0%, respectively) than for placebo (26.9 and 27.6%, respectively; $p < 0.001$ for all comparisons). Similarly evaluated at day 14 patients' discomfort due to rhinitis and investigators' GCI indicated that both bilastine and cetirizine were more effective than placebo.²⁴

Similar efficacy of bilastine in SAR was shown in a study that used controlled allergen exposure in a Vienna Challenge Chamber.²⁵ Bilastine at 20 mg was as effective as cetirizine at 10 mg or fexofenadine at 120 mg during the first 4 hours after administration, being significantly more effective than placebo in reducing TSS. However, 22–26 hours after administration of the last dose of bilastine and cetirizine were more effective than fexofenadine and placebo.²⁵

In a large, international, double-blind, placebo-controlled study evaluating efficacy of 4-week therapy of PAR bilastine at 20 mg once daily bilastine was as effective as cetirizine at 10 mg once daily and more effective than placebo only in a subgroup of patients from Europe and South America.²⁶ Lack of efficacy of bilastine in the whole group resulted from great variability of symptom scores reported in different countries, particularly in South Africa.²⁶

Safety

Generally, bilastine was safe and well tolerated at doses of 2.5–80 mg/day.^{16,17,22,23,24} Both preclinical and clinical studies included >2000 individuals in which it was established that in patients receiving 20 mg of bilastine once daily the most common adverse effects of headache, somnolence, fatigue and dyspnea were reported less frequently than in patients receiving first-generation H₁-antihistamine hydroxyzine and also less frequently than in patients receiving cetirizine at 10 mg once daily.^{23,24} The frequency of adverse effects of bilastine at 20 mg once daily used in therapy of AR were comparable with that of desloratadine.²³ The frequency of somnolence and impaired psychomotor performance greater than in the placebo group was shown only in persons treated with doses of bilastine for >40 mg/day.²² However, it was still less frequent than that observed in subjects treated with cetirizine at 10 mg once daily.²²

No significant anticholinergic effects, such as dry mouth, have been reported with any of the bilastine doses (20, 40, or 80 mg).^{22–24} This is consistent with high selectivity of bilastine established in *in vitro* experiments.⁹

No significant cardiovascular adverse effects, including no significant effect on QTc interval, were observed in subjects receiving bilastine doses up to 100 mg/day.^{16,21–24} Similarly, coadministration of bilastine with ketoconazole, a medication known to prolong QTc interval, did not show any amplification of QTc prolongation by bilastine.¹⁹ Ketoconazole prolonged QTc interval to the same extent whether given alone or in combination with bilastine.¹⁹

No significant carcinogenic effects have been established in rats and mice.

CONCLUSIONS

Bilastine is a potent and highly selective second-generation antihistamine. It is effective and safe for treatment of SAR. No impairment of psychomotor performance at therapeutic doses is seen.

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