Review Article

Bilastine: A Novel Antihistamine

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Abstract

Bilastine is a new second generation H1-antihistamine approved for the symptomatic treatment of allergic rhinitis (AR) and chronic urticaria (CU) in patients older than 12 years of age. AR and urticaria are very common clinical conditions that represent one of the most frequent reasons for a patient to visit their general practitioner or allergist or dermatologist. Bilastine, with its efficacy and safety profile epitomizes the evolution of research on antihistamines.

Keywords: Bilastine, chronic urticaria, antihistamine

INTRODUCTION

Bilastine is a new second-generation H1-antihistamine approved for the symptomatic treatment of allergic rhinitis (AR) and chronic urticaria (CU) in patients older than 12 years of age. AR and urticaria are very common clinical conditions that represent one of the most frequent reasons for a patient to visit their general practitioner or allergist or dermatologist. AR and urticaria respond to antihistamine treatment and current international guidelines recommend nonsedating second-generation antihistamines as first-line treatment for both.[1-3]

Bilastine, or 2-[4-(2-(4-(1-(2-ethoxyethyl)-1H–benzimidazole–2-yl) piperidine-1–yl) ethyl) phenyl]-2-methyl propionic acid, is a new next-generation antihistamine.[4] It is a new piperidine molecule and belongs to the same chemical group as many new antihistamines (ebastine, fexofenadine, loratadine, desloratadine, rupatadine, levocabastine, emedastine, and epinastine). Within this group, it is chemically close to the piperidine-benzimidazole subgroup, which also includes molecules such as norastemizole and mizolastine.[5]

PHARMACODYNAMICS AND PHARMACOKINETICS

Bilastine belongs to piperidine derivatives and is not structurally derived from any other currently available antihistamines. Bilastine exerts a potent and specific H1-antihistamine activity. Bilastine is an H1 receptor inverse agonist. Bilastine has high specificity for H1-receptors. The affinity for the H1 receptor is 3 and 6 times higher than for cetirizine and fexofenadine, respectively. In vitro data have shown that bilastine also exerts anti-inflammatory activity by inhibiting the release of histamine, interleukin-4, and tumor necrosis factor-α from human mast cells and granulocytes.[6]

Absorption

Bilastine has a T[subscript max] of 1.13 h. The absolute bioavailability is 61%. No accumulation is observed with daily dosing of 20–100 mg after 14 days. C[subscript max] decreased by 25% and 33% when taken with a low fat and high fat meal compared to fasted state. It does not undergo presystemic hepatic metabolism and has no active metabolites. It does not interact with the cytochrome P450 system and consequently is unlikely to be involved in drug–drug interactions. Like many other antihistamines, plasma levels of bilastine are increased by the concomitant administration of erythromycin, ketoconazole, or diltiazem, all inhibitors of P-glycoprotein (P-gp), and/or organic anion-transporting polypeptide (OATP) modulators of intestinal absorption.[4]

Distribution

The binding of bilastine to plasma proteins is 84%–90%. Radiolabelled molecule availability studies in rats and dogs using (14C)-bilastine show wide tissue distribution, predominantly in organs involved in absorption, metabolism,

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and excretion (gastrointestinal tract, biliary tract, and kidneys). No Bilastine was detected in the brain.

Compartmental analyses in healthy volunteers show that, at a daily dose of bilastine 20 mg, the distribution volume is about 59 liters for the central compartment (VcF) and 30 liters for the peripheral compartment (VpF), which corresponds with a Vda of 1.29 l/kg.

No tissue accumulation was found after single or multiple doses of bilastine.

The half-life for bilastine (t½) is estimated at 14.53 h, similar to that of fexofenadine and intermediate between published values for cetirizine/levocetirizine (8–10 h) and desloratadine (26.8 h).

These data in healthy volunteers indicate that a once-daily dose of bilastine 20 mg maintains a sufficient plasma level to maintain its therapeutic activity for 24 h.

**Route of elimination**

Bilastine is mainly excreted in the feces (66.5%) with some excreted in the urine (28.3%). Nearly, all is excreted as the parent compound.

Bilastine has a total clearance is 9.20 L/h and a renal clearance of 8.7 L/h.

**BILASTINE IN SPECIAL SITUATIONS**

**Age and sex**

A study was conducted in 32 healthy volunteers divided into four homogeneous groups (males 18–35 years, males >65 years, females 18–35 years, and females >65 years).

Following single oral doses of bilastine 20 mg, there were minimal differences in Cmax for the group of females, without statistical significance, and no differences by gender or age for the other pharmacokinetic parameters.

**Hepatic impairment**

Since the hepatic metabolism of bilastine is negligible and biliary excretion is believed to be minimal, a specific pharmacokinetic study on patients with liver impairment has not been performed.

**Renal impairment**

Since the mass balance studies indicate that 28%–33% of bilastine administered undergoes renal excretion, a study was conducted to determine the pharmacokinetics and tolerance of bilastine in patients with varying degrees of renal impairment.

The study showed that:

- The renal route is the main excretory route for bilastine in the plasma
- Bilastine clearance is proportional to renal function
- Patients with renal impairment have increased Cmax and AUC, with no significant differences in Tmax or t1/2 values
- In patients with severe renal failure, Cmax values did not reach concentrations higher than those that could potentially cause adverse effects.

Thus, it can be concluded that no dose adjustment is necessary when administering bilastine to patients with renal impairment.

**Children**

A study has been started on 44 children with AR and/or CU, in the age ranges of 2–6 years and 6–12 years. A secondary end point is to assess the safety and tolerability of bilastine in these age ranges.

**Drug Interactions**

P-gp is a drug transport pump in the blood–brain barrier (BBB), the intestinal wall, and proximal renal tubules. It is important in drug bioavailability, distribution, and elimination.

**Table 1: Adverse events of Bilastine**

| Study             | Number of patients | Duration of study | Disease                  | Adverse event       |
|-------------------|--------------------|-------------------|--------------------------|---------------------|
| Zuberbier T et al. | 525                | 28 days           | Chronic idiopathic urticaria | Any: 30.1%          |
|                   |                    |                   |                          | Headache: 12.1%     |
|                   |                    |                   |                          | Somnolence: 5.8%    |
|                   |                    |                   |                          | Fatigue: 2.9%       |
| Sastre J et al.   | 650                | 4 weeks           | Persistent allergic rhinitis | Any: 23.4%          |
|                   |                    |                   |                          | Headache: 10.7%     |
|                   |                    |                   |                          | Somnolence: 13.7%   |
| Bachert et al.    | 721                | 14 days           | Seasonal allergic rhinitis | Any: 28.3%          |
|                   |                    |                   |                          | Headache: 12.0%     |
|                   |                    |                   |                          | Somnolence: 3.9%    |
|                   |                    |                   |                          | Fatigue: 2.6%       |
| Kuna P et al.     | 683                | 14 days           | Seasonal allergic rhinitis | Any: 24.7%          |
|                   |                    |                   |                          | Headache: 10.6%     |
|                   |                    |                   |                          | Somnolence: 3.9%    |
|                   |                    |                   |                          | Fatigue: 0.4%       |
|                   |                    |                   |                          | Dyspnea: 0.9%       |
OATPs (organic anion transporting polypeptides) are protein carriers with the ability to uptake drugs, drug metabolites, or toxins into the cell, i.e. they have the opposite effect of P-gp. They are also present in many tissues and like P-gp, can be activated and inhibited by many substances.

Interaction studies performed with bilastine show that:

- The absorption of bilastine is significantly increased when administered together with erythromycin and ketoconazole. These drugs are themselves inhibitors of cytochrome P450 (mainly CYP3A4) and also of P-gp and OATP-dependent transport systems.
- Since bilastine is negligibly metabolized and considering that at in vitro therapeutic concentrations, it does not inhibit or induce the activity of cytochrome P450 isoenzymes, it is believed that the interactions occur in the transport systems.

**With erythromycin**

$C_{\text{max}}$ and AUC values of bilastine were significantly increased when administered with erythromycin, confirming higher bioavailability in the presence of erythromycin. Neither the plasma concentration profile of erythromycin nor its elimination parameters were affected by coadministration with bilastine.

**With ketoconazole**

$C_{\text{max}}$ and AUC values of bilastine were significantly increased when administered with ketoconazole, confirming higher bioavailability in the presence of ketoconazole.

Neither the plasma concentration profile of ketoconazole nor its elimination parameters were affected by coadministration with bilastine.

**With diltiazem**

Co-administration of bilastine and diltiazem caused an increase of 62% and 40% in the $C_{\text{max}}$ and AUC values of bilastine, respectively, suggesting higher bioavailability.

**Clinical Efficacy**

In clinical trials, bilastine, at a single daily dose of 20 mg, has shown to be more effective antihistamine than placebo, and at least as effective as cetirizine, desloratadine, and fexofenadine in controlling the symptoms of allergic rhinoconjunctivitis. It has also demonstrated to be at least as effective as levocetirizine in controlling pruritus and the number and size of wheals in urticaria.[5]

**Safety and Tolerability**

All clinical studies have demonstrated the safety and tolerability of bilastine with no statistically significant differences between the therapeutic dose (20 mg) and placebo.[5]

- Headache, drowsiness, and lethargy are the most common adverse events reported by patients.
- Bilastine does not prolong the QT/QTc interval and it does not cause significant changes on ECG at the studied doses, even in the case of interaction with drugs that increase its plasma levels, such as ketoconazole.
- At therapeutic doses, bilastine does not have anticholinergic effects and does not affect psychomotor performance, assessed by means of objective psychometric tests and subjective perceptive tests.
- Bilastine is a good substrate for P-gp which would limit its passage across the blood–brain barrier into the brain.
- At therapeutic doses, bilastine does not affect psychomotor performance or enhance the effects of alcohol or the benzodiazepine and lorazepam.
- In on-the-road driving test studies, bilastine does not show significant differences versus placebo.

**Dosage**

The recommended dose of bilastine is 20 mg in single daily dose, best taken at least 1 h before or 2 h after the intake of food or fruit juice.[8]

- It is not necessary to make dose adjustments in patients over 65 years.
- No dose adjustment is necessary when administering bilastine to patients with renal impairment. Concomitant administration of bilastine and P-gp inhibitors must be avoided in patients with moderate-to-severe renal impairment.
- Since bilastine is not metabolized in liver and its main route of elimination is renal, it does not seem likely that hepatic impairment could lead to bilastine bioavailability in excess of its safety range. For these reasons, it is not necessary to make dose adjustments in patients with hepatic impairment.
- Safety and efficacy of bilastine in children below 12 years has not been determined.
- Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, parturition, or postnatal development, but as a precautionary measure, it is preferable to avoid the use of bilastine during pregnancy.
- With respect to lactation, it is unknown whether bilastine is excreted in human breast milk.

The excretion of bilastine in milk has not been studied in animals. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with bilastine should be made taking into account the benefit of breastfeeding to the child and the benefit of bilastine therapy to the mother.

- For AR, the treatment should be limited to the period of exposure to allergens.
- For seasonal AR, treatment could be discontinued after the symptoms have resolved and reinitiated upon their reappearance.
- In perennial AR, continued treatment may be proposed to the patients during the allergen exposure periods.
- For urticarial, the duration of treatment depends on the type, duration, and course of the complaints.
**ADVERSE EVENTS**

Headache, drowsiness, dizziness, and fatigue are the most common adverse events reported by patients with an incidence similar to placebo [Table 1].

**CONCLUSION**

Bilastine is a new-generation, nonsedating H1 antihistamine of piperidine family.

With a high affinity for H1 receptors, has high receptor selectivity, a potent in vitro and in vivo activity, at least equal to cetirizine and higher than fexofenadine. It has rapid and sustained action, with an 8 h duration of maximum effect and significant activity for at least 24 h following a single dose. Its clinical efficacy is at least comparable to cetirizine, desloratadine, and fexofenadine in the treatment of allergic rhinoconjunctivitis, and at least comparable to levocetirizine in the treatment of urticaria.

- A similar safety and tolerability profile to the other new H1 antihistamines, without anticholinergic effects, no significant effects on cognition or psychomotor performance (CNS), and no cardiovascular or electrocardiographic changes at the doses studied, even in case of drug interactions.

Therefore, the authors concluded that bilastine meets current EAACI/ARIA criteria for medications used in the treatment of AR.

Bilastine epitomizes the evolution of research on antihistamines concerning both efficacy and safety.

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**Conflicts of interest**

There are no conflicts of interest.

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