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Safety profile of Bilastine: 2nd generation h1-antihistamines

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Abstract. – Bilastine is a new H1 antagonist with no sedative side effects, no cardiotoxic effects, and no hepatic metabolism. In addition, bilastine has proved to be effective for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria.

Pharmacological studies have shown that bilastine is highly selective for the H1 receptor in both *in vivo* and *in vitro* studies, and with no apparent affinity for other receptors. The absorption of bilastine is fast, linear and dose-proportional; it appears to be safe and well tolerated at all doses levels in healthy population. Multiple administration of bilastine has confirmed the linearity of the kinetic parameters. The distribution in the brain is undetectable. The safety profile in terms of adverse effects is very similar to placebo in all Phase I, II and III clinical trials. Bilastine (20 mg), unlike cetirizine, does not increase alcohol effects on the CNS. Bilastine 20 mg does not increase the CNS depressant effect of lorazepam. Bilastine 20 mg is similar to placebo in the driving test. Therefore, it meets the current criteria for medication used in the treatment of allergic rhinitis and urticaria.

Key Words:
H(1)-antihistamine, Bilastine.

Introduction

Although histamine exerts important physiologic functions in human health through 4 subtypes of receptors[1-5], it is the activity at H1 histamine receptors that is involved in allergic reactions[6].

Histamine plays an important role in the pathophysiology of allergic disorders, including allergic rhinitis and urticaria[7,8].

Through the H1-receptor, histamine increases release of some mediators from mast cells and basophils, downregulates humoral immunity, increases antigen-presenting cell capacity and upregulates TH1 priming and proliferation, IFN-production, cellular adhesion molecule expression, and chemotaxis of eosinophils and neutrophils[9].

Drugs that bind to H1-receptors and act as inverse agonists, reduce allergic inflammation directly through the H1-receptor by interfering with histamine action at H1-receptors, either on sensory neurons or on small blood vessels. Involving the ubiquitous transcription factor nuclear factor-kB, they also decrease expression of proinflammatory cytokines, cell adhesion molecules and chemotaxis[10,11].

However, through the H1-receptor, histamine contributes to regulation of cell proliferation and differentiation, hematopoiesis, embryonic development, regeneration, and wound healing and plays an important role in neurotransmission in the central nervous system (CNS). It has anticonvulsant activity and contributes to regulation of vigilance (alertness and attention), cognition, learning, memory, and the circadian sleep-wake cycle, as well as to energy and endocrine homeostasis[12].

Since histamine trough the H1-receptor exerts many functions, it appear that drugs blocking this receptor in all body including CNS, may have many side effects beside its beneficial effects.

H1-antihistamines are functionally classified into 2 groups. First-generation medications readily cross the blood-brain barrier (BBB) and occupy H1-receptors located on postsynaptic membranes of histaminergic neurons throughout the CNS. Second generation H1-antihistamines do not cross the BBB readily[6].

First-generation antihistamines are effective in controlling allergic rhinitis symptoms, but they are also associated with side effects such as sedation and antimuscarinic effects[12,13]. These side effects may interfere with daily activities and increase the risk of accidents in situations such as driving or operating machinery, where high levels of alertness are required. Furthermore, they are likely to reduce compliance because of excessive fatigue and malaise. For these reasons were practically abandoned as anti allergic drugs.

Second-generation H1 receptor antagonists have largely superseded their first-generation

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counterparts, owing to more favourable pharmacokinetics and reduced (or negligible) sedative effects. The most frequently used second-generation H1-receptor antagonists are desloratadine, loratadine, fexofenadine, cetirizine, levocetirizine and bilastine.

Second-generation antihistamines are less sedating than the first generation agents for their limited penetration across the blood-brain barrier[6,14], and a major reason for this is thought to be P-glycoprotein-mediated efflux of the drug from the CNS[15,16], but also for their less lipid solubility than the first-generation agents[17]. In addition, these new-generation agents are more selective for H1 receptors and, hence, are not associated with adverse events arising from interactions at other receptor types[6]. Finally, their drug-drug, drug-food, and drug–herbal product interactions, if any, are less clinically relevant[14].

The main purpose of this report is to evaluate the safety profile of bilastine, the most recent second-generation H1-receptor antagonists introduced in clinical practice. The clinical efficacy of bilastine has recently been assessed[18], for which will not be extensively evaluated in this report.

Bilastine

Bilastine is a new antihistamine that is not structurally derived from any antihistamines currently on market, nor is it an active metabolite or enantiomer of another antihistamine. From a structural point of view is 2-[4-(2-(4-(1-(2-ethoxyethyl)-1Hbenzimidazol-2-yl)piperidin-1-yl)ethyl)phenyl]-2-methyl propionic acid, with a molecular weight of 463.6 daltons and a chemical structure similar to piperidinyl-benzimidazole (Figure 1)[19,20]. This chemical structure, with the hydrophilic carboxylic substituent, contributes to the low penetration into CNS. Bilastine is a potent, effective, non-sedating antihistamine, without cardiac toxicity, absence of metabolism, and

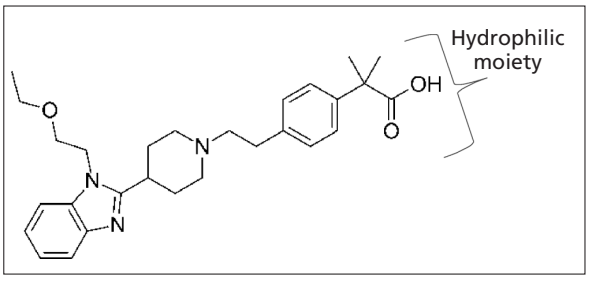

Figure 1. Chemical structure of Bilastine. The hydrophilic carboxylic substituent, contribute to the low penetration into CNS.

it does not interact with cytochrome P450. Therefore, it meets the current European Academy of Allergy and Clinical Immunology (EAACI) and Allergic Rhinitis and its Impact of Asthma (ARIA) criteria for medication used in the treatment of allergic rhinitis[21]. Bilastine was approved for use in the European Union in 2010[22], and is currently being introduced into clinical practice in 28 Countries of the European Union (EU) for the symptomatic treatment of allergic rhinoconjunctivitis (perennial and seasonal) and urticaria in adults and children over 12 years.

Pharmacological Profile

Pharmacological studies have shown that bilastine is highly selective for the H1-receptor in both *in vivo* and *in vitro* studies, and with no apparent affinity for other receptors.

These preclinical studies provide evidence that bilastine has H1-antihistamine activity, with high specificity for H1-receptors, and poor or no affinity for other receptors such as serotonin, bradykinin, leukotriene D4, calcium, muscarinic M3-receptors, alpha1-adrenoceptors, beta2-adrenoceptors, and H2- and H3-receptors. Moreover, in the *in vitro* Schultz-Dale reaction bilastine demonstrated anti-inflammatory activity[23].

In vivo preclinical studies confirmed those obtained from previously conducted *in vitro* experiments of bilastine, and provide evidence that bilastine possesses antihistaminic as well as antiallergic properties, with similar potency to cetirizine and superior potency to fexofenadine[24].

Pharmacokinetics

Bilastine, studied in single- and multiple-dose trials in healthy volunteers, presents linear pharmacokinetics with regard to maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) in the dose range studied (2.5 to 220 mg), with a low interindividual variability. The drug is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1 hour. No drug accumulation was observed with repeated bilastine administration. The mean value of bilastine oral bioavailability was found about 61%[24]. In a population pharmacokinetic model the predicted median value for Cmax was 220 ng/mL, and the apparent volume of distribution was 59.2 L for the central compartment and 30.2 L for the peripheral compartment. At therapeutic doses bilastine is 84-90% bound to plasma proteins[25,26], and the mean AUC from time zero

to 24 hours was 990 ngh/mL after a single 20 mg dose of bilastine in 48 healthy volunteers[27].

Bilastine is a substrate of P-glycoprotein (P-gp) and organic anion transporter inhibitor (OATP)-1A2[12,13]. Bilastine does not appear to be a substrate of the transporter BCRP or renal transporters OCT2, OAT1 and OAT3. Based on *in vitro* studies, bilastine is not expected to inhibit the following transporters in the systemic circulation: P-gp, MRP2, BCRP, BSEP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and NTCP, since only mild inhibition was detected for P-gp, OATP2B1 and OCT1, with an estimated IC_{50} 300 μM, much higher than the calculated clinical plasma Cmax and, therefore, these interactions will not be clinically relevant. However, the inhibition by bilastine of transporters present in the intestinal mucosa, e.g. P-gp, cannot be excluded[28].

Bilastine is not metabolized and not induces or inhibits activity of CYP450 isoenzymes in *in vitro* studies.

In healthy volunteers, after administration of a single dose of 20 mg 14C-bilastine, almost 95% of the administered dose was recovered in urine (28.3%) and faeces (66.5%) as unchanged bilastine, confirming that bilastine is not significantly metabolized in humans. The mean elimination half-life calculated in healthy volunteers was 14.5 h and the apparent total plasma clearance is 18.1L/h (population pharmacokinetic model estimates)[29-31].

Safety in Clinical Trials

As mentioned above, the complete clinical evaluation of bilastine is out of this review. Here, the summary is reported. The clinical efficacy of bilastine in allergic rhinitis (AR) and urticaria has been assessed in a number of clinical trials in which over 4,600 patients were involved (32). In all of these studies bilastine was compared with placebo and another second-generation antihistamine with confirmed efficacy. There were no significant differences in primary endpoint results between bilastine and any of the active comparators used in these trials (i.e. cetirizine, levocetirizine and desloratadine)[18].

In one of the first studies performed under controlled conditions of allergen exposure and time of exposure with sensitised volunteers using the Vienna Challenge Chamber, bilastine 20 mg shows similar efficacy to that of cetirizine 10 mg for the relief of symptomatic seasonal AR (SAR). The duration of the effect of both compounds was higher than that of fexofenadine at a dose of 120 mg[33].

The type and frequency of adverse events, tolerability, and general safety of treatment were evaluated in all clinical trials.

Bilastine was generally well tolerated in patients with seasonal or perennial allergic rhinitis or chronic urticaria[34-37].

The overall prevalence of treatment-related adverse events was 15-30% and 19-28% in bilastine and in placebo recipients respectively[34-37]. The most frequently reported adverse events associated with bilastine were headache, somnolence, fatigue and dizziness[34-37]. The adverse events that were at least possibly related to bilastine occurred at a frequency of about 0.5%. No serious adverse events or deaths were reported in clinical studies[34-37]. No clinically significant changes in any laboratory parameters, ECG recordings or vital sign measurements were observed in bilastine recipients.

The nature and occurrence of adverse events appeared similar between bilastine and the active comparator for each study, with headache and somnolence being the most frequently occurring adverse events in all treatment arms[34-37]. However, in one study, the appearance of treatment-related adverse events, somnolence and fatigue were significantly lower in bilastine than cetirizine recipients[35] showing that the tolerability of bilastine appeared more favourable than that of cetirizine. Additionally, in a pooled analysis the treatment-related somnolence occurred at a significantly lower rate in bilastine than cetirizine recipients [3.52% vs 7.58% – ($p < 0.0001$)], while occurred in a similar proportion in bilastine and placebo recipients[38].

The Table I offers a summary of the most frequent adverse events reported during the clinical trials carried out with bilastine compared to desloratadine or cetirizine[32].

Organ Related Tolerability

From the point of view of drug safety, absence, or only minimum presence of adverse CNS, or cardiac effects are the requirements any new antihistamine must fulfill.

CNS Tolerability

A double-blind, cross-over placebo-controlled study compared the effects upon the CNS of three different doses of bilastine (20, 40 and 80 mg) once a day after 7 consecutive days, using hydroxyzine as a positive control[39]. Objective evaluations of motor activity, perception, attention and associative integration were performed,

Table I. Most frequent adverse events reported during the clinical trials carried out with bilastine and comparators. Bilastine exhibited a statistically significant better profile of adverse events than cetirizine[32].

Adverse events	Placebo	Cetirizine	Desloratadine	Bilastine	Statistical significance
Headache	4.8% (35/734	9.5% (23/241)	4.5% (11/242)	6.4% (101/1573)	$p < 0.05$*
Somnolence/sedation	3.3% (24/734)	9.1% (22/241)	3.7% (9/242)	4.1% (65/1573)	$p < 0.05$*
Fatigue/asthenia	2.3% (17/734)	3.7% (9/241)	1.7% (4/242	1.3% (21/1573)	$p < 0.05$*
ECG abnormalities	2.0% (15/734)	2.1% (5/241)	1.7% (4/242)	1.7% (27/1573)	N.S.
Dizziness	0.8% (6/734)	1.7% (4/241)	1.2% (3/242)	1.6% (25/1573)	N.S.

*vs cetirizine.

as well as the subjective changes in mood state through a visual analogue scale and an specific questionnaire. Bilastine at the dose of 20 mg, used in clinical practice, showed no significant differences versus placebo. The 40 mg dose induced subjective drowsiness, but no objective alterations in the psychomotor tests were observed. Only the 80 mg dose (i.e. 4 times the recommended dose) caused a discrete impairment of the psychomotor test results. Thus, the 20 mg dose was seen to be completely safe as regards the adverse effects upon the CNS.

Interaction with Alcohol

It is well known that alcohol potentiates the effects of first-generation antihistamines upon subjective drowsiness and psychomotor skills. In the case of bilastine, a double-blind, cross-over placebo-controlled study was carried out to evaluate the interaction of two different doses of bilastine (20 and 80 mg) with alcohol (0.8 g/kg), together with two comparator drugs (cetirizine 10 mg and hydroxyzine 25 mg)[40]. The effect of 20 mg of bilastine plus alcohol was equivalent to that obtained by placebo with alcohol, while cetirizine 10 mg, and hydroxyzine 25 mg enhanced significantly the effects of alcohol. At the dose of 80 mg bilastine enhanced significantly the effects of alcohol similar to cetirizine 10 mg, and hydroxyzine 25 mg.

Interaction with Benzodiazepines

First-generation antihistamines interact with benzodiazepines, increasing their sedative effects. However, this phenomenon is not observed with second-generation antihistamines. Bilastine 20 mg, in the context of a double-blind, crossover placebo-controlled study, did not increase the central depressant effects of 3 mg of lorazepam in either single or multiple administration during 8 consecutive days[41].

Effects on the Ability to Drive

The effect of bilastine on the ability to drive was evaluated in a recent double-blind, cross-over placebo-controlled study[42]. Two doses of bilastine (20 and 40 mg) were compared with hydroxyzine 50 mg as positive control, in single and multiple administration during 8 consecutive days. The primary endpoint of this study was the Deviation of the Lateral Position, which is a measure of vehicle zigzagging. Bilastine, in contrast to hydroxyzine, induced no alterations in the ability to drive and both the 20 mg and the 40 mg dose were seen to be safe in single and repeated administration.

Cardiovascular Safety

Some studies have demonstrated the cardiovascular safety of bilastine using doses up to ten times the therapeutic dose in healthy volunteers with results not very different from those of the placebo controls. Single doses of bilastine up to 220 mg and multiple doses up to 200 mg (10 times higher than the therapeutic dose) during 7 days did not result in a statistically significant QT/QTc interval prolongation as compared with results from baseline vs. placebo[32].

Another study[43] investigates, according with the International Conference of Harmonisation (ICH) E14 guideline, whether a composite ECG measure of T-wave morphology (Morphology Combination Score [MCS]) can be used together with the heart rate corrected QT interval (QTc) to exclude clinically relevant repolarization effects of bilastine. The study showed that there were no effects of bilastine monotherapy (20 and 100 mg) on MCS or QTc at those study times where the bilastine plasma concentrations were highest. MCS changes for bilastine monotherapy did not exceed the normal intrasubject variance of T-wave shapes for triplicate ECG recordings. Authors concluded that bilastine, at therapeutic

and supratherapeutic dosages, does not induce any effects on T-wave morphology or QTc.

The safe cardiac profile was confirmed in another recent study[44] where the effect of bilastine multiple-dose on cardiac repolarization was evaluated in 30 healthy subjects. The study compared bilastine at therapeutic and supratherapeutic doses (20 mg and 100 mg once daily, respectively), with placebo, active control (400 mg moxifloxacin), and bilastine 20 mg administered with ketoconazole 400 mg. Bilastine did not clinically significantly increase QTc intervals at therapeutic and supratherapeutic doses. Although a statistically significant QT prolongation was observed after the concomitant administration of bilastine and ketoconazole, it was most likely related to ketoconazole as no PK-QT relationship with bilastine alone at 20 mg and 100 mg was observed.

These studies confirm the absence of any effect for bilastine on cardiac repolarization.

Reasons that May Explain the Higher Safety of Bilastine

Bilastine is a new second generation H-1-antihistamine with similar efficacy of desloratadine and cetirizine but with better tolerability, at least compared to the latter.

Several pharmacological properties of bilastine may explain this property.

Selectivity: Binding studies performed in animal tissues with a high density of H1-receptors show that bilastine has a moderate-high affinity for histamine H1-receptors, with values 3 times higher than those of cetirizine and 5 times higher than those of fexofenadine. These studies have also revealed that at a high concentration, bilastine does not show affinity for the 30 other receptors that have been assessed (including muscarinic receptors), nor for the other histamine receptor subtypes H2, H3 and H4. Bilastine binds specifically and selectively to histamine H1-receptor[23,24].

CNS penetration: The tissue distribution of bilastine has been examined in three types of mice using whole body autoradiography, no detectable drug levels being seen in the CNS in any of them at the different measured time points between 15 minutes and 336 hours after the administration of 20 mg/kg of bilastine[45].

Moreover, 2 hours after administration of oral 14C-bilastine 20 mg/kg to rats, no radioactivity was observed in the brain while diffuse radioactivity was detected throughout the peripheral tissues, particularly in the gastrointestinal system and liver[19].

Bilastine may have a limited penetration across the blood-brain barrier because it is a good P-glycoprotein substrate[15], additionally the relative high molecular weight (Table II), the relative lower lipophilicity may play a role.

Metabolism: Bilastine metabolism has been studied by *in vitro* incubation with hepatic microsomes, and human and other species hepatocytes. Bilastine does not induce the enzymatic activity of CYP450 family (CYP2B6, CYP2A6, CYP2C8, CYP2C19, CPY3A4, CYP1A2, CYP2C9 and CYP2E1). No interaction clinically relevant can be expected between bilastine and drugs or food[29]. Even if the metabolism is not directly involved in CNS tolerability, the expected absence of interaction with drugs affecting the CNS may contribute to the safety of bilastine.

Conclusions

Bilastine is a new second-generation antihistamine with a better pharmacological profile compared to other second generation H1-antihistamine. Clinical efficacy at a dose of 20 mg for the treatment of allergic rhinoconjunctivitis (perennial and seasonal) and urticaria has been demonstrated and it is similar to cetirizine. Therefore, bilastine appeared more safer than cetirizine in terms of adverse effects upon the CNS. The imaging studies having revealed no penetration into the CNS and no significant differences have been observed versus placebo in terms of the objective psychomotor test results or subjective assessments of drowsiness. Likewise, bilastine does not interact with alcohol, and does not enhance the central depressant effect of lorazepam. Regarding the ability to drive, a dose of up to 40 mg (i.e. twice the standard recommended dose) has been shown to be safe for the patient, is well tolerated, without objective alterations in driving ability. These characteristics define bilastine as an interesting drug from the therapeutic perspective and extremely safe regarding CNS effects.

Table II. Molar mass (molecular weight) of some second-generation H1-antihistamines.

Drug	Molar mass (g mol^{-1})
Desloratadine	310.82
Loratadine	382.88
Cetirizine	388.89
Bilastine	463.6

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