Bilastine and the Central Nervous System

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Abstract

Antihistamines have been classified as first or second generation drugs, according to their pharmacokinetic properties, chemical structure and adverse effects. The adverse effects of antihistamines upon the central nervous system (CNS) depend upon their capacity to cross the blood-brain barrier (BBB) and bind to the central H1 receptors (RH1). This in turn depends on the lipophilicity of the drug molecule, its molecular weight (MW), and affinity for P-glycoprotein (P-gp) (CNS xenobiotic substances extractor protein). First generation antihistamines show scant affinity for P-gp, unlike the second generation molecules which are regarded as P-gp substrates. Histamine in the brain is implicated in many functions (waking-sleep cycle, attention, memory and learning, and the regulation of appetite), with numerous and complex interactions with different types of receptors in different brain areas. Bilastine is a new H1 antihistamine that proves to be effective in treating allergic rhinoconjunctivitis (seasonal and perennial) and urticaria. The imaging studies made, as well as the objective psychomotor tests and subjective assessment of drowsiness, indicate the absence of bilastine action upon the CNS. This fact, and the lack of interaction with benzodiazepines and alcohol, define bilastine as a clinically promising drug with a good safety profile as regards adverse effects upon the CNS.

Key words: H1 antihistamines. Bilastine. Adverse effects. Histamine. Histamine Receptors. CNS. Histaminergic system.

Resumen

Los antihistámicos han sido clasificados en primera y segunda generación atendiendo a sus propiedades farmacocinéticas, estructura química y efectos adversos. Los efectos adversos de los antihistámicos sobre el sistema nervioso central (SNC) dependen de su capacidad de atravesar la barrera hematoencefálica (BHE) y fijarse a los receptores H1 centrales (RH1), y esto depende a su vez, de la lipofilia de la molécula, de su peso molecular (PM) y de su afinidad por la glucoproteína P (P-gp) (proteína extractor de sustancias xenobióticas del SNC). Los antihistámicos de primera generación presentan escasa afinidad por la P-gp, al contrario que los de segunda que se consideran sustratos de esta proteína. La histamina a nivel cerebral está implicada en múltiples funciones (ciclo vigilia-sueño, atención, memoria-aprendizaje, regulación del apetito), con interacciones numerosas y complejas con diferentes tipos de receptores en distintas áreas cerebrales. Bilastina es un nuevo antihistámico H1 eficaz en el tratamiento de la rinoconjuntivitis alérgica (estacional y perenne) y de la urticaria. Tanto las pruebas de imagen realizadas, como las psicomotoras objetivas, y la valoración subjetiva de la somnolencia, demuestran una ausencia de acción de la bilastina sobre el SNC; y junto con la falta de interacción con lorazepam y el alcohol, la convierten en un fármaco clínicamente prometedor y con un buen perfil de seguridad en cuanto a sus efectos adversos sobre el SNC.

Introduction

Antihistamines have been classified as first or second generation drugs, according to their pharmacokinetic properties, structural characteristics and adverse effects.

The effects exerted by these substances upon the central nervous system (CNS) are fundamentally determined by their capacity to cross the blood-brain barrier (BBB) and bind to the central H\(_1\) receptors (RH\(_1\)). This capacity to cross the BBB depends on the lipophilicity of the drug molecule and their affinity for P-glycoprotein (P-gp).

P-gp is a transmembrane transport protein that regulates the exchange of biologically important molecules such as hormones, nutrients and xenobiotic substances across the cell membrane. This is done in an active way, independently of their concentration gradient on both sides of the cell membrane. The extraction of substances takes place thanks to the energy produced by the adenosine triphosphate hydrolysis (ATP)[1]. P-gp is located in the luminal surface of renal tubular cells, hepatocytes, enterocytes, and on the endothelial surface of testicular and brain blood vessels [2]. Cerebral capillaries present airtight intercellular junctions and virtually no transendothelial conduits, so that only soluble molecules may cross by passive diffusion. Other components of the BBB are the microglia, astrocytes, pericytes (essential for maintaining the structure of the airtight intercellular junctions) and the neurons themselves. All these structures are globally referred to as the neurovascular unit, which is crucial for correct function and integrity of the CNS [3].

First generation antihistamines are lipophilic, with scant affinity for P-gp, unlike second generation molecules, which are lipophobic and are regarded as P-gp substrates. The distinction based on their different molecular weight (smaller molecules theoretically may cross the BBB more easily) is less important. For example, desloratadine has a molecular weight (310.8) similar to that of hydroxyzine (374.9), but its permanence within the brain tissue after administration is different.

Antihistamines are classified as non sedative if they minimally fulfill three requirements:

a) Subjective incidence of sleepiness (assesses the presence of sleepiness after being administered the antihistamine).

b) Objective evaluations of possible alterations in cognitive and psychomotor performance.

c) Central H\(_1\) receptor occupancy studies. In this context, positron emission tomography (PET) has become the technique of choice for studying antihistamine penetration into brain tissue. This technique allows the correlation of central H\(_1\) receptor occupation to psychometric and functional studies [4].

Although the last two criteria are particularly important, all three must be present in order to classify the drug as a non-sedative antihistamine [5,6].

Chen et al. showed the brain tissue penetration of a first-generation antihistamine to be about 5.5 times greater than that of a second-generation antihistamine [7].

The Brain Histaminergic System

Histamine is an endogenous neurotransmitter exclusively synthesized in the neurons of the mammillary tubercles, located in the posterior hypothalamus, projecting from there to the rest of the brain [8].

The morphological characteristics of the histaminergic system are similar to those of other biogenic amine systems (norepinephrine, serotonin), i.e., it possesses a compact neuronal nucleus from which many fibers emerge in all directions. Within the CNS, histamine interacts with specific H\(_1\)-H\(_2\)-H\(_3\)-H\(_4\) receptors distributed throughout the CNS to induce different activities. The distribution of the H\(_1\) receptors in the human brain is very extensive, being the main locations the frontal, temporal and occipital cortex, the cingulate cortex, caudal nucleus, putamen and thalamus [9]. This distribution differs according to gender, with a higher density of H\(_1\) receptors in all areas in females [10].

Histamine in the brain is implicated in many functions, such as the waking-sleep cycle, attention, memory and learning, and the regulation of appetite [4]. It acts as a regulatory center for global brain activity. Recently, histamine has been attributed with a neuroprotective role in cases of brain ischemia and neurodegenerative disorders [11].

The histaminergic system interacts with other systems and with other neuropeptides to exert the following actions:

a) Modulation of acetylcholine (ACh) release, acting upon the magnocellular basal nucleus, which supplies the cortex with most of its cholinergic innervation. Local histamine application reduces cholinergic tone via the H\(_1\) receptors, potentially causing learning difficulties and cognitive impairment.

b) Modulation of emotional memory acquisition, acting upon the basolateral amygdala.

c) Modulation of alertness; during sleep the histaminergic neurons are activated at low level, and at high level during attention and in the waking state. Histamine interacts with orexin-secreting neurons (this being a peptidergic neurotransmitter affecting alertness – its deficiency causing narcolepsy). Histamine also interacts with the principal noradrenergic nucleus of the brain (the locus coeruleus). Histamine administration in this nucleus increases neuronal excitation in the latter [12]. Finally, the histaminergic system interacts with and excites the serotonergic neurons of the nucleus raphe dorsalis [13].

d) Regulation of food intake: histamine is one of the appetite-suppressing neurotransmitters. Noradrenaline, present in the paraventricular nucleus of the hypothalamus, stimulates food ingestion. Histamine has been shown to inhibit noradrenaline release from the nerve endings of the paraventricular nucleus, thereby suppressing appetite [14].

e) Control of oxytocin secretion under different physiological conditions, including delivery and lactation. Histamine acts upon the paraventricular nucleus of the hypothalamus, increasing intranuclear and systemic oxytocin release [15].
Antihistamines and the CNS

Tagawa et al., in the context of a PET-based study comparing ebastine versus chlorpheniramine, showed that increased brain H1 receptor occupancy was correlated to increased plasma levels of chlorpheniramine, and therefore to impaired cognitive function – though this was not seen to occur with ebastine (specifically with its active metabolite, carebastine). Ebastine 10 mg occupied approximately 10% of the H1 receptors, while chlorpheniramine 2 mg exceeded 50% [16]. This higher tissue penetration of first-generation antihistamines was subsequently demonstrated for second-generation drugs, specifically cetirizine, which shows 13% occupancy at a dose of 10 mg and 25% at a dose of 20 mg – though no correlation to subjective sleepiness could be established in this case [17].

Therapeutic doses of second-generation (or non-sedative) antihistamines occupy between 10-30% of the brain H1 receptors, with the possible exception of fexofenadine, which has been associated with practically zero occupation of these receptors [18].

In order to define an antihistamine as being non-sedative, its occupancy of central receptors should not exceed 20%, when administered at the recommended maximum dose [5].

Central effects appear after a 50% of occupancy of brain H1 receptors [16], although some authors consider that occupancy must reach 60% or even 70% [19].

The table shows the incidence of drowsiness with different second-generation antihistamines in studies of allergic rhinitis and chronic urticaria.

Bilastine

Bilastine, or 2-[4-(2-(4-[(1-(2-ethoxyethyl)-1H-benzimidazol-2-yl)piperidin-1-yl]ethyl)phenyl]-2-methyl propionic acid, is a new second-generation antihistamine

### Table. Incidence of drowsiness produced by different second-generation antihistamines in the treatment of allergic rhinitis and idiopathic chronic urticaria.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses (mg)</th>
<th>Time (week)</th>
<th>SAR</th>
<th>PER</th>
<th>IAR</th>
<th>PAR</th>
<th>UCI</th>
</tr>
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<tbody>
<tr>
<td>Bilastine</td>
<td>20</td>
<td>2</td>
<td>1.8%[20], 3.9%[21]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>4</td>
<td>NA</td>
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<td>NA</td>
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<tr>
<td>Cetirizine</td>
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<td>2</td>
<td>6%[23], 7.5%[20], 8.5%[24]</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
<td>10</td>
<td>4</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Desloratadine</td>
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<td>2</td>
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<td>NA</td>
<td>1.1%[28]</td>
<td>NA</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4</td>
<td>NA</td>
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<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
<td>5</td>
<td>12</td>
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<td>NA</td>
<td>NA</td>
<td>2.2%[31]</td>
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<tr>
<td>Ebastine</td>
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<td>1.6%[32], 2.7%[32]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&lt;2%[33]</td>
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<tr>
<td></td>
<td>10</td>
<td>12</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
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<tr>
<td></td>
<td>20</td>
<td>12</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ebastine 10-20 mg.</td>
<td>Patient &gt;12 years 3%, &lt;12 years 1.25% [35]</td>
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<thead>
<tr>
<th>Drug</th>
<th>Doses (mg)</th>
<th>Time (week)</th>
<th>SAR</th>
<th>PER</th>
<th>IAR</th>
<th>PAR</th>
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<td>Fexofenadine</td>
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<td>2</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td></td>
<td>180</td>
<td>4</td>
<td>3%[23]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&lt;2%[37]</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>4</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
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<td>180</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4.5%[28]</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>5</td>
<td>2</td>
<td>0.7%[38], 4%[39]</td>
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<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
<td>5</td>
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<td></td>
<td>5</td>
<td>8</td>
<td>NA</td>
<td>6%[40]</td>
<td>NA</td>
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<tr>
<td></td>
<td>5</td>
<td>26</td>
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<td>NA</td>
<td>NA</td>
<td>3.3%[41]</td>
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<tr>
<td>Loratadine</td>
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<td>1</td>
<td>5%[42]</td>
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<tr>
<td></td>
<td>10</td>
<td>2</td>
<td>2.2%[36]</td>
<td>NA</td>
<td>NA</td>
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<tr>
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<td>10</td>
<td>4</td>
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<td>NA</td>
<td>NA</td>
<td>6.6%[43], 2.8%[44]</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>10</td>
<td>2</td>
<td>7%[43]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>10</td>
<td>4</td>
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<td>3.8%[46]</td>
<td>NA</td>
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<td>3.8%[44]</td>
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<tr>
<td>Rupatadine</td>
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<td>2</td>
<td>9.6%[34]</td>
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<td>NA</td>
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<td></td>
<td>10</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.7%[48]</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>12</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10%[27]</td>
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<tr>
<td></td>
<td>10</td>
<td>26</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7.7%[47]</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>52</td>
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<td>NA</td>
<td>NA</td>
<td>5.8%[47]</td>
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<tr>
<td></td>
<td>20</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>8.3%[48]</td>
</tr>
</tbody>
</table>

indicated for the treatment of allergic rhinoconjunctivitis (perennial and seasonal) and urticaria [49].

In vitro studies have shown bilastine to have a high specificity for the H\(_1\) receptor and very little affinity for other receptors – thereby reducing the possibility of adverse effects [50]. In vivo studies of the antihistaminic and antiallergic activity of the drug have shown bilastine behaviour to be similar to that of cetirizine and superior to that of fexofenadine [51].

The molecular weight of bilastine is 463.61 g/mol, i.e., the molecule is larger than that of cetirizine and superior to that of fexofenadine [51]. In vivo studies of the antihistaminic and antiallergic activity of the drug have shown bilastine behaviour to be similar [50]. In vivo studies of the antihistaminic and antiallergic activity of the drug have shown bilastine behaviour to be similar [50].

In murine models, bilastine has shown to be a P-gp substrate [52] – this being a feature common to new second-generation antihistamines and greater barrier to brain tissue penetration, thereby reducing adverse effects at CNS level.

The phase II trials with bilastine, involving a total of 1111 randomized patients, concluded that the optimum dose for the treatment of both allergic rhinoconjunctivitis and urticaria, taking into account clinical efficacy and safety, is 20 mg a day [53].

Bilastine and the CNS

From the point of view of drug safety, absence, or only minimum presence of adverse CNS effects is one of the requirements any new antihistamine must fulfill, [54-56]. Most of the studies performed to evaluate the central effects of antihistamines, when administered at therapeutic doses, are comparative studies between second and first generation molecules, and refer to the disorders caused by the latter upon reaction capacity, attention, learning capacity or sedation, versus second-generation molecules. Nowadays, as to ensure the maximum precision of the results, objective measurements are being used, since subjective measurements of drowsiness or tiredness do not adequately correlate to the objective results of functional tests, such as the quantification of reaction time, or of accuracy of a given response [19]. In this sense, 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. Objective evaluations of motor activity, perception, attention and associative integration were performed, as well as the subjective changes in mood state through a visual analog scale and a specific questionnaire. Bilastine at the dose of 20 mg 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 [57].

Although PET is the imaging technique of choice for the evaluation of the H\(_1\) receptor occupancy in the CNS, there are several indirect techniques used in preclinical studies that allow the identification of the molecule in body tissues, such as whole body autoradiography. This method allows us to examine the pharmacokinetics at tissue level, the elimination routes, interactions among drugs, distribution in the tissues, the places where the drug is located and retained after administration, enzyme participation in drug metabolism, drug penetration in certain tissues (e.g., tumors), or the comparative kinetics among different species [58]. Animal (usually murine) models are used for this kind of studies. The tissue distribution of bilastine has been examined with this technique in three types of mice - no detectable drug levels being seen in the CNS in any of them at the different measured timepoints between 15 minutes and 336 hours after the administration of 20 mg/kg of bilastine [59].

Phase II and III studies, some of which have been published [20-22], in patients with perennial and seasonal allergic rhinoconjunctivitis, and with idiopathic chronic urticaria, have included over 4650 patients, 2186 of whom received bilastine (1358 involving the 20 mg/day dose of the drug). Depending on the type of study, treatment was maintained for 14 or 28 days, except for 513 patients, who completed one year of therapy. After evaluating the results, it was concluded that bilastine 20 mg/day shows no significant differences versus placebo as regards the outcome of adverse effects in general, nor those affecting the CNS in particular [53].

Preclinical and clinical studies in all phases carried out with a broad range of bilastine doses, indicate that this is a non-sedating antihistamine [53], with no effects upon the CNS when administered at therapeutic doses, as corresponds to the new (second-generation) antihistamines.

Special Situations

Adolescents

A total of 198 adolescents (aged 12 to 18 years) took part in four phase III trials (perennial and seasonal allergic rhinoconjunctivitis, urticaria) throughout the clinical development of bilastine. Of the adolescents, 81 received bilastine 20 mg – the dose being administered daily for 12 months in 68 cases. The conclusion was that this dose is effective and safe in terms of adverse effects (including CNS) in patients belonging to this age group [data not published].

Interaction with alcohol

It is well known that alcohol potentiates the effects of first-generation antihistamines upon subjective drowsiness and psychomotor skills [60-63]. In most cases such effects have not been observed with second-generation antihistamines [61,63,64].

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). All groups administered alcohol showed a worse psychomotor performance, although the effect of 20 mg of bilastine plus alcohol was equivalent to that obtained by placebo with alcohol. Cetirizine 10 mg, bilastine 80 mg and hydroxyzine 25 mg did enhanced the effects of alcohol [65].
**Interaction with benzodiazepines**

First-generation antihistamines interact with benzodiazepines, increasing their sedative effects – though this phenomenon is not observed with second-generation antihistamines [61,66,67].

Bilastine 20 mg, in the context of a double-blind, cross-over 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 [53].

**Real on the road driving test**

A recent double-blind, cross-over placebo-controlled study has been made to determine whether bilastine affects the ability to drive. Two bilastine doses (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 Standard 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 [68].

**Conclusions**

Bilastine is a new second-generation antihistamine with a pharmacological profile indicating clinical efficacy at a dose of 20 mg for the treatment of allergic rhinoconjunctivitis (perennial and seasonal) and urticaria. In addition, it is safe 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 has been shown to be safe for the patient, i.e., twice the standard recommended dose specified in the Summary of Product Characteristics, is well tolerated, without objective alterations in driving ability. These characteristics define bilastine as a promising drug from the therapeutic perspective and extremely safe regarding CNS effects.

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**Conflicts of interest**

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