

## REVIEW ARTICLE

**Bilastine in allergic rhinoconjunctivitis and urticaria**C. Bachert<sup>1</sup>, P. Kuna<sup>2</sup> & T. Zuberbier<sup>3</sup>

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**Abstract**

Allergic rhinoconjunctivitis and urticaria are increasing in prevalence in many developed countries. The role of histamine in such conditions is well documented and clinical guidelines recommend non-sedating H<sub>1</sub>-receptor antagonists as first-line treatment choices. Bilastine is a novel non-sedating histamine H<sub>1</sub>-receptor antagonist developed for the treatment of allergic rhinoconjunctivitis and urticaria. The aim of this review is to critique the scientific evidence relating to the pharmacological properties of bilastine and the clinical evidence regarding its potential as an antihistamine. *In vitro* binding studies and investigations in animal tissue have demonstrated the high specificity of bilastine for H<sub>1</sub>-receptors, and preclinical animal studies have also yielded promising results in terms of a reduction of histamine-mediated inflammatory effects, including capillary permeability and bronchospasm. In pharmacodynamic studies bilastine was found to down-regulate histamine-induced flare and wheal responses in healthy volunteers. Preclinical and clinical pharmacokinetic studies showed that bilastine has dose-dependent kinetics following oral administration. Excretion is almost exclusively via urine and faeces as unchanged drug. Early clinical trials have shown that bilastine has similar efficacy to other second-generation H<sub>1</sub>-receptor antagonists such as cetirizine, desloratadine, fexofenadine and levocetirizine, in terms of reducing allergic symptoms. Clinical findings also indicate that bilastine has a rapid onset of action and a 20 mg single dose is effective throughout a 24-h period. Furthermore, bilastine has been associated with improved quality of life in allergic rhinoconjunctivitis and urticaria patients. Adverse effects have generally been minimal in these studies and doses up to twice those proposed did not exhibit differences in adverse events compared to placebo. Moreover, *in vivo* investigations have found no evidence of accumulation of bilastine in the central nervous system, and various studies have confirmed minimal effects on psychomotor performance in healthy volunteers administered up to four times the usual dose. Clinical studies have also found no effect of bilastine on the QTc interval and other ECG parameters, even at supratherapeutic dosages, confirming the good cardiac safety profile of this newer antihistamine. Given its pharmacodynamic profile, which appears to be similar to other second-generation H<sub>1</sub>-receptor antagonists, and its favourable safety and tolerability, bilastine has the attributes of a potentially clinically useful non-sedating antihistamine. Larger clinical studies are now necessary to fully elucidate the clinical potential of this novel antihistamine.

Diseases such as allergic rhinoconjunctivitis and urticaria are becoming increasingly prevalent in many developed countries (1–3). Estimates suggest that approximately 10–40% of the global population is affected by allergic rhinoconjunctivitis (4–7). The prevalence of urticaria is similar, with a lifetime incidence of approximately 20% (8). The reasons for the increased prevalence of allergic diseases are largely unexplained, although potential causes are proposed by two diver-

gent theories. The first suggests that reduced exposure to allergens during childhood increases the risk of allergy and is referred to as the 'hygiene hypothesis' (9). In contrast, the 'pollution hypothesis' proposes that the risk of developing allergic diseases is potentiated by atmospheric pollution (10). The impact of these diseases on the patient's quality of life (QoL) can be significant as a result of loss of sleep and fatigue, headache, irritability and the inability to concentrate.

Such symptoms can ultimately impair performance in school and the workplace (7, 11, 12). Given the high prevalence of allergic rhinoconjunctivitis in particular, the costs to society can be extremely high, with estimates suggesting that indirect costs due to loss of productivity are greater than those incurred for providing healthcare to this patient group (13). Thus, development of effective treatments should not only provide symptomatic relief and increase the QoL of the patient, they should also improve individual performance, reduce clinic visits and increase productivity. The benefits for overburdened healthcare systems and resources, and society in general, are potentially enormous (13).

The role of histamine in allergic diseases is well described in the literature (14–16). In brief, immunoglobulin E (IgE) antibodies are recognised at the surface of mast cells and on exposure to the appropriate antigen following an allergic stimulus, trigger the release of histamine via mast cell degranulation. Histamine mediates its effects via activity at several receptors including the H<sub>1</sub>-, H<sub>2</sub>-, H<sub>3</sub>- and H<sub>4</sub>- receptors. Biological effects of histamine involved in allergic reactions are related to activity at H<sub>1</sub>-receptors and include smooth muscle contraction, bronchospasm, increased endothelial permeability and stimulation of sensory nerves and cough receptors (17). Therefore, treatments blocking the effects of histamine at H<sub>1</sub>-receptors (antihistamines) play a vital role in the management of diseases including allergic rhinoconjunctivitis and urticaria.

Allergic rhinoconjunctivitis is a chronic respiratory illness, characterised by rhinorrhoea, nasal congestion, sneezing and nasal itch, and is often accompanied by lacrimation, ocular redness and itching of the ears and palate (11). Histamine is an important mediator of these symptoms although other mediators including leukotrienes, prostaglandins and kinins contribute to pro-inflammatory cellular effects, such as up-regulation of endothelial and epithelial adhesion molecules, cytokines and chemokines and activation of leukocytes (6, 18, 19). Allergic rhinoconjunctivitis has traditionally been categorised into seasonal and perennial allergic rhinoconjunctivitis, mainly based on the time of exposure. Seasonal allergic rhinoconjunctivitis (SAR) is associated with a wide variety of pollen allergens and thus is dependent upon geographic location and time of year, whereas perennial allergic rhinoconjunctivitis (PAR) is most frequently caused by pollen, mites and/or animal dander (6). However, there are exceptions to both categories and thus the Allergic Rhinitis and its Impact on Asthma (ARIA) workshop, in conjunction with the WHO, introduced a new classification for allergic rhinoconjunctivitis, based on duration and severity of symptoms (4, 20, 21) (Table 1). The ARIA classification recognises allergic rhinoconjunctivitis as a chronic respiratory illness and provides guidance which may aid treatment. This is important given that allergic rhinoconjunctivitis is one of the top ten reasons for patients visiting their general practitioner (22). Indeed, a two-step, cross-sectional, population-based survey reported a mean incidence of 23% (range 17–29%) in six European countries (23). Furthermore, allergic rhinoconjunctivitis is often associated with other respiratory conditions including asthma, sinusitis, nasal polyposis

**Table 1** Allergic Rhinitis and its Impact on Asthma (ARIA) classification system for allergic rhinoconjunctivitis (21)

| Classification                            | Definition                                                                                                                                                  |
|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Intermittent allergic rhinoconjunctivitis | Symptoms are present for <4 days a week or <4 weeks.                                                                                                        |
| Persistent allergic rhinoconjunctivitis   | Symptoms are present for >4 days a week and for >4 consecutive weeks.                                                                                       |
| Mild allergic rhinoconjunctivitis         | No impairment of sleep, daily activities, sport or leisure, work or school and no disruptive symptoms.                                                      |
| Moderate to severe allergic rhinitis      | Presence of one of the following events: abnormal sleep, impairment of daily activities, sport or leisure; impaired work or school; or disruptive symptoms. |

and lower respiratory tract infection, emphasising the importance of effective treatment for this patient population.

The term urticaria refers to: physical urticarias, acute urticaria, chronic 'idiopathic' urticaria, and urticarial vasculitis, defined by spontaneously occurring wheals and/or angioedema (24, 25). Wheals are characterised by central swelling of variable size, associated itching or burning and are generally fleeting in nature; the skin usually recovers within 24 h (26). Angioedema has a slower resolution and is associated with swelling of the lower dermis and subcutis, pain rather than itching and involvement of mucous membranes. Different types of urticaria are associated with a common, complex pathogenesis, involving increased cytokine expression, oedema, leukocyte infiltration to the perivascular space, and mast cell degranulation (26–29). These varied effects are indicative of a multi-factorial process involving many mediators, in addition to mast cell-induced production of histamine. EAACI/GA<sup>2</sup>LEN/EDF/WAO guidelines for the management of urticaria recommend avoidance of allergic stimuli and treatment with non-sedating H<sub>1</sub>-receptor antagonists (26, 30, 31). In non-responding patients, higher doses (up to 4-fold) are recommended. For this reason and as daily drug administration may be required for longer periods (weeks to years), H<sub>1</sub>-receptor antagonists must have a good tolerability profile (32).

Several national and international clinical guidelines have recommended that H<sub>1</sub>-receptor antagonists should be regarded as the first-line treatment for allergic rhinoconjunctivitis (4, 6, 11, 33, 34) and urticaria (26, 31). First-generation antihistamines were defined by their ability to antagonise H<sub>1</sub>-receptors and thereby effectively control allergic symptoms. However, they were frequently associated with adverse events, especially sedation. This led to development of second-generation H<sub>1</sub>-antihistamines, which were designed to be less lipophilic so as to minimise transfer across the blood-brain barrier and thus avoid producing sedative effects. The ultimate goal was to improve the therapeutic index, but some second-generation H<sub>1</sub>-receptor antagonists have been associated with adverse effects such as weight gain, drug-drug interactions and of most concern, potentially life threatening

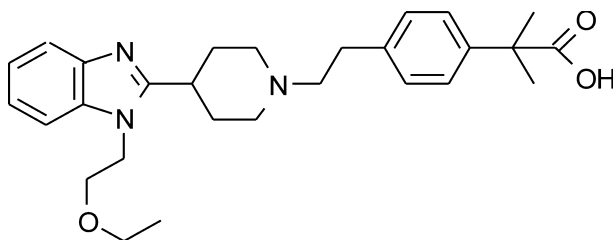


**Figure 1** Chemical structure of bilastine.

cardiotoxicity (2). Bilastine, F-96221-BM1, 2(2-[4-(2-(4-(1-(2-ethoxyethyl) benzimidazole-2-yl) piperidine-1-yl) ethyl) phenyl]-2-methylpropanoic acid) (Fig. 1), is a novel non-sedating histamine  $H_1$ -receptor antagonist developed for the treatment of allergic rhinoconjunctivitis and urticaria. The aim of this review is to critique the current literature relating to the pharmacological properties of bilastine and to evaluate the preliminary scientific evidence regarding its clinical efficacy and safety.

### Preclinical and clinical pharmacology

The preclinical pharmacology of bilastine was presented in detail by Corcóstequi et al. (17) and the main findings are summarised below.

#### Preclinical: *in vitro* studies

*In vitro* radioligand-receptor binding studies have clearly demonstrated the affinity of bilastine for histamine  $H_1$ -receptors. Bilastine inhibited binding of [ $H^3$ ]-pyrilamine in a dose-dependent manner in guinea pig cerebellum and human embryonic kidney (HEK)-293 cells expressing human recombinant  $H_1$ -receptors. A mean affinity value ( $K_i$ ) for bilastine of 64 nM was calculated in the HEK-293 cell line. This was similar to the mean value calculated in  $H_1$ -receptors from guinea pig cerebellum membranes ( $K_i = 44$  nM). This affinity observed for bilastine was 5-fold greater than values for fexofenadine and 3-fold greater than values for cetirizine (Table 2).

These findings were supported by isolated organ studies in guinea pig ileum and trachea smooth muscle. In guinea pig ileum, bilastine displayed competitive properties up to 33 nM

and non-competitive antagonistic properties from 100 nM. Bilastine was approximately 5.5 times more potent than cetirizine as a competitive antagonist and ~10 times more potent than cetirizine as a non-competitive antagonist. In guinea pig tracheal preparations, bilastine exhibited non-competitive antagonism (Table 2). Interestingly, in guinea pig ileum bilastine demonstrated a residual effect as  $H_1$ -receptors did not recover contractile activity to histamine following several washes (17).

Additional isolated organ studies confirmed the specificity of bilastine for  $H_1$ -receptors compared with other histamine receptor subtypes. For example, it did not alter the positive chronotropic effect of the  $H_2$ -agonist dimaprit in guinea pig right atria and responses to bilastine on electrical twitches in guinea pig jejunum were considered to be unrelated to activity at  $H_3$  receptors. Furthermore, bilastine 10  $\mu$ M did not inhibit the specific binding of [ $H^3$ ]-histamine to human recombinant histamine  $H_4$ -receptors stably transfected and expressed in HEK-293 cells (17).

The effects of bilastine at a variety of other receptor types were investigated using *in vitro* methods. Radioligand binding studies assessed the specificity of bilastine for a range of 30 different receptors including serotonin, bradykinin, leukotriene, calcium, muscarinic and adrenergic receptors. No significant displacement of other radioligands was found with bilastine at a concentration of 10  $\mu$ M. Indeed, bilastine at this concentration demonstrated no significant anti-muscarinic activity in C6 rat glioma cell lines expressing one of the five human muscarinic receptors ( $M_1$ – $M_5$ ) (35). Studies in guinea pig ileum are consistent with a lack of effect at muscarinic receptors as bilastine did not alter  $M_3$ -mediated contraction (17).

Findings from several isolated organ experiments using high concentrations of bilastine further confirmed bilastine as a selective  $H_1$ -receptor antagonist. Thus, bilastine at a concentration of 10  $\mu$ M or higher, did not modify the concentration-response curves induced by serotonin, bradykinin, noradrenaline, leukotriene and calcium in rat, rabbit or guinea pig specific isolated organs (caudal artery, thoracic aorta and ileum or trachea, respectively). Similar effects were also reported for cetirizine and fexofenadine (17).

The greater selectivity of bilastine for  $H_1$ -receptors is a promising finding in these early studies as activity at other receptors is often associated with a poor tolerability profile (36). These findings suggest that bilastine may be a more attractive treatment in allergic conditions compared to other, less selective, antihistamines.

In addition to effects mediated via  $H_1$ -receptor blockade, second-generation antihistamines putatively produce a variety of effects through modulation of anti-inflammatory activity. Reported down-regulatory activity of bilastine on inflammatory agents provides optimism that it could be effective in allergic diseases via inhibition of histamine-producer cells (37). *In vitro* studies in human mast cells (HMC-1) and granulocytes showed that bilastine inhibited both spontaneous and activated histamine, interleukin-4 (IL-4) and tumour necrosis factor- $\alpha$  (TNF $\alpha$ ) release (37).

**Table 2** Histamine  $H_1$ -receptor binding and antagonism of bilastine compared with cetirizine and fexofenadine.  $K_i$  values were obtained from binding studies in guinea pig cerebellum whereas  $pA_2$  and  $pD'_2$  values were obtained from antagonism studies in guinea pig ileum (17).  $pA_2$  and  $pD'_2$  are mathematical parameters that define the *in vitro* ability of the antagonist to inhibit the agonist

| $H_1$ -antagonist | $K_i$ (nM) | $pA_2$ | $pD'_2$ |
|-------------------|------------|--------|---------|
| Bilastine         | 44         | 8.0    | 6.2     |
| Cetirizine        | 143        | 7.3    | 5.2     |
| Fexofenadine      | 246        | –      | 6.2     |

**Table 3** Antihistaminic effects of bilastine *in vivo* compared to other H<sub>1</sub>-receptor antagonists (38)

| Study                                                        | Measurement                                                     | Species/Strain                         | Administration of H <sub>1</sub> -receptor antagonists                                     | Potency of bilastine compared to cetirizine and fexofenadine                       |
|--------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Histamine-induced capillary permeability in dorsal skin      | Determination of Evans Blue (EB) leakage in dorsal skin papules | Male Wistar rats                       | Oral, 1 h prior to allergic stimulus                                                       | ED <sub>50</sub> (mg/kg)<br>Bilastine: 2.5<br>Cetirizine: 2.3<br>Fexofenadine: 10  |
| Histamine-induced capillary permeability in dorsal skin      | Determination of EB leakage in dorsal skin papules              | Male Wistar rats                       | Intravenous, 5 min prior to allergic stimulus                                              | ED <sub>30</sub> (µg/kg)<br>Bilastine: 83<br>Cetirizine: 281                       |
| Histamine-induced microvascular extravasation                | Determination of EB leakage in trachea                          | Male albino Dunkin-Hartley guinea pigs | Intravenous, 5 min prior to allergic stimulus                                              | ED <sub>50</sub> (µg/kg)<br>Bilastine: 185<br>Cetirizine: 168<br>Fexofenadine: 773 |
| Histamine-induced bronchospasm                               | Measurement of bronchospasm                                     | Male albino Dunkin-Hartley guinea pigs | Intravenous, prior to allergic stimuli at 2, 10, 20, 30, 40, 50 and 60 min post-treatment. | ED <sub>50</sub> (µg/kg)<br>Bilastine: 4.6<br>Cetirizine: 53.3                     |
| Lethality induced by subcutaneous injection of histamine     | Measurement of the number of deaths over 24 h.                  | Male albino Dunkin-Hartley guinea pigs | Oral, 1 h prior to allergic stimulus                                                       | ED <sub>50</sub> (mg/kg)<br>Bilastine: 0.2<br>Cetirizine: 0.2<br>Fexofenadine: 1.7 |
| Lethality induced by intravenous injection of Compound 48/80 | Measurement of the number of deaths over 2 h.                   | Wistar rats                            | Oral, 1 h prior to injection of Compound 48/80                                             | ED <sub>50</sub> (mg/kg)<br>Bilastine: 2.3<br>Cetirizine: 1.2<br>Fexofenadine: 6.8 |

### Preclinical: *in vivo* studies

The inhibitory effects of bilastine on histamine release and activity at H<sub>1</sub>-receptors have translated into beneficial effects in animal models of histamine-mediated inflammation (Table 3). For example, it decreased microvascular leakage from the trachea of guinea pigs and from the dorsal skin of rats, and reduced histamine-induced bronchospasm and histamine- and compound 48/80-induced lethality in guinea pigs (38). In general, bilastine exhibited similar efficacy to cetirizine in terms of antihistaminic activity, although there were differences in some *in vivo* assays. Of note, repeating histamine-mediated capillary permeability studies showed that bilastine was more potent than cetirizine following intravenous administration and both drugs were more potent than fexofenadine (38).

*In vivo* investigations have also assessed the efficacy of bilastine in reducing allergic responses to stimuli other than histamine (Table 4). Bilastine was effective in reducing permeability mediated via the passive cutaneous anaphylaxis (PCA) reaction in rats; the Schultz–Dale reaction in guinea pig ileum; IgG-dependent active cutaneous anaphylaxis (ACA) reaction or an IgE-dependent ACA reaction in mice; and passive Arthus reaction in mice induced by sheep red blood cells. Bilastine was at least as effective as cetirizine and more effective than fexofenadine in reducing these different allergic responses (Fig. 2) (17, 38).

Evidence from preclinical investigations highlights the specificity of bilastine for H<sub>1</sub>-receptors compared with other histamine receptors and other receptor subtypes. *In vivo* experimentation confirmed the antihistaminic and antiallergic activity which was comparable to that of the established second-generation H<sub>1</sub>-antagonist cetirizine.

### Preclinical: toxicology

*In vivo* studies have investigated the toxicology of bilastine for periods of up to 2 years. For example in a 2-year oncogenicity study, bilastine administered at a dosage of 2000 mg/kg per day to mice and 5000, 15 000 and 30 000 ppm to rats resulted in similar survival rates and causes of death as placebo in these rodent species (39). In this study, bilastine displayed no carcinogenic potential in rats or mice. Bilastine was considered to display no carcinogenic potential as the type and incidence of lesions diagnosed during the course of the study are commonly diagnosed in animals of the strains and ages used (39).

### Preclinical: pharmacokinetic studies

*In vivo* studies have investigated the pharmacokinetic properties of bilastine in various species, primarily dogs and rodents. C<sub>max</sub> and area under the curve (AUC) of bilastine increased proportionally to dose, up to a single oral dose of 50 mg/kg (40). The values for these parameters were

**Table 4** Antiallergic effects of bilastine *in vivo* compared to other H<sub>1</sub>-receptor antagonists (38)

| Study                                                                                | Measurement                                                     | Species/Strain   | Administration of H <sub>1</sub> -receptor antagonists | Potency of bilastine compared to cetirizine and fexofenadine                      |
|--------------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------|--------------------------------------------------------|-----------------------------------------------------------------------------------|
| Passive cutaneous anaphylaxis (PCA) reaction induced by homologous serum             | Determination of Evans Blue (EB) leakage in dorsal skin papules | Male Wistar rats | Oral, 1 h prior to allergic stimulus                   | ED <sub>50</sub> (mg/kg)<br>Bilastine 7.6<br>Cetirizine 2.2<br>Fexofenadine 62.6  |
| PCA induced by monoclonal antibodies                                                 | Determination of EB leakage in dorsal skin papules              | Male Wistar rats | Oral, 1 h prior to allergic stimulus                   | ED <sub>50</sub> (mg/kg)<br>Bilastine 6.0<br>Cetirizine 4.3<br>Fexofenadine 58.8  |
| IgG-dependent active cutaneous anaphylaxis (ACA) reaction                            | Determination of EB leakage in mouse ear                        | Male CD1 mice    | Oral, 1 h prior to allergic stimulus                   | ED <sub>30</sub> (mg/kg)<br>Bilastine 4.2<br>Cetirizine 1.1<br>Fexofenadine 8.9   |
| IgE-dependent active cutaneous anaphylaxis (ACA) reaction                            | Determination of EB leakage in mouse ear                        | Male CD1 mice    | Oral, 1 h prior to allergic stimulus                   | ED <sub>30</sub> (mg/kg)<br>Bilastine 3.8<br>Cetirizine 0.7<br>Fexofenadine 9.4   |
| Type III allergic reaction: Passive Arthus reaction induced by sheep red blood cells | Measurement of paw swelling                                     | Male CD1 mice    | Oral                                                   | Bilastine: 28% inhibition at 50 mg/kg<br>No effect of cetirizine or fexofenadine. |
| Type IV allergic reaction: contact dermatitis induced by oxazolone                   | Measurement of ear swelling                                     | Male CD1 mice    | Oral, topical                                          | No effect of bilastine, cetirizine or fexofenadine.                               |

generally 10-fold greater in dogs than in rats at equivalent doses. Dose-dependent kinetics were also demonstrated in mice, rats and dogs and in female rabbits, over a range of oral doses up to a maximum of 2000 mg/kg per day in a long-term administration study (41).

Bioavailability measurements have varied between species and gender. For example, while bilastine exhibited no differences in plasma levels between the sexes in rats and dogs, there were significant differences between male and female mice (41). In dogs, values of 42–69% were reported for bioavailability with a clear trend of increasing bioavailability with dosage (from 10 to 50 mg/kg). In contrast, bioavailability in rats was 25–61% with no observable increase with dose (40). The liver and lungs have virtually no intrinsic ability to metabolise bilastine (42). An *in vitro* study confirmed this finding as no metabolism of [<sup>14</sup>C]-bilastine was reported in rat, dog or human hepatocytes demonstrating its stability in this *in vitro* system (43).

The tissue distribution of bilastine was assessed via quantitative whole body radiography in male and female Sprague Dawley rats and male Lister Hooded rats following oral administration of [<sup>14</sup>C]-labelled drug. Radioactivity was widely distributed to tissues, with higher values found in the gastrointestinal tract, liver and kidneys, correlating with patterns of elimination. There was no accumulation of radioactivity in the brain or other peripheral tissues (44). A long term study involving several species of laboratory animals including Wistar rats, Sprague–Dawley rats, rabbits, CD1 mice and beagle dogs reported no evidence of accumulation

over the period of the study, which was 26 weeks in rats and mice and 56 weeks in dogs (following oral or iv administration of doses up to 2000 mg/kg per day in rodents and 800 mg/kg per day in dogs) (41).

New antihistamines should be developed with minimal ability to enter the brain. This is dependent upon several factors including p-glycoprotein-mediated transport. Studies in rats assessed the p-glycoprotein sensitivity of bilastine at a dose of 20 mg/kg using the p-glycoprotein inhibitor, valspodar. Measurement of maximal plasma bilastine concentration indicated that bilastine is a good substrate for p-glycoprotein and thus will be prevented from entering the brain (42). This suggests that bilastine will have minimal impact on the central nervous system (CNS).

Preclinical assessment of the pharmacokinetic profile of bilastine indicates dose-dependent kinetics following oral administration. Bioavailability estimates are between 25% and 69%, with considerable variation between species. The fact that bilastine undergoes minimal hepatic clearance, and is eliminated in the faeces and urine as unchanged drug, supports a reduced possibility of interactions with other drugs. No accumulation was observed in the CNS, a promising finding in terms of minimising possible sedative/psychomotor effects.

#### Clinical pharmacodynamic studies

Given the promising *in vitro* and *in vivo* evidence regarding bilastine as an antihistaminic and antiallergic agent, early

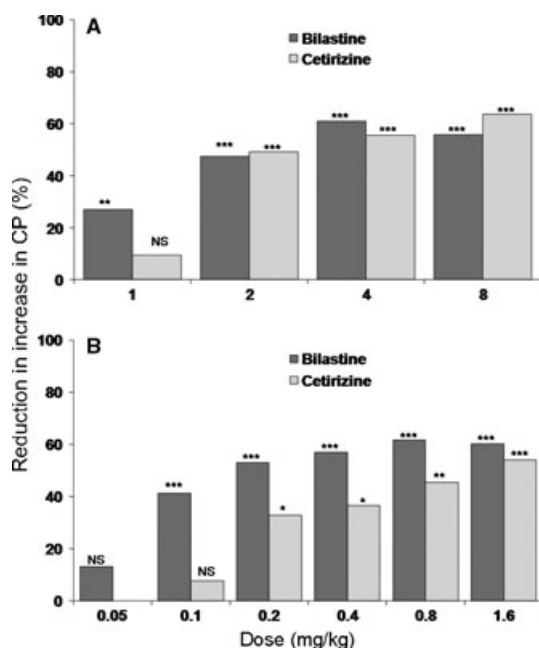


**Figure 2** Reduction in the histamine-induced increase in capillary permeability (CP) in rats following (A) oral and (B) intravenous administration of bilastine or cetirizine (38). NS, not significant; \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

pharmacological studies have aimed to assess these properties in healthy volunteers (Table 5).

When selecting an  $H_1$ -antihistamine, patients are concerned with a rapid onset of action, good efficacy, a long duration of action and freedom from unwanted effects. A widely used model to determine these parameters is the wheal and flare reaction following histamine skin prick testing.

A recent phase I study in healthy male volunteers evaluated the effect of five different bilastine single doses (2.5, 5, 10, 20 and 50 mg) on histamine-induced wheal and flare over a 24 h period, compared with a single 10 mg oral dose of cetirizine (45). The results of this investigation indicated that bilastine was at least as effective as cetirizine in reducing histamine-mediated effects in healthy volunteers. Importantly, 20 and 50 mg of bilastine reduced the wheal and flare response significantly more rapidly than cetirizine, an established second-generation  $H_1$ -antihistamine (Fig. 3).

### Clinical pharmacokinetic studies

The clinical pharmacokinetic properties of bilastine are summarised in Table 6. Studies in human volunteers demonstrated that bilastine is rapidly absorbed after oral treatment, reaching maximal plasma concentrations 1–1.5 h after administration of both single and multiple doses (46, 47). Assessment of pharmacokinetic parameters including  $AUC_{(0-t)}$  and  $C_{max}$  have indicated a linear profile within the 10–220 mg dose range for both single and multiple doses of

bilastine in healthy male volunteers (46). This was confirmed in simulated computer models using concentration-time data from 310 healthy volunteers. These programs indicated that bilastine fits a two-compartmental population model with first-order absorption and elimination (46). The apparent volume of distribution of the central compartment ( $V_c/F$ ) was 59.2 l and the apparent volume of distribution of the peripheral compartment ( $V_p/F$ ) was 30.2 l. Determination of pharmacokinetic parameters following single and 14 days once daily administration provided no evidence of accumulation (47).

A Phase I mass balance study in healthy volunteers investigated absorption, metabolism and excretion following a single oral dose of [ $^{14}C$ ]-bilastine 20 mg. Radiolabelled bilastine was eliminated exclusively in the faeces (67%) and urine (33%). Measurement of metabolites in the plasma, urine and faeces indicated that bilastine is not metabolised in humans and is almost exclusively eliminated as unchanged drug (48). Bilastine metabolism was additionally defined using Caco-2 cells, with and without induction of the two main cytochromes involved in intestinal metabolism: CYP1A1 and CYP3A4. No metabolites were produced as a result of cellular activity, indicating an absence of intestinal metabolism (49). Additional *in vitro* studies in human microsomes and hepatocytes showed that bilastine is neither an inducer nor an inhibitor of CYP450 isoenzymes (50).

Studies in healthy male and female volunteers reported no clinically significant gender-related differences in  $C_{max}$ ,  $AUC_{(0-t)}$  and  $AUC_{(0-inf)}$ . In contrast, mean peak plasma concentrations were higher in younger subjects (18–35 years) than in those aged  $>65$  years. In this study, highest values for  $C_{max}$  were observed in young females, although total exposure to bilastine ( $AUC_{(0-inf)}$ ) was very similar in all groups studied (51). Simulated pharmacokinetic models have also assessed parameters such as age, gender, body weight, height, pulse rate, and albumin, bilirubin and creatinine plasma concentrations, but none of these variables had a significant effect on the pharmacokinetic profile of bilastine (46).

Due to the frequent and often long-term administration of antihistamines, clinical assessment of drug interactions is necessary in the development of newer agents. Studies in healthy volunteers assessed the potential interaction between bilastine and the known p-glycoprotein and cytochrome P450 3A4 inhibitors ketoconazole (52), erythromycin and diltiazem (50). Co-administration of bilastine with either erythromycin or ketoconazole resulted in a significant increase in the  $AUC$  and  $C_{max}$  values for bilastine, whilst the duration of exposure remained unchanged. The pharmacokinetic parameters of erythromycin and ketoconazole were unaltered in the presence of bilastine. Increases in the  $C_{max}$  and  $AUC$  of bilastine were also observed when co-administered with diltiazem, although at a lower level compared with erythromycin or ketoconazole. These changes in the pharmacokinetic parameters of bilastine are almost certainly due to the inhibition of p-glycoproteins by ketoconazole, erythromycin and diltiazem, resulting in an alteration in intestinal transport systems and increased absorption.

**Table 5** Studies comparing the efficacy and safety of bilastine in reducing allergic symptoms

| Aim                                                                                                                                                                                | Type of trial                                                                                    | Dosing regimen                                                          | Number and type of subjects                                                                   | Main findings                                                                                                                                                                                                                                    | Safety                                                               |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| <b>Allergic rhinitis studies</b>                                                                                                                                                   |                                                                                                  |                                                                         |                                                                                               |                                                                                                                                                                                                                                                  |                                                                      |
| To assess the effects of bilastine on allergic symptoms in patients exposed to aeroallergen in the Vienna Challenge Chamber (VCC) compared with cetirizine and fexofenadine. (55). | Phase II study. Randomised, double-blind, placebo-controlled, single oral dose, crossover study. | 20 mg bilastine, 10 mg cetirizine, 120 mg fexofenadine or placebo.      | 75 Seasonal allergic rhinoconjunctivitis (SAR) patients (symptom-free prior to study period). | Bilastine reduced allergic symptoms with a rapid onset and a long duration of action. Bilastine was similar in activity to cetirizine and maintained the effect for longer than fexofenadine.                                                    | Well tolerated, similar safety profile to placebo.                   |
| To compare the efficacy of bilastine with cetirizine and placebo in the symptomatic treatment of SAR. (15).                                                                        | Phase III study. Randomised, double-blind, placebo-controlled study.                             | 20 mg bilastine, 10 mg cetirizine or placebo, once daily for 14 days.   | 683 SAR patients                                                                              | Bilastine reduced symptoms of SAR more effectively than placebo. Bilastine and cetirizine were equally effective.                                                                                                                                | Similar safety profile to placebo. Better tolerated than cetirizine. |
| To compare the safety and efficacy of bilastine to desloratadine in SAR patients (11).                                                                                             | Phase III study. Randomised, double-blind, placebo-controlled study.                             | 20 mg bilastine, 5 mg desloratadine or placebo. Once daily for 14 days. | 721 SAR patients                                                                              | Bilastine reduced symptoms of SAR more effectively than placebo. Bilastine and desloratadine were equally effective.                                                                                                                             | Well tolerated, similar safety profile to placebo.                   |
|                                                                                                                                                                                    |                                                                                                  |                                                                         |                                                                                               |                                                                                                                                                                                                                                                  |                                                                      |
| To compare the efficacy of bilastine to cetirizine in perennial allergic rhinoconjunctivitis (PAR) patients (50).                                                                  | Phase III study. Randomised, double-blind, placebo and active-controlled study.                  | 20 mg bilastine, 10 mg cetirizine or placebo once daily for 28 days     | 651 PAR patients                                                                              | Bilastine reduced total symptom score (TSS) and improved quality of life (QoL) compared with placebo. Bilastine and cetirizine produced comparable effects in reducing TSS from baseline. However these effects were not different from placebo. | Well tolerated; see 'Safety studies' section.                        |
| To assess the long term effects of bilastine over a 12 month period (50).                                                                                                          | Open label extension study.                                                                      | 20 mg bilastine once daily                                              | 513 PAR patients                                                                              | Bilastine significantly reduced nasal symptom scores (NSS) and non-NSS, as well as individual symptom scores (sneezing, runny nose, nasal itching, nasal congestion, tearing and ocular redness) compared with baseline values.                  | Well tolerated; see 'Safety studies' section                         |

**Table 5** (Continued)

| Aim                                                                                                                            | Type of trial                                                                                                  | Dosing regimen                                                                               | Number and type of subjects    | Main findings                                                                                                                                                                                      | Safety                                                                                                                                                         |
|--------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Urticaria studies</b>                                                                                                       |                                                                                                                |                                                                                              |                                |                                                                                                                                                                                                    |                                                                                                                                                                |
| To assess the effect of bilastine on histamine-induced wheal and flare, compared to cetirizine (58)                            | Phase I study. Randomised, double-blind, placebo-controlled, single oral dose, crossover study                 | 2.5, 5, 10, 20 and 50 mg bilastine, 10 mg cetirizine or placebo                              | 21 healthy male volunteers     | 20 mg bilastine inhibited histamine-induced wheal and flare at levels comparable to cetirizine.                                                                                                    | Well tolerated, similar safety profile to placebo.                                                                                                             |
| To assess the efficacy of bilastine administered at different doses in patients with chronic idiopathic urticaria (55).        | Phase II study. Randomised, double-blind, placebo-controlled study.                                            | 10, 20, 30 mg bilastine or placebo.                                                          | 152 chronic urticaria patients | All doses of bilastine were superior to placebo in terms of reducing TSS.                                                                                                                          | Well tolerated, similar safety profile to placebo.                                                                                                             |
| To assess the clinical efficacy and safety of bilastine in patients with chronic idiopathic urticaria. (32).                   | Phase III study. Randomised, double-blind, placebo-controlled study.                                           | 20 mg bilastine, levocetirizine 5 mg or placebo. Once daily for 28 days.                     | 516 chronic urticaria patients | Bilastine reduced TSS compared to placebo. Bilastine and levocetirizine were equally effective.                                                                                                    | Well tolerated, similar safety profile to placebo.                                                                                                             |
| <b>Safety studies</b>                                                                                                          |                                                                                                                |                                                                                              |                                |                                                                                                                                                                                                    |                                                                                                                                                                |
| To assess the CNS effects of the possible interaction between bilastine and alcohol, compared to hydroxyzine and placebo (58). | Pharmacodynamic interaction study. Randomised, double-blind, placebo and positive-controlled, crossover study. | 20, 80 mg bilastine, 25 mg hydroxyzine, 10 mg cetirizine or placebo. Alcohol: 0.8 g/kg       | 24 healthy volunteers          | Bilastine did not affect psychomotor scores when administered with alcohol. Cetirizine and hydroxyzine both significantly enhanced the effects of alcohol.                                         | Well tolerated, similar safety profile to placebo.                                                                                                             |
| To assess the effect of therapeutic and supratherapeutic doses of bilastine on the QTc interval (59).                          | Thorough QT/QTc study. Randomised, double-blind, placebo- and positive-controlled crossover study              | 20, 100 mg bilastine, 20 mg bilastine + 400 mg ketoconazole, 400 mg moxifloxacin or placebo. | 30 healthy volunteers          | Bilastine did not produce any significant effects on QTc interval at either dosage. Small changes occurring when bilastine was co-administered with ketoconazole were due to the antifungal agent. | Well tolerated, similar safety profile to placebo.                                                                                                             |
| To assess the long term safety of bilastine over a 12 month period (50).                                                       | Open label extension safety study.                                                                             | 20 mg bilastine                                                                              | 513 PAR patients               |                                                                                                                                                                                                    | Bilastine was well tolerated, with only 18 subjects (3.5%) withdrawing from the study due to AEs. These AEs were not considered to be due to study medication. |
| To determine the peripheral and central effects of single and repeated doses of bilastine (57)                                 | Phase I study. Randomised, double-blind, placebo-controlled study.                                             | 20, 40, 80 mg bilastine, 25 mg hydroxyzine or placebo.                                       | 21 healthy volunteers          | Psychomotor impairment was not observed with the 20 and 40 mg doses of bilastine. 80 mg: minor CNS effects.                                                                                        | Well tolerated, similar safety profile to placebo.                                                                                                             |

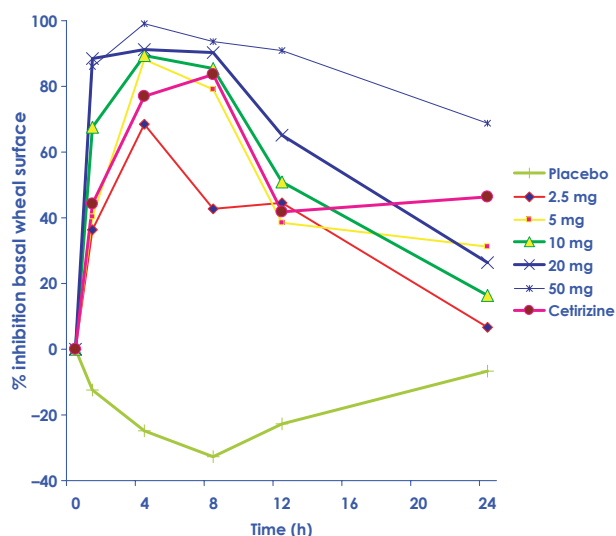


**Figure 3** Percentage inhibition of histamine-induced wheal surface area over time in subjects treated with bilastine (2.5, 5, 10, 20 and 50 mg), cetirizine 10 mg or placebo (45).

**Table 6** Overview of the pharmacokinetic properties of bilastine 20 mg based upon data from single- and multiple dose studies applied to a two-compartmental model with first-order absorption and elimination (47)

| Parameters                       | Pharmacokinetic values |
|----------------------------------|------------------------|
| $C_{max}$ (ng/ml)                | 220                    |
| $T_{max}$ (h)                    | 1.3                    |
| $AUC_{0-t}$ (h*ng/ml)            | 1105                   |
| $K_a$ (per hour)                 | 1.5                    |
| $K_e$ (per hour)                 | 0.3                    |
| $V_d/F$ (l)                      | 59.2                   |
| $V_p/F$ (l)                      | 30.2                   |
| Plasma binding (%)               | 85                     |
| $Q/F$ (l/h)                      | 1.6                    |
| $CL/F$ (l/h)                     | 18.1                   |
| Distribution $t_{1/2\alpha}$ (h) | 2.1                    |
| Elimination $t_{1/2\beta}$ (h)   | 14.5                   |

$C_{max}$ , maximum plasma concentration;  $T_{max}$ , time taken to reach  $C_{max}$ ;  $AUC$ , area under the curve;  $K_a$ , absorption rate constant;  $K_e$ , elimination rate constant;  $V_d$ , volume of distribution in central compartment;  $V_p$ , volume of distribution in peripheral compartment;  $Q$ , clearance between the compartments;  $CL$ , clearance;  $F$ , bioavailability.

Co-administration with grapefruit juice reduced plasma  $C_{max}$ ,  $AUC_{(0-t)}$ , and  $AUC_{(0-inf)}$  values for bilastine by 33%, 24% and 24% respectively, compared to bilastine alone, in a randomised two-way crossover study in healthy adults. These data demonstrate that grapefruit juice reduces the systemic exposure of bilastine (53). This is most probably due to the effects of grapefruit flavonoids on intestinal transporter systems such as p-glycoproteins and organic anion transporting peptide.

Two single dose (20 mg) studies in healthy volunteers investigated the effect of food intake on the bioavailability of bilastine. Bioavailability was reduced by 30% when bilastine was taken with high fat food, and by 25% with standard low fat food, compared with values obtained under fasting conditions (50). This observation should be taken into account when considering the administration of bilastine.

## Clinical properties

### Clinical efficacy in rhinoconjunctivitis

Preliminary clinical studies with bilastine in allergic rhinoconjunctivitis patients have yielded promising results (Table 5). Seventy-five asymptomatic volunteers with SAR were challenged with grass pollen in the Vienna Challenge Chamber. This is an experimental setting in which subjects are exposed to specific allergens for prolonged periods, under controlled and reproducible conditions. In this study, subjects were challenged with grass pollen for 6 h on two consecutive days. A single oral dose of bilastine 20 mg taken 2 h after the start of the allergic provocation effectively reduced nasal symptom scores (NSS), global symptom scores, nasal secretions and eye symptoms compared to placebo on day 1 (54). Similar results were obtained with cetirizine 10 mg. Although the effects of bilastine and fexofenadine 120 mg were similar during the first 4 h after administration, bilastine was significantly more effective than fexofenadine between 22 and 26 h after drug intake. Furthermore, bilastine was shown to have a rapid onset of action (1 h) and a long duration of action (>26 h). Like cetirizine and fexofenadine, bilastine was safe and well tolerated in this short term study.

Bilastine 20 mg also effectively improved total symptom score (TSS), compared with placebo over a 14 day period in two randomised, double-blind, placebo controlled, studies performed in allergic rhinoconjunctivitis patients ( $n = 721$ ,  $n = 683$ ) (11, 15). Total symptom score incorporated NSS (sneezing, rhinorrhoea, nasal itching, and nasal congestion) and non-NSS (ocular tearing and redness, itching of the ears/palate). Two other second-generation antagonists, cetirizine (15) and desloratadine (11), were also assessed in these studies and bilastine proved to be as efficacious as these drugs (Fig. 4). Bilastine had a better tolerability profile than cetirizine in terms of CNS effects, particularly with regards to a lower incidence of somnolence. Additional parameters measured to assess the efficacy of bilastine included patient-evaluated discomfort associated with rhinoconjunctivitis and QoL. Bilastine improved both of these endpoints compared with placebo ( $P < 0.001$ ), and the findings were comparable to those produced by desloratadine (11) and cetirizine (15).

In a 28 day multicentre study involving 651 patients with perennial allergic rhinoconjunctivitis, bilastine 20 mg and cetirizine 10 mg both reduced TSS compared to baseline. However, these effects were not significantly different to placebo (Table 5). *Post hoc* analysis showed this was indicative of a considerable placebo effect in one region of the study. Following the short-term double-blind trial, subjects ( $n = 513$ ) received bilastine 20 mg once daily for 12 months

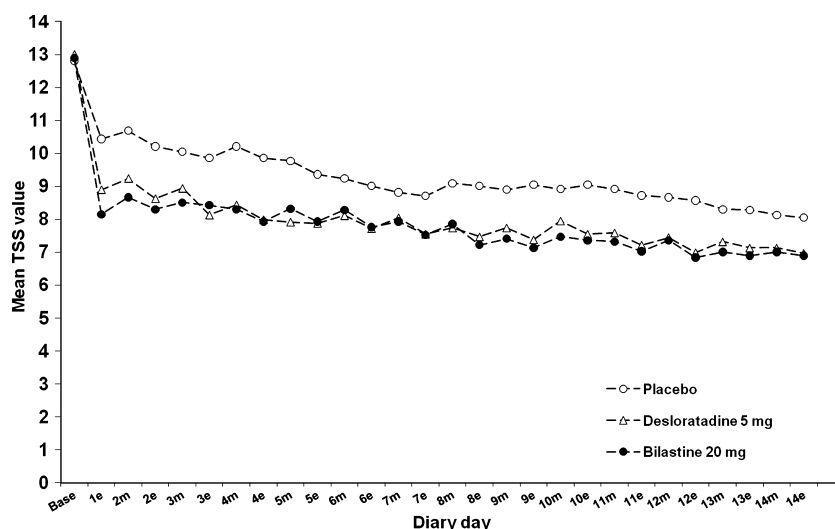


**Figure 4** Effect of treatment with bilastine 20 mg, desloratadine 5 mg, or placebo, on mean total symptom score, recorded as reflective 12 hourly scores in the morning (m) and evening (e) over a period of 14 days (11).

in an open-label extension study. Whilst safety was the primary endpoint (see Tolerability and safety section; Table 5), over the course of the 12 months' follow-up bilastine significantly reduced NSS and non-NSS, as well as individual symptom scores (sneezing, runny nose, nasal itching, nasal congestion, tearing and ocular redness) compared with baseline values (50).

These results indicate that bilastine 20 mg once daily was significantly superior to placebo and comparable to cetirizine 10 mg and desloratadine in relieving symptoms of SAR, and furthermore, it demonstrated a significantly better adverse event profile than cetirizine. Despite a significant placebo effect, bilastine 20 mg decreased nasal and non-nasal symptoms for up to 12 months and was well tolerated in a group of PAR patients.

#### Clinical efficacy in urticaria

Bilastine doses of 10, 20 and 30 mg were all superior to placebo in terms of reducing TSS ( $P = 0.003$ ), based on the variables of itching and number and diameter of wheals in 218 chronic urticaria patients (55). The efficacy of bilastine (20 mg) was also compared with levocetirizine 5 mg in a recent double-blind, placebo-controlled, randomised, parallel group phase III study in 516 chronic urticaria patients (32). Bilastine and levocetirizine were equally effective, significantly reducing TSS and sleep disturbances, and improving QoL and urticaria-associated discomfort compared with placebo ( $P < 0.001$ ), from day 2 to the end of the 28-day treatment period.

As estimates suggest that up to 40% of children in some developed countries suffer from allergies (11) it is necessary to establish a dose of bilastine for the paediatric population. A simulated model of pharmacokinetic parameters based on data from adults was recently developed (56). Simulations of

plasma concentrations over time for bilastine after four consecutive oral doses of 5, 10 and 20 mg of the drug were performed in order to determine the optimal dosage relative to the therapeutic endpoint of wheal/flare inhibition described for adults. This study concluded that four consecutive doses of 10 mg/day in children (aged 2, 6 and 12 years) maintained bilastine concentrations above the  $IC_{50}$  value required for wheal inhibition. Therefore, in this simulated setting, bilastine 10 mg was considered effective in children aged 2–12 years. In infants, a dose of 5 mg/day was calculated to maintain antihistaminic activity throughout the treatment period (56). Clinical studies to confirm the efficacy and safety of these doses in children are on-going.

#### Tolerability and safety

Assessment of the safety of bilastine indicates that it is a well tolerated antihistamine and doses of 20–100 mg were no different in terms of Adverse Events (AEs) profile from placebo in studies involving healthy volunteers who received the drug for up to 14 days (47). Similar tolerability was also reported for bilastine and placebo in clinical trials in patients with allergic rhinoconjunctivitis (11, 15). Furthermore, bilastine (20 mg) had an improved safety profile, with reduced incidences of fatigue and somnolence, compared with cetirizine (10 mg) over a 14 day period (15). A recent 28-day double-blind study was followed by a 12 month open-label safety extension and involved a total of 513 patients treated with bilastine 20 mg daily. Of this population, 18 subjects (3.5%) withdrew due to AEs. However, these AEs were not considered by the investigator to be due to study medication (50). Based upon these early findings bilastine appears to very well tolerated at usual dosages and may prove to be an attractive alternative compared to some of the more established  $H_1$ -receptor antagonists (15).

### Lack of CNS effects

Criteria for determining whether a new antihistamine may be classified as non-sedating have been proposed by the Consensus group On New Generation Antihistamines (CONGA) (2). These factors are (i) incidence of subjective sleepiness, (ii) objective cognitive and psychomotor functions and (iii) positron emission tomography (PET) measurement of H<sub>1</sub>-receptor occupancy. Balancing the beneficial peripheral H<sub>1</sub> inhibitory effects with unwanted CNS effects involves determining at what dose the drug is clinically effective, whilst minimising adverse effects. A clinical study was performed to characterise the CNS response to three doses of bilastine (20, 40 and 80 mg) compared with that of placebo and hydroxyzine 25 mg (a sedating antihistamine included as positive control) in healthy young volunteers (57). The greatest motor impairment was documented for hydroxyzine 25 mg. As motor impairment was not observed with the 20 and 40 mg doses of bilastine, these results provide optimism for bilastine as a potential treatment in allergic conditions. The data also suggest that there is dissociation between the peripheral and central antihistamine effects of bilastine. Subjective reports on mood indicated that the greatest negative impact was with hydroxyzine 25 mg, while bilastine 20 mg was no different from placebo.

A number of studies have assessed the CNS effects of bilastine in combination with others drugs known to cause sedation. For example, in a double-blind, crossover study, bilastine 20 mg once daily for 8 days did not increase the sedative effects of lorazepam 3 mg (as assessed by objective psychomotor testing) in healthy volunteers (50). In a similarly designed study, bilastine 20 mg did not affect psychomotor scores when administered with alcohol. This is an encouraging finding since other antihistamines evaluated in this study (cetirizine 10 mg and hydroxyzine 25 mg) both significantly enhanced the effects of alcohol (58). A phase I study in healthy volunteers investigated the effects of repeated doses of bilastine (20 and 40 mg) on driving ability compared with hydroxyzine 50 mg and placebo. Bilastine had no effect on the primary efficacy variable, Standard Deviation of Lateral Position (SDLP) in the Road Tracking Test. However, SDLP was significantly altered by hydroxyzine 50 mg, in comparison to placebo in this setting (50). In terms of the incidence of subjective sleepiness and objective cognitive and psychomotor performance, bilastine 20 mg demonstrates a promising profile as a non-sedative H<sub>1</sub>-receptor antagonist. However, given the CONGA recommendations, PET measurement of H<sub>1</sub>-receptor occupancy is recommended to fully explore this potential.

### Cardiac safety

The second-generation antihistamines astemizole and terfenadine have been associated with severe adverse cardiac effects including QT interval prolongation and *torsades de pointes* ventricular tachyarrhythmias and were withdrawn from the market. Such effects are attributed to direct blockade of potassium channels controlling the repolarisation of the car-

diac action potential and are not related to H<sub>1</sub>-receptor antagonism, i.e. it is not a class effect (2). However, given the seriousness of the effects, the development of any new antihistamine now involves vigorous testing of cardiotoxicity, including assessment of the QTc interval.

Bilastine, fexofenadine, desloratadine and cetirizine dose-dependently blocked human ether-a-go-go-related gene (HERG) current in HEK-293 cells transfected through the lipofectamine method with the HERG clone. IC<sub>50</sub> values of 6.5, 12.5, 1.4 and 1.1 µM, respectively were calculated. Bilastine was 5-fold less potent than cetirizine in this model (50).

Recently the effect of therapeutic (20 mg) and supratherapeutic (100 mg) doses of bilastine on QTc interval was assessed in accordance with FDA and ICH guidelines (ICH E14). This was a multiple-dose, randomised, double-blind, crossover trial with placebo and active control (moxifloxacin 400 mg). Bilastine did not produce any significant effects on QTc interval at either dosage. Furthermore, changes that occurred when co-administered with ketoconazole 400 mg were relatively small and likely to be due to the antifungal agent (59).

### Place in therapy

Current antihistamines have –in most clinical circumstances– a good level of efficacy and therefore development of new antihistamines is primarily concerned with improving their tolerability and decreasing the incidence of AEs, increasing their potency, extending their duration of action and/or producing agents which act more quickly. *In vitro* studies have confirmed the specificity of bilastine for H<sub>1</sub>-receptors, and both preclinical and clinical investigations have shown that bilastine has similar efficacy to cetirizine, desloratadine and levocetirizine in terms of reducing allergic symptoms. Clinical findings indicate that bilastine has a rapid onset of action and a 20 mg single dose is effective throughout a 24-h period. Furthermore, bilastine has been associated with improved QoL in allergic rhinoconjunctivitis and urticaria patients.

In terms of safety and tolerability, early evidence indicates that bilastine 20 mg is very well tolerated with minimal adverse effects. Indeed, in clinical trials it was no different from placebo in terms of tolerability and this makes this novel antihistamine a potentially exciting treatment for allergic diseases. The removal of astemizole and terfenadine from the marketplace has raised the awareness and some concerns regarding antihistamines and cardiotoxicity (60). In this regard bilastine underwent a well-controlled QTc assessment according to FDA/ICH guidelines, and even at supratherapeutic dosages it was not associated with adverse effects on the QTc interval and this highlights its cardiovascular safety. In addition, bilastine appears to have minimal potential for drug-drug interactions given that it is not metabolised in the liver and does not affect CYP450 isoenzymes.

Thus, based on its pharmacological properties and early clinical trials experience it appears that bilastine has a similar efficacy to other second-generation H<sub>1</sub>-receptor

antagonists, but may possess a more favourable safety profile. Larger, long term trials are required to fully elucidate this potential and to help determine its overall

place in the treatment of diseases for which an antihistamine is advocated such as allergic rhinoconjunctivitis and urticaria.

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