

Article Type: Review Article

JEADV-2017-0398

Bilastine: a new H₁-antihistamine with an optimal profile for up dosing in urticaria

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Short Title: Bilastine in urticaria

Keywords: bilastine, H₁-antihistamine, urticaria, P-glycoprotein

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This review was funded by FAES Pharma, Bilbao, Spain.

MKC has honoraria from FAES Farma. LL is an employee of FAES Farma.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jdv.14305

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Abstract

This review set out to examine published papers detailing the efficacy of bilastine in skin models and urticaria to assess whether it meets the optimal profile for up dosing in urticaria, i.e. strong clinical efficacy and freedom from unwanted side effects, particularly sedation. Bilastine is a highly effective H₁-antihistamine even when used at the basic dose of 20 mg daily. Its facilitated uptake after oral dosage gives it a rapid onset and long duration of action. In both wheal and flare studies and in urticaria up dosing four fold showed increased effectiveness. With respect to somnolence, bilastine is a substrate for P-glycoprotein, a membrane pump which prevents it crossing the blood–brain barrier. Consequently, bilastine is a practically ‘non-sedating’ H₁-antihistamine. In conclusion, the excellent profile of bilastine in both efficacy and safety make it the ideal H₁-antihistamine for up dosing the daily dose fourfold in difficult-to-treat urticaria as recommended by the EAACI/GALEN/EDF/WAO guideline for the management of urticaria.

1. Introduction

Urticaria is one of the most frequent skin diseases. It is characterized by pruritic wheal and flare-type skin reactions with or without angioedema that usually persist for less than 24 hours. As mast cell-derived histamine is the major mediator of these conditions, second generation H₁-antihistamines (SGAHs) are the mainstay of treatment ¹⁻³. However, authorised doses of SGAHs are ineffective in completely relieving symptoms in many patients because histamine may reach very high concentrations in the skin, due to its poor diffusibility in the dermis ^{4, 5}. In these patients, the EAACI/GA2LEN/EDF/WAO guidelines recommend increasing the dosage up to fourfold ⁶.

Even with up dosing to four times the standard dose a, specialist review has estimated that a good outcome in occurs in only 78% of patients ⁷. Furthermore, although SGAHs have a much reduced brain penetration compared with their first generation counterparts, most may only be referred to as 'minimally sedating' rather than 'non-sedating'. For example, in a study of patients' perspective of effectiveness and side effects of H₁-antihistamine up dosing in chronic spontaneous urticaria (CSU), more than 20% of patients reported sedation is a side effect of SGAHs ⁸. It is clear, therefore, that for use in urticaria, two major factors are of importance. First is freedom from unwanted side effects, particularly sedation, so that up dosing may occur safely. Second is strong clinical efficacy, preferably with a rapid onset and long duration of action.

This review will examine published papers detailing particularly the efficacy of bilastine in skin models and urticaria to assess whether it meets effective and non-sedating criteria for the treatment of up dosing in urticaria. The papers on the safety profile will be summarized very briefly as they have already been explained in many reviews.

2. *In Vitro* and Pharmacokinetic Studies of Bilastine

Bilastine, 2-[4-(2-(4-(1-(2-ethoxyethyl)benzimidazole-2-yl)piperidine-1-yl)ethyl)phenyl]-2-methylpropanoic acid, is a new SGAH indicated for the treatment of allergic rhinoconjunctivitis and urticaria ⁹⁻¹¹. Like all other antihistamines bilastine is an inverse agonist ^{12, 13}. Preclinical studies have shown the drug to be highly selective for histamine H₁-receptors, with little or no affinity for other receptors,

including other histamine receptor subtypes and muscarinic and serotonin receptors^{9, 14, 15}. Bilastine is rapidly absorbed after oral administration, followed by an exponential decay of plasma levels over the ensuing 48 hours¹⁶. After administration of a single oral 20-mg dose to healthy volunteers, bilastine reached a mean peak plasma concentration of 220 ng/ml at 1.3 hours, an apparent volume of distribution of 1.29 l/kg, a terminal elimination half-life of 14.5 h and plasma binding of 84 - 90%^{15, 16}.

3. Effectiveness of Bilastine in Preclinical Skin Models

A range of preclinical studies of bilastine in rats and guinea pigs have been performed by Corcóstegui and colleagues⁹. In rats, oral administration bilastine showed a dose-dependent inhibition of histamine-induced capillary permeability with a 50% effective dose (ED₅₀) of 2.4 mg/kg. Cetirizine had a similar effectiveness but fexofenadine was weaker with an ED₅₀ of ~10 mg/kg.⁹ When the histamine releaser compound 48/80 was used to induce capillary permeability, the oral ED₅₀ values for bilastine and cetirizine were 3.47 and 5.32 mg/kg respectively⁹.

In the IgE-dependent passive cutaneous anaphylactic reaction in rats⁹ oral bilastine showed significant activity with an ED₅₀ value of 7.6 mg/kg while cetirizine was more effective (ED₅₀ 2.2 mg/kg). However, when the reaction was induced by monoclonal IgE antibodies, bilastine and cetirizine were of similar potency with ED₅₀ values of 6.0 and 4.3 mg/kg respectively. Fexofenadine was some 10-fold less effective than bilastine in both studies. In the active cutaneous reaction in the mouse induced by both IgE and IgG antibodies, cetirizine was marginally more effective than bilastine. Both drugs were more effective than fexofenadine.

The results of the *in vivo* preclinical studies corroborate those obtained in *in vitro* experiments conducted previously, and provide evidence that in preclinical histamine-related skin models, bilastine possesses antihistaminic and anti-allergic properties with similar potency to cetirizine and superior potency to fexofenadine.

4. Clinical Pharmacokinetics of Bilastine

Before looking at comparative wheal and flare studies and urticaria trials, it is worth addressing that absorption and distribution of bilastine.

While the presence of P-glycoprotein (P-gp) in the blood brain barrier is beneficial in preventing the penetration of bilastine into the brain, this efflux transporter is also present in the intestine. Based on its hydrophobicity and P-gp-mediated efflux, the absorption of bilastine would be expected to be low as ¹⁷. However, the mean oral bioavailability of bilastine has been estimated to be around 61% in healthy human volunteers ¹⁶. A possible explanation for this (Figure 1) is that bilastine is also a substrate for the human intestinal drug transporter OATP1A2 that has already been implicated in the facilitated intestinal absorption of fexofenadine ¹⁸. This explanation for bilastine is supported by the reduction of bilastine absorption by co-administration with grapefruit juice, an inhibitor of OATP1A2 ¹⁸⁻²⁰. However, further investigations into the human transporter systems are necessary to explain with certainty the rapid and effective absorption of bilastine.

5. Bilastine in histamine-induced wheal and flare responses

Perhaps the most appropriate model to assess the potential speed of onset and efficacy of an H₁-antihistamine in urticaria is the histamine-induced wheal and flare response (W&F) ²¹. Four such studies have been performed.

The first of these ²² compared the speed of onset of action after single oral doses of 20, 40 and 80 mg bilastine and 25 mg hydroxyzine in 20 healthy volunteers. The W&F response was induced by intradermal injection of histamine 5 µg. The results showed that bilastine achieved maximal activity within 1 hour at 40 and 80 mg and within 2 hours at 20 mg. In contrast, it took hydroxyzine four hours to achieve maximal activity. Dosing was then continued daily for seven days when a further comparison of efficacy was performed with similar results.

In the second study ²³ 21 healthy male volunteers were randomised receive single oral doses of bilastine 20 mg, cetirizine 10 mg or placebo before provocation of W&F responses to 100 mg/ml histamine by skin prick 1.5, 4, 8, 12 and 24 hours later. The results showed bilastine 20 mg to be faster in onset of action than cetirizine 10 mg, inhibitions of both the W&F responses at 1.5 hours being significantly ($P < 0.02$) greater with bilastine (Figure 2). There were no significant differences between the two drugs at later time points. The drug effects were also assessed by the number of individuals experiencing more than 70% inhibition of the effects of histamine. At 1.5 hours, both wheal and flare were inhibited in 11/12 individuals taking bilastine but in only 3/11 of those taking cetirizine ($P = 0.003$, Fisher's exact test). There were no significant differences in response rates at later times.

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In the third study ²⁴, 24 healthy volunteers were randomized to receive single doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo in a double-blind crossover manner (Figure 3). W&F responses were induced by intradermal injection of histamine 5 µg and were evaluated before treatment and at 0.5, 1, 2, 4, 6, 9, 12 and 24 hours. Pruritus was also evaluated using a 100 mm visual analogue scale. The results showed bilastine to be more rapid in onset than the other two drugs showing a highly significant ($P < 0.001$) inhibition of both wheal and flare at 1 hour while significant ($P < 0.01$) inhibition with desloratadine and rupatadine occurred only at four hours. Also, maximum wheal inhibition at 6 hours of bilastine 83% was significantly than those of 38% for desloratadine and 37% for rupatadine. Similar results were seen for flare. Bilastine also significantly reduced pruritus between 2 and 12 hours. In contrast, neither desloratadine nor rupatadine significantly reduced pruritus compared with placebo. In conclusion, this study showed bilastine to be more rapid in onset of action and more effective than two competitor H₁-antihistamines.

The fourth study in this series ²⁵ assessed possible ethnic differences by studying bilastine in 60 healthy Japanese individuals. After single oral doses, maximum plasma concentrations were reached at 1 –1.5 hours after dosing. The maximum plasma concentration increased dose-proportionally with single doses of 10–50 mg. No remarkable differences were seen with 14 daily doses. Bilastine at 20 and 50 mg showed significant inhibition of histamine-induced W&F response (prick test with histamine 10 mg/ml) from 1.5 h after administration and persisted for 24 hours..

6. Bilastine in Urticaria

a) Bilastine in chronic spontaneous urticaria (CSU)

Bilastine was initially studied in CSU in doses of 10, 20 and 30 mg versus placebo control in a dose ranging phase II study involving 222 patients²⁶. Using the number of wheals and itching as endpoints, all doses were statistically different from placebo. Although there was a dose related trend, there were no statistically significant differences between the doses.

More recently, bilastine 20 mg was compared with levocetirizine 5 mg and placebo in a multicentre study across Europe and Argentina of 525 urticaria patients²⁷. Drugs were dosed daily for 28 days. Bilastine significantly ($P < 0.001$) reduced the total symptoms scores from day 2 onwards. The results showed different from placebo. Dermatology Life Quality Index (DLQI), chronic urticaria-associated discomfort and sleep disturbance were also significantly improved. Bilastine and levocetirizine were equally efficacious and equally safe and well tolerated.

Perhaps the biggest test for an antihistamine is to relieve symptoms of CSU where other SGAHs, including loratadine, cetirizine, rupatadine, ebastine, fexofenadine and desloratadine, have failed. Such a study was performed by Weller and colleagues²⁸ in which 31 CSU patients who had previously failed treatment with a SGAH other than bilastine in licensed doses. These patients had a mean UAS7 $\pm$ SD of 24.7 ± 8.0 at baseline. Following a 2-week baseline phase in which only rescue medication was permitted patients received bilastine 20 mg daily for 2 weeks. If they were not complete responders they then received 40 mg daily for 2 weeks and then 80 mg

daily for a final 2 weeks. This procedure followed the EAACI/GA²LEN/EDF/WAO guideline for the management of urticaria ⁶ and represented the first and authentic up dosing pilot study with bilastine in clinical practice. The results showed that 6 (19%) patients gained complete (UAS7 $\leq$ 3) relief with bilastine 20 mg and a further 3 (10%) patients with bilastine 40 mg. Seven patients (23%) gained complete from itching with bilastine 20 mg and a further 3 (10%) with 40 mg. If minimal urticarial symptoms (UAS7 $\leq$ 6) were taken as the endpoint then the number of patients responding to 20, 40 and 80 mg bilastine was 8 (26%), 2 (6%) and 1 (3%) respectively. Similarly, if minimal pruritus (Pruritus 7 $\leq$ 3) was taken as the endpoint then the number of patients responding to 20, 40 and 80 mg bilastine was 10 (32%), 5 (16%) and 1 (3%) respectively. The study concluded that bilastine is effective and safe in moderate to severe CSU patients not responding sufficiently to other SGAHs in licensed doses.

The possible ethnic differences in the efficacy and safety of bilastine were assessed in a study of Japanese patients with CSU ²⁹. In this 14-day study, 101 patients received daily doses 20 mg bilastine, 100 patients 10 mg bilastine and 103 patients placebo. Total symptom scores for both doses of bilastine significantly ($P < 0.001$) improved from day and were maintained during the following two-week treatment period. DLQI scores were also improved in bilastine. Both doses of bilastine were safe and well tolerated.

In a further long-term study, 122 Japanese patients with CSU were treated with 20 mg bilastine daily for 52 weeks ³⁰. Total symptom score was significantly ($P < 0.001$) improved by two weeks and remained the same thereafter. Similar efficacy patterns

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were observed for rash and itch scores. Bilastine-related adverse events were reported in only 2.5% of patients. All adverse events were mild to moderate in severity. Somnolence related to bilastine was reported in only two patients. The authors concluded that the long-term treatment with bilastine 20 mg once daily for 52 weeks is safe and well tolerated in Japanese patients with CSU or pruritus associated with skin diseases. Also, bilastine improved disease symptoms of both conditions early in treatment, and the efficacy was maintained throughout the treatment.

b) Bilastine in cold-contact urticaria

This double blind crossover study of 20 patients assessed the effects of bilastine in reducing the symptoms of cold contact urticaria, at a standard 20 mg dose, and updosing to 40 and 80 mg³¹. The results showed (Figure 4) that whealing to a challenge of 4°C was completely abolished by bilastine 20 mg in 7 patients (35%). Updosing to bilastine 40 and 80 mg completely prevented whealing in 11 (55%) and 12 (60%) of patients respectively. One person reported sedation at 40 mg but there were no reports at bilastine 20 and 80 mg³¹. Two conclusions may be drawn from the results of this severe challenge model. First is the high effectiveness of the standard dose of bilastine. Second is the significant increase in effectiveness with up dosing of bilastine in the absence of somnolence.

The secondary readout of this study was pruritus³¹. Pruritus is probably the most bothersome of symptoms in urticaria¹. Following treatment with bilastine 20 mg daily, the median pruritus score (with 75% confidence limits) was reduced from the placebo level of 2.0 (1.25–3.0) to 0 (0–1) ($P = 0.001$), with 13 of the 20 patients

reporting no itch. There was no significant increase in effectiveness with up dosing to 40 mg and 80 mg bilastine. These results suggest that, even in the standard dose of 20 mg daily, bilastine is particularly effective against pruritus. This result contrasts with other SGAHs in which up dosing was required to significantly improve the control of pruritus³².

7. Safety of Bilastine

Basic safety studies, including lack of cardiovascular effects and freedom from cardiac toxicity are well documented and will not be repeated here^{14, 15, 33-35}.

However, it is necessary to highlight the freedom from somnolence that is a cardinal feature of bilastine.

It is well established that, because of their lipophilic nature, first-generation H₁-antihistamines readily cross the blood-brain barrier to cause drowsiness, sedation, somnolence and fatigue, leading to impairment of cognitive function, memory and psychomotor performance^{36, 37}. SGAHs, such as cetirizine, loratadine and levocetirizine, because of their more hydrophilic nature, cross the blood brain barrier less well. However, they should be referred to as 'minimally sedating' rather than 'non-sedating' as sedation has been reported, particularly with increased dose levels^{38, 39}. For example, in a study of patients' perspective of effectiveness and side effects of H₁-antihistamine up dosing in chronic spontaneous urticaria, more than 20% of patients reported sedation is a side effect of SGAHs⁸.

More recently, studies have suggested hydrophilicity alone is not sufficient to keep drugs from entering the brain but that an active efflux transporter in the blood brain

barrier may be involved. The most extensively studied of the active efflux proteins is P-glycoprotein (P-gp), which is known to efflux a wide variety of structurally dissimilar drugs^{40, 41}. This work has been extended Comparison of P-gp-mediated efflux from caco-2 cells⁴² showed cetirizine and desloratadine and hydroxyzine to have weak but significant efflux ratios while that of fexofenadine was much greater. More recently similar studies have shown bilastine also had a high efflux ratio⁴³. The failure of bilastine and fexofenadine to enter the brain and occupy histamine H₁-receptors has been confirmed using positron emission tomography^{44, 45}. It is also important to note that total H₁-receptor occupancy (H₁RO) in the brain for bilastine and fexofenadine was less than zero. Thus, these two drugs appear to be truly 'non-sedating' H₁-antihistamines and the most likely reason for their lack of brain penetration is that they are actively pumped out of the blood–brain barrier by P-gp (Figure 5)^{15, 40, 46, 47}.

The lack of central nervous system effects of bilastine, both objective and subjective, has been confirmed in several studies. These studies, including interactions with lorazepam and alcohol, which have been detailed previously^{15, 22, 48}, showed clearly that bilastine at the licenced dose of 20 mg daily is a 'non-sedating' antihistamine.

More recently, the effects bilastine has been examined in two situations highly relevant to their potential use in real life. These are effects on driving a motor vehicle and on airline pilots. In the former study⁴⁹ bilastine 20 and 40 mg and hydroxyzine 50 mg were administered daily for eight days to 22 healthy volunteers tested in a placebo-controlled, randomized, double blind, four-way cross over design. On day 1 and 8 of each treatment period participants performed an actual highway-driving test

in which a measure of weaving was assessed. Results showed that, unlike hydroxyzine, bilastine did not produce any driving impairment after single or repeated doses and can be safely used in traffic in doses up to 40 mg⁴⁹. In the second study⁵⁰ bilastine 20 mg was compared with hydroxyzine 50 mg in 24 healthy volunteers on flying-related performance under hypobaric conditions that prevail in an airliner. Assessments were made before and up to 6 hours after administration of the study medication using the vigilance and tracking task, multi-attribute task battery, and Stanford sleepiness scale. The results showed that, unlike hydroxyzine, bilastine 20 mg did not cause sleepiness or impaired performance on tasks related to flying. The authors concluded that bilastine may provide a safe therapeutic alternative for pilots suffering from allergic rhinitis or urticaria⁵⁰.

Conclusions

This review set out to examine published papers detailing the efficacy of bilastine in skin models and urticaria to assess whether it meets the optimal profile for up dosing in urticaria. The conclusion is that it has an excellent profile for both efficacy and safety. Bilastine is a highly effective H₁-antihistamine even when used at the basic dose of 20 mg daily. It is a practically non-brain penetrating antihistamine and its freedom from sedative effects, even at 80 mg daily, make it the ideal H₁-antihistamine for up dosing the daily dose fourfold in difficult-to-treat urticaria as recommended by the EAACI/GA(2) LEN/EDF/WAO guideline for the management of urticaria⁶. However there is a need for controlled clinical trials to compare efficacy of bilastine in a real life up dosing study in patients with urticaria, paying special attention to itch control.

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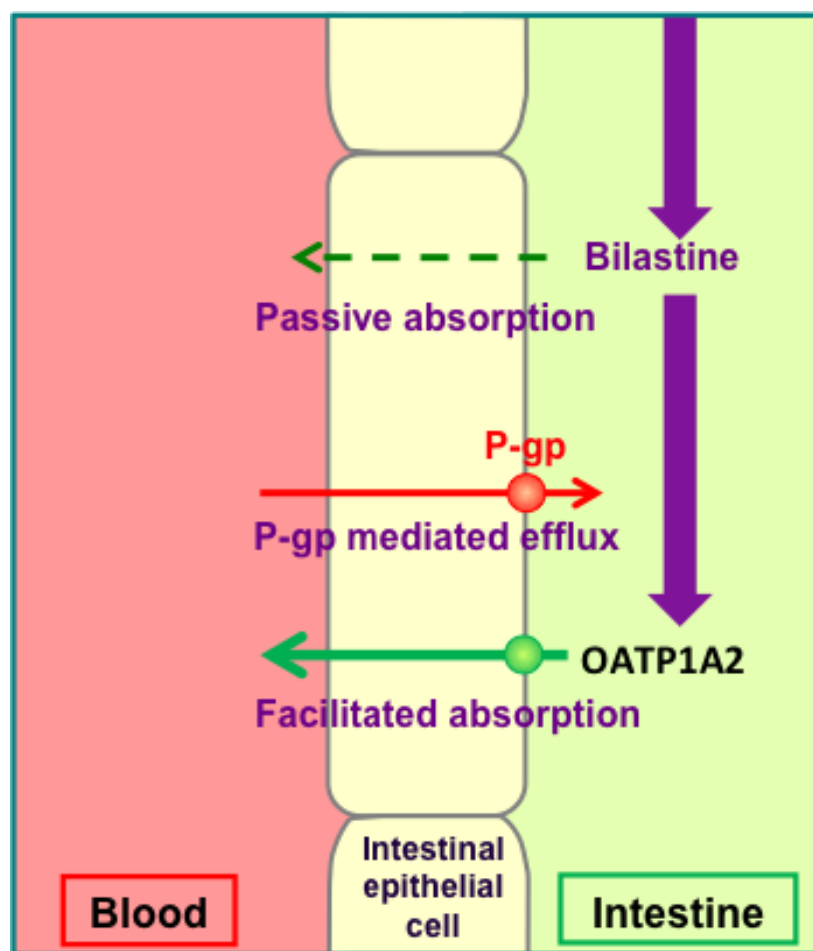


Figure 1. Purported facilitated intestinal uptake of bilastine. The diagram shows an initial passive uptake of bilastine into the blood followed by a P-glycoprotein (P-gp) facilitated excretion of bilastine into the intestine. Finally, the diagram shows the purported facilitated uptake of bilastine by Organic Anion Transporting Polypeptide 1A2 (OATP1A2). References ^{15, 20}.

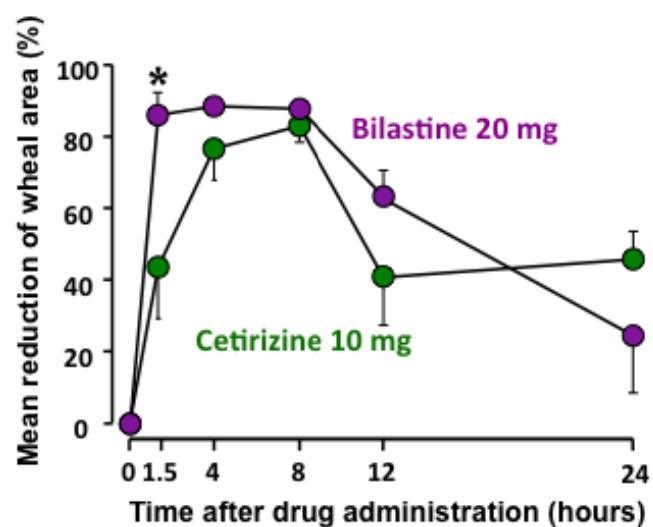


Figure 2. Inhibition of histamine induced wheal and flare responses by bilastine 20 mg (purple circles) and cetirizine 10 mg (green circles).

*Indicates significance ($P < 0.02$) of difference between bilastine and cetirizine at 1.5 h. Each point is the mean $\pm$ SEM of measurements in 12 healthy volunteers.

Reference²³.

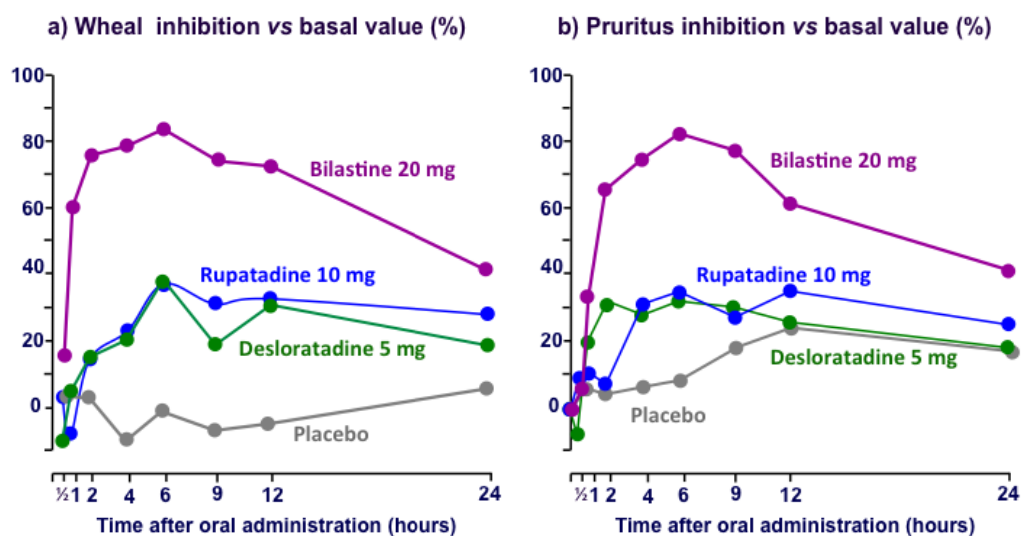


Figure 3. Percentage inhibition of a) wheal area and b) pruritus after crossover treatment with single oral doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo. Each result is the mean of observations in 24 individuals. Redrawn from reference ²⁴.

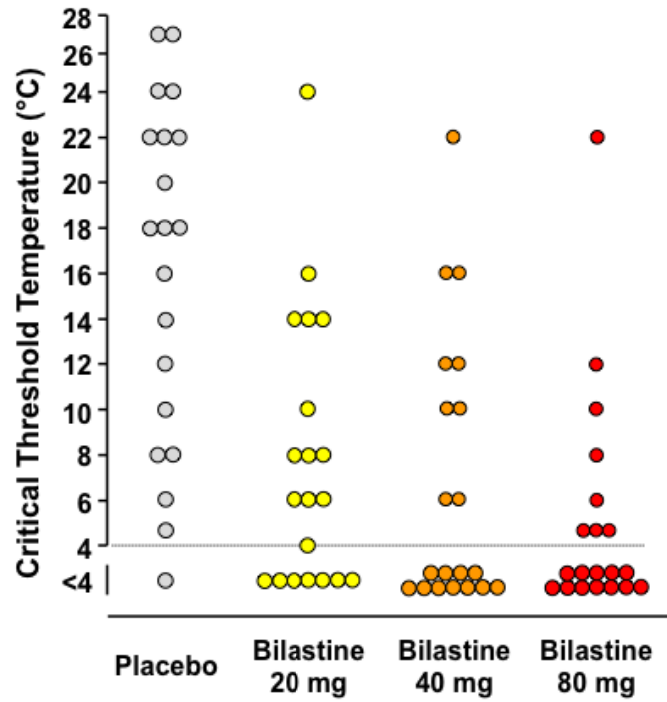


Figure 4. Critical temperature thresholds for the production of wheals following cold provocation in 20 cold urticaria patients. Redrawn from reference ³¹.

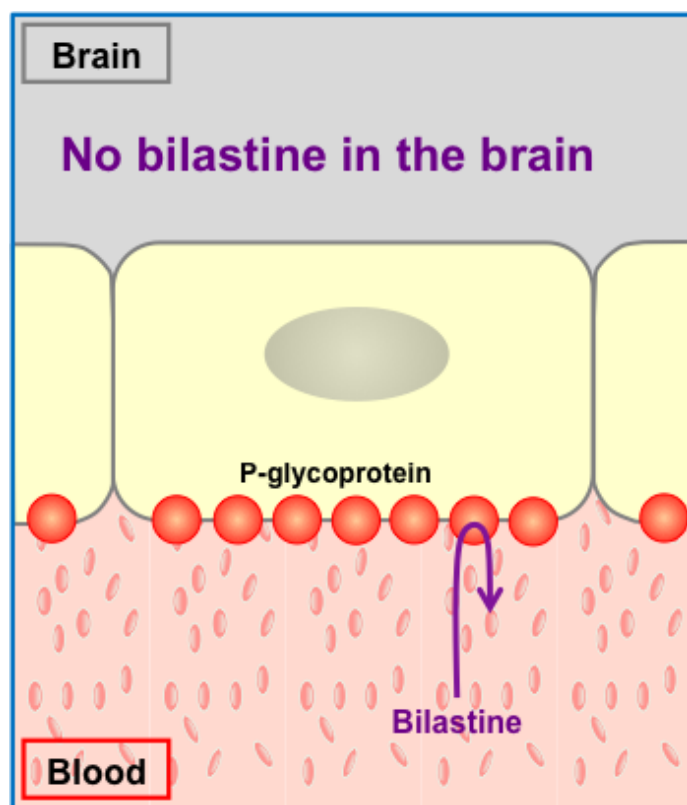


Figure 5. Diagrammatic representation of P-glycoprotein, an active efflux transporter in the blood brain barrier, preventing the uptake of bilastine into the brain.