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Lack of Clinical Relevance of Bilastine-Food Interaction in Healthy Volunteers: A Wheal and Flare Study

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Keywords
Bilastine · Food interaction · Pharmacodynamics · Antihistaminic effect · Pharmacokinetics

Abstract
Introduction: The aim of this study was to compare the pharmacodynamic activity of bilastine administered under fasting and fed conditions in healthy volunteers. ***Methods:*** In this randomized, open-label, two-period, crossover study involving 24 healthy subjects, once-daily oral bilastine 20 mg was administered for 4 days under fasting and fed conditions, with a 7-day washout period. Bilastine plasma concentrations were measured for 24 h after the first and fourth doses in each period. Pharmacodynamic activity was assessed by wheal and flare surface inhibition and subjective assessment of itching, after intradermal injection of histamine 5 µg. ***Results:*** When administered under fed versus fasting conditions, exposure to bilastine 20 mg decreased (mean maximum plasma concentration and area under the curve from time 0 to 24 h decreased by 34.27% and 32.72% [day 1], respectively, and 33.08% and 28.87% [day 4]). Despite this, the antihistaminic effect of bilastine 20 mg was not altered by food. On day 1, as assessed by wheal and flare surface inhibition, the maximum effect and duration of action of bilastine did not differ to a significant extent between fasting and fed conditions, with only a short 30-min delay in the onset of wheal inhibition. At steady state (day 4), bilastine's pharmacodynamic effects were not significantly affected under fasting or fed conditions. ***Conclusion:*** The pharmacokinetic interaction of bilastine with food does not imply a significant reduction of its peripheral antihistaminic efficacy. Despite a slight delay in onset of action on the first treatment day, the global clinical efficacy of bilastine is not affected by coadministration with food.

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Introduction

Bilastine is a second-generation antihistamine, has good selectivity for H_1-receptors, and is considered a non-brain-penetrating antihistamine [1]. Bilastine was approved for the symptomatic treatment of allergic rhinoconjunctivitis (perennial and seasonal) and urticaria in Europe in 2010 and has been introduced into clinical practice in about 120 countries worldwide. At the recommended adult dose of 20 mg once daily, clinical trials have demonstrated good efficacy, an excellent safety profile, and improvements in quality of life in patients with allergic rhinitis or chronic urticaria [2, 3].

The pharmacokinetic profile of bilastine has been reported in healthy Caucasian [4] and Japanese adults [5], as well as in children with allergic rhinoconjunctivitis or chronic urticaria [6]. After administration of a single oral 20 mg dose, bilastine had a mean peak plasma concentration of about 220 ng/mL at 1.3 h, an apparent volume of distribution of 1.29 L/kg, a terminal elimination half-life of 14.5 h, and reached steady state in 72–96 h in Caucasian adults [4]. The pharmacokinetic profile of bilastine 20 mg in Japanese adults [5] was similar to that previously reported in Caucasian adults, and the pharmacokinetics of bilastine 10 mg in pediatric patients [6] were consistent with those of bilastine 20 mg in adult subjects. The absolute oral bioavailability of bilastine is 60.67% [7], and no accumulation pattern was shown after repeated dosing in a 14-day pharmacokinetic study [8].

Bilastine is not metabolized and does not interact, either as an inhibitor or inducer, with the cytochrome P450 enzyme system, suggesting a low probability for drug-drug interactions when this metabolic pathway is involved [9]. However, the bioavailability of bilastine was reduced by 30% when it was administered with high-fat food and by 25% with standard low-fat food, compared with values obtained under fasting conditions, indicating a significant pharmacokinetic food interaction [10, 11]. The most widely used human model for assessing the onset of action, efficacy, and duration of action for an antihistamine drug is the wheal and flare response after a cutaneous prick-test or intradermal injection of histamine [12–14]. It is possible that the antihistaminic effect of bilastine remains unaffected by concomitant administration with food. This is the main prediction obtained in a recent analysis conducted by nonlinear mixed-effect modeling performed under both fed and fasting conditions using a developed pharmacokinetic food-effect model and an already available pharmacokinetic/pharmacodynamic model [15].

The main objective of this clinical study, therefore, was to verify whether the pharmacokinetic interaction of bilastine with food leads to a significant reduction in antihistamine activity, as assessed by the reduction of the surfaces of wheal and flare induced by histamine injection. Wheal and flare responses were evaluated on the first (day 1) and fourth day (day 4) of bilastine administration (steady-state concentrations of bilastine are achieved on day 4).

Methods

Objectives

The primary objective was to compare the efficacy of bilastine administered under fasting and fed (with a moderate-fat breakfast) conditions in reducing histamine-induced skin reactivity (wheal and flare) in healthy volunteers, assessed on the first day of treatment (day 1) and at steady state (day 4). Secondary objectives were to evaluate the onset of action, maximum effect, time to maximum effect, duration of effect, subjective sensation of itching after histamine inoculation, and the safety and tolerability of bilastine.

Study Design

The study design is shown in Figure 1. This was a randomized, open-label, crossover study (EudraCT number: 2018-000913-19; protocol code BILA-3818/PD) conducted at Hospital Santa Creu i Sant Pau, Barcelona, in 24 healthy volunteers. Subjects were recruited between May 17 and July 3, 2018. Four weeks before the beginning of the experimental phase (from day −28 onwards), signed informed consent was obtained from all willing participants who met the study inclusion criteria prior to performing any study evaluation. On the day before the start of the experimental phase (day −1), all subjects selected for the study were randomly allocated (1:1) to the fasting or fed group, followed by treatment with oral bilastine 20 mg once daily for 4 days. After a 7-day washout period, the groups' diets were switched, and all subjects received another 4-day treatment period with bilastine at the same dosage but under opposite conditions to those in the first period. The trial medication was administered orally with mineral water (240 mL) in the presence of a member of the investigator team and a witness at the clinical trial unit.

Selection Criteria

Subjects had to be healthy volunteers (normal medical records and physical examination at screening, no clinically significant abnormalities on laboratory tests, vital signs, and ECG record within the normal range), aged 18–45 years, and with a body mass index of ≥18.0 and ≤28.0 kg/m^2. Participants had to have induced wheal area values within the reference range of the research institute (0.5521–2.5941 cm^2) in the histamine-induced skin reactivity test.

Subjects were excluded on the following grounds: history of allergy, idiosyncrasy, or hypersensitivity to drugs or any related products (including excipients of the formulations); heavy consumers of stimulating drinks (>5 cups of coffee, tea, chocolate, or cola drinks per day); history of alcohol dependence or drug abuse in the last 5 years, or daily consumption of alcohol >40 g/day for men or >24 g/day for women; intake of any medication (except

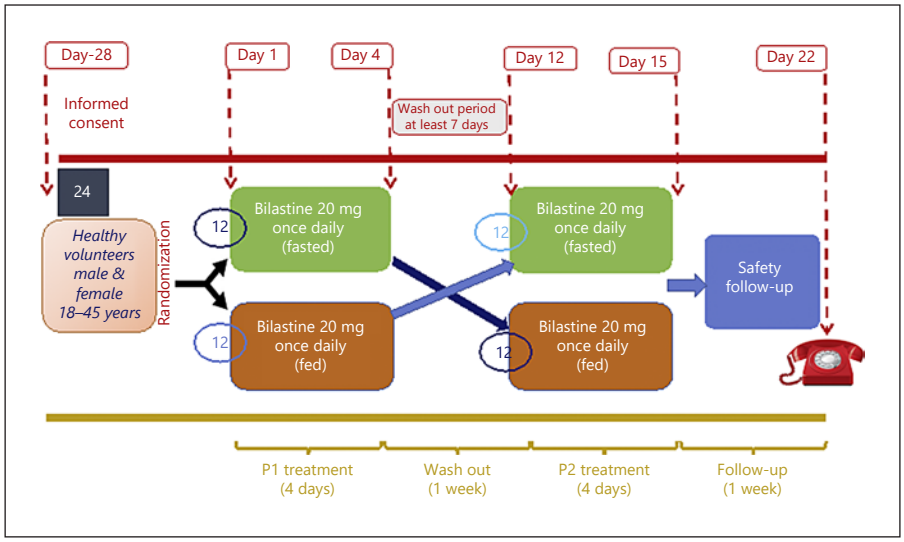

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Fig. 1. Study design scheme.

acetaminophen [paracetamol] for short-term symptomatic treatment) within 2 weeks prior to taking the study medication, including over-the-counter products (including natural food supplements, vitamins, and medicinal plant products); positive test results for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus; positive results for abuse drugs in urine test or ethanol in breath test; background or clinical evidence of chronic disease; rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption; pregnant or breast-feeding women; smokers (use of any tobacco product, including smokeless tobacco, nicotine patches, electronic cigarettes, etc.) within 6 months prior to the study medication intake; participation in another clinical drug trial during the previous 3 months; blood donation within 4 weeks of inclusion in the study; mental or legal incapacity at screening; unwillingness or inability to follow the procedures outlined in the protocol; history of difficulty in swallowing; positive dermographism or any other condition that, in the investigator's opinion, may have jeopardized the trial execution.

Fasting and Fed Conditions

Subjects in the fed arm of the study received a moderate-fat breakfast 30 min before each bilastine dose. This comprised whole milk (200 mL), white sugar (7 g), bread (40 g), toast (34 g), olive oil (10 mL), and ham (30 g) (approximately 480 kcal [144 kcal as fat], 15.83% protein, 54.17% carbohydrate, and 30.0% fat). Fruit or fruit juices were not allowed.

Subjects in the fasting arm of the study received the daily bilastine dose after a minimum of 10 h since the last food intake. On days 1 and 4, all subjects received a snack 4 h after bilastine administration, lunch 6 h post-medication, and another snack 10 h post-medication. Water was not permitted from 1 h before until 2 h after administration of bilastine.

Pharmacokinetic and Pharmacodynamic Evaluations

Recruited subjects attended the clinic by 7 p.m. the day prior to the first treatment day (day −1) and remained hospitalized until 12 h after the first bilastine dose (day 1). They returned at 24 h (morning of day 2) and 48 h (morning of day 3) for subsequent doses and monitoring and were then hospitalized again by 7 p.m. on day 3 until 12 h after the fourth dose (day 4). Participants returned for clinical and safety evaluation 24 h after the fourth dose (day 5).

On day 1 and day 4 of each crossover treatment period, skin reactivity and itching sensation were evaluated, and blood samples were collected. The safety and tolerability of bilastine were also assessed, including systolic and diastolic blood pressure, heart rate, ECG, and recording of adverse events.

On day −1, all participants were randomized to one of two extraction groups (group A or group B), which determined the time points for blood sampling in each crossover period. Blood collection and plasma preparation procedures were approved by the analytical laboratory before starting the study. The extraction of blood samples for the determination of bilastine plasma concentrations was performed on all volunteers. Five samples were collected from each subject on days 1 and 4 of each crossover period. In group A, samples were collected at baseline (predose) and +0.5, +2, +6, and +12 h post-bilastine administration; in group B, samples were collected at baseline (predose) and +1, +4, +9, and +24 h post-bilastine administration. A cannula was placed in the forearm to permit repeated sampling. Drug plasma concentrations were determined under Good Laboratory Practices by Anapharm Europe S.L.

Skin reactivity test and subjective evaluation of itching were conducted at baseline (predose) and +0.5, +1, +2, +4, +6, +9, +12, and +24 h after the first and last bilastine doses in each experimental period. The skin reactivity test involved intradermal injection of 0.05 mL of a histamine solution (100 mg/mL) in the ventral forearm. Each ventral forearm (right and left) was divided into four zones based on proximity to the main body mass (proximal and distal) and to the midline of the body (external vs. internal). Each histamine injection was performed in a different zone, randomly assigned, leaving a minimum distance of 2.5 cm between different evaluations. The application was performed by inserting the needle (tuberculin syringe) tip at a 45° angle and moving it forwards and upwards. The wheal and flare surfaces induced were measured 15 min after histamine injection, drawing the contours

Table 1. Demographic details and baseline vital signs of randomized subjects ($n = 24$)

Parameter	Mean	SD	Median	Minimum	Maximum
Age, years	27.29	4.89	26	19	40
Body weight, kg	66.52	10.14	63.25	52.00	91.00
Height, cm	169.29	8.57	168.50	152.00	182.00
BMI: Quetelet's index, kg/m^2	23.18	1.97	22.60	20.50	27.70
Systolic BP, mm Hg	118.21	12.19	117	100	139
Diastolic BP, mm Hg	62.04	6.63	10.69	51	75
Heart rate, bpm	69.96	10.02	69.50	52	92
Temperature, °C	35.94	0.43	36.05	35.30	36.70

BMI, body mass index; BP, blood pressure; bpm, beats per minute; SD, standard deviation.

with a permanent marker pen onto a transparent film, and quantifying the surface area using Visitrak System™. The left and right arms were used alternately for successive evaluations.

The intradermal injection of histamine induces a wheal and flare response. In this study, wheal and flare surface areas were measured on days 1 and 4 in each group and during each crossover period (fasting and fed conditions). The primary endpoint was the change from baseline in the mean area under the curve (AUC) by time over 24 h ($AUC_{0-24\,h}$) of the wheal and flare surface areas on days 1 and 4 under fasting and fed conditions.

The efficacy of bilastine was assessed as the ability to reduce wheal and flare areas (percentage of reduction in these areas) versus baseline values at each time point. The curves were built with the percentage of reduction of wheal and flare areas by time, both before (baseline curve) and after bilastine administration, and the mean change in AUC was calculated as the main outcome.

The itching sensation was evaluated 5 min after each histamine application using a visual analog scale. This consisted of a 100-mm horizontal line on which subjects marked a vertical line at the point corresponding to their subjective itching sensation. The left end of the line corresponded to "no itching" and the right end to "very much itching." The recorded score was the distance in millimeters from the left end to the subjects' mark.

Safety Assessment

All adverse events occurring after the first study medication intake and within a week after the last dose were considered treatment-emergent adverse events (TEAEs). The investigator assessed the severity of any adverse event and likely causality. Biochemical and hematological laboratory tests were conducted and ECG and vital signs recorded at initial screening and the end of the study (24 h after the last bilastine dose of the second crossover period).

Statistics

The study sample size was calculated considering a variation coefficient of 25% for the primary endpoint and a significance level of 5%. A sample size of 22 subjects provided a power of 80% for detecting a minimum difference between treatments of 15%. Because of the high risk of dropouts as a result of the prolonged study duration, it was decided to increase the sample size to 24 subjects.

Statistical analysis and data management were performed using IBM-SPSS (version 22.0). The default summary statistics for quantitative variables were the number of observations, mean, standard deviation, median, minimum, and maximum. For qualitative variables, the number and percentage of patients with nonmissing data per category were the default frequency tabulation.

Each of the variables obtained in the objective skin reactivity evaluations were evaluated by means of two-way analysis of variance (ANOVA) of repeated measures, considering the factors of treatment and time. The analysis was performed in two different ways:

- Expressing the data as percentage reduction with respect to baseline values, to compare $AUC_{0-24\,h}$ of day 1 and day 4 under fasting and fed conditions;
- Expressing the data as direct values, in order to obtain information on the possible effect of the time course.

The four AUCs for each individual (days 1 and 4, fasting and fed) were evaluated by means of two-way ANOVA of repeated measures, considering day and food. This was used to evaluate whether the change between day 1 and day 4 was similar with and without food.

The second analysis involved a three-way ANOVA; the factors being time, day, and food. When statistically significant differences were detected in a time factor, a detailed analysis was performed evaluating the differences between groups at each evaluation time and the differences between evaluation times after each group, using a simple-main-effects omnibus test and pairwise comparisons.

For all statistical analyses, the level of significance was set at 5% (alpha value 0.05), two-sided.

Results

Study Population

Among the 41 subjects screened for this trial, 29 met the selection criteria. Seven subjects were excluded for personal reasons, three for positive dermographism, and two for altered laboratory tests. Twenty-four subjects (12 men and 12 women), all Caucasian, were randomized and 23 completed the study. One subject withdrew from the study after the first treatment period, for personal reasons. Demographic details and baseline vital signs for the 24 randomized subjects are presented in Table 1. None of the randomized subjects were smokers. With regard to alcohol consumption, 13 subjects did not drink at all and

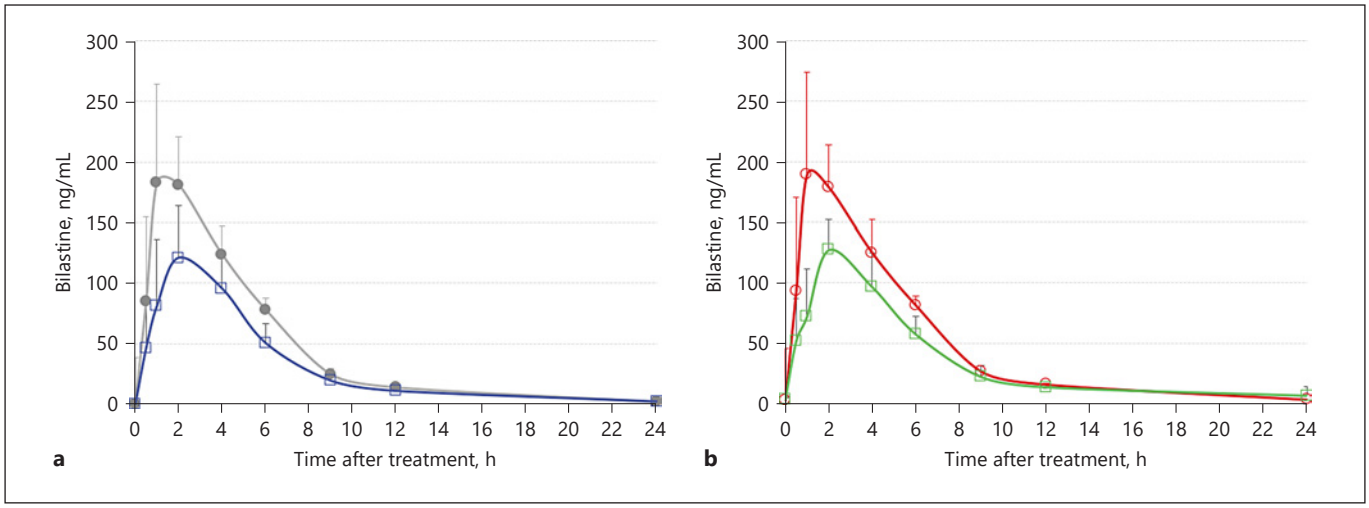

Fig. 2. Bilastine plasma concentrations (mean ± standard deviation) on day 1 in fasting (grey line) and fed (blue line) subjects (**a**) and on day 4 in fasting (red line) and fed (green line) subjects (**b**).

the remaining 11 subjects consumed a maximum of 17.5 g alcohol/day (mean 6.15 g/day). Regarding the consumption of xanthines (tea, coffee, chocolate, etc.), 20 subjects consumed xanthines daily (mean 6 units/week). The only concomitant medication used during the study was acetaminophen for a headache in one subject and nasal congestion in another.

Pharmacokinetic Evaluation

In this study, moderately fatty food had a significant effect on the pharmacokinetics of oral bilastine 20 mg. On day 1, the mean maximum plasma concentration (C_{max}) of bilastine was reduced by 34.27% with food, from 183.13 ± 70.34 ng/mL (fasting) to 120.38 ± 41.25 ng/mL (fed) (Fig. 2a). The mean plasma $AUC_{0-24\,h}$ of bilastine was reduced by 32.72%, from 1,037.23 (fasting) to 697.82 ng×h/mL (fed), and the mean time to C_{max} was extended from 1 h to 2 h postdose. Similarly, on day 4, the mean C_{max} and plasma $AUC_{0-24\,h}$ of bilastine were reduced by food, from 189.46 ± 77.31 (fasting) to 126.78 ± 23.51 ng/mL (fed; 33.08% reduction), and from 1,088.21 (fasting) to 774.05 ng×h/mL (fed; 28.87% reduction), respectively, while the time to C_{max} was extended from 1 to 2 h postdose (Fig. 2b).

Pharmacodynamic Evaluation

Skin Reactivity Test: Wheal Area

The percentage inhibition of wheal area (compared with baseline) was statistically significantly greater in fasting subjects than fed subjects at 30 min ($p < 0.05$) and 1 h ($p < 0.001$) after the first dose of bilastine. However, this delay in onset of action of bilastine in the fed group was brief, and the profiles of wheal inhibition in fasting and fed subjects on day 1 were broadly the same (Fig. 3a), with no statistically significant differences between both groups from 2 h after bilastine administration and onwards. Peak inhibition, which indicates the maximum effect of bilastine, was 75.2% and occurred at 4 h under fasting conditions, compared with 75.1% at 6 h under fed conditions. In both groups, the percentage inhibition at 24 h, compared with baseline, remained statistically significant: 41.5% ± 12.1 fasting ($p < 0.001$) versus 40.3% ± 15.4 fed ($p < 0.001$).

On day 4, there was no statistically significant difference between the percentage of wheal area inhibition from baseline at any time point under fasting versus fed conditions (Fig. 3b). Peak inhibition was 73.3% at 12 h postdose under fasting conditions and 76.6% at 9 h postdose under fed conditions.

ANOVA evaluation (1-, 2-, and 3-way) failed to identify any statistically significant effect of food on the percentage inhibition of wheal area in the skin reactivity test. The two-way ANOVA (day/food) applied to the mean AUC of percentages of reduction revealed a statistically significant effect of the day factor ($p = 0.004$) but not the food factor ($p = 0.415$) nor the interaction day × food factor ($p = 0.196$).

Skin Reactivity Test: Flare Area

The profiles of percentage inhibition of flare area from baseline were substantially the same under fasting and fed

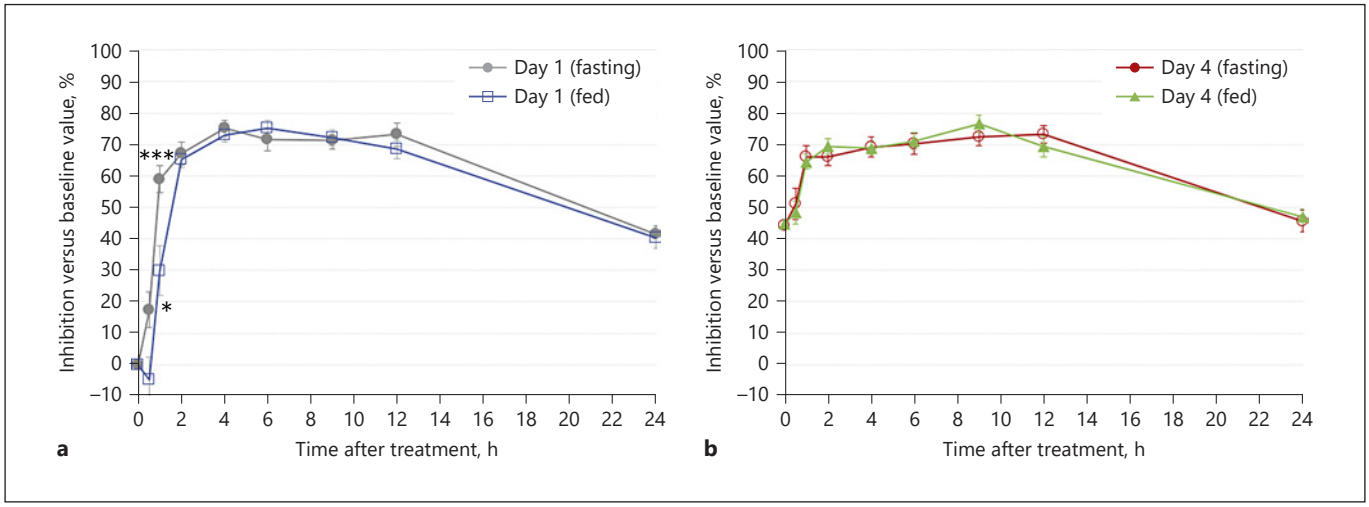

Fig. 3. Percentage wheal inhibition from baseline to 24 h after the first dose of bilastine (day 1), fasting (grey line) or fed (blue line), (**a**) and the last dose of bilastine (day 4), fasting (red line) or fed (green line) (**b**). Statistically significant differences between fasting and fed conditions on day 1. *$p < 0.05$ and ***$p < 0.001$.

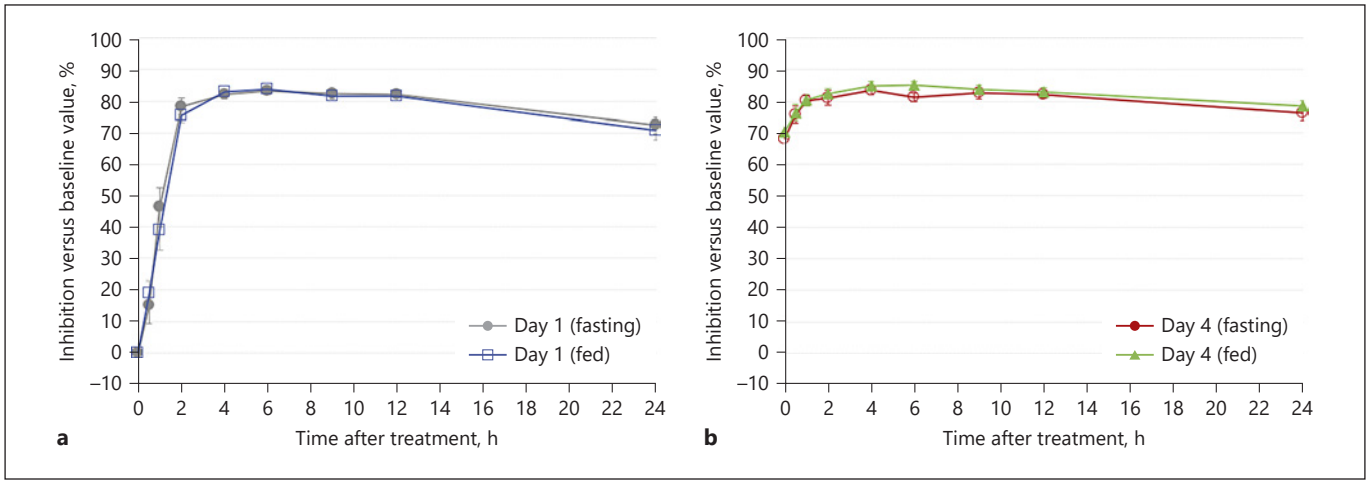

Fig. 4. Percentage flare inhibition versus baseline to 24 h after the first dose of bilastine (day 1), fasting (grey line) and fed (blue line), (**a**) and the last dose of bilastine (day 4), fasting (red line) or fed (green line) (**b**).

conditions, on both day 1 (Fig. 4a) and day 4 (Fig. 4b). The mean maximum effect of bilastine ranged from 83.3% to 84.2% and occurred between 4- and 6-h postdose in subjects in both groups (fasting and fed) and on both days (days 1 and 4). This antihistamine effect was well maintained at 24 h postdose on both days.

ANOVA evaluation (1-, 2-, and 3-way) failed to identify any statistically significant effect of food on the percentage inhibition of flare area in the skin reactivity test. The two-way ANOVA (day/food) applied to the mean AUC of percentages of reduction revealed a statistically significant effect of the day factor ($p < 0.001$) but not the food factor ($p = 0.933$). The interaction day × food factor was statistically significant ($p = 0.025$).

Skin Reactivity Test: Subjective Assessment of Itching

Compared with baseline values, there were statistically significant reductions ($p < 0.01$) in itching, under both fed and fasting conditions, from 2 to 12 h postdose on day 1. On day 4, the reductions were statistically significant at

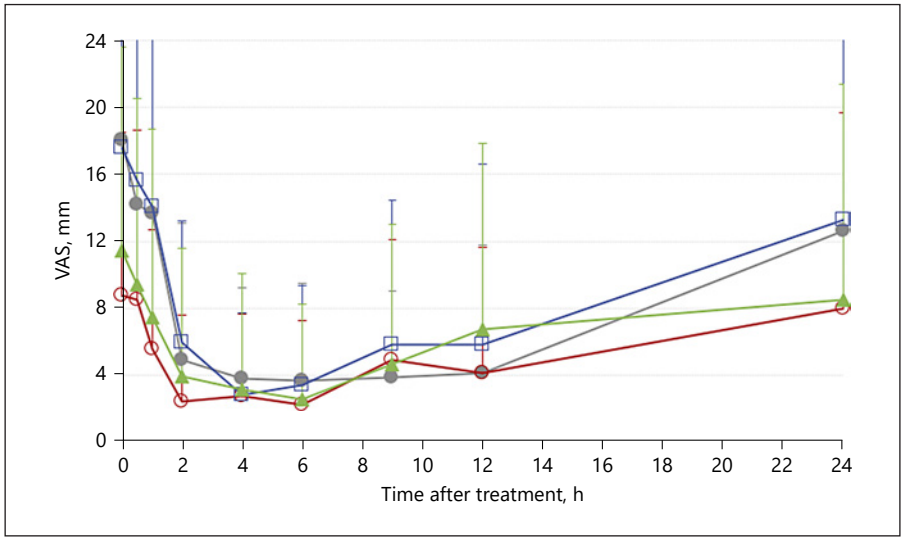

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Fig. 5. Subjective assessment of itching on a visual analog scale (VAS; 0 = no itching, 100 = worst itching), mean ± standard deviation, over a 24-h period after oral bilastine 20 mg, in fasting subjects on day 1 (grey line), fed subjects on day 1 (blue line), fasting subjects on day 4 (red line) and fed subjects on day 4 (green line).

all postdose time points from 0.5 to 24 h under both conditions (Fig. 5).

Food had no statistically significant effect on itching sensation, as determined by ANOVA evaluation (1-, 2-, or 3-way). The two-way ANOVA (day/food) applied to the mean AUC of percentages of reduction revealed a statistically significant effect of the day factor ($p = 0.011$) but not the food factor ($p = 0.448$) nor the interaction day × food factor ($p = 0.850$).

Safety

Five TEAEs were recorded in five different subjects during the study: mild dyspnea in one subject on day 1 in the fasting group; mild nasal congestion in one subject on day 4 in the fasting group; mild vomiting in one subject on day 1 in the fed group; and headache in two subjects (1 mild, 1 moderate) on day 1 in the fed group. Acetaminophen was administered for the cases of moderate headache and nasal congestion. The case of nasal congestion was considered unrelated to bilastine administration, while the other 4 cases were considered possibly related. All TEAEs resolved without consequences.

No clinically significant changes were observed in laboratory tests (hematology and biochemistry) carried out during the study. Changes observed in vital signs (systolic and diastolic blood pressure and heart rate) did not show any clinically relevant abnormalities, and all parameters remained within the normal range. No clinically significant changes were observed in ECG data recorded during the study, neither did physical examinations show any clinically important changes.

Discussion

This study compared the pharmacokinetic and pharmacodynamic profiles of oral bilastine 20 mg per day under fed and fasting conditions in healthy volunteers. Overall, the pharmacokinetic difference observed between both conditions (an $AUC_{0-24\,h}$ reduction of about 33% with fed vs. fasting on days 1 and 4 [steady state]) only led to a short delay in the onset of action to 1-h postadministration with respect to wheal inhibition on the first day of treatment. No difference was found in flare inhibition or itching sensation.

Previous studies have evaluated the pharmacokinetics of bilastine coadministered with or without food, obtaining similar results to the present study. A reduction of 30% and 25% in bioavailability was observed when bilastine was taken with high-fat and low-fat food, respectively, relative to fasting conditions [16].

In this study, the pharmacodynamic profile was evaluated as the wheal and flare response after an intradermal injection of histamine. Four previous wheal and flare clinical studies have been performed in healthy Caucasian or Japanese volunteers after administration of bilastine 20 mg under fasting conditions [5, 17–19]. In two of these studies, the wheal and flare response was induced by histamine using the skin prick-test method [5, 17], and, in the other two studies, the wheal and flare response was induced by intradermal injection of histamine 5 μg [18, 19]. In all of these studies, no remarkable differences were seen regarding onset of action, maximum effect, and duration of action. When the wheal and flare pharmaco-

dynamic effect was assessed in addition to the 24-h pharmacokinetic profile in healthy volunteers, a hysteresis phenomenon was observed [5, 17]. That means bilastine remains highly effective even when its plasma concentration is very low. In other words, the marginal decrease in efficacy is not in line with the much faster decline in plasma concentrations. Recently, the long duration of antihistaminic effect with bilastine, albeit at low plasma concentrations, has been shown to be related to its long residence time at the human histamine H_1 receptor [20]. This could explain why, in the current study, although the AUC is decreased by around 30% when bilastine is coadministered with food, the pharmacodynamic effect is only slightly altered in the first hour on day 1 but remains similar during the remaining days of treatment, independent of the fasting or fed condition.

The methodology used in this study is well documented, and the study design (crossover, young volunteers) was chosen to minimize interindividual variability. In fact, baseline values obtained for wheal and flare areas did not differ between both treatment sequences, showing similar conditions for each treatment period. Wheal and flare results are normally considered with caution because some data suggest that histamine challenge tests do not necessarily correlate with clinical responses [21]. However, at the same time, some authors describe the wheal and flare response as the "best indicator we have of the effectiveness of H_1 antihistamines in clinical practice" [22]. In fact, a recent study demonstrated that efficacy in chronic spontaneous urticaria could be predicted by >75% inhibition of the histamine wheal at 24 h after administration of an antihistamine [23].

Prior to the current study, a pharmacokinetic-pharmacodynamic modeling study of the antihistaminic activity of bilastine was performed, extracting data from 12 different clinical trials [15]. Simulations performed showed that the pharmacodynamics of bilastine remained unchanged despite the decreased bioavailability with food. The present study corroborates these findings at steady state since no differences in wheal and flare $AUC_{0-24\,h}$ between the fed and fasting conditions were observed on day 4. Only a small difference in the reduction of wheal area by bilastine was observed in the first hour on day 1 of treatment. Although the bilastine European Summary of Product Characteristics (SmPC) advises that bilastine should be taken without food (i.e., 2 h before or 1 h after food) [10], this advice was based on evidence from previous in vitro and in vivo pharmacokinetic studies [16]. The results of this study suggest that interaction between bilastine and food is not clinically relevant as a whole. Nevertheless, if rapid relief of symptoms is needed, taking the first dose without food may be better than taking it with food.

Fexofenadine and bilastine are quite similar in some pharmacological aspects, including alterations in their pharmacokinetic profile when administered with food. Similar to bilastine, fexofenadine plasma AUC and C_{max} are reduced by 17% and 11%, respectively, for a capsule formulation, and by 24% and 25%, respectively, for a tablet formulation, when the drug is administered 30 min after a high-fat breakfast versus a 10-h fast [24]. In addition, fexofenadine and bilastine are non-brain-penetrating antihistamines and zwitterions, display similar binding to H_1-receptors, have similar acid-base dissociation constants, have larger molecular weights than other nonsedating antihistamines, and exhibit the hysteresis phenomenon [1, 25, 26]. However, in the case of fexofenadine, drug-food interactions are not reflected with a warning in its SmPC; therefore, taking the current study results into consideration, one can argue that maybe the same should also apply to bilastine.

The effects of food on the pharmacokinetic profiles of other second-generation H_1-antihistamines are variable. The plasma AUC for cetirizine appears to be unaffected by food [27], while that for ebastine [28] and rupatadine [29] may be increased. For desloratadine, in one early study in healthy volunteers, food had no significant impact on the drug´s pharmacokinetic profile [30]. However, plasma AUC and C_{max} were reduced by over 30% when food was coadministered in most subjects in a Chinese study, in which almost all subjects (97.8%) were desloratadine-extensive metabolizers [31].

None of the previously mentioned studies of the interaction of food with other second-generation antihistamines measured pharmacodynamic activity. Thus, the present study makes an important contribution to knowledge about the clinical relevance of food-drug pharmacokinetic interactions, at least for bilastine. Although the current study was not designed to evaluate safety and tolerability, no serious adverse events were recorded during drug administration and bilastine was well-tolerated, with no relevant changes in vital signs, hematology, or biochemistry, as previously shown in other studies [2, 3].

Conclusions

The pharmacokinetic interaction of bilastine with food does not imply a significant reduction of its peripheral antihistaminic efficacy. Despite a slight delay in onset

of action on the first treatment day, the global clinical efficacy of bilastine is not affected by coadministration with food.

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Statement of Ethics

This study (EudraCT: 2018-000913-19) was conducted following the international recommendations for clinical research gathered in the last revision of the Declaration of Helsinki and according to the Guidelines for Good Clinical Practice (GCP) and the current applicable Spanish and European legislation. Independent Ethics Committee approval and Spanish Agency authorization were obtained. Prior to admission, all subjects provided written informed consent and were advised that they were free to withdraw from the study at any time without specifying a reason. The study design and methodology ensured subject confidentiality.

Conflict of Interest Statement

Jimena Coimbra, Montserrat Puntes, Ignasi Gich, Joan Martínez, Pol Molina, and Rosa Antonijoan; they are part of the research team (CIM. Hospital Sant Pau). Cristina Campo and Luis Labeaga are employees of FAES.

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Author Contributions

Rosa Antonijoan and Jimena Coimbra participated in the design of the trial. Jimena Coimbra, Montserrat Puntes, Joan Martínez, and Pol Molina conducted the research and investigation process. Ignasi Gich contributed to data analysis. Jimena Coimbra and Rosa Antonijoan revised the manuscript. Luis Labeaga and Cristina Campo designed the trial and contributed to the writing and revision of the paper.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1 Kawauchi H, Yanai K, Wang DY, Itahashi K, Okubo K. Antihistamines for allergic rhinitis treatment from the viewpoint of nonsedative properties. Int J Mol Sci. 2019;20(1):21.
2 Ridolo E, Montagni M, Bonzano L, Incorvaia C, Canonica GW. Bilastine: new insight into antihistamine treatment. Clin Mol Allergy. 2015;13(1):1.
3 Church MK, Tiongco-Recto M, Ridolo E, Novák Z. Bilastine: a lifetime companion for the treatment of allergies. Curr Med Res Opin. 2020;36(3):445–54.
4 Jauregizar N, de la Fuente L, Lucero ML, Sologuren A, Leal N, Rodríguez M. Pharmacokinetic-pharmacodynamic modelling of the antihistaminic (H1) effect of bilastine. Clin Pharmacokinet. 2009;48(8):543–54.
5 Togawa M, Yamaya H, Rodríguez M, Nagashima H. Pharmacokinetics, pharmacodynamics and population pharmacokinetic/pharmacodynamic modelling of bilastine, a second-generation antihistamine, in Healthy Japanese Subjects. Clin Drug Investig. 2016;36(12):1011–21.
6 Rodríguez M, Vozmediano V, García-Bea A. Pharmacokinetics and safety of bilastine in children aged 6 to 11 years with allergic rhinoconjunctivitis or chronic urticaria. Eur J Pediatr. 2020;179(5):801–5.
7 Sádaba B, Gómez-Guiu A, Azanza JR. Oral availability of bilastine. Clin Drug Investig. 2013;33(5):375–81.
8 Crean C, Roupe K, Sologuren A. The pharmacokinetics of bilastine after single and 14 days once daily administration [abstract no. P252]. Basic Clin Pharmacol Toxicol. 2007;101(Suppl 1):148.
9 Lucero ML, Gonzalo A, Mumford R, Betanzos M, Alejandro A. An overview of bilastine metabolism during preclinical investigations. Drug Chem Toxicol. 2012;35 Suppl 1:18–24.
10 Faes Farma . Bilaxten (bilastine) 20 mg tablets, 10 mg orodispersible tablets and 2.5 mg/mL oral solution: EU summary of product characteristics. Faes Farma; 2020.
11 Bachert C, Kuna P, Zuberbier T. Bilastine in allergic rhinoconjunctivitis and urticaria. Allergy. 2010;65(s93):1–13.
12 Purohit A, Melac M, Pauli G, Frossard N. Twenty-four-hour activity and consistency of activity of levocetirizine and desloratadine in the skin. Br J Clin Pharmacol. 2003;56(4):388–94.
13 Denham KJ, Boutsiouki P, Clough GF, Church MK. Comparison of the effects of desloratadine and levocetirizine on histamine-induced wheal, flare and itch in human skin. Inflamm Res. 2003;52(10):424–7.
14 Clough GF, Boutsiouki P, Church MK. Comparison of the effects of levocetirizine and loratadine on histamine-induced wheal, flare, and itch in human skin. Allergy. 2001;56(10):985–8.
15 Rodriguez M, Leal N, Campo C. Lack of influence of food in the pharmacodynamic profile of bilastine in humans [abstract no. 1085]. Allergy. 2018;73(S105):566.
16 Church MK. Safety and efficacy of bilastine: a new H1-antihistamine for the treatment of allergic rhinoconjunctivitis and urticaria. Expert Opin Drug Saf. 2011;10(5):779–93.
17 Church MK. Comparative inhibition by bilastine and cetirizine of histamine-induced wheal and flare responses in humans. Inflamm Res. 2011;60(12):1107–12.
18 Antonijoan R, Coimbra J, García-Gea C, Puntes M, Gich I, Campo C, et al. Comparative efficacy of bilastine, desloratadine and rupatadine in the suppression of wheal and flare response induced by intradermal histamine in healthy volunteers. Curr Med Res Opin. 2017;33(1):129–36.

19 García-Gea C, Martínez-Colomer J, Antonijoan RM. Comparison of peripheral and central effects of single and repeated oral dose administrations of bilastine, a new H1 antihistamine: a dose-range study in healthy volunteers with hydroxyzine and placebo as control treatments. J Clin Psychopharmacol. 2008; 28(6):675–85.
20 Bosma R, van den Bor J, Vischer HF. The long duration of action of the second generation antihistamine bilastine coincides with its long residence time at the histamine H(1) receptor. Eur J Pharmacol. 2018;838:107–11.
21 Devillier P, Bousquet J. Inhibition of the histamine-induced weal and flare response: a valid surrogate measure for antihistamine clinical efficacy? Clin Exp Allergy. 2007;37(3): 400–14.
22 Church MK, Maurer M. H1-antihistamines and urticaria: how can we predict the best drug for our patient? Clin Exp Allergy. 2012; 42(10):1423–9.
23 Sánchez J, Zakzuk J, Cardona R. Prediction of the efficacy of antihistamines in chronic spontaneous urticaria based on initial suppression of the histamine- induced wheal. J Investig Allergol Clin Immunol. 2016;26(3): 177–84.
24 Stoltz M, Arumugham T, Lippert C, Yu D, Bhargava V, Eller M, et al. Effect of food on the bioavailability of fexofenadine hydrochloride (MDL 16455A). Biopharm Drug Dispos. 1997;18(7):645–8.
25 Yanai K, Yoshikawa T, Yanai A, Nakamura T, Iida T, Leurs R, et al. The clinical pharmacology of non-sedating antihistamines. Pharmacol Ther. 2017;178:148–56.
26 Schoepke N, Church MK, Maurer M. The inhibition by levocetirizine and fexofenadine of the histamine-induced wheal and flare response in healthy Caucasian and Japanese volunteers. Acta Derm Venereol. 2013;93(3): 286–93.
27 Barnes CL, McKenzie CA, Webster KD, Poinsett-Holmes K. Cetirizine: a new, nonsedating antihistamine. Ann Pharmacother. 1993; 27(4):464–70.
28 Pentikis HS, Huang MY, Dorr MB, Heald DL. The effect of food on the bioavailability of ebastine. Am J Ther. 1997;4(2–3):80–4.
29 Solans A, Carbó ML, Peña J, Nadal T, Izquierdo I, Merlos M. Influence of food on the oral bioavailability of rupatadine tablets in healthy volunteers: a single-dose, randomized, open-label, two-way crossover study. Clin Ther. 2007;29(5):900–8.
30 Gupta S, Banfield C, Affrime M, Marbury T, Padhi D, Glue P. Oral bioavailability of desloratadine is unaffected by food. Clin Pharmacokinet. 2002;41 Suppl 1:7–12.
31 Wang T, Zhang K, Li T, He L, Xie H, Jiang X, et al. Prevalence of desloratadine slow-metabolizer phenotype and food-dependent pharmacokinetics of desloratadine in healthy Chinese volunteers. Clin Drug Investig. 2015; 35(12):807–13.