

Oral Availability of Bilastine

B. Sádaba · A. Gómez-Guiu · J. R. Azanza ·
I. Ortega · R. Valiente

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Abstract

Background and Objective Bilastine (BilaxtenTM) is a novel non-sedating H₁ receptor antagonist (antihistamine) developed in the dosage form of oral tablets and indicated for the treatment of allergic rhinitis (seasonal and perennial) and urticaria. Several clinical trials have been performed in order to determine the efficacy and safety of bilastine. The aim of this trial was to study the absolute oral bioavailability of bilastine in humans.

Methods Twelve male and female adults were recruited into a single centre for a randomized, single-dose, open-label, controlled two-arm crossover study with a minimum 14-day washout period between the two single doses. Two single doses of bilastine were administered: a 20-mg oral tablet and a 10-mg intravenous formulation. Blood and urine samples were collected between 0 and 72 h post each administration. The clinical trial was carried out under quality assurance and quality control systems with standard operating procedures to ensure that the study was conducted and data generated in compliance with the protocol, Good Clinical Practice standards, International Conference on Harmonisation and other applicable regulations.

Results Oral bioavailability of bilastine was 60.67 % with a 90 % parametric confidence interval of 53.79–67.56.

Trial Registration ClinicalTrials.gov identifier: NCT01124123.

B. Sádaba (✉) · A. Gómez-Guiu · J. R. Azanza
Clinical Research Unit, Servicio de Farmacología Clínica,
Clínica Universidad de Navarra, c/Pío XII, n° 36,
31008 Pamplona, Navarra, Spain
e-mail: bsadaba@unav.es

I. Ortega · R. Valiente
Research, Development and Innovation Department,
FAES FARMA, S.A, Bilbao, Spain

The maximum bilastine concentration was measured 1.31 h after oral administration. Pharmacokinetic parameters were similar to those observed in previous studies. Tolerance to treatment was good, with no adverse events related to study medication.

Conclusion The absorption of bilastine after oral administration to healthy subjects was rapid. The absolute oral bioavailability was moderate.

1 Introduction

Bilastine is a novel second-generation H₁ receptor antagonist (antihistamine) developed for the treatment of symptomatic chronic urticaria, seasonal allergic rhinitis and perennial allergic rhinitis. Preclinical studies have demonstrated that bilastine is a highly selective and potent H₁-antihistamine. In vitro, bilastine displayed higher affinity for the histamine H₁ receptor than other histamine H₁ receptor antagonists such as cetirizine and fexofenadine [1, 2]. In addition to histamine H₁ receptor antagonism, bilastine has been shown to inhibit histamine and interleukin IL-4 release from human mast cells and peripheral blood granulocytes, in contrast to other H₁ antagonists, which enhanced the release of these inflammatory mediators from human mast cells [3].

The safety and efficacy of bilastine for the relief of allergic rhinitis symptoms have been confirmed in two pivotal clinical trials evaluating over 1,400 patients. Bilastine was found to be not inferior to the standard seasonal allergic rhinitis treatment with desloratadine or with cetirizine [4, 5]. Bilastine has also demonstrated therapeutic potential in the management of chronic idiopathic urticaria [6].

Bilastine has been shown to be rapidly absorbed after oral administration in humans, with a time to reach peak

concentration ($t_{\max}$) of 1–1.5 h and a half-life close to 10 h [7]. Bilastine is not significantly metabolised in humans and is largely eliminated unchanged both in urine and faeces [9]. In cell cultures (hepatocytes and liver microsomes) bilastine is not metabolised and does not inhibit or induce the activity of cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1 and 3A4 [8]. Its excretion was mostly faecal, with 67 % of the administered dose recovered in faeces, although urinary excretion was also detected (33.1 %) [9]. The pharmacokinetic profile of bilastine was not modified by age or sex [10].

Linear pharmacokinetics were observed within the dose range of 2.5–220 mg/day. Compartmental analysis showed that the pharmacokinetics of bilastine after oral administration followed a two-compartment model with first-order absorption and elimination (first-order absorption rate constant $K_a = 1.5 \text{ h}^{-1}$). The population pharmacokinetic estimates for clearance (CL), volume of distribution of the central (V_c) and peripheral (V_p) compartments and inter-compartmental clearance (Q) were 18.1 L/h, 59.2 L, 30.2 L and 1.59 L/h, respectively [11].

The coadministration of bilastine and grapefruit significantly reduced systemic bilastine exposure. Maximum concentration ($C_{\max}$) and total area under the plasma concentration-time curve (AUC) from time zero to infinity (AUC_{∞}) were 33 and 24 % lower, respectively, when 240 mL of grapefruit juice was administered with bilastine [12].

While several preclinical studies [2] and clinical trials of the efficacy, safety and pharmacokinetics (including mass balance analysis) of bilastine have been conducted [4–7, 9], none has evaluated the absolute oral bioavailability of this agent in humans.

The present study was designed to evaluate the bioavailability of bilastine after oral administration of a single dose (20 mg) to healthy subjects under dietary restrictions.

2 Methods

The protocol design of the study was based on the general criteria for bioavailability studies set out in the “Investigation of Bioavailability and Bioequivalence” guide (CPMP/EWP/QWP/1401/98) of the European Medicines Agency [13].

2.1 Subjects

Twelve healthy subjects, six males and six females, aged 18–24 years with body weight ranging from 50 to 80.6 kg and body mass index (BMI) between 19 and 25 kg/m² (Table 1), were enrolled in the trial. All subjects were non-smokers, and had no evidence of any clinically significant abnormalities at medical screening. Before the beginning

of the study and 7 days after its completion they were determined to be healthy by a medical history, a physical examination, an electrocardiogram and a blood chemistry test (including a complete blood count, electrolytes, glucose, protein and liver function). They were excluded if they had previously participated in another clinical trial or donated blood during the preceding 3 months, showed evidence of drug abuse in urine testing, were on continuous medication, had a previous history of surgery of the gastrointestinal tract, or had an electrocardiogram-corrected QT interval (QTc) >430 ms for males and QTc >450 ms for females, or heart rate less than 55 beats/min, respectively. The subjects must not have taken any prescription or over-the-counter drugs for at least 30 days prior to the study day. No caffeinated or alcoholic beverages were to be consumed at least 72 h prior to and during the study days. The subjects agreed not to ingest cranberries, grapefruit or any other citrus fruits, fruit juices and other fruit derivatives within 7 days prior to the first drug administration until last blood draw 72 h post-administration of the second period.

2.2 Study Design

The study was conducted at the Clinical Research Unit of the University Hospital of Navarra in compliance with Good Clinical Practice (GCP). The study was performed according to the revised Declaration of Helsinki. The Regional Ethics Committee (Pamplona, Spain) approved the study protocol. The protocol was also reviewed and approved by the Spanish Agency for Medicines and Health Products and registered at ClinicalTrials.gov (identifier: NCT01124123).

Each subject provided his or her written consent after comprehensive verbal and written information on aims and possible risks of the study.

This was a single-centre, randomized, open-label, single-dose, two-arm crossover controlled trial. Every subject received a single 20-mg bilastine oral tablet (BilaxtenTM, FAES FARMA, Bilbao, Spain) and a single 10-mg bilastine intravenous injection (IDD-Tech, Dardilly, France) over a 5-min period, with a minimum washout period of 14 days. The sequence of administration was determined by a randomization schedule in a balanced manner (blocks of six subjects).

Subjects fasted for 10 h prior to until 4 h after drug administration at approximately 8:00 am; water intake was not allowed during this interval. Subjects were confined to the clinical trial unit for the first 10 h after dosing. They received standard meals during both treatment periods. Meals were served at 4 h and between 6 and 8 h after dosing. During the study period, no medication was allowed unless required to treat any adverse event (AE).

Table 1 Demographic characteristics of subjects included in the study ($n = 12$)

Measure	Age (years)	Height (m)	Weight (kg)	BMI (kg/m ²)
Mean $\pm$ SD	20.8 $\pm$ 2.0	1.708 $\pm$ 0.093	65.9 $\pm$ 10.5	22.47 $\pm$ 1.85
Minimum	18.0	1.570	50	19.41
Maximum	24	1.850	80.6	25.40
Median	21.5	1.704	62	22.58

BMI body mass index

Some vital signs such as arterial blood pressure and heart rate were measured before dose administration and 2, 4 and 10 h post-dose. Subjects were questioned during blood extraction about potential AEs.

2.3 Sample Collection

After each drug administration, blood samples were drawn and urine samples were collected to measure bilastine concentration up to 72 h post-dose. Blood samples for determination of the concentrations of bilastine were collected (5 mL) predose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 7, 12, 24, 48 and 72 h after bilastine administration.

Blood was drawn from the antecubital vein, using a peripheral venous catheter or directly by venipuncture. Blood draws were made using a different venous access to that used for administering the drug. Samples of venous blood were obtained in 5-mL sodium heparin vacutainer tubes. Immediately after drawing the blood, the tube was gently turned upside down several times to mix the anti-coagulant with the blood. Within 1 h of drawing blood, the plasma fraction was separated from the formed elements by centrifugation for 15 min at 2,000 rpm in a refrigerated centrifuge (4 °C). The resulting plasma was rapidly separated and distributed in two aliquots of almost 0.3 mL, and immediately frozen at -20 °C.

Urine samples were collected for determination of bilastine at the following time intervals: 0–2, 2–6, 6–12, 12–24, 24–48 and 48–72 h after study drug administration. Subjects were instructed to void just prior to administration of the medication and to void at the end of each subsequent interval in order to collect the total urine volume for the interval. The urine sample prior to the 0–2 h collection served as the predose blank.

Urine was stored in a 24-h container after each micturition. The subjects kept the urine containers in a cool place, away from heat sources. Prior to dose administration (time 0), and at the end of each subsequent interval, total urine volumes were measured and two aliquots (25 mL each) were transferred to labelled, non-breakable polypropylene containers and stored at -20 °C.

Bilastine concentrations were measured by the analytical laboratory Anapharm Europe (Barcelona, Spain).

The analytical phase was conducted in compliance with International Conference on Harmonisation Good Laboratory Practice guidelines.

2.4 Analytical Methods

Bilastine concentrations were determined in heparinized human plasma by a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method using a solid-phase extraction procedure.

In brief, 500 μ L of each plasma or urine sample was spiked with internal standard (100 μ L of 500 ng/mL of trandolapril in water) and combined with 300 mL of water and 100 μ L of 1 % (v/v) trifluoroacetic acid. The sample was vortex-mixed and centrifuged for 1 min at 3,000 rpm and purified by solid-phase extraction procedure. The cartridges (IsoluteC8, EC; Biotage AB, Uppsala, Sweden) were processed subsequently with 2 mL of methanol and 2 mL of 0.1 % (v/v) trifluoroacetic acid. Thereafter, samples were transferred to the cartridges, and were washed with 2 mL of 0.1 % (v/v) aqueous trifluoroacetic acid. Finally, the sample was eluted with 2 mL of 5 mmol/L ammonium acetate in 90 % (v/v) aqueous methanol. The eluent was evaporated using a vacuum centrifuge (SpeedVac; Savant Instruments, Life Sciences International, Runcorn, UK) and the residue was reconstituted in 200 μ L of mobile phase (1 % [v/v] formic acid in 50 % [v/v] aqueous acetonitrile), vortex-mixed for 1 min and transferred into a polypropylene auto sampler vial.

LC–MS/MS analysis was performed using a Perkin-Elmer LC system combined with a Sciex API 3000 mass spectrometer equipped with a Turbo Ion Spray source (GenTech Scientific, Inc., Arcade, NY, USA). A 10- μ L aliquot of the reconstituted sample was injected using a reverse phase column (Waters XBridge, RP18, 3.5 μ m 2.1 $\times$ 30 mm for plasma and Waters XBridge, RP18, 3.5 μ m 4.6 $\times$ 50 mm for urine; Waters Corporation, Milford, MA, USA) at a temperature of 50 °C and a constant mobile phase flow of 0.15 mL/min. Mass transitions of 464 $\rightarrow$ 272 for bilastine and 431 $\rightarrow$ 234 for trandolapril were selected for quantification in multiple-reaction monitoring mode. The retention times were 0.7 min for bilastine and 0.9 min for trandolapril. The assay was validated over a linear range (0.2–400 ng/mL for plasma, and

5–500 ng/mL for urine) [11]. The lower limit of quantification was 0.2 ng/mL for plasma and 4.33 ng/mL for urine.

2.5 Data Analysis

$C_{\max}$, AUC from time zero to 72 h (AUC_{72}), AUC_{∞} , $t_{\max}$, terminal half-life ($t_{1/2}$) and cumulative amount of unaltered drug excreted in the urine (A_e) were calculated by non-compartmental methods. All calculations were carried out using WinNonlin Professional Version 5.3 (Pharsight Company, Palo Alto, CA, USA). AUC_{∞} was used to calculate the bioavailability of bilastine administered by oral route.

$C_{\max}$, AUC and A_e were normalized by dose (D).

Absolute bioavailability (F) was calculated as the ratio between the dose-normalized AUC_{∞} value obtained after oral administration ($AUC_{\infty, \text{oral}}$) and the dose-normalized AUC_{∞} value obtained after intravenous (iv) administration ($AUC_{\infty, \text{iv}}$), using the following equation:

$$F = (AUC_{\infty, \text{oral}} / \text{oral dose}) / (AUC_{\infty, \text{iv}} / \text{iv dose})$$

It was also possible to calculate absolute bioavailability with urine data as the ratio between dose-normalized A_e values, using the following equation:

$$F = (A_{e, \text{oral}} / \text{oral dose}) / (A_{e, \text{iv}} / \text{iv dose})$$

Renal clearance (CL_R) of bilastine was calculated using the following formula:

$$CL_R = A_{e, \text{last}} / AUC_{\text{last}}$$

where AUC_{last} is the area under the plasma concentration-time curve from time zero to time of the last measurable concentration of the last plasma sample with quantifiable concentrations of bilastine, and also the end of the last urine collection period, or the last time at which these values coincide.

2.6 Adverse Events

AEs were categorized as mild, moderate or severe. Subjects were questioned at each visit during blood extraction about potential AEs. Tolerability and safety were evaluated according to occurrence of AEs, physical examination results, ECGs and the periodic assessment of clinical laboratory values and vital signs. All the AEs were characterized by type, onset, duration, intensity and causality throughout the trial. Clinical and laboratory parameters of tolerability were evaluated in a descriptive manner (haematological parameter values and blood pressure, heart rate, respiratory rate and temperature). AEs were coded using MedDRA (Medical Dictionary for Regulatory Activities) version 13.0.

2.7 Statistical Analysis

Laboratory data, blood pressure, heart rate, respiratory rate and temperature were also presented with their descriptive parameters, which were evaluated using Student's *t* test for paired data, Wilcoxon's test for non-parametric samples, or analysis of variance (ANOVA) for repeated measures. The 90 % confidence interval (CI) for geometric mean ratios of the test and reference products was calculated, as recommended in previous guidelines [13]. Statistical significance was established at $p < 0.05$. The statistical analysis was done with SPSS version 15 (Lead Technologies Inc., Chicago, IL, USA).

3 Results

Twelve subjects participated in the study, six women and six men. Demographic characteristics were similar in all subjects, as can be seen from Table 1. All subjects completed both study arms.

The mean plasma concentration versus time profiles of bilastine after the single oral (20 mg) and intravenous (10 mg) doses are presented in Figs. 1 and 2. Bilastine cumulative urinary excretion data 72 h after the individualized administration of the two treatments are shown in Fig. 3.

The pharmacokinetic parameter values obtained after a non-compartmental pharmacokinetic analysis of the concentration-time profiles of bilastine in plasma and urine are presented in Table 2.

The bilastine $C_{\max}$ was measured 1.31 h after oral administration and 0.25 h after intravenous administration. The $t_{1/2}$ value obtained after oral administration was 9.05 ± 5.55 h (mean $\pm$ SD). The cumulative amount of unaltered drug excreted in urine over a period of 72 h related to dose (A_e/D) was slightly higher after bilastine intravenous administration (mean $\pm$ SD 0.66 ± 0.11) than after oral administration (mean $\pm$ SD 0.42 ± 0.24). CL_R was similar for both routes of administration, with an average value of 9.2 for oral administration and 8.3 L/h for intravenous administration (Table 2). The mean F value was 60.67 % with a 90 % parametric CI of 53.79–67.73. Bilastine bioavailability was also calculated from urinary data, obtaining similar values to those obtained with the plasma data. The mean value of absolute bioavailability was 63.61 % with a 90 % parametric CI of 48.58–78.63 (Fig. 3).

No serious AE was reported during the study, nor any other significant AE. Only one AE was reported by one subject during the study. One subject complained of gastroenteritis 44 h after oral administration of bilastine. No drug treatment was required. It was considered that it was

Fig. 1 Mean ($\pm$ SD) plasma concentration–time curves for bilastine following a single 20-mg oral dose and a single 10-mg intravenous dose

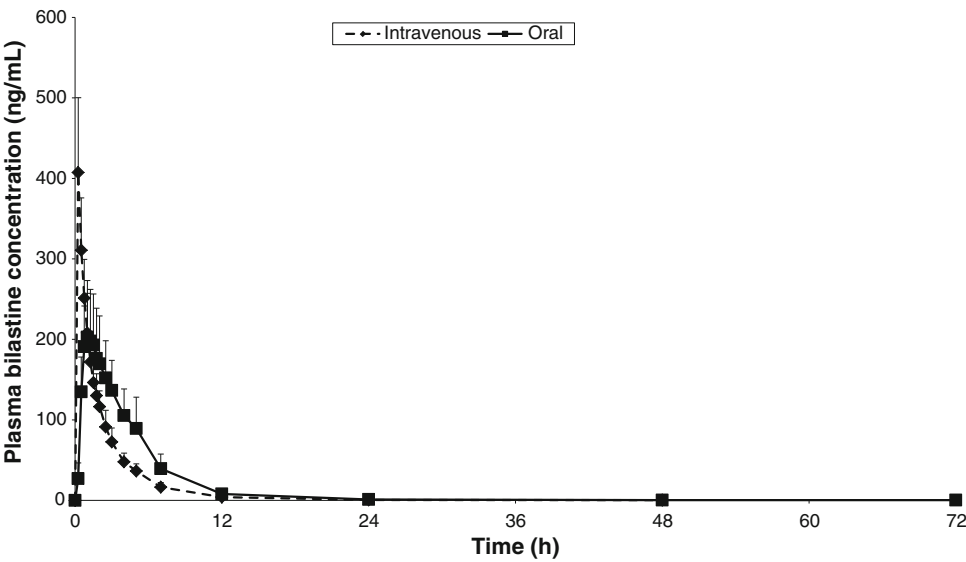


Fig. 2 Mean ($\pm$ SD) plasma concentration–time curves for bilastine following a single 20-mg oral dose and a single 10-mg intravenous dose on a semi-log scale

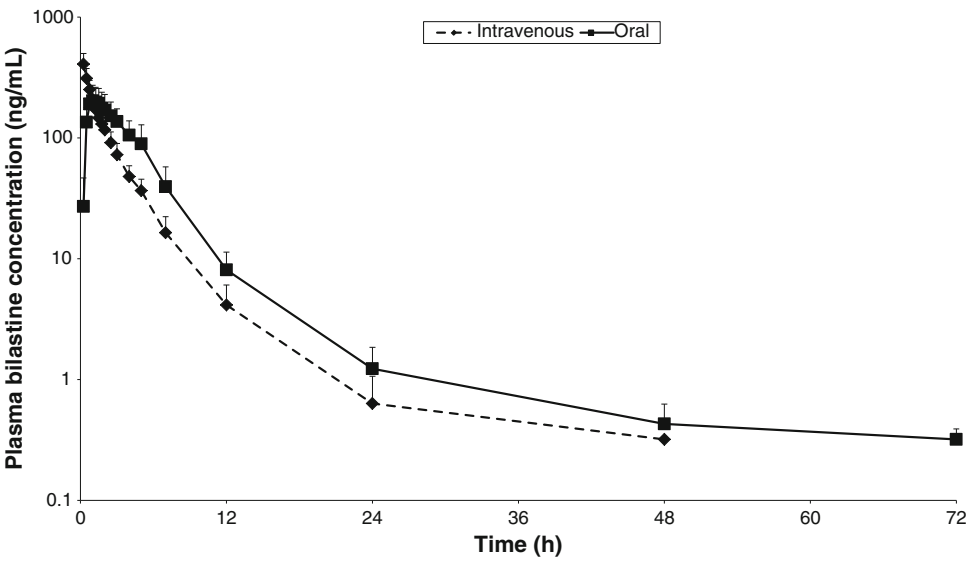


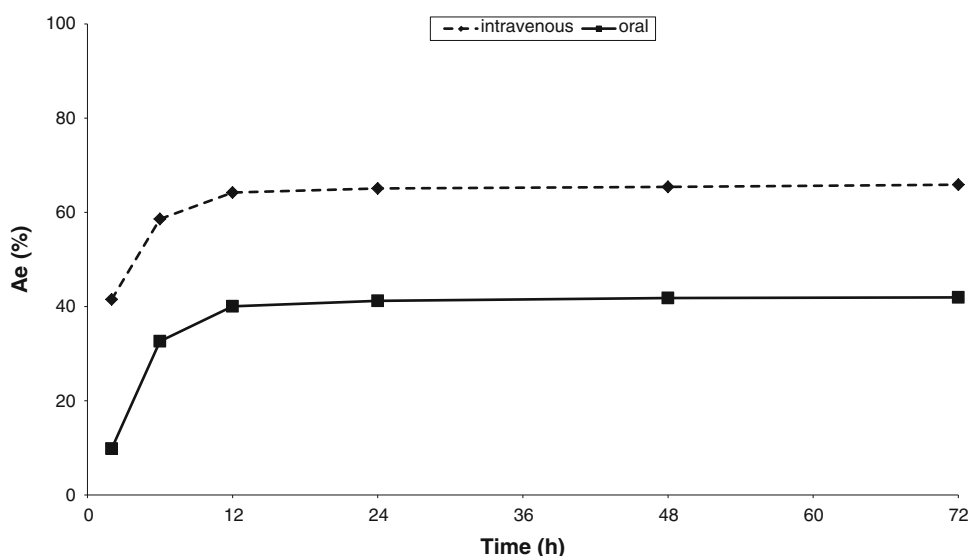
Table 2 Pharmacokinetic parameters of bilastine after a single oral dose of 20 mg and after a single intravenous dose of 10 mg ($n = 12$)

Parameter	Intravenous (10 mg)		Oral (20 mg)	
	Mean	SD	Mean	SD
AUC_{72}/D (ng·h/mL/mg)	82.04	14.22	49.70*	14.00
AUC_{∞}/D (ng·h/mL/mg)	82.32	14.25	49.87*	13.99
C_{max}/D (ng/mL/mg)	41.09	9.15	10.98*	3.10
t_{max} (h)	0.27	0.07	1.31	0.72
F (%)			60.67	14.50
Ae/D	0.66	0.11	0.42*	0.24
CL_R (L/h)	8.27	2.44	9.20	7.35

* $p < 0.001$ vs. intravenous, Student's t test

Ae cumulative amount of unaltered drug excreted in the urine, AUC area under the plasma concentration–time curve, AUC_{∞} AUC from time zero to infinity, AUC_{72} AUC from time zero to 72 h, CL_R renal clearance, C_{max} maximum plasma concentration, D dose, F bioavailability, t_{max} time to reach C_{max}

Fig. 3 Mean cumulative urinary excretion of bilastine following a single 20-mg oral dose and a single 10-mg intravenous dose. *Ae* cumulative amount of unaltered drug excreted in the urine



not related to the study medication, and was mild in intensity. No AE analysis was implemented as only one event was described.

4 Discussion

The purpose of this study was to determine the bioavailability of bilastine after oral administration of a single dose of 20 mg. A recently developed intravenous formulation of 10 mg was employed with this aim. Bilastine exhibits linear pharmacokinetics in healthy adult subjects after oral administration in the 2.5–220 mg dose range. Both the $C_{\max}$ and the AUC of bilastine increased proportionally to the administered doses. The $t_{1/2}$ and the other pharmacokinetic parameters of bilastine remained constant over the entire dose range studied [11]. Therefore, the AUC can be normalized by the dose, and the absolute bioavailability can be calculated.

Following intravenous administration, plasma concentrations of bilastine appeared to decline in a multiphasic manner and were measurable for up to 72 h post-dose in all subjects after oral and intravenous administration. The pharmacokinetic parameters obtained after single oral doses of 20 mg bilastine were similar to those previously reported in other studies. The values of $C_{\max}$ and AUC_{∞} are within the $C_{\max}$ (182.4–256.56 ng/mL) and AUC (876–1289.2 ng·h/mL) ranges obtained from previous single-dose studies [10–12].

The $t_{1/2}$ after 20 mg bilastine orally in a single dose was similar to that previously described [10–12].

The results of the study demonstrate that absolute oral bioavailability was 61 %, similar to that observed in dogs (42–69 %) [14]. The absolute bioavailability of bilastine

obtained from plasma concentration data is similar to that observed with urine data. This is due to the fact that bilastine is not metabolised in humans and is largely eliminated unchanged both in faeces (67 %) and in urine (33 %) [9].

Despite the fact that grapefruit does not have a relevant influence on the absorption of bilastine [12], the study was designed to prevent potential effects of diet on absorption of bilastine.

Bilastine is rapidly absorbed after oral administration, with a mean $t_{\max}$ value of 1.31 h. Although the absorption mechanism of bilastine has not yet been completely elucidated, it could reasonably be expected that there are no saturable transport mechanisms involved.

Bilastine was shown to be safe and effective at a therapeutic dose of 20 mg [15]. Moreover, studies in healthy subjects have demonstrated that doses of bilastine 20–100 mg are devoid of any sedative or cardiotoxic effects [16, 17] and do not significantly potentiate sedating adverse effects when interacting with alcohol [16].

5 Conclusion

Bilastine showed a moderate bioavailability after oral administration in healthy subjects. The absorption was rapid, with $C_{\max}$ being attained after 1.31 h. Pharmacokinetic parameters are similar to those observed in previous studies. Both bilastine 20 mg orally and 10 mg intravenously were well tolerated.

Conflicts of interest The study was sponsored by FAES FARMA, S.A. Spain. R. Valiente and I. Ortega are employees of FAES FARMA, S.A. Spain. All other authors have no other potential conflicts of interest.

References

1. Corcóstequi R, Labeaga L, Inneráriti A, Berisa A, Orjales A. In vivo pharmacological characterisation of bilastine, a potent and selective histamine H1 receptor antagonist. *Drugs R D*. 2006;7(4):219–31.
2. Corcóstequi R, Labeaga L, Inneráriti A, Berisa A, Orjales A. Preclinical pharmacology of bilastine, a new selective histamine H1 receptor antagonist: receptor selectivity and in vitro antihistaminic activity. *Drugs R D*. 2005;6(6):371–84.
3. Alvarez-Mon M, San Antonio E, Lucero M, Sanz E, Ledo F, De la Hera A. Bilastine a novel antihistamine that preferentially inhibits histamine and interleukin-4 release from human mast cells and granulocytes (abstract no. 1454). *Allergy*. 2009;64 (Suppl 90):555.
4. Bachert C, Kuna P, Sanquer F, et al. Comparison of the efficacy and safety of bilastine 20 mg vs desloratadine 5 mg in seasonal allergic rhinitis patients. *Allergy*. 2009;64(1):158–65.
5. Kuna P, Bachert C, Nowacki Z, et al. Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo for the symptomatic treatment of seasonal allergic rhinitis: a randomized, double-blind, parallel-group study. *Clin Exp Allergy*. 2009;39(9):1338–47.
6. Zuberbier T, Oanta A, Bogacka E, et al. Comparison of the efficacy and safety of bilastine 20 mg vs levocetirizine 5 mg for the treatment of chronic idiopathic urticaria: a multi-centre, double-blind, randomized, placebo-controlled study. *Allergy*. 2010;65(4):516–28.
7. Crean C, Roupe K, Sologuren A, Valiente R. The pharmacokinetics of bilastine after single and 14 days once daily administration (abstract no. P252). *Basic Clin Pharmacol Toxicol*. 2007;101(Suppl 1):148.
8. Sádaba Díaz de Rada B, Azanza Perea JR, Gomez-Guiu Hormigos A. Bilastine for the relief of allergy symptoms. *Drugs Today* 2011;47(4):251–62.
9. Sologuren A, Lucero ML, Valiente R, Charles H, Mair SJ. Human mass balance with [14C]-bilastine following oral administration to healthy volunteers (abstract no. TP85). *Basic Clin Pharmacol Toxicol*. 2009;105(Suppl. 1):106–7.
10. Roupe K, Sologuren A, Crean C, Valiente R. Effect of age and gender on the pharmacokinetics and pharmacodynamics of bilastine (abstract no. 70). *J Clin Pharmacol*. 2007;47(9):1198.
11. 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.
12. Crean C, Valiente R, Sologuren A, McLaverty D. Effect of grapefruit juice on the pharmacokinetics of bilastine (abstract no. 71). *J Clin Pharmacol*. 2007;47(9):1198.
13. Investigation of Bioavailability and Bioequivalence guide (CPMP/EWP/QWP/1401/98) of the EMA. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed Jul 2012.
14. Gonzalo A, Lucero ML, Orjales A. Preclinical pharmacokinetics of bilastine, a new antihistamine drug, in rats and dogs (abstract no. W4463). *AAPS J*. 2007;9(S2):2867.
15. Bilastine (F-96221-BMI). A novel antihistamine compound for the treatment of allergic rhinitis and chronic idiopathic urticaria. <http://www.faes.es>. Accessed Jul 2008.
16. García-Gea C, Martínez-Colomer J, Antonijoan RM, Valiente R, Barbanoj MJ. 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;28:675–8.
17. Sologuren A, Valiente R, Allison M, Tyl B. A Lack of significant effect of bilastine on ventricular repolarization: a thorough QT/QTc study [abstract no. 189]. *Allergy*. 2008;63(Suppl 88):85.

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