

Food Effects on the Pharmacokinetics of Doxylamine Hydrogen Succinate 25 mg Film-Coated Tablets

A Single-Dose, Randomized, Two-Period Crossover Study in Healthy Volunteers

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Abstract

Background: Doxylamine succinate, an ethanolamine-based antihistamine, is used in the short-term management of insomnia because of its sedative effects. The data available on the pharmacokinetic profile of doxylamine in humans are limited, notwithstanding that this drug has been marketed in European countries for more than 50 years. In fact, no data on the effect of food on the pharmacokinetic parameters of doxylamine are available.

Objective: The objective of this study was to evaluate the pharmacokinetic parameters of doxylamine following a single oral dose of doxylamine hydrogen succinate 25 mg in healthy human subjects under fed and fasting conditions.

Study Design: This was a single-center, randomized, single-dose, laboratory-blinded, two-period, two-sequence, crossover study.

Setting: The study was conducted in a phase I clinical unit.

Subjects and Methods: A single oral dose of doxylamine hydrogen succinate 25 mg (equivalent to 17.4 mg of doxylamine base) was administered to healthy volunteers under either fed conditions (high-fat, high-calorie food intake) or fasting conditions in each study period. The drug administrations were separated by a wash-out period of seven calendar days. Plasma samples were collected for up to 60 hours postdose, and plasma doxylamine concentrations were determined by a high-performance liquid chromatography method with tandem mass spectrometry detection. Pharmacokinetic parameters were calculated using noncompartmental analysis. Safety was evaluated through assessment of adverse events, standard laboratory evaluations, vital signs, and 12-lead electrocardiography.

Results: In total, 24 healthy subjects (12 male and 12 female) were included in the study. Doxylamine succinate 25 mg tablets exhibited similar oral bioavailability of doxylamine in the fasting state (mean maximum plasma drug

concentration [C_{\max}] 118.21 ng/mL, coefficient of variation [CV] 19.2%; mean area under the plasma concentration time curve from time zero to time t [AUC_t] 1746.97 ng • h/mL, CV 31.6%) and in the fed state (mean C_{\max} 120.99 ng/mL, CV 15.0%; mean AUC_t 1712.20 ng • h/mL, CV 26.7%). No statistically significant between-treatment differences were observed for any of the pharmacokinetic parameters under study. The fed : fasting ratios of the geometric least squares means with corresponding 90% confidence intervals for C_{\max} and AUC_t were within the range of 80–125%.

Conclusion: High-fat, high-calorie food intake does not affect the kinetics of doxylamine in healthy subjects. The drug was safe and well tolerated by the subjects in this study.

Introduction

Antihistamines were first introduced in the 1940s and represent one of the most commonly used medications today.^[1] The first-generation antihistamine doxylamine succinate is a member of the ethanolamine class and was introduced into clinical use in the EU in the late 1950s. It acts by competitively inhibiting histamine at H_1 receptors, the binding being readily reversible. It has hypnotic, anticholinergic, and local anesthetic effects, and shares the actions and uses of other antihistamines. The effects upon the central nervous system are fundamentally determined by the capacity to cross the blood–brain barrier and bind to the central H_1 receptors.^[2–4] Although sedation sometimes limits the clinical usefulness of doxylamine when that effect is not desirable, it also provides an additional indication, shared by other antihistamines in the ethanolamine group: symptomatic treatment of insomnia.^[1–3,5,6]

Currently, doxylamine medicinal products have been authorized for more than 50 years, with an appropriate extent of use, for symptomatic treatment of occasional insomnia, making doxylamine a drug with a well established use. In fact, doxylamine alone or in combination with other drugs is available over the counter in Australia, Belgium, Canada, France, Germany, Hungary, Ireland, Italy, Korea, New Zealand, Poland, Portugal, Slovenia, Spain, Switzerland, the UK, and the US.

Dormidina[®] has been marketed in Spain since 1990 with a unique active ingredient: doxylamine

hydrogen succinate 25 mg or 12.5 mg. Doxylamine hydrogen succinate 25 mg (salt) corresponds to doxylamine 17.4 mg (base). Doxylamine is indicated for the symptomatic treatment of occasional insomnia in adults aged 18 years and over, particularly those with difficulty in falling asleep, frequent interruptions during sleep, or early waking in the morning. Because its marketing authorization was approved before the implementation of the present regulatory standards, pharmacokinetic studies of doxylamine hydrogen succinate in its current pharmaceutical presentation (film-coated tablets) have never been performed under fed conditions. The main objectives of this study, therefore, were to evaluate the pharmacokinetic properties of doxylamine following single oral dose administration of a doxylamine hydrogen succinate 25 mg film-coated tablet to healthy human subjects under fed and fasting conditions and to assess the relative bioavailability of doxylamine under those conditions.

Subjects and Methods

Study Design

This was a single-center, randomized, single-dose, laboratory-blinded, two-period, two-sequence, crossover study. A single oral dose of doxylamine hydrogen succinate 25 mg was administered under either fed or fasting conditions in each study period. A 25 mg dose was used, since this is the recommended dosage regimen. No higher doses

of the drug are currently recommended. Since the Physician's Desk Reference rates doxylamine as being in pregnancy category B, it was acceptable to include women in the present study. To ensure that no carryover effect was observed, a wash-out period of seven calendar days was observed between drug administrations, corresponding to more than 10 times the expected half-life of the moiety to be measured. It should be noted that the randomization code was not made available to the personnel in charge of the determination of plasma drug concentrations (Algorithme Pharma Inc., Laval, QC, Canada) until the analytical tables were finalized and audited by the quality assurance department.

The protocol and the informed consent forms were approved by an independent review board (ETHIPRO) on June 17, 2010. All subjects voluntarily agreed to participate in this study and signed the informed consent form after having fully comprehended its contents and prior to initiation of the study procedures. This study was performed in compliance with Good Clinical Practice.^[7]

Study Population

Subject screening procedures included informed consent, an inclusion/exclusion check, demography, medical history, medication history, physical examination, height, weight, body mass index, and a concomitant medication check. Subjects were in good health as determined by the medical history, physical examination (including vital signs), 12-lead electrocardiogram, and the usual clinical laboratory tests (hematology, biochemistry, urinalysis), including negative HIV, hepatitis B, and hepatitis C tests, negative screening for ethanol and drugs of abuse in urine, and a negative pregnancy test (for female subjects).

All participating subjects were judged to be eligible for the study when assessed against the inclusion and exclusion criteria. Tolerability was evaluated through assessment of adverse events (AEs), standard laboratory evaluations, and vital signs.

The predetermined reason for excluding subjects from the study was for any safety issues as determined by the investigator. Also, subjects

could be withdrawn because of protocol violations, administrative problems, difficulties in blood collection, occurrence of emesis during the time interval described in the protocol, or other reasons described in the protocol. Furthermore, subjects were allowed to discontinue their participation in the study at any time. In the event of such a discontinuation, the subject was requested to complete a safety assessment at the time of discontinuation, and the reason for discontinuation was to be documented.

Blood Sample Collection: Method of Measurement

Blood samples were collected prior to and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48, and 60 hours after drug administration. This sampling was planned in order to provide a reliable estimate of the extent of absorption, as well as the terminal elimination half-life ($t_{1/2}$), and to ensure that the area under the plasma concentration–time curve (AUC) from time zero to time t (AUC_t) was at least 80% of the AUC from time zero extrapolated to infinity (AUC_{∞}). Samples were processed and stored under conditions (frozen) that have been shown not to cause significant degradation of the analyte.

The experimental samples were assayed for doxylamine at the analytical facility of Algorithme Pharma Inc. Sample pretreatment involved protein-precipitation extraction of doxylamine from 0.100 mL of human plasma. Doxylamine-D5 was used as the internal standard. The compounds were identified and quantified using reverse-phase high-performance liquid chromatography with tandem mass spectrometry detection over a theoretical concentration range of 1.00–200.00 ng/mL. A gradient of acetonitrile was used for the mobile phase. A low volume was injected at room temperature, using a Turbo Ionspray in positive mode, and the mass : charge ratio (m/z) was monitored according to the optimization of the analytical facility. Between-day variability was evaluated for all calibrants and quality-control samples during the study; within- and between-day variability was also evaluated during the validation of the doxylamine method.

Treatment Schedule

Subjects received the investigational product (Dormidina® [Laboratorios del Dr. Esteve SA, Barcelona, Spain]; a doxylamine hydrogen succinate 25 mg film-coated tablet) on two occasions (once under fed conditions and once under fasting conditions) according to the randomization list. The randomization scheme was computer generated.

Food was controlled and standardized for each treatment period and for all subjects.

The Fed State: Following an overnight fast of at least 10 hours, subjects received a high-fat, high-calorie breakfast 30 minutes prior to drug administration. Afterward, a single dose of the investigational product was administered orally with approximately 240 mL of water at ambient temperature.

The high-fat breakfast, equivalent to approximately 900 kcal, consisted of about 240 mL of whole milk, two large eggs, four ounces of hash brown potatoes (two potato patties), one English muffin with approximately 4.5 g of butter, and two strips of bacon. The subjects ate the total contents of this meal in 30 minutes or less. Furthermore, a standardized lunch was served at least 4 hours after dosing. A supper and a light snack were then served at appropriate times thereafter. Water was allowed ad libitum until 2 hours pre-dose and from 2 hours after drug administration.

The Fasting State: The subjects fasted overnight for at least 10 hours prior to drug administration. A single dose of the investigational product was thereafter administered orally with approximately 240 mL of water at ambient temperature.

Fasting continued for at least 4 hours following drug administration, after which a standardized lunch was served. A supper and a light snack were also served at appropriate times thereafter, but not before 9 hours after dosing. Water was allowed ad libitum until 2 hours pre-dose and from 2 hours after drug administration.

Statistical Analysis

Sample Size

The sample size was calculated, taking into consideration that the intrasubject variations in the maximum plasma drug concentration (C_{\max})

and AUC_t following a single dose of doxylamine appear to be around 10%. Therefore, it was estimated that 24 subjects were sufficient to evaluate the bioavailability of a single 25 mg dose of doxylamine after single oral dose administration under fed and fasting conditions.

Statistical Comparison

Descriptive statistics were used to summarize AEs, safety results, and demographic variables (age, height, weight, and body mass index). Pharmacokinetic parameters such as C_{\max} , the time to reach C_{\max} (t_{\max}), AUC_t , AUC_{∞} , $AUC_t : AUC_{\infty}$, the elimination rate constant (k_e), and $t_{1/2}$ were calculated. For statistical analysis of relative bioavailability, the main pharmacokinetic parameters of interest were C_{\max} and AUC_t . The natural logarithmic transformation of C_{\max} , AUC_t , and AUC_{∞} was used for all statistical inferences. The main absorption and disposition parameters were estimated using a noncompartmental approach with a log-linear terminal phase assumption. The trapezoidal rule was used to estimate the area under the concentration–time curve, and the terminal phase was estimated by maximizing the coefficient of determination estimated from the log-linear regression model. They were not to be estimated for individual concentration–time profiles, where the terminal log-linear phase could not be reliably characterized. The mean, median, minimal value, maximal value, standard deviation, and coefficient of variation were calculated for plasma concentrations at each individual timepoint and for all pharmacokinetic parameters. t_{\max} was analyzed using a nonparametric approach. Testing of fixed period, sequence, and treatment effects was based on the Wilcoxon rank sum test (the Mann–Whitney U-test). All other untransformed and log-normal (ln)-transformed pharmacokinetic parameters were statistically analyzed using a random analysis of variance (ANOVA) model. The fixed factors included in this model were the treatment received, the period in which it was given, and the sequence in which each treatment was received. A random factor was also added for the subject effect (nested within sequence).

The sequence, period, and treatment effects were assessed at the 5% two-sided level. The in-

trasubject coefficient of variation was calculated, where the mean square error was obtained from the ANOVA model of the ln-transformed parameters. If a pharmacokinetic parameter could not be determined for one period in an individual subject, that subject was excluded from that particular statistical comparison.

To assess bioavailability, the ratios of the geometric least squares (LS) means with corresponding 90% confidence intervals were calculated from the exponential of the difference between the fed and fasting conditions for the ln-transformed parameters C_{\max} and AUC_t .

Furthermore, an exploratory analysis was carried out to explore the sex effect.

Statistical and pharmacokinetic analyses were generated using Kinetic, a software application developed at Algorithm Pharma Inc., and SAS[®] software (version 9.1 or higher), using the mixed procedure.

Results

Subject Recruitment

A total of 24 healthy volunteers were included (12 male and 12 female), with a median age of 36 years (range 20–53), weight of 75.4 kg (range 53.4–99.7), height of 173 cm (range 149–188), and body mass index of 25.5 kg/m² (range 19.6–28.6). Twenty-one subjects (88%) were White, two (8%) were Black, and one (4%) was Asian.

Of these 24 subjects, 23 completed the crossover design and received a single oral dose of the assigned treatment on day 1 and day 8. One subject was withdrawn before dosing in period 2 for safety reasons (eczema of severe intensity) and received only one single oral dose of doxylamine hydrogen succinate under fed conditions. This subject was excluded from the statistical comparison of relative bioavailability but was included in the safety analysis.

Treatment Compliance

All subjects took the study medication according to the protocol. The investigational product was administered under the supervision of the qualified investigator or his designees. The film-

coated tablet was to be swallowed whole and was not to be chewed or broken. Following administration of the drug, each subject's hands and mouth were checked in order to confirm the consumption of the medication. The physician in charge remained at the clinical site for at least the first 4 hours following each drug administration and remained available at all times during the entire period of the study.

Pharmacokinetic Assessments

Tables I and II depict the doxylamine pharmacokinetic results: C_{\max} , t_{\max} , AUC_t , AUC_{∞} , $AUC_t:AUC_{\infty}$, k_e , and $t_{1/2}$ in both the fed and fasting states. No statistically significant between-treatment differences were observed for any of the pharmacokinetic parameters under study. The usual criteria used to assess the food effect of the test formulation were fulfilled. The fed : fasting ratio of the geometric LS means and corresponding 90% confidence intervals for C_{\max} and AUC_t were within the range of 80–125%. Figures 1 and 2 show the linear and logarithmic profiles of the mean plasma concentrations of doxylamine. Table III shows the main pharmacokinetic parameters of doxylamine, analyzed by sex.

Tolerability and Safety

No deaths or serious AEs were reported during this study. Twenty-one (87.5%) of the 24 subjects included in the study experienced a total of 54 AEs.

Seventeen subjects (70.8%) reported 33 AEs (five different system organ classes [SOCs] and eight different preferred terms [PTs]) after single-dose administration of the test product under fed conditions, and 15 subjects (65.2%) reported 21 AEs (five different SOC and six different PTs) after single-dose administration of the test product under fasting conditions. The most frequently reported AE was somnolence (reported in 70.8% of the subjects under fed conditions and in 56.5% of the subjects under fasting conditions).

The severity of AEs ranged from mild to severe. Five severe AEs (four in the fed state: eczema, headache, somnolence [two occurrences]; one in the fasting state: somnolence) were observed

Table I. Summary of the main pharmacokinetic parameters of doxylamine

Parameter	Mean [CV (%)]	
	Fed ^a	Fasting ^a
C_{max} (ng/mL)	120.99 [15.0]	118.21 [19.2]
ln C_{max}	4.7846 [3.2]	4.7559 [3.9]
t_{max} (h) ^b	2.50 [41.7]	2.00 [27.7]
AUC_t (ng • h/mL)	1712.20 [26.7]	1746.97 [31.6]
ln AUC_t	7.4150 [3.3]	7.4279 [3.6]
AUC_{∞} (ng • h/mL)	1798.14 [29.6]	1830.05 [33.6]
ln AUC_{∞}	7.4580 [3.6]	7.4698 [3.8]
$AUC_t : AUC_{\infty}$ (%)	95.84 [3.2]	95.91 [2.2]
k_e (h ⁻¹)	0.0544 [22.3]	0.0553 [24.4]
$t_{1/2}$ (h)	13.49 [28.1]	13.11 [19.5]

a The p-values for all comparisons between the fed and fasting states were nonsignificant (i.e., $p \geq 0.05$).

b For t_{max} , median values are presented, and the statistical analysis is based on a nonparametric approach.

AUC = area under the plasma concentration–time curve; **AUC_t** = AUC from time zero to time t; **AUC_∞** = AUC from time zero extrapolated to infinity; **C_{max}** = maximum plasma drug concentration; **CV** = coefficient of variation; **k_e** = elimination rate constant; **ln** = log-normal; **t_{1/2}** = elimination half-life; **t_{max}** = time to reach C_{max} .

during the study. Of all AEs, four (blood potassium level increased, feeling cold, and hypoesthesia [two occurrences]) were unexpected and possibly drug related.

No significant alterations were found in the laboratory evaluations and the electrocardiogram repeated at the end of the study.

Discussion

To our knowledge, this is the first time that the effect of food on the pharmacokinetic parameters of doxylamine has been studied. The results of this study show that the fed : fasting ratios of the geometric LS means and corresponding 90%

confidence intervals for C_{max} and AUC_t were within the range of 80–125%. Consequently, the test formulation of doxylamine hydrogen succinate 25 mg film-coated tablets manufactured by Laboratorios del Dr. Esteve SA (Barcelona, Spain) was judged to be bioequivalent under fed and fasting conditions.

Data available on the pharmacokinetic profile of doxylamine in humans are limited, notwithstanding that this drug has been marketed in European countries for more than 50 years. In fact, the available studies on pharmacokinetic parameters after an oral dose of doxylamine succinate 25 mg were published more than 20 years ago.^[6,8-10] It should be noted that this phase I clinical trial was one of the first to be performed in compliance with Good Clinical Practice and under the current regulatory standards. In the present study conducted under fasting and fed conditions, the pharmacokinetic parameters of doxylamine were not significantly affected by high-fat, high-calorie food intake. No statistically relevant differences in pharmacokinetic parameters between the two states were found. Although some slight differences in some pharmacokinetic parameters (without clinical significance) might be found in comparison with other published studies, the overall results of this study are in line with studies performed with oral doses of doxylamine succinate 25 mg tablets^[6,8,9] and with oral doses of doxylamine succinate 20 mg solution.^[10,11] These slight differences could be explained by the analytical method that was used.^[11,12] On the other hand, the fact that no significant sequence effect was observed in either the fasting or the fed treatment period of the study indicates that the washout period was appropriate and that no carryover effect was present. The effect of sex was studied as

Table II. Standards for comparative bioavailability of doxylamine

Parameter	Intrasubject CV (%)	Geometric LS mean		Fed : fasting ratio ^a (% [90% CI])
		Fed	Fasting	
C_{max}	8.9	119.59 ng/mL	116.07 ng/mL	103.03 [98.50–107.77]
AUC_t	6.2	1657.34 ng • h/mL	1678.16 ng • h/mL	98.76 [95.72–101.90]

a The p-values for all comparisons between the fed and fasting states were nonsignificant (i.e., $p \geq 0.05$).

AUC_t = area under the plasma concentration–time curve from time zero to time t; **CI** = confidence interval; **C_{max}** = maximum plasma drug concentration; **CV** = coefficient of variation; **LS** = least squares.

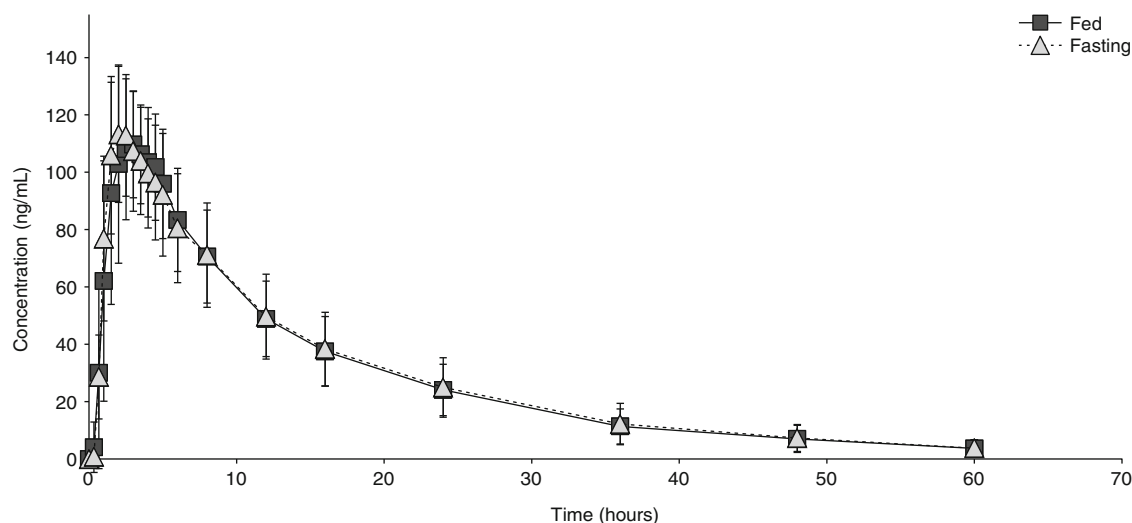


Fig. 1. Linear profile of the mean plasma concentrations of doxylamine in the fed and fasting states.

a descriptive analysis. No statistically significant differences in the pharmacokinetic parameters between male and female subjects were observed in either the fasting or the fed states. It should be noted that female subjects had a longer t_{max} in the fed state than in the fasting state.

Doxylamine succinate is available as an over-the-counter hypnotic agent and in many cough

and cold formulations. The healthy subjects included in this study were young (between 20 and 53 years old). The absorption, distribution, metabolism, and excretion of doxylamine did not seem to be significantly affected by the age or by the sex of the subjects, although the clearance of doxylamine could be reduced in elderly men but not in elderly women.^[8,9] In a *post hoc* analysis,

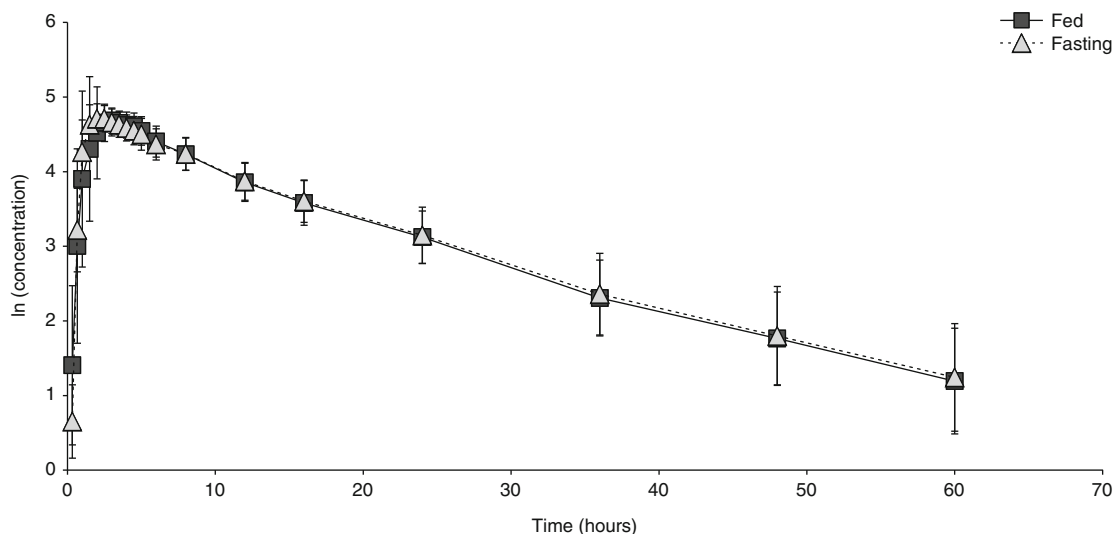


Fig. 2. Logarithmic profile of the mean plasma concentrations of doxylamine in the fed and fasting states. \ln = log-normal.

Table III. Summary of the main pharmacokinetic parameters of doxylamine, analyzed by sex

Parameter	Mean [CV (%)]			
	Male (n = 12)		Female (n = 11)	
	Fed ^a	Fasting ^a	Fed ^a	Fasting ^a
C_{max} (ng/mL)	117.65 [13.4]	111.84 [13.8]	124.63 [16.6]	125.16 [22.3]
ln C_{max}	4.7593 [2.9]	4.7082 [3.0]	4.8123 [3.6]	4.8081 [4.5]
t_{max} (h) ^b	2.00 [35.2]	2.25 [23.6]	3.50 [34.6]	2.00 [32.8]
AUC_t (ng • h/mL)	1563.45 [25.0]	1636.83 [24.3]	1874.47 [25.9]	1867.11 [36.6]
ln AUC_t	7.3292 [3.1]	7.3757 [3.1]	7.5086 [3.2]	7.4848 [4.1]
AUC_{∞} (ng • h/mL)	1649.33 [29.6]	1712.44 [25.8]	1960.49 [28.2]	1958.35 [39.0]
ln AUC_{∞}	7.3745 [3.5]	7.4180 [3.2]	7.5490 [3.4]	7.5264 [4.3]
$AUC_t : AUC_{\infty}$ (%)	95.63 [3.7]	95.88 [2.1]	96.07 [2.6]	95.94 [2.4]
k_e (h ⁻¹)	0.0524 [25.2]	0.0546 [20.0]	0.0567 [19.6]	0.0561 [29.3]
$t_{1/2}$ (h)	14.23 [32.6]	13.09 [16.8]	12.68 [20.3]	13.13 [23.0]

a The p-values for all comparisons between the fed and fasting states were nonsignificant (i.e., $p \geq 0.05$).

b For t_{max} , median values are presented, and the statistical analysis is based on a nonparametric approach.

AUC = area under the plasma concentration–time curve; **AUC_t** = AUC from time zero to time t; **AUC_∞** = AUC from time zero extrapolated to infinity; **C_{max}** = maximum plasma drug concentration; **CV** = coefficient of variation; **k_e** = elimination rate constant; **ln** = log-normal; **t_{1/2}** = elimination half-life; **t_{max}** = time to reach C_{max} .

no sex effect was observed. The results obtained in this study could be extrapolated to the general population, although studies in an elderly population would be necessary.

Overall, the doxylamine hydrogen succinate 25 mg film-coated tablet was generally safe and well tolerated by the subjects in this study. It should be noted that most of the subjects experienced somnolence under both fasting and fed conditions when administered doxylamine hydrogen succinate 25 mg, although somnolence and sleep induction seemed to be more frequent under fed conditions.

Certain aspects of the study design should be considered before drawing conclusions for future users of doxylamine hydrogen succinate, as the open-label, single-dose design and the fact that the study population consisted of healthy subjects could lead to underestimation or overestimation of the generalizability of the results beyond the population and conditions that were studied.

Conclusion

The usual criteria used to assess the food effect of the test formulation were fulfilled. The fed : fasting ratio of the geometric LS means and the corresponding 90% confidence intervals for C_{max}

and AUC_t were within the range of 80–125%. Doxylamine hydrogen succinate 25 mg film-coated tablets are judged to be bioequivalent under fed and fasting conditions. Consequently, high-fat, high-calorie food intake does not affect the kinetics of doxylamine in healthy subjects.

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Sebastián Videla and Mounia Lahjou contributed equally to this study. This work was supported by Laboratorios del Dr. Esteve SA.

Conflicts of Interest: Sebastián Videla, Zhengguo Xu, Carles Tolrà, Gregorio Encina, and Artur Sans are employees of Laboratorios del Dr. Esteve SA. Mounia Lahjou, Pascal Guibord, and Eric Sicard are employees of the clinical research organization Algorithme Pharma Inc., contracted by Laboratorios del Dr. Esteve SA.

Author Contributions: Mounia Lahjou, Artur Sans, and Sebastián Videla designed and wrote the study protocol; Eric Sicard visited and supervised the study subjects, and was the person in charge of the clinical part of the study; Carles Tolrà and Artur Sans monitored the study; Zhengguo Xu and Gregorio Encina were in charge of the analytical results; Pascal Guibord was in charge of the statistical analysis and the data management; and Sebastián Videla, Mounia Lahjou, and Artur Sans wrote the manuscript. All authors have read and approved the final manuscript.

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