ORIGINAL ARTICLE

Absorption and disposition of levocetirizine, the eutomer of cetirizine, administered alone or as cetirizine to healthy volunteers

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ABSTRACT

The primary objective of the present study was to compare the absorption and disposition of levocetirizine, the eutomer of cetirizine, when administered alone (10 mg) or in presence of the distomer. An additional objective was also to investigate the configurational stability of levocetirizine in vivo in humans. The study was performed in a randomized, two-way cross-over, single-dose design with a wash-out phase of 7 days between the two periods. A total of 12 healthy male and 12 healthy female volunteers were included in the study. Bioequivalence can be concluded from the analysis of the pharmacokinetic parameters of levocetirizine when administered alone or as the racemate cetirizine. No chiral inversion occurs in humans when levocetirizine is administered, i.e. there is no formation of the distomer. When comparing the pharmacokinetic characteristics of levocetirizine and the distomer, the apparent volume of distribution of the eutomer is significantly smaller than that of the distomer (0.41 and 0.60 L/kg, respectively). For an H_1-antagonist a small distribution volume can be considered as a positive aspect, both in terms of efficacy and safety. Moreover the non-renal clearance of levocetirizine is also significantly lower than that of the distomer (9.70 and 28.70 mL/min, respectively), which constitutes an additional positive aspect particularly as far as metabolism-based drug interactions are concerned. The information collected in the present study on the pharmacokinetics of levocetirizine and the distomer provide additional reasons for eliminating the distomer and developing levocetirizine as an improvement on cetirizine.

INTRODUCTION

Cetirizine dihydrochloride (available under the trademark Zyrtec; UCB Pharma, Braine L'Alleud, Belgium) is an antihistamine of the second generation, approved world-wide for the relief of symptoms of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. Cetirizine is a racemate whose R- and S-enantiomers are ucb 28556 (levocetirizine dihydrochloride) and ucb 28557, respectively. When developing an enantiomer from an existing marketed racemate, it is important to know whether the removal of the inactive/less active enantiomer (distomer or isomeric ballast) alters the pharmacokinetics of the active/more active enantiomer (eutomer) [1,2]. It is indeed theoretically possible, when the racemate is administered, that the pharmacokinetics of one enantiomer be influenced by the concomitant administration of the other enantiomer as far as absorption, distribution, metabolism or excretion are concerned. The primary objective of the present study was therefore to compare the absorption and disposition of levocetirizine, the eutomer of cetirizine [3–6], when administered alone or in presence of the distomer ucb 28557.

For a chiral drug the low configurational stability resulting in racemization can be a problem either of

pharmacological-clinical or pharmaceutical significance according to whether the half-life of racemization is of the order of minutes/h or of months/years, respectively. A fast method exists to determine the configurational stability of drug candidates that have a chiral centre of the type R″R′RC-H, namely proton–deuterium exchange. The reaction has the considerable advantage that it can be performed with the racemate, which allows chiral drug candidates to be screened for configurational stability prior to their resolution [7]. As cetirizine is a racemic drug with a chiral carbon atom of the type R″R′RC-H, the configurational stability of cetirizine enantiomers is of interest for the possible development of the R-enantiomer as a drug. This configurational stability has been investigated following the proton–deuterium substitution, which can easily be monitored by proton nuclear magnetic resonance (^{1}H-NMR) [8]. The configuration of cetirizine was found to be fully stable, despite of the substitution of the chiral centre by three acid-strengthening groups. This stability might be explained by the inaccessibility of the chiral centre due to the influence of solvation and steric effects. These data however, reported only the configurational stability of cetirizine in the test tube and were not transposable to in vivo conditions, although it seemed improbable that an enzyme system might catalyse the chiral inversion of cetirizine as postulated and/or described for other compounds [9–12].

The configurational stability of cetirizine enantiomers was therefore studied in vivo in a number of laboratory animals. Studies in the rat, rabbit and dog showed that there is no interconversion of cetirizine enantiomers in vivo. The investigation of the configurational stability of levocetirizine in vivo in humans was therefore an additional objective of the present study.

MATERIALS AND METHODS

Chemicals

Materials administered

The test materials were levocetirizine dihydrochloride (UCB-Group) and cetirizine dihydrochloride (UCB-Group). Sparteine sulfate (AAI Deutschland GmbH & Co KG, Neu-Ulm, Germany) was also administered.

Other materials

The compounds ucb 28556 (UCB-Group), ucb 28557 (UCB-Group) and ucb 20028 {[2-[2-[4-(diphenyl methylene)-1-piperidinyl]ethoxy]ethoxy]acetic acid hydrochloride} were provided by the Department of Chemistry, UCB S.A.-Pharma Sector, R & D. They were stored at room temperature in the dark and used without further chemical treatment.

Methods

Overall study design and plan

The study was performed in a randomized, two-way cross-over, single dose design with a wash-out phase of 7 days between the two periods. A total of 12 healthy male and 12 healthy female volunteers were included in the study. The study protocol was submitted to and approved by an Ethics Committee. Before entering the study, all volunteers had to undergo a medical examination including 12-lead electrocardiograms (ECG) and clinical laboratory screening to check the inclusion criteria. Prior to any study activity, all volunteers were informed of the aim, design, risks and steps of the study orally in a detailed conversation with a physician as well as in writing. They declared their consent and voluntary nature of participation by signing the informed consent form before any study-related procedure was initiated. Before starting the randomization phase, subjects were phenotyped with sparteine in order to determine if they were poor or extensive metabolizers. The randomization phase consisted of two periods during which the subjects were administered a single dose of levocetirizine hydrochloride (10 mg) or cetirizine hydrochloride (20 mg).

Selection of study population

The study was conducted on healthy female and male Caucasians aged between 20 and 55 years (35 ± 9.5 years, mean ± SD). The selected subjects' weight (50.3–88.0 kg; 67.3 ± 11.4 kg, mean ± SD) ranged within ± 10% of normal for height, sex and frame as defined by the Metropolitan Life Insurance Company Tables. Smokers up to 15 cigarettes/day ($n = 14$) or/and able to restrict from smoking during the period of confinement ($n = 10$) were accepted. Pregnant or lactating females were excluded, as well as candidates having positive Hepatitis B Antigen (HBsAg) or Human Immunodeficiency Virus infection (HIV). Participation in another clinical trial within 30 days of study start, blood donation or loss ≥ 450 mL within the previous 12 weeks, as well as alcohol or drug addiction were not acceptable. The subjects were not allowed to take any other drug (including over-the-counter products) for the 14 days preceding the study (2 months for enzyme-inducing drugs). This prohibition did not include daily vitamin supplements and female hormonal contraception.

Treatments

Administration of levocetirizine and cetirizine will be reported throughout the text as Treatment 1 and Treatment 2, respectively. Prior to dosing, levocetirizine and cetirizine dihydrochlorides in powder (10 mg and 20 mg, respectively) were dissolved by adding 50 mL of non-carbonated water at ambient temperature. The resulting solution was immediately ingested by the subjects after a supervised overnight fast, according to a randomization scheme. An additional 50 mL of non-carbonated water was added to the vial and swirled prior to immediate ingestion. Afterwards the subjects drank an additional 180 mL of non-carbonated water. They were then required to fast for 4 h after dosing. Water was not permitted for 1 h before and after dosing, but allowed at all other times. Standard meals were provided at approximately 4 and 9 h after dosing and at appropriate times thereafter.

The dose of sparteine sulfate (100 mg/subject in a capsule) used for phenotyping at pre-study was much smaller than the daily dose of 200–1000 mg used for the treatment of cardiac dysrhythmia and was administered with approximately 200 mL of non-carbonated water at ambient temperature. Prior to drug intake, the volunteers were requested to empty their urinary bladder. To ensure sufficient urine production, they were required to drink 200 mL of non-carbonated water 3 h post-dose. There was no restriction of food intake before or during urine collection.

Collection, storage and transport of biological samples

Blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36 and 48 h after administration of levocetirizine and cetirizine. A blood sample was also collected pre-dose. Each time, 10 mL blood was drawn by single venous puncture or indwelling venous catheter into Li-heparinized Becton-Dickinson Vacutainers (Becton-Dickinson, Heidelberg, Germany). Blood samples were centrifuged within 30 min at 4 °C and at 1600 g for 10 min Plasma samples were stored at −20 °C. Urines were collected in the intervals 0–3, 3–6, 6–9, 9–12, 12–24, 24–36 and 36–48 h post-dose and stored at −20 °C after measurement of the volume of each fraction. Plasma and urine samples were shipped via courier in insulated containers with sufficient dry ice to transport and maintain samples at −20 °C until arrival and storage at the analysis site (UCB S.A. Pharma Sector, Laboratory of Drug Metabolism and Pharmacokinetics). Urine was also collected after administration of sparteine in the interval 0–12 h and stored at −20 °C until analysis at AAI Deutschland GmbH & Co. KG.

Safety assessments

Vital signs [heart rate (HR), systolic and diastolic blood pressure (BP)] were monitored at screening (no more than 21 days prior to the start of the study) and then during each period before dosing and approximately 10 min before the scheduled blood draws at 1, 2 and 24 h following drug administration, in addition to before discharge from the clinic. ECG were recorded using a 12-lead ECG at screening and before discharge from the clinic (two days after the last drug administration). Blood samples were taken for haematology and clinical chemistry at screening and before discharge from the clinic. Urinalysis was performed at screening and before discharge from the clinic. Complete physical examination was performed at screening and before discharge from the clinic. Adverse events were monitored and recorded throughout the study.

Determination of the concentrations of the two enantiomers of cetirizine in plasma and urine

Samples were analysed following the recommendations of the Conference of Washington [13]. Briefly, aliquots of plasma (2 mL) or urine (1 mL), diluted if necessary by blank plasma or urine, were added to the structurally related internal standard ucb 20028 (100 μL) and citrate-phosphate buffer (0.5 mL, pH 5, 1 mol/L). The solutions obtained were transferred onto Chemelut columns. Levocetirizine (ucb 28556), ucb 28557 and the internal standard were extracted twice with 6 mL ethyl acetate (solid phase extraction). Phosphoric acid (1.7% v/v, 0.6 mL) was added to the pooled organic extracts. The mixture was then shaken (vortex), centrifuged and the organic phase discarded. A gentle stream of dry oxygen-free nitrogen was passed over the acidic extracts for a few minutes to remove any residual ethyl acetate. The acidic extract was then transferred into vials and 100 μL portions were injected into the chromatograph. A Hewlett-Packard 1090 liquid chromatograph (Hewlett-Packard, Waldbronn, Germany), equipped with a variable wavelength detector operating at 230 nm, was used to measure ucb 28557, ucb 28556 and the internal standard in the extracts. The chromatograph was fitted with an analytical column (Chiralcel OD-H, 5 μm, 250 × 4.6 mm; Baker, Deventer, Holland) equipped with a precolumn (ODS-hypersil, 5 μm, 100 × 4.6 mm; company, Baker, Deventer, Holland) which was protected by

a guard column (ODS-hypersil, 5 μm, 20 × 4 mm; HP, Brussels, Belgium). The analysis were performed at room temperature. The wavelength of the UV detector was set at 230 nm. The mobile phase was a mix of HClO4 (0.2 mol/L)-acetonitrile (65/35 v/v) added with diethylamine (0.4 vol percentage) and adjusted to pH 2.5 with KOH (0.5 mol/L). The flow was set to 0.6 mL/min. Under these conditions, the internal standard, ucb 28557 and ucb 28556 were eluted from the column with retention times of approx. 33.5, 37.8 and 40.6 min, respectively. Calibration curves ranging from 20 to 1000 ng/mL and from 0.1 to 10 μg/mL were used for plasma and urine, respectively. ucb 28556 and ucb 28557 were reliably quantitated in plasma and in urine down to concentrations of 20 ng/mL and 0.1 μg/mL, respectively.

Another enantioselective determination of cetirizine in human urine by HPLC has been described by Choi et al. [14], where a chiral stationary phase of α_1-acid glycoprotein was used to separate the enantiomers and roxatidine was employed as the internal standard. However the minimum detectable concentration of the cetirizine enantiomers in urine was 0.4 μg/mL.

Determination of the concentrations of sparteine and its metabolites in urine

Sparteine and its metabolites 2-dehydrosparteine (2-DHSP) and 5-dehydrosparteine (5-DHSP) were determined by gas chromatography with a nitrogen specific detector (GC-NFID). Aliquots of urine (0.5 mL) were added with 100 μL of internal standard (17-ethylsparteine diperchlorate, 37.8 mg/20 mL of 0.1 N HCl) and 50 μL of 12.5 N NaOH. The samples were then extracted with 600 μL of dichloromethane. The mixture was then shaken (vortex), centrifuged and the organic phase analyzed by GC-NFID, essentially as described by Osikowska-Evers and Eichelbaum [15]. The volunteers were characterized as poor metabolizers for sparteine [cytochrome P-450 2D6 isozyme (CYP 2D6)] when at least one of the following criteria was met:

1 metabolic ratio [amount of sparteine in urine/(amount of 2-DHSP + 5-DHSP in urine)] > 20 [16,17];
2 more than 50% of the dose excreted in urine as sparteine within 12 h;
3 less than 2% of the dose excreted as 2- and 5-DHSP within 12 h.

The ratio of the peak areas [peak area of sparteine in urine/(peak area of 2-DHSP + 5-DHSP in urine)] in the chromatogram was used as measure for the metabolic ratio.

Calculations of the pharmacokinetic parameters

Pharmacokinetic parameters for cetirizine enantiomers in plasma and urine were calculated by AAI Deutschland GmbH & Co KG. AUC is the area under the plasma concentration vs. time curve from time 0 to infinity, calculated as the sum of the $AUC_{0\text{-}t} + C_t/\lambda_z$. C_{max} and t_{max} are the maximum measured plasma concentration and the time of the maximum measured plasma concentration, respectively. λ_z is the apparent first-order terminal rate constant calculated from a semilog plot of the plasma concentration vs. time curve and t½ is the terminal half-life calculated as $(\ln 2)/\lambda_z$. CL/F is the apparent total body clearance calculated by dividing the dose administered by AUC and V_z/F the apparent volume of distribution relative to the bioavailability (F), calculated as $CL/F/\lambda_z$. Ae is the total amount of cetirizine enantiomers excreted over the entire urine sample collection period, calculated as the sum of the amounts excreted during each collection interval, whereas Fe is the relative cumulative urinary excretion calculated as 100 × Ae/dose. CL_R is the renal clearance calculated as $Ae/AUC_{0\text{–}48\ h}$.

Statistical analysis

Statistical analyses for pharmacokinetic parameters of ucb 28556 in plasma and urine were performed by AAI Deutschland GmbH & Co KG. Standard procedures for bioequivalence studies were used to investigate whether the pharmacokinetics of ucb 28556 are bioequivalent when given as a single enantiomer or as the racemate. Bioequivalence (therefore similarity in disposition when ucb 28556 is administered alone or as the racemate) was to be concluded when the 90% confidence interval (CI) for the treatment ratio was fully contained within the 80–125% acceptance range for ln-transformed data. For variables that were not ln-transformed, the CI for the treatment difference had to be fully contained within –20% and + 20% of the reference value. Statistical tests were applied to the primary pharmacokinetic parameters of ucb 28556, i.e. AUC, C_{max}, t_{max} and Ae (see *Table I*). The analysis of variance performed on AUC, C_{max} and Ae included gender, sequence, subjects within gender and sequence group, period and drug formulation as factors. The above mentioned statistical analyses were performed using the statistical analysis system general linear models (SAS GLM) procedure. Previous investigations with cetirizine resulted in an ANOVA coefficient of variation (CV) of 15% for the log-transformed cumulative excretion of cetirizine (UCB, data on files). This corresponds to a sample size of 12 subjects to allow a reasonable chance for a statistical conclusion of bioequivalence by the

Table I Comparative disposition of levocetirizine dihydrochloride (ucb 28556) in all subjects.

	Ae (mg)	AUC (h × ng/mL)	C_{max} (ng/mL)	t_{max} (h)
Statistics	ANOVA	ANOVA	ANOVA	Non parametric
Transformation	ln	ln	ln	no
Geometric mean (min-max)				Median
Treatment 1*	6.74 (4.8–8.7)	4072.5 (2828.6–5654.1)	501.4 (294–709)	0.5 (0.5–1.5)
Treatment 2†	7.15 (5.5–10.1)	4043.9 (3175.5–5444.6)	499.1 (331–698)	1.0 (0.5–1.5)
Ratio (%)	94.1	100.7	100.4	0‡
90% CI	89.6–99.0	97.1–104.5	95.6–105.5	–0.25–0§

*Oral extemporaneous solution in water containing 10 mg of levocetirizine (ucb 28556); †oral extemporaneous solution in water containing 20 mg of cetirizine.2HCl; ‡Difference instead of ratio; §90% CI of the difference.

assessment of CIs. In order to allow analysis by sex, 12 males and 12 females were included. Descriptive statistics were carried out concerning statistical analysis of safety data [vital signs, ECG parameters (PR, QT, QTc, QRS)].

RESULTS

Sparteine phenotype

All the subjects included in the study were fast metabolizers excepted two, one male and one female, who were poor metabolizers.

Safety

No subject discontinued the study prematurely due to intolerable adverse events. No serious adverse events occurred during the study. No clinically relevant differences in mean systolic or diastolic blood pressure or heart rate were observed between the treatments. No clinically relevant findings were detected in the post-study ECGs. The tolerability of both study preparations was comparable. The adverse events judged to be at least possibly related to the study drug were: tiredness (6 subjects), abdominal discomfort (1 subject) and headache (2 subjects) after Treatment 1 and tiredness (2 subjects), weariness (1 subject), dizziness (1 subject) and headache (1 subject) after Treatment 2.

Plasma concentrations and urinary excretion of levocetirizine when administered alone or in presence of the distomer

Plasma concentrations of levocetirizine (mean ± SD) following Treatments 1 and 2 are presented in *Figure 1* whereas the corresponding pharmacokinetic parameters are presented in *Table II*. Cumulative amounts of levocetirizine (mean ± SD) excreted in urine following Treatments 1 and 2 are presented in *Figure 2* whereas the corresponding pharmacokinetic parameters are presented

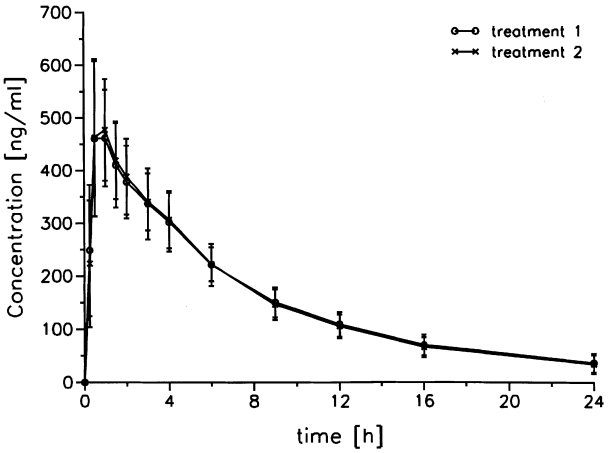

Figure 1 Mean plasma concentrations (± SD) of ucb 28556.

in *Table II*. Statistical results on primary pharmacokinetic parameters of ucb 28556 are presented in *Table I*. The geometric mean ratio for the AUC was 101% with a 90% CI ranging from 97 to 105%, which is within the acceptance range. The geometric mean ratio for C_{max} was 100% with a 90% CI ranging from 96 to 106%. Medians of t_{max} were 0.5 and 1 h for Treatment 1 and 2, respectively, and the difference was estimated to 0 min with – 15–0 min (–0.25–0 h) as 90% CI. The amounts of ucb 28556 excreted in urine (Ae) within 48 h after dosing ranged from 4.9 to 10.1 mg and agreed well between treatments with geometric means of 6.74 and 7.15 mg for Treatment 1 and 2, respectively. The mean ratio was estimated at 94% with a CI ranging from 90 to 99%.

Configurational stability of levocetirizine in vivo in humans

The plasma concentrations of ucb 28557 were not only below the limit of quantitation (20 ng/mL) but under the limit of detection for all subjects at all sampling times

Table II Plasma and urinary pharmacokinetic parameters of levocetirizine (ucb 28556) and ucb 28557 in males and females following treatments 1 and 2 (means ± SD).

Pharmacokinetic parameter	Treatment 1			Treatment 2					
	ucb 28556			ucb 28556			ucb 28557		
	Males	Females	Males + Females	Males	Females	Males + Females	Males	Females	Males + Females
AUC (ng.h/ml)	3984.5 ± 803.58	4288.3 ± 664.32	4136.4 ± 737.6	3968.3 ± 637.68	4213.8 ± 658.47	4091.0 ± 646.2	1765.6 ± 410.76	2041.5 ± 340.11	1909.5 ± 392.92
C_{max} (ng/ml)	465.83 ± 95.94	558.67 ± 95.61	512.25 ± 104.98	456.67 ± 82.38	561.17 ± 91.76	508.92 ± 100.61	255.33 ± 51.71	324.92 ± 53.82	290.13 ± 62.67
t_{max} (h)	0.58 ± 0.19	0.88 ± 0.38	0.73 ± 0.33	0.80 ± 0.34	0.79 ± 0.26	0.80 ± 0.29	0.80 ± 0.34	0.82 ± 0.33	0.82 ± 0.33
$t_{½}$ (h)	8.46 ± 1.68	7.05 ± 1.16	7.76 ± 1.59	8.83 ± 1.90	6.77 ± 1.45	7.80 ± 1.96	6.21 ± 2.21	4.83 ± 1.10	5.52 ± 1.85
Cl/F (ml/min)	43.45 ± 8.87	39.72 ± 6.13	41.58 ± 7.70	42.91 ± 6.25	40.45 ± 6.36	41.68 ± 6.30	98.21 ± 18.40	83.62 ±13.06	90.60 ± 17.16
V_d/F (l)	31.41 ± 7.79	23.88 ± 3.21	27.65 ± 6.98	32.57 ± 7.56	23.21 ± 4.12	27.89 ± 7.64	47.00 ± 6.36	34.26 ± 6.48	40.35 ± 9.04
Ae (µg)	6624.7 ± 918.8	6995.9 ± 1126.5	6810.3 ± 1023.1	6996.4 ± 1204.0	7523.2 ± 1359.9	7259.8 ± 1284.6	5985.9 ± 1314.7	6737.4 ± 1289.8	6361.6 ± 1330.2
fe (%)	66.25 ± 9.19	69.96 ± 11.27	68.10 ± 10.23	69.96 ± 12.04	75.23 ± 13.60	72.6 ± 12.9	59.86 ± 13.15	67.37 ± 12.90	63.6 ± 13.30
Cl_r (ml/min)	30.75 ± 8.51	28.80 ± 7.06	29.78 ± 7.71	32.01 ± 8.06	31.94 ± 8.92	31.98 ± 8.32	62.79 ± 19.26	60.06 ± 16.65	61.43 ± 17.66

after administration of levocetirizine. The urinary concentrations of ucb 28557 were also undetectable in all urinary fractions for all subjects. There was therefore no evidence of conversion of ucb 28556 into ucb 28557 in vivo in humans.

Pharmacokinetic parameters of levocetirizine in the fast and poor metabolizers

The pharmacokinetics of both levocetirizine and the distomer were not different in the two poor metabolizers compared to the extensive metabolizers, e.g. mean AUC of levocetirizine in poor and extensive metabolizers after Treatment 1 was 4086 and 4141 ngh/mL, respectively. The isozyme CYP2D6 should not therefore be involved in the metabolism of these compounds or if so, its contribution cannot be evidenced from a study design where only the parent compounds are measured. In another study where ^{14}C-levocetirizine was administered to healthy volunteers, the compound was very poorly metabolized: the cumulative 48 h excretion as parent compound accounted for 85.8% of the oral dose. Thirteen minor metabolites were detected in urine and represented 2.4% of the dose at 48 h [18]. Independently from the design of the present study where the main objectives were not to determine the contribution of CYP2D6 to the metabolism of levocetirizine, a previous in vitro metabolism study with human liver microsomes in the absence and presence of quinidine, a selective inhibitor of CYP2D6, has shown that CYP2D6 is practically not involved in the metabolism of these compounds (UCB, data on file).

Pharmacokinetic parameters of the cetirizine enantiomers in males and females

The plasma and urinary pharmacokinetic parameters of levocetirizine and the distomer in males and females following Treatments 1 and 2 are presented in *Table II*. In general female subjects showed higher AUCs and C_{max} than males despite a slightly shorter half-life. This was probably due, at least partly, to the relatively higher dose received by the female subjects when expressed as mg/kg, as their mean weight was 58.9 kg compared with 75.7 kg for the males. These differences could be observed for both treatments and for both levocetirizine and the distomer. However no statistically significant difference was found in AUC between males and females (mean AUC of levocetirizine = 3976 and 4251 ngh/mL, respectively; ANOVA, $P = 0.296$). When the AUC of levocetirizine and the distomer were adjusted to a 1 mg/kg dose, statistically significant differences were observed

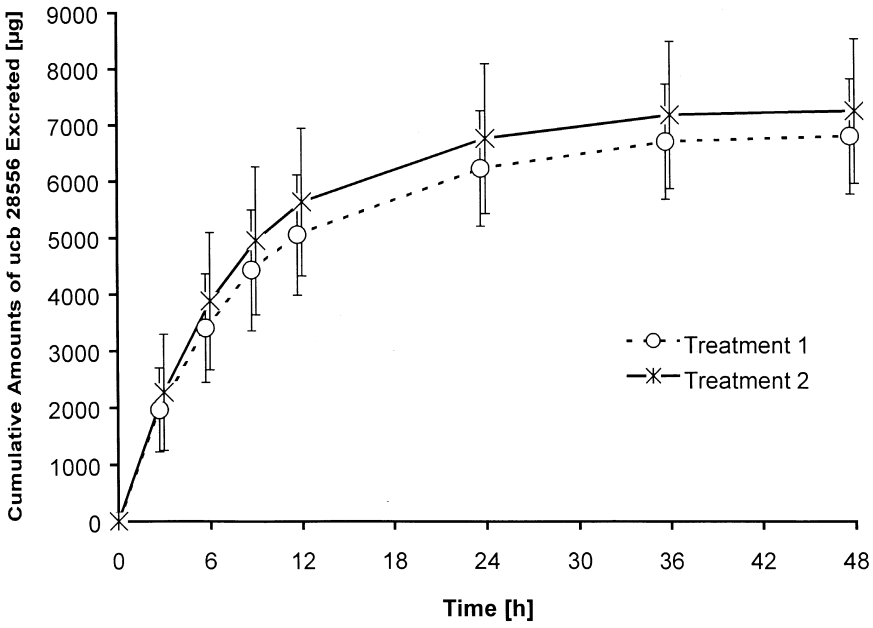

Figure 2 Mean cumulative amounts (± SD) of ucb 28556 excreted in urine.

between males and females (mean AUC of levocetirizine = 29.92 and 24.94 µgh/mL, respectively; ANOVA, $P = 0.015$). Moreover when Cl/F of levocetirizine and the distomer were expressed per kg body weight, significant differences between males and females were observed (mean Cl/F of levocetirizine = 0.572 and 0.689 mL/min/kg, respectively; ANOVA, $P = 0.017$). A statistically significant difference between males and females was also found in the half-life of levocetirizine and the distomer (mean t1/2 of levocetirizine = 8.65 and 06.91 hours, respectively; ANOVA, $P = 0.007$). In contrast, when the V_z/F of levocetirizine and the distomer were expressed per kg body weight, no statistically significant differences were obtained. The 90% CI of the geometric means ratio (females/males) was not fully contained in the 0.8–1.25 interval only for the half-life of levocetirizine and the distomer (ratio = 0.80 and 90% CI = 0.75–0.86 for levocetirizine). Smoking did not appear to modify the pharmacokinetics of levocetirizine, whatever the gender. In non-smoker and smoker males following Treatment 1, half-life ranged from 9.95 to 10.51 hours and from 5.21 to 9.82 hours, apparent total body clearance from 33.44 to 55.70 mL/min and from 32.41 to 58.92 mL/min, respectively. In non-smoker and smoker females following the same treatment, half-life ranged from 6.03 to 9.13 and from 5.11 to 8.94 hours, apparent total body clearance from 33.88 to 48.71 mL/min and from 29.48 to 48.28 mL/min, respectively.

Pharmacokinetic characteristics of the eutomer compared to the distomer

The pharmacokinetic parameters of levocetirizine and the distomer are presented in *Table II*. The AUC and C_{max} of levocetirizine are higher than those of the distomer (mean AUC of eutomer/mean AUC of distomer = 2.14; mean C_{max} of eutomer/mean C_{max} of distomer = 1.75). Moreover, levocetirizine has a longer half-life, a lower apparent total body clearance, a lower renal clearance and a significantly smaller apparent volume of distribution than the distomer (Student's *t*-test for paired data, P less than 0.001). The non renal clearance calculated as the difference of the total apparent body clearance and the renal clearance is 9.70 ± 5.96 mL/min (mean ± SD) for levocetirizine compared to 28.70 ± 15.74 mL/min (mean ± SD) for the distomer (Student's *t*-test for paired data, $P < 0.001$).

DISCUSSION

The primary objective of this study was to compare the absorption and disposition of levocetirizine when administered alone or in the presence of the distomer: bioequivalence can be concluded from the analysis of the pharmacokinetic parameters of levocetirizine when administered alone or as the racemate cetirizine.

It is interesting to observe that the interindividual variability of levocetirizine pharmacokinetics is rather low, e.g. the coefficient of variation (CV) of the AUC and

Ae is 17.8 and 15%, respectively, after administration of levocetirizine. The CV values of these levocetirizine parameters are very similar when cetirizine is administered. The secondary objective was to prove that no chiral inversion occurs in humans when levocetirizine is administered, i.e. that there is no formation of the distomer, which has also been demonstrated.

Levocetirizine is so poorly metabolized that the knowledge of the isozymes involved in its metabolism is probably not particularly relevant. Anyway, the fact that CYP2D6 does not appear to be practically involved in the metabolism of levocetirizine is interesting not only because poor metabolizers behave like rapid metabolizers following administration of the compound but also because many commonly used drugs belonging to different therapeutic classes are metabolized by this isozyme or can inhibit it [19,20]. Therefore the noninvolvement of CYP2D6 in the metabolism of levocetirizine is in favour of a lack of metabolism-based drug interactions.

The differences between males and females in dose adjusted AUC, Cl/F expressed per kg body weight, and t1/2 of levocetirizine, although statistically significant, are of no clinical relevance.

When comparing the pharmacokinetic characteristics of levocetirizine and the distomer, it is important to emphasize that the apparent volume of distribution of the eutomer is significantly smaller than that of the distomer (27.89 and 40.35 L, respectively, or 0.41 and 0.60 when expressed as l/kg, respectively). For an H_1-antagonist, a small distribution volume can be considered as a positive aspect, both in terms of efficacy and safety [21]. Moreover the non renal clearance of levocetirizine is also significantly lower than that of the distomer (9.70 and 28.70 mL/min, respectively), which constitutes an additional positive aspect particularly as far as metabolism-based drug interactions are concerned.

In conclusion, the information collected in the present study on the pharmacokinetics of levocetirizine and the distomer provide additional reasons for eliminating the distomer and developing levocetirizine as an improvement on cetirizine.

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