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Steady-State Pharmacokinetics of the Enantiomers of Citalopram and Its Metabolites in Humans

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ABSTRACT The steady-state pharmacokinetics in serum and urine of the enantiomers of citalopram and its metabolites, demethylcitalopram (DCT) and didemethylcitalopram (DDCT), were investigated after multiple doses of *rac*-citalopram for 21 consecutive days (40 mg per day) to healthy human subjects who were extensive metabolisers of sparteine and mephenytoin. Comparable pharmacokinetic variability was noted for (+)-(S)-, (−)-(R)- and *rac*-citalopram. Enantiomeric (S/R) serum concentration ratios for citalopram were always less than unity and were constant during the steady-state dosing interval. A modest, but statistically significant, stereoselectivity in the disposition of citalopram and its two main metabolites was observed. Serum levels of the (+)-(S)-enantiomers of citalopram, DCT, and DDCT throughout the steady-state dosing interval investigated were 37 ± 6%, 42 ± 3% and 32 ± 3%, respectively, of their total racemic serum concentrations. The (+)-(S)-enantiomers of citalopram, DCT, and DDCT were eliminated faster than their antipodes. For (−)-(R)- and (+)-(S)-citalopram, respectively, the serum $t_{1/2}$ averaged 47 ± 11 and 35 ± 4 h and AUC_{ss} averaged 4,193 ± 1,118 h · nmol/l and 2,562 ± 1,190 h · nmol/l. The observed enantiospecificities were apparently more related to clearance, rather than to distributional mechanisms. *Chirality 9:686–692, 1997.*

KEY WORDS: citalopram; metabolites; enantiomer pharmacokinetics; stereospecific HPLC analysis; DCT; DDCT

Citalopram (Fig. 1) is a bicyclic phthalane derivative belonging to a class of antidepressants that preferentially increases 5-HT transmission by inhibiting 5-HT uptake. Citalopram is the most selective of the selective serotonin reuptake inhibitors (SSRIs), having no, or very little, affinity for noradrenaline or dopamine uptake sites, and does not inhibit monoamine oxidase.[1] The elimination of citalopram is largely mediated via oxidative metabolism with N-demethylation (and subsequent retention of the chiral centre), generating demethylcitalopram (DCT) and didemethylcitalopram (DDCT), appearing to be the quantitatively most important step.[2] Based on potency relative to citalopram, these metabolites are not considered to make major contributions to its antidepressant effect.[3] In vitro and animal in vivo studies have demonstrated IC_{50} values for inhibition of 5-HT uptake in rat brain synaptosomes of 1.5 nM for the (+)-enantiomer of citalopram with the 1-(S) absolute configuration and 250 nM for (−)-(R)-citalopram.[4]

Whereas the pharmacokinetics of *rac*-citalopram have been well described, only sparse information regarding the disposition of its individual enantiomers is available. In addition to describing a stereoselective HPLC assay for the quantitation of the enantiomers of citalopram, DCT and DDCT, we present an investigation undertaken to elucidate the steady-state pharmacokinetics in serum and urine of the enantiomers of citalopram and two of its metabolites in healthy subjects.

MATERIALS AND METHODS

Experimental Design

The study was approved by the ethics committee of Lower Normandy, Caen, France. Ten subjects (6 females and 4 males, age 23–32 years, weight 51–74 kg) phenotyped as extensive metabolisers of sparteine (cytochrome P450 (CYP) 2D6 substrate) and mephenytoin (CYP2C19 substrate) gave informed, written consent to the study. Complete physical examination, as well as routine biochemical and haematological tests, were performed to ensure that the subjects were medically fit. Both non-smoking and smoking (<10 cigarettes/day; n = 6) subjects were studied. Subjects received *rac*-citalopram orally as a 40 mg (0.7 ± 0.1 mg/kg) tablet (containing equal amounts

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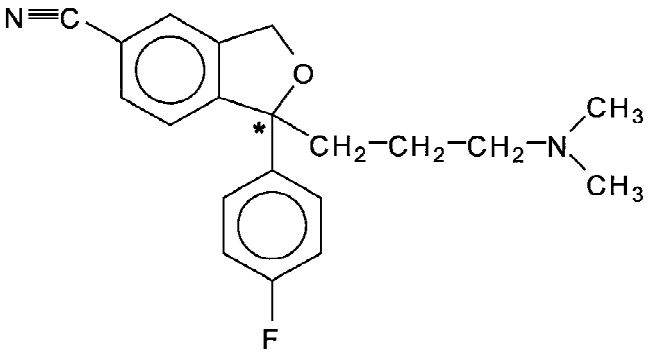

Fig. 1. Structure of citalopram. Asterisk denotes the chiral centre.

of (+)-(S)- and (−)-(R)-citalopram; H. Lundbeck A/S, Copenhagen, Denmark) once daily for 21 consecutive days. They refrained from consuming alcoholic beverages and grapefruit juice a day before and during the study period. In general, no concomitant medication was allowed in the study. If the subjects were in need of an analgesic, paracetamol was permitted. Laboratory analyses (haematology, blood chemistry, and urinalysis) and cardiovascular monitoring (ECG, blood pressure, and pulse rate) were conducted prior to and on the last day of the study. The occurrence of adverse events was recorded throughout the study. Blood samples for pharmacokinetic analysis were drawn from an antecubital vein into glass tubes immediately before citalopram administration on Days 1, 18, 19, 20, and 21 and at 1, 1.5, 2.5, 4, 6, 8, 12, 48, 72, 96, 120, 144, 168, 192, 216, and 240 h following drug intake on Day 21. Serum samples obtained following coagulation and centrifugation were stored at −20°C until analysed. After emptying the bladder immediately before drug administration on Day 21, urine was collected over the following periods: 0–6, 6–12, 12–24, 24–48, 48–72, 72–96, 96–120, 120–144, 144–168, 168–192, 192–216, and 216–240 h. Urine samples were immediately frozen and stored at −20°C until analysed.

Stereospecific HPLC Assay

The racemate and enantiomers of citalopram, DCT, and DDCT were of >99% purity. A ring-opened citalopram analogue, (+)-4-(4-Dimethylamino-1-(4′-fluorphenyl)-1-hydroxybutyl)-3-hydroxymethylbenzonitrile, hemi-(−)-O,O′-di(4′-toluoyl)-L-tartrate, was used as an internal standard. HPLC-grade n-heptane and methanol were purchased from Rathburn Chemicals Ltd. (Walkerburn, Scotland) and 96% ethanol was of European Pharmacopoeia quality. Water was purified by an Elgastat Maxima apparatus (Elga Ltd., Bucks, England).

Levels of the (+)-(S)- and (−)-(R)-enantiomers of citalopram, DCT, and DDCT in serum and urine were determined by a direct stereospecific HPLC method using a derivatised β-cyclodextrin 5-µm column (Cyclobond I 2000 DMP, Astec Inc., Whippany, NJ; 250 × 4.6 mm I.D.). The Cyclobond column was thermostated at 30°C with a Universal Thermostat Oven (Mikrolab Aarhus A/S, Århus, Denmark). The mobile phase was 0.05 M citric acid buffer, pH 6.0, with 30–40% methanol. The flow rate was 1.0–1.5 ml/min and the eluates were monitored by fluorescence detection with excitation wavelength of 240 nm and emission wavelength of 296 nm. Stock solutions of the reference compounds and the internal standard (1 mg/ml in 96% ethanol) were kept refrigerated for up to 1 month. Calibration standards in serum and urine were prepared by spiking blank samples with freshly prepared standard solutions of citalopram, DCT, and DDCT in water.

After alkalisation with 50 µl 1 *N* NaOH and addition of 100 ng of internal standard, serum and urine samples (1.0 ml) were extracted with 6.0 ml of n-heptane containing 1.5% isoamyl alcohol. The mixture was shaken for 15 min followed by centrifugation at 2,000*g* for 5 min. The organic layer was transferred to another tube containing 100 µl 0.1 *N* HCl. Following mixing for 15 min and centrifugation at 2,000*g* for 5 min, the organic layer was discarded and 50 µl of the aqueous phase was injected into the chromatographic system. As separation of the enantiomers of DDCT was a critical factor in sample analyses, chromatographic conditions were optimised to provide a resolution factor of >1 (Fig. 2). Standard curves for (+)-(S)- and (−)-(R)-enantiomers were linear over concentration ranges of 15–450 nmol/l for citalopram, 8–240 nmol/l for DCT, and 3–100 nmol/l for DDCT, for R/S or S/R ratios of 0.5 and 1.0. The analytical procedure was validated and the lower limits of quantification (LOQs) in both serum and urine were 15.4, 8.1, and 3.4 nmol/l for both enantiomers of citalopram, DCT, and DDCT, respectively. For citalopram, DCT, and DDCT, respectively, the within-day coefficients of variation were 7–10% for concentrations of 385, 200, and 85 nmol/l and 9–17% for the LOQ concentrations.

Pharmacokinetic Analysis

Serum data. Values for the time (t_{max}) to achieve maximal concentration ($C_{max,ss}$) at steady-state (SS; Day 21) were both obtained directly from the data. The terminal elimination rate constant (λ_z) was determined by linear least squares regression of the terminal portion of the serum concentration-time curve and the apparent terminal half-life ($t_{1/2}$) was calculated as $\ln(2)/\lambda_z$. The area under the serum concentration vs. time curve (AUC_{ss}) at steady-state was estimated using the linear trapezoidal rule. Average steady-state concentration ($C_{av,ss}$) was derived as AUC_{ss}/τ, where τ is the dosing interval. For citalopram, the total oral clearance (CL/F) was calculated by dividing the administered dose by the AUC_{ss}, where F is the oral bioavailability of the drug. A value of 0.5 · dose was used in calculating CL/F for the individual enantiomers of citalopram. The steady-state distribution volume (V_{ss}/F) was calculated noncompartmentally.[5] The enantiomeric ratio in serum at steady-state was defined as $AUC_{ss,(+)\text{-}(S)}/AUC_{ss,(-)\text{-}(R)}$. For DCT and DDCT, the metabolic ratio was defined as $AUC_{ss,metabolite}/AUC_{ss/citalopram}$.

Urinary data. The urinary recoveries of citalopram and its metabolites (Ae) were calculated up to 240 h after dosing on Day 21. The percentage of the dose excreted in

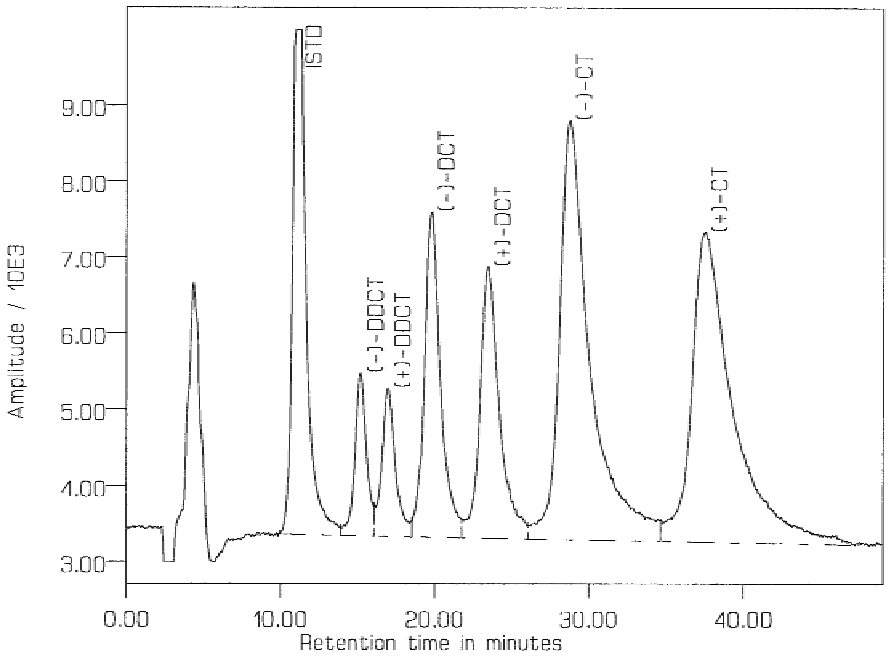

Fig. 2. Chromatogram from the analysis of 1.0 ml of human serum spiked with racemic citalopram (CT), DCT, DDCT, and internal standard (ISTD) corresponding to 150, 80, 30, and 150 µmol, respectively, of the enantiomers of each compound. Chromatographic profiles for urine were the same as those observed for serum.

urine during the steady-state dosing interval ($Ae_{\%dose}$) as citalopram, DCT, and DDCT was calculated from the molar ratio of Ae/Dose. Urinary half-lives were calculated from the slope of the terminal linear portion of the log urinary excretion rate vs. midpoint of the collection time curves. Renal clearance (CL_R) was calculated from urinary recovery (Ae_{ss}) divided by AUC_{ss}. Nonrenal clearance for citalopram was calculated as $CL_{NR} = CL/F–CL_R$. For DCT and DDCT, the excretion ratio in urine, relative to the parent compound, was defined as $Ae_{ss,metabolite}/Ae_{ss,citalopram}$.

In Vitro Interconversion Study

The stereochemical stability of each compound was investigated by spiking blank human serum and urine samples with the individual enantiomers of citalopram (460 nmol/l), DCT (240 nmol/l), and DDCT (100 nmol/l) under three storage conditions: (1) at room temperature for up to 2 days, (2) at −20°C for 2 weeks with thawing and refreezing on Days 4 and 7, and (3) at −20°C for 4 weeks.

Statistical Analysis

Normally distributed pharmacokinetic parameters of the enantiomers of citalopram, DCT, and DDCT were compared using paired *t*-tests. The Wilcoxon rank sum test was used for comparison of non-normally distributed parameters ($C_{max,ss}$ and t_{max}). The level of significance was set at $P < 0.05$. SAS software (SAS Institute, Cary, NC) was used for all statistical calculations.

RESULTS AND DISCUSSION

The study medication was well tolerated and no serious adverse events were reported during the study period. No clinically significant changes in ECG, vital signs, or in clinical chemistry were observed in the study. Pharmacokinetic parameters are summarised in Table 1 and mean serum concentration profiles are presented in Figure 3. Pre-dose serum concentrations of the enantiomers of citalopram and its metabolites on Days 18 to 21 showed that steady-state had been reached by that time (results not shown). Racemic $C_{av,ss}$ values averaged (±SD) 281 ± 96 nmol/l for citalopram, 96 ± 22 nmol/l for DCT, and 17 ± 4 nmol/l for DDCT.

Citalopram is a drug of low intrinsic clearance and its kinetics have been found to be linear over a dose range of 10–60 mg.[3] The plasma protein-binding of citalopram and its demethylated metabolites is approximately 80% and the absolute bioavailability of citalopram tablets is about 80% of the intravenous dose.[3] In this study, CL/F and V_{ss}/F for *rac*-citalopram were 0.33 ± 0.10 l/h/kg and 17.0 ± 4.4 l/kg, respectively. Serum half-lives for *rac*-citalopram, DCT, and DDCT averaged 38.4 ± 7.8, 50.8 ± 11.4, and 108.2 ± 27.7 h, respectively. The total amount of the administered dose recovered in urine was 36 ± 5%. Overall, the pharmacokinetics of *rac*-citalopram and its metabolites in this study are in close agreement with pharmacokinetic data derived using non-chiral analytical methods.[3] Importantly, pharmacokinetic variability was comparable between the enantiomers of citalopram and, in turn, this variability was similar to that observed for *rac*-citalopram.

The (+)-(S)-enantiomers of citalopram and its metabolites were found to undergo a more rapid elimination than their optical antipodes. Except for t_{max} and V_{ss}/F, comparison of the pharmacokinetic parameters of the enantiomers of citalopram and its metabolites reached statistical significance. Serum (+)-(S)-citalopram levels throughout the

TABLE 1. Pharmacokinetic parameters (mean ± SD) of citalopram (CT), demethylcitalopram (DCT), and didemethylcitalopram (DDCT) in humans following 21 days once-daily oral administration of *rac*-CT

	(−)-(R)-CT	(+)-(S)-CT	(−)-(R)-DCT	(+)-(S)-DCT	(−)-(R)-DDCT	(+)-(S)-DDCT
t_{max} (h)	3.3 ± 1.4	3.3 ± 1.4**	7.6 ± 7.0	6.5 ± 6.6**	19.6 ± 17.4	17.6 ± 29.0**
$C_{max,ss}$ (nmol/l)	228.4 ± 63.6	154.2 ± 64.5*	62.7 ± 17.5	46.3 ± 9.3*	13.4 ± 3.2	6.4 ± 1.4*
AUC_{ss} (h · nmol/l)	4193 ± 1181	2562 ± 1190*	1343 ± 357	967 ± 172*	284 ± 71	133 ± 21*
$C_{av,ss}$ (nmol/l)	174.7 ± 49.2	106.7 ± 49.6*	55.9 ± 14.9	40.3 ± 7.2*	11.9 ± 3.0	5.5 ± 0.9*
CL/F (l/h/kg)	0.26 ± 0.06	0.48 ± 0.22*	na	na	na	na
V_{ss}/F (l/kg)	16.4 ± 4.5	18.3 ± 4.7**	na	na	na	na
$t_{1/2}$ serum (h)	46.9 ± 10.6	34.8 ± 4.3[b,*]	69.8 ± 18.8	50.6 ± 12.7*	175.0 ± 83.3	nd
$t_{1/2}$ urine (h)	46.9 ± 7.5	31.3 ± 6.9*	64.5 ± 15.7	42.3 ± 8.7*	101.6 ± 29.0[c]	59.9 ± 11.8[d,*]
CL_R (l/h/kg)	0.06 ± 0.02	0.06 ± 0.02*	0.13 ± 0.03	0.13 ± 0.03*	0.16 ± 0.02	0.13 ± 0.03*
CL_{NR} (l/h/kg)	0.19 ± 0.04	0.42 ± 0.21*	na	na	na	na
$Ae_{\%dose}$ (%)	12.1 ± 2.1	6.6 ± 2.3*	8.1 ± 2.2	6.2 ± 1.1*	2.2 ± 0.6	0.9 ± 0.2*
Enantiomeric ratio (AUC_{ss})	0.59 ± 0.15		0.74 ± 0.08		0.48 ± 0.06	

[a]na, not applicable, [b]n = 6, [c]n = 8, [d]n = 9: serum $t_{1/2}$ values in several subjects could not be determined due to an inadequate number of data points in the terminal elimination phase.
*Significant ($P < 0.05$) and **not significant in statistical comparison of (−)-(R) and (+)-(S) enantiomers.

steady-state dosing interval investigated were 37 ± 6% (range: 21–46%) of *rac*-citalopram concentrations. This compares favourably with the 24–49% value for plasma concentration ratios of (+)-(S)/(R,S)-citalopram recently reported in depressive patients.[6] Steady-state levels of (+)-(S)-DCT and (+)-(S)-DDCT were 36–48% and 24–39%, respectively, of their racemic concentrations. Based on comparisons of individual data, the serum $t_{1/2}$ of (−)-(R)-citalopram was 46 ± 25% longer, CL/F 41 ± 16% lower, CL_R 9 ± 6% higher, and AUC_{ss} 83 ± 55% higher than respective values for (+)-(S)-citalopram. Enantiomeric differences in the pharmacokinetic parameters of DCT and DDCT were of the same order of magnitude. These enantiomeric differences were consistent between smokers and nonsmokers.

Compared with citalopram, there was markedly greater variability in t_{max} for DCT and DDCT, reflecting interindividual variability in metabolic formation rates. Importantly, variability in pre-dose concentrations, which themselves are governed by intrinsic clearance, were similar between the (−)-(R)- and (+)-(S)-enantiomers of each compound.

There may be several explanations behind the observed enantiomeric differences in the pharmacokinetics of citalopram and its metabolites. Although not presently or previously investigated, enantiospecificity in drug release from dosage form and in absorption of citalopram is not considered likely to be a contributory factor. This view finds support in the identical t_{max} values observed for the enantiomers of citalopram. In addition, enantioselectivity in absorption is only to be expected for active processes, e.g., as for L-dopa and methotrexate.[7]

In pharmacological investigations of stereoisomeric compounds it is important to understand the configurational lability of the individual enantiomers. For the majority of chiral compounds, the barriers to racemisation are usually too great for this phenomenon to occur readily in relation to the time of drug residence in the body under physiological conditions.[7] The in vitro racemisation investigation undertaken in this study showed no interconversion of individually spiked enantiomers of citalopram, DCT, and DDCT in human plasma and urine under various storage conditions. In addition, the enantiomers of citalopram and its metabolites have been shown to be configurationally stable under various analytical working conditions.[8] Enzymatically mediated chiral interconversion, as has been reported to occur for the (R)-enantiomers of 2-arylpropionic acids via coenzyme *A* thioester formation,[9] typically results from a sequence of several reactions.[10] For citalopram, this phenomenon would not appear to be facile as it would necessitate ring opening and a subsequent ring closure. Thus, we do not consider racemisation to be a credible factor in understanding the enantiomeric disposition of citalopram and its metabolites.

Nonrenal clearances (87 ± 5% and 76 ± 4% of CL/F for (+)-(S)- and (−)-(R)-citalopram, respectively) demonstrated a significant biotransformation of both citalopram enantiomers. Citalopram is metabolised mainly by demethylation to DCT, DDCT, and by deamination and dehydrogenation to a propionic acid derivative, but also by N-oxidation and glucuronide conjugation.[3,8] Compared with citalopram, the metabolites are less potent SSRIs in vitro, enter the brain less readily, and are present in lower concentrations.[1,3] The propionic acid derivative is without any pharmacological activity.[3] The observations with nonrenal and oral clearances suggest some enantiomeric specificity in these metabolic pathways involved in the elimination of citalopram and its metabolites. The *N*-demethylation of citalopram is thought to be mediated by CYP3A4 and CYP2C19, whereas that of DCT is largely under the control of CYP2D6.[11,12] More specifically, there is in vitro and some in vivo evidence that (+)-(S)-citalopram is preferentially metabolised by CYP3A4 and CYP2C19 and that CYP2D6 also contributes to citalopram demethylation, but with opposite stereoselectivity.[13]

In this study, enantiomeric (S/R) ratios for citalopram and its metabolites were always less than unity and were

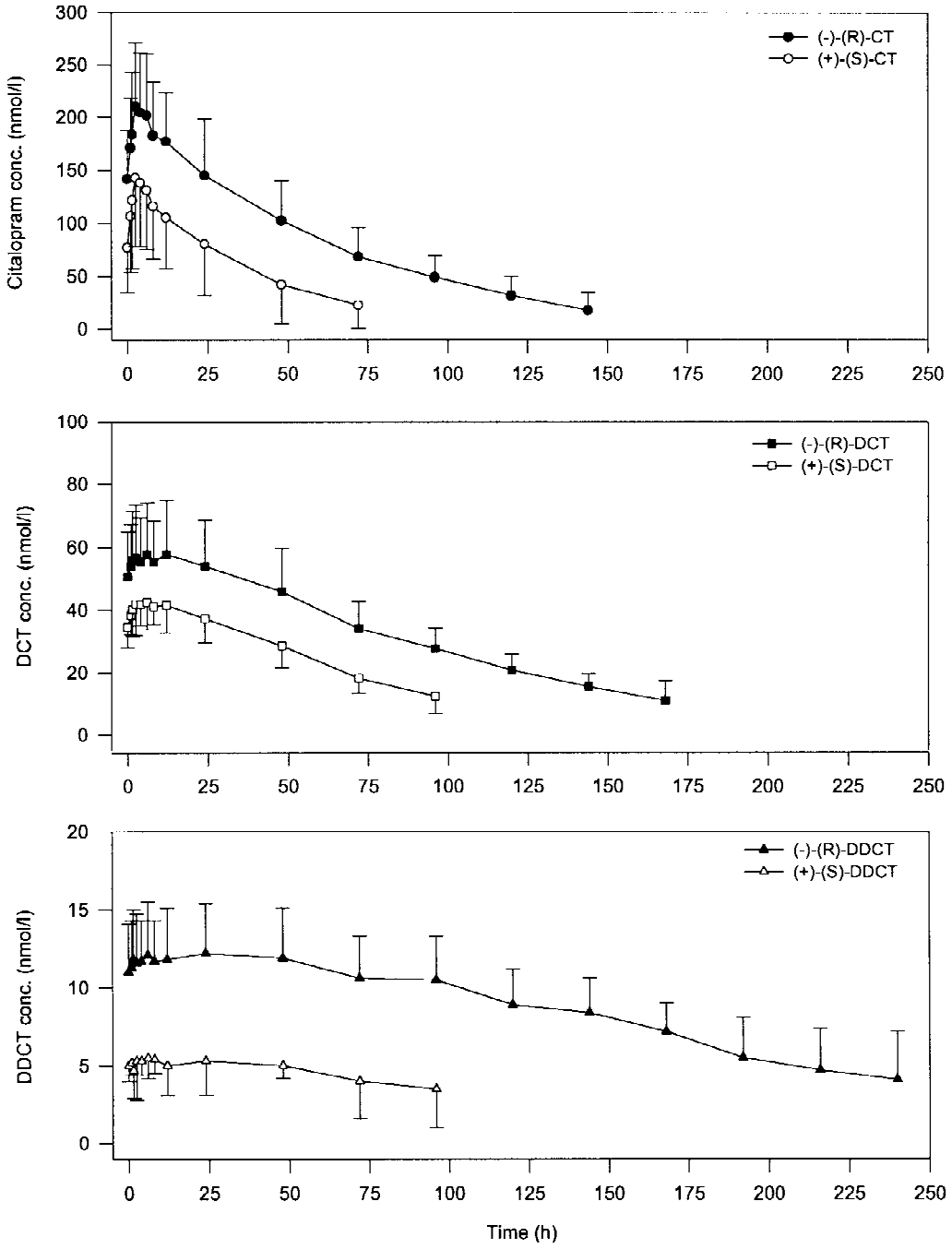

Fig. 3. Mean (±SD) serum concentration vs. time profiles for citalopram (CT), DCT, and DDCT on Day 21 following once-daily oral administration of 40 mg *rac*-citalopram to ten healthy subjects. Mean concentrations below the limit of quantification are not plotted.

consistent with those reported (0.7 ± 0.1 for citalopram and 0.8 ± 0.1 for DCT) for 5 patients in whom plasma samples were collected at least 12 h postdose after more than a week of citalopram dosing.[8] Similar (S/R) ratios have been found in a cohort of female patients.[13] In addition, (S/R) serum concentration ratios in the present study were fairly constant throughout the steady-state dosing interval. That the enantiomeric ratios were higher and closer to unity for DCT than for citalopram may indicate intrinsically less stereoselectivity in the disposition of this chiral metabolite or, alternatively, reflect the lower demethylation rate of the (−)-(R)- relative to the (+)-(S)-enantiomer. Further credence to this point may lie in the metabolic ratio for DCT, which was slightly, though significantly, lower for the (−)-(R)- than for the (+)-(S)-enantiomer. Similarly, concentration ratios of citalopram/DCT of 1.9 ± 0.6 and 2.5 ± 0.7 for (+)-(S)- and (−)-(R)-enantiomers, respectively, have recently been reported in female patients.[13]

A slight degree of stereoselectivity (in favour of the (−)-(R)-enantiomer for citalopram and DDCT and of the (+)-

TABLE 2. Excretion (ER) and metabolic (MR) ratios for (−)-(R) and (+)-(S) enantiomers of DCT and DDCT at steady-state after repeated oral administration of *rac*-citalopram to healthy subjects

	ER	MR
(−)-(R)-DCT	0.69 ± 0.25	0.33 ± 0.09
(+)-(S)-DCT	1.09 ± 0.61*	0.46 ± 0.23*
(−)-(R)-DDCT	0.19 ± 0.06	0.07 ± 0.03
(+)-(S)-DDCT	0.15 ± 0.07**	0.06 ± 0.04**

*Significant ($P < 0.05$) and **not significant in statistical comparison of (−)-(R) and (+)-(S) enantiomers.

(S)-enantiomer of DCT) was noted in CL_R, though the significance of this is questionable in light of the small magnitudinal differences involved and the predominance of hepatic clearance in the overall elimination of citalopram. It was also observed that excretion ratios for the metabolites were approximately twice as high as their metabolic ratios (Table 2). Importantly, the differences between the ratios were magnitudinally similar for the enantiomers of each metabolite. The higher excretion ratios may be explained by a greater urinary excretion of the (more polar) metabolite relative to the parent compound and by a greater contribution of renal secretion to the CL_R of the metabolites. In an earlier investigation, cimetidine, a known inhibitor of the carrier-mediated secretion of organic bases,[14] was shown to significantly decrease the CL_R of DCT and DDCT but not of citalopram.[15]

A further explanation to the enantiospecificity seen in citalopram pharmacokinetics could lie in distribution volume. However, the enantiomeric difference in V_{ss}/F was slight (9 ± 18% lower for (−)-(R)- relative to (+)-(S)-citalopram) and statistically insignificant, and discordant with the observed enantiomeric differences in citalopram half-lives. Although not presently investigated, enantiospecificity in protein binding would be of minor importance in light of the observed enantiomeric differences in citalopram CL/F as citalopram is only moderately bound to plasma proteins.

A gender-related difference was noted in the pharmacokinetics of citalopram, which resulted in an approximately 80% higher AUC_{ss} of *rac*-citalopram in females compared with males. Both CL/F (0.41 ± 0.11 vs. 0.28 ± 0.06 l/h/kg) and V_{ss}/F (20.8 ± 4.4 vs. 14.4 ± 1.9 l/kg) for *rac*-citalopram were higher in males than in females. Accordingly, half-life values were similar between the genders. These gender differences were not present for DCT or DDCT, were greater for (+)-(S)- than for (−)-(R)-citalopram, and could not be accounted for by smoking. Enantiomeric ratios for citalopram were lower in males (0.46 ± 0.14 vs. 0.68 ± 0.09). There were no apparent gender differences in renal clearances for the various compounds. Notably, there was similar pharmacokinetic variability for citalopram and its metabolites between the genders. Times to achieve maximal serum citalopram concentrations were slightly longer (on average 13%) in females, though this difference from males was not enantiospecific. With the present data it is difficult to elucidate the mechanisms behind the observed gender-related differences. With similar terminal-phase half-lives between males and females, a gender-related difference in F, the fraction of the dose reaching the systemic circulation, appears to be implicated. It is of interest to note that a multicentre trial of citalopram in 520 patients aged between 18–65 years (dose: 10–60 mg/day) did not show any gender difference in citalopram levels once body weight was taken into consideration (Overø, personal communication). Further, in 169 psychiatric patients (10–84 years), weight-related total citalopram and DCT levels were reported not to be consistently different between men and women, nor were there gender differences in the demethylated fraction.[16]

CONCLUSION

In this group of healthy subjects, a modest, but statistically significant, stereoselectivity in the disposition of citalopram and its two main metabolites (DCT and DDCT) was observed after steady-state *rac*-citalopram dosing. The precise nature of the stereoselective differences in the pharmacokinetics of citalopram and its primary metabolites (e.g., differences in renal secretion, macromolecular binding, or in metabolic pathways) was not discernible in the present study. However, it is apparent that the observed enantiospecificites were more related to clearance, rather than to distribution mechanisms.

In conclusion, this investigation in healthy subjects demonstrated that the variability in the pharmacokinetic parameters of citalopram was comparable between its enantiomers. Further, (S/R) serum concentration ratios for citalopram were always less than unity throughout a 240 h blood sampling period and were constant during the steady-state dosing interval.

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