Investigation of multiple dose citalopram on the pharmacokinetics and pharmacodynamics of racemic warfarin

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Aims An open, controlled, randomized, crossover study was conducted in healthy males to assess the possible occurrence of a pharmacokinetic/pharmacodynamic interaction between warfarin and the selective serotonin re-uptake inhibitor citalopram.

Methods Twelve subjects received a single 25 mg dose of racemic warfarin either alone or on Day 15 of a 21-day oral dosing regimen of 40 mg citalopram daily. Blood samples for pharmacokinetic analysis were obtained over a 168 h period after warfarin dosing. The degree of anticoagulation was assessed by the prothrombin time.

Results Citalopram produced no change in the pharmacokinetics of (R)- and (S)-warfarin, indicating that citalopram does not alter the metabolism of warfarin mediated via CYP1A2, CYP3A4 and CYP2C9. Citalopram coadministration resulted in a statistically significant increase in the maximum prothrombin time (R_{max}; by 1.6 ± 3.0 s) and the area under the prothrombin time-time curve (AUC_{PT}; by $5.0 \pm 5.7\%$). The 90% confidence intervals for R_{max} and AUC_{PT} ratios (citalopram + warfarin/warfarin alone) were $1.01-1.10$ and $1.03-1.07$, respectively.

Conclusions The small increase in prothrombin time observed in this study with coadministration of citalopram and warfarin is not considered to be of importance in the clinical setting.

Keywords: (R)- and (S)-warfarin, citalopram, drug-drug interaction, pharmacokinetics, pharmacodynamics

Introduction

Citalopram is an antidepressant belonging to a class of drugs that selectively and potently inhibit serotonin re-uptake into central neurons [1]. The oral chiral anticoagulant warfarin has been shown to be involved in a number of drug-drug interactions resulting in changes in its pharmacokinetics as well as in hypoprothrombinaemic response [2]. (R)-warfarin is approximately 5–8 times less potent an oral anticoagulant than (S)-warfarin in humans [3]. Warfarin is eliminated almost entirely by hepatic CYP450 enzymes, in a partially stereospecific manner. Stereoselective metabolism by the CYP2C9 isozyme leads to the 7-hydroxylation of (S)-warfarin [4, 5] and CYP1A2 and CYP3A4 may contribute to (S)-warfarin's elimination [4]. CYP3A4 may also be involved in the metabolism of (R)-warfarin [4] and there is also nonstereoselective degradation of warfarin. Thus, the possibility of metabolic interactions cannot be discounted. Citalopram elimination is largely mediated via oxidative metabolism, with *N*-demethylation being the quantitatively most important step [6]. Though citalopram has not been observed to be an inhibitor of CYP1A2 or CYP3A *in vitro* [7], a weak inhibition of CYP2D6 and of the metabolism of mephenytoin (CYP2C19) *in vivo* has been reported [8].

The present study was undertaken to evaluate the effects of chronic citalopram dosing on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects.

Methods

Twelve, healthy male subjects aged between 21 and 32 years and weighing between 63 and 90 kg participated in the study, which was approved by the Medeval Independent Ethics Committee. A complete physical examination as well as routine biochemical and haematological tests were performed to ensure that the subjects were medically fit. No abnormalities in the haematological tests were accepted for study inclusion. Each subject provided his written approval for participation before entering the study.

The study consisted of an open, controlled, randomized, two-way cross-over design. Each subject received a single dose of 25 mg *rac*-warfarin (5 × 5 mg Marevan® tablets) either alone (Treatment A) or on Day 15 (Treatment B) of a 21-day dosing regimen of 40 mg citalopram (H. Lundbeck A/S, Copenhagen, Denmark) administered as a single daily dose. A washout period of at least 14 days occurred between treatments. Blood samples were taken from an indwelling venous catheter (no heparin) at 0, 0.5, 1, 2, 4, 8, 10, 12, 24, 36, 48, 60, 72, 96, 120, 144, and 168 h after warfarin administration. On Days 12, 13 and 14 of the 21-day dosing regimen of citalopram, blood samples were taken and analysed to assure that steady-state was reached. The degree of anticoagulation was assessed by the prothrombin time as

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described by Quick [9]. Prothrombin times were determined daily on the 3 days preceding warfarin administration to determine baseline values and to evaluate whether citalopram had any anticoagulant effect. Subsequently, prothrombin times were determined at 0, 4, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144 and 168 h after warfarin administration.

The concentrations of warfarin enantiomers in plasma were measured simultaneously by h.p.l.c. analysis with fluorescence detection [10]. Neither citalopram nor its metabolites, demethylcitalopram or didemethylcitalopram, were found to interfere with the analysis. The lower limit of quantification for (S)- and (R)-warfarin in plasma was $0.15 \, \text{mg} \, \text{l}^{-1}$, with linearity up to $2.38 \, \text{mg} \, \text{l}^{-1}$. The within-day imprecision was below 8% for both enantiomers. Predose citalopram concentrations were quantified by h.p.l.c. based on the method of Øyehaug *et al.* [6].

Pharmacokinetic parameters of (S)- and (R)-warfarin were determined by non-compartmental methods [11]. The pharmacokinetic and pharmacodynamic parameters (maximal concentration (C_{max}), AUC(0, 168h), oral clearance (CL/F), apparent volume of distribution (V_z/F), maximum prothrombin time (R_{max}) and the area under the prothrombin

time *vs* time curve (AUC_{PT})) between treatment groups were compared using two-way analyses of variance on the log transformed data. Times to reach maximum plasma concentration (t_{max}) and to reach maximum prothrombin time ($t_{max,PT}$) were compared using a Wilcoxon's matched-paired test. With 12 subjects, there was a 90% power to detect a 3% difference in AUC_{PT} between treatments.

Results and discussion

Measurement of pre-dose serum citalopram concentrations (Day 12 (mean $\pm$ s.d.): $205 \pm 47 \, \text{nmol} \, \text{l}^{-1}$, Day 13: $201 \pm 46 \, \text{nmol} \, \text{l}^{-1}$ and Day 14: $200 \pm 44 \, \text{nmol} \, \text{l}^{-1}$; intra-individual variability (CV) $= 4.1 \pm 2.5\%$.) indicated that steady-state had been reached. Baseline prothrombin times were not affected by repeated administration of citalopram.

The pharmacokinetic [12, 13] and pharmacodynamic [13] outcomes for warfarin in this study are consistent with that previously reported. Major drug interactions involving warfarin that result in marked changes in the hypoprothrombinaemic response in most individuals have been found to arise from changes in the pharmacokinetics of (S)-warfarin
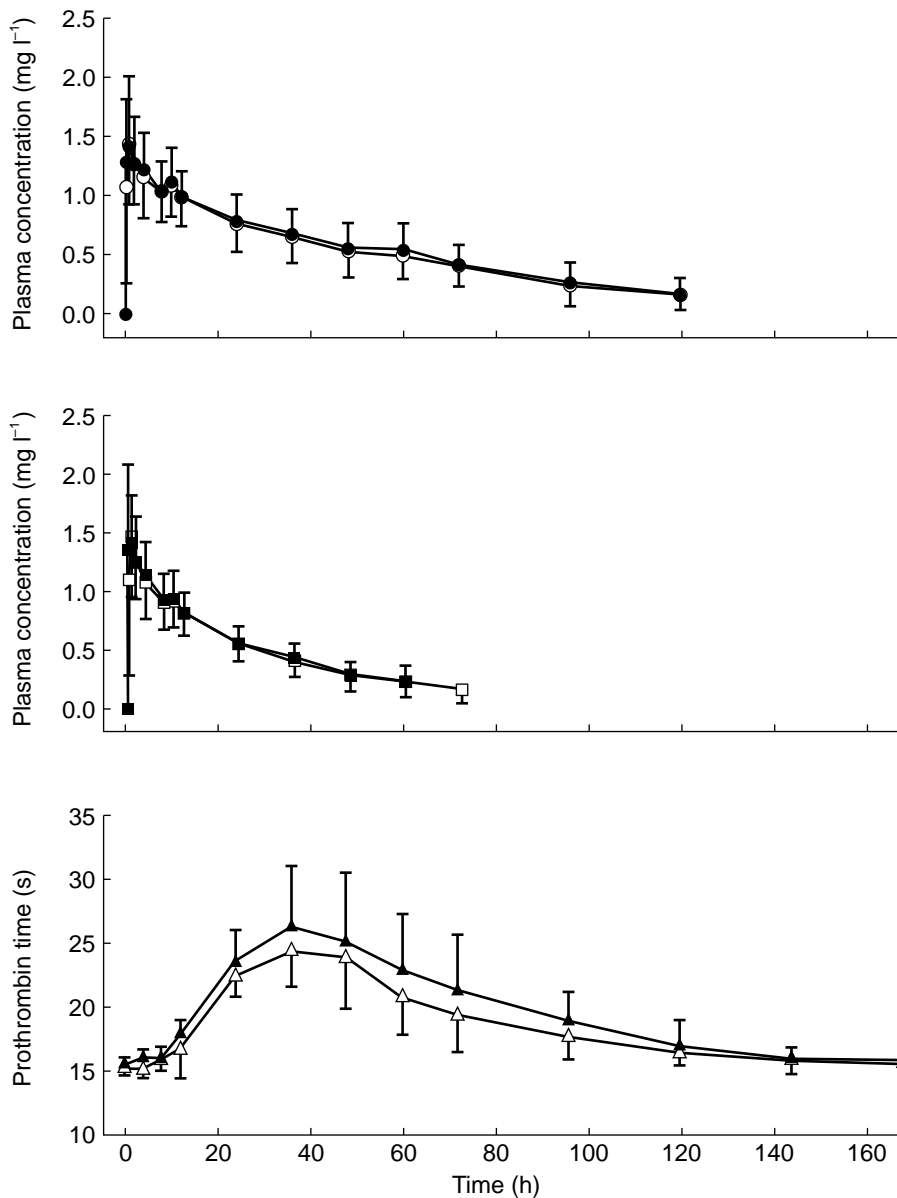
Figure 1 Effects of citalopram on (R)- (○ alone; ● +citalopram) and (S)- (□ alone; ■ +citalopram) warfarin plasma concentrations (mean $\pm$ s.d.; $n = 12$) and on prothrombin time (△ warfarin alone; ▲ warfarin + citalopram). Mean plasma levels below the limit of quantification ($0.15 \, \text{mg} \, \text{l}^{-1}$) are not plotted.

Table 1 Mean (s.d.) pharmacokinetic and pharmacodynamic parameters for (R)- and (S)-warfarin alone and in the presence of repeated citalopram administration ($n = 12$/treatment).

Parameter	Warfarin alone		Warfarin + citalopram	
	(R)-warfarin	(S)-warfarin	(R)-warfarin	(S)-warfarin
C_{max} (mg l^{-1})	1.6 (0.6)	1.6 (0.6)	1.6 (0.5)	1.6 (0.5)
t_{max} (h)[#]	1 (0.5–10)	1 (0.5–2)	0.75 (0.5–4)	0.5 (0.5–4)
AU(0, 168h) (mg h l^{-1})	79.7 (30.1)	46.3 (14.9)	80.1 (29.3)	46.5 (13.7)
$t_{1/2,z}$ (h)	47.0 (8.7)	32.8 (12.0)	44.4 (6.5)	31.2 (9.4)
CL/F (l h^{-1})	0.18 (0.07)	0.31 (0.13)	0.18 (0.06)	0.29 (0.09)
V_z/F (l)	11.7 (3.3)	13.1 (3.3)	10.9 (2.9)	12.5 (2.9)
R_{max} (s)	25.1 (3.7)		26.7 (5.1)★	
$t_{max,PT}$ (h)[#]	36 (24–48)		36 (24–48)	
AUC_{PT} (s h)	3098 (248)		3260 (402)★	

[#]median (range). $P < 0.05$ for statistical comparison between treatment groups.

[14, 15]. Concomitant administration of citalopram did not affect the plasma levels of either (R)- or (S)-warfarin (Figure 1). In this acute study, the single dose pharmacokinetics of warfarin did not show any statistically significant changes between treatment groups (Table 1), indicating that citalopram does not alter the metabolism of warfarin mediated via CYP1A2, CYP3A4 and CYP2C9. Such single dose studies undertaken to investigate warfarin-drug interactions have effectively reflected changes observed clinically during chronic warfarin dosing [14, 15].

Citalopram coadministration resulted in slight, though statistically significant, changes in warfarin pharmacodynamics (Figure 1 and Table 1). Notably, R_{max} increased by 1.6 ± 3.0 s (range: -2.7 to 7.0 s) and AUC_{PT} values increased by $5.0 \pm 5.7\%$ in the presence of citalopram compared with warfarin given alone. The 90% confidence intervals for R_{max} and AUC_{PT} ratios (Treatment B/Treatment A) were 1.01–1.10 and 1.03–1.07, respectively.

The slight increase in warfarin's anticoagulant effect observed during citalopram coadministration is consistent with that reported for another selective serotonin reuptake inhibitor, sertraline (8.9% increase in prothrombin time) [16]. Similarly, paroxetine has been found to increase bleeding time during warfarin dosing [17]. During coadministration with warfarin, fluvoxamine has been reported to increase plasma warfarin levels by 65%, resulting in an increase in the prothrombin time [18]. In addition, fluoxetine was noted to decrease the warfarin induced prothrombin time in three healthy subjects [19].

In conclusion, no pharmacokinetic interaction between citalopram and warfarin was found. The small increase in prothrombin time observed in this study with coadministration of citalopram and warfarin is not considered to be of importance in the clinical setting.

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