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Warfarin Enantiomers Pharmacokinetics by CYP2C19

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1. Introduction

Warfarin, a coumarin vitamin K antagonist, is the most widely prescribed anticoagulant agent for the control and prevention of atrial fibrillation-related thrombus formation, stroke, and arterial and venous thrombembolism (Hirsh J et al., 1998). The recommend warfarin therapy consists of the lowest dose required to maintain the target international normalized ratio (INR) because of the drug's narrow therapeutic window. However, there can be a 20-fold difference in the dose required by patients to achieve this target INR. It is well known that cytochrome P450 (CYP), predominantly CYP2C9, activity is an important source of variability (Kaminsky LS and Zhang ZY, 1997) . Additionally, Rieder et al. (2005) have reported that an effect of the vitamin K epooxide reductase complex subunit 1 gene (VKORC1) has an important role on dose requirement. However, Takahashi et al. (2006) shows that Caucasians and African-Americans have high frequencies of VKORC1 and CYP2C9 genotypes, which lead to either reduced metabolic activity or attenuated sensitivity to warfarin, whereas only about 20% of the Japanese population possesses these genotypes. Therefore, further study of sources of variability in warfarin dose requirements among Japanese patients is warranted.

Warfarin is administered clinically as a racemic mixture of the *S*- and *R*-enantiomer (Fig. 1), however *S*-warfarin is 3–5 times more potent than *R*-enantiomer. Both enantiomers are extensively metabolized in the liver (Chan E et al., 1994; Takahashi H and Echizen H, 2001). The more potent *S*-enantiomer is metabolized mainly to *S*-7-hydroxywarfarin by CYP2C9, whereas *R*-enantiomer is metabolized to *R*-6, *R*-7, *R*-8 and *R*-10-hydroxywarfarin by several CYPs involving CYP1A2, CYP3A4 and CYP2C19 (Kaminsky LS and Zhang ZY, 1997). Among these CYPs, it has been shown that both CYP2C9 and CYP2C19 are subject to single nucleotide polymorphisms (SNPs). In Japanese, because the heterozygous frequency of the CYP2C9 Leu359 allele is 3.5% (Takahashi H et al., 1998) and the frequency of the defective CYP2C19 alleles is 18.8% (Kubota T et al., 1996), the latter may be more closely associated with the clinical effect of warfarin. In this chapter, we therefore focus on the effect of CYP2C19 genotypes on the pharmacokinetics and pharmacodynamics of warfarin enantiomers. In addition, we characterize the impact of omeprazole, a CYP2C19 inhibitor, on the stereoselective pharmacokinetics and pharmacodynamics of warfarin between CYP2C19 genotypes.

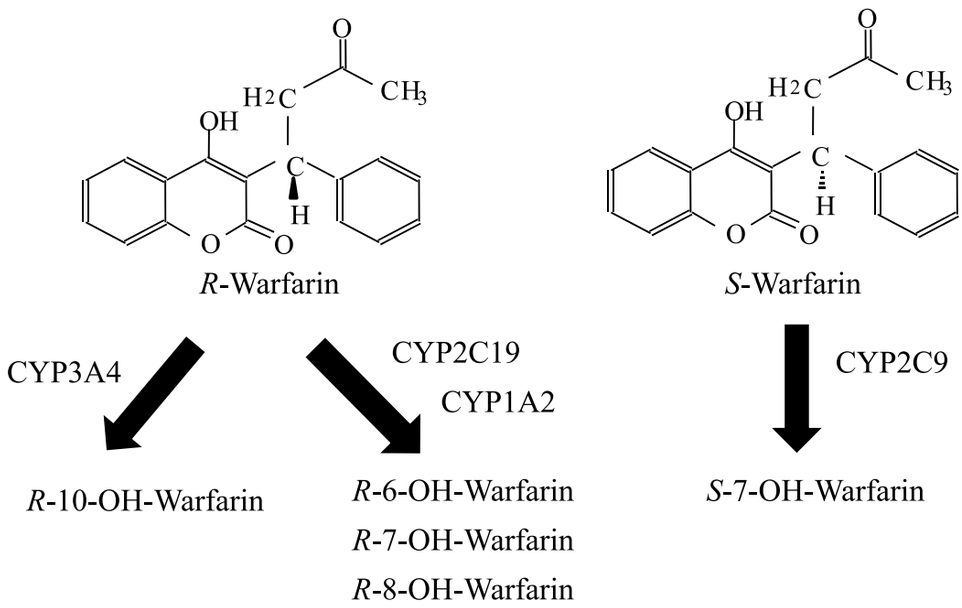

Fig. 1. Metabolic pathways of *R*-warfarin and *S*-warfarin.

2. Analytical methods

2.1 Genotypic identification

17 healthy Japanese volunteers (12 males and 5 females) were enrolled in this study after giving written informed consent. All subjects were enrolled in this study after giving written informed consent. Each Subject underwent a CYP2C19 genotyping test by use of a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method with allele–specific primer for identifying the *CYP2C19* wild-type (*1) gene and the 2 mutated alleles, *CYP2C19**2 (*2) in exon 5 and *CYP2C19**3 (*3) in exon 4 (De Morais SM et al., 1994), and they were classified into 2 genotype groups as follows: homozygous extensive metabolizers (hmEMs, *1/*1, 10 subjects), poor metabolizers (PMs, *2/*2 or *2/*3, 7 subjects). Similarly, CYP2C9 genotyping test by use of a PCR-RFLP method with allele–specific primer was performed for identifying the *CYP2C9* wild-type (*1) gene and the 2 mutated alleles, *CYP2C9*2* (Arg144Cys) and *CYP2C9*3* (Ile359Leu) (Yasar U et al., 1999). Alleles in which neither *CYP2C9**2 nor *CYP2C9**3 variants were identified were regarded as wild type in all subjects.

2.2 Assay

Plasma concentrations of warfarin enantiomers and *S*-7-hydoxywarfarin were determined using high performance liquid chromatography (HPLC) method developed in our laboratory (Uno T et al., 2007). In brief, warfarin enantiomers, *S*-7-hydroxywarfarin and an internal standard, diclofenac sodium, were extracted from 1 ml of plasma sample using diethyl ether-chloroform (80:20, v/v). The extract was injected onto column I (TSK precolumn BSA-C8, 5 μm, 10 mm x 4.6 mm i.d.) for clean-up and column II (Chiralcel OD-RH analytical column, 150 mm x 4.6 mm i.d.) coupled with a guard column (Chiralcel OD-

RH guard column, 10 mm x 4.6 mm i.d.) for separation. The mobile phase consisted of phosphate buffer-acetonitrile (84:16 v/v, pH 2.0) for clean-up and phosphate buffer-acetonitrile (45:55 v/v, pH 2.0) for separation. The peaks were monitored with an ultraviolet detector set at a wavelength of 312 nm, and total time for chromatographic separation was about 25 minutes. The retention times of *S*-7-hydoxywarfarin, *R*-warfarin, I.S. and *S*-warfarin were 17.6 min, 19.1 min, 20.0 min and 21.2 min, respectively. The validated concentration ranges of this method were 3-1000 ng/ml for *R*- and *S*-warfarin, and 3-200 ng/ml for *R*- and *S*-7-hydroxywarfarin, respectively. Intra- and inter-day coefficients of variation were less than 4.4 and 4.9% for *R*-warfarin and 4.8 and 4.0% for *S*-warfarin, and 5.1 and 4.2% for *R*-7-hydroxywarfarin and 5.8 and 5.0% for *S*-7-hydroxywarfarin at the different concentrations. The limit of quantification was 3 ng/ml for both warfarin and 7-hydroxywarfarin enantiomers. Plasma samples for the pharmacokinetic study were stored at -20 ˚C and analyzed within 3 months after sampling, and then were stable at -70 ˚C for 12 months.

Plasma concentrations of omeprazole and 5-hydroxyomeprazole were quantitated using HPLC method developed in our laboratory (Shimizu M et al., 2006). In brief, after alkalization with 0.1 mL of 0.5 M disodium hydrogen phosphate, 1 mL plasma was extracted with 4 mL of diethyl ether-dichloromethane (55:45, v/v). The organic phase was evaporated at 60 ˚C to dryness. The residue was dissolved with 30 μL of methanol and 100 μL of 50 mM disodium hydrogen phosphate buffer (pH 9.3), and then a 30-μL aliquot was injected to an HPLC system (SHIMADZU CLASS-VP, SHIMADZU Corporation, Kyoto, Japan), with a Inertsil ODS-80A column as an analytical column (particle size 5 μm; GL Science Inc, Tokyo, Japan). The mobile phase consisted of phosphate buffer-acetonitrile-methanol (65:30:5 v/v/v, pH6.5). Flow rate was 0.8 mL/min and wavelength was set at 302 nm. Limit of quantification was 3 ng/mL for omeprazole and 5-hydroxyomeprazole. Intra- and inter-day coefficient variations were less than 5.1 and 6.6% for omeprazole concentrations ranging from 4 to 1600 ng/mL and 4.6 and 5.0% for 5-hydroxyomeprazole concentration ranging from 4 to 400 ng/mL, respectively.

3. Pharmacokinetics of warfarin enantiomers

We examined the pharmacokinetics of warfarin enantiomers by administering 10 mg of racemic warfarin to 17 healthy volunteers (Uno T et al., 2008). Blood samples were obtained before and over the course of 120 hours after dosing for the determination plasma warfarin enantiomer concentrations and prothrombin time-INR (PT-INR). Fig. 2 shows the mean plasma concentration-time curves for *R*- and *S*-warfarin between the CYP2C19 genotypes. The mean pharmacokinetic parameters of these compounds are summarized in Table 1.

In this study, the area under the plasma concentration-time curve ($AUC_{0-\infty}$) and the elimination half-life ($t_{1/2}$) of *R*-warfarin were about 2-fold greater than those of *S*-warfarin in 17 subjects (Table 1). These values of *R*- and *S*-warfarin were in line with a previous report in which the same dose of racemic warfarin was administered (Lilja JJ et al., 1984). Additionally, $AUC_{0-\infty}$ and $t_{1/2}$ of *R*-warfarin in PMs were significantly greater than those in hmEMs ($P < 0.001$ and $P = 0.010$, respectively). Similarly, there is a significant difference ($P = 0.007$) in the apparent oral clearance (CL) in hmEMs compared with that in PMs. The *S*/*R* ratios of $AUC_{0-\infty}$ of warfarin enantiomers were 0.51 in hmEMs and 0.37 in PMs ($P = 0.005$). Whereas, no difference was found in all pharmacokinetic parameters of *S*-warfarin and *S*-7-hydroxywarfarin in hmEMs compared with PMs of CYP2C19.

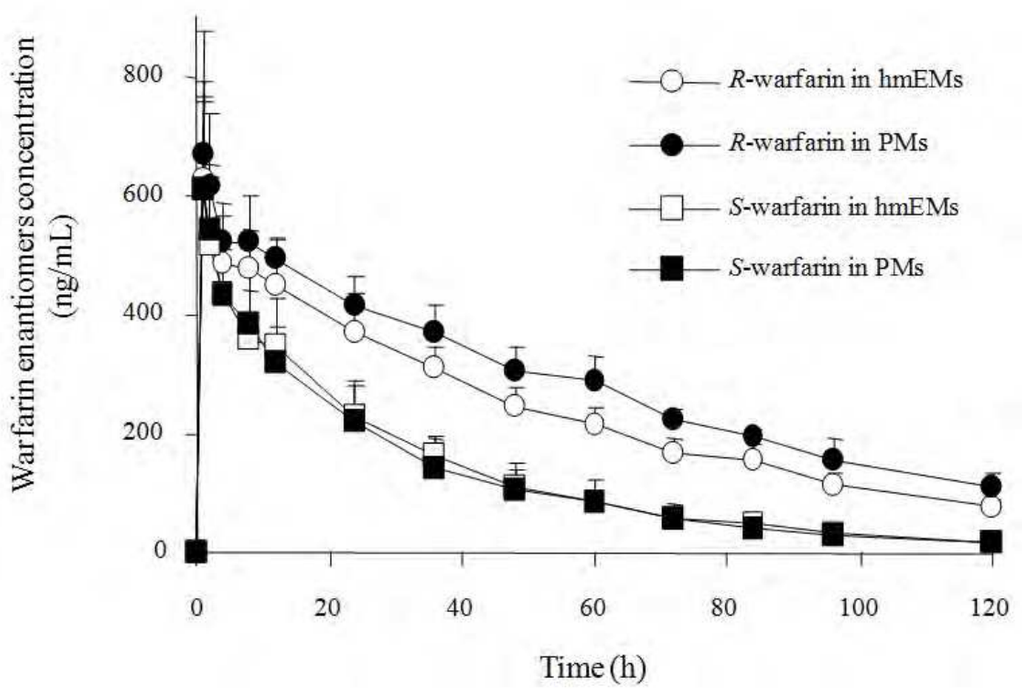

Fig. 2. Plasma concentrations-time curves (mean + S.D.) of *R*-warfarin or *S*-warfarin in hmEMs (*R*-; open circles, *S*-; open square) and PMs (*R*-; closed circles, *S*-; closed square) after a single dose of 10 mg warfarin.

4. Drug interaction between omeprazole and warfarin enantiomers

Omeprazole 20 mg/daily was given orally to 17 healthy volunteers for 11 days, and on day 7, a single dose of racemic warfarin 10 mg was added (Uno T et al., 2008).

The pharmacokinetic parameters are summarized in Table 1. In hmEMs, the omeprazole treatment significantly increased *R*-warfarin $AUC_{0-\infty}$ ($P = 0.004$), and prolonged its $t_{1/2}$ ($P = 0.017$) without any effect on *R*-warfarin C_{max} or t_{max}. However, the omeprazole treatment did not alter any pharmacokinetic parameters of *S*-warfarin in both hmEMs and PMs as well as those of *R*-warfarin in hmEMs. Consequently, the omeprazole treatment decreased the *S*/*R* enantiomer ratio of warfarin $AUC_{0-\infty}$ from 0.51 to 0.43 in hmEMs ($P = 0.010$), but not in PMs.

In addition, significant differences were found in mean C_{max} ($P < 0.001$), $t_{1/2}$ ($P = 0.005$), and AUC_{0-24} ($P < 0.001$) of omeprazole between different CYP2C19 genotypes, though there was no difference in mean C_{max} or AUC_{0-24} of 5-hydroxyomeprazole between hmEMs and PMs.

Variable	hmEMs			PMs		
	Control	Omeprazole	Fold change	Control	Omeprazole	Fold change
***R*-warfarin**						
C_{max} (ng/mL)	692 (616, 768)	629 (556, 702)	0.92 (0.70-1.18)	706 (599, 813)	589 (474, 703)	0.84 (0.55-1.08)
t_{max} (h)	1.4 (0.8, 2.0)	3.3 (1.3, 5.3)	3.02 (0.25-12)	2.6 (0.6, 4.5)	3.6 (0.6, 6.5)	2.79 (0.5-12)
$t_{1/2}$ (h)	40.8 (36.1, 45.6)	46.4 (44.2, 48.7)†	1.12 (0.96-1.27)	49.6 (46.9, 52.3)*	48.8 (42.5, 55.0)	0.97 (0.63-1.18)
$AUC_{0-\infty}$ (ng*h/mL)	34613 (32702, 36524)	41387 (37221, 45552)††	1.19 (1.02-1.39)	42938 (39342, 46533)**	39100 (34802, 43399)	0.92 (0.74-1.08)
CL (mL*kg/h)	2.4 (2.1, 2.5)	2.1 (1.8, 2.2)††	0.87 (0.72-1.09)	1.9 (1.6, 2.3)**	2.1 (1.6, 2.6)	1.12 (0.93-1.36)
***S*-warfarin**						
C_{max} (ng/mL)	659 (570, 748)	600 (528, 673)	0.93 (0.62-1.36)	630 (520, 739)	554 (469, 638)	0.90 (0.69-1.12)
t_{max} (h)	1.3 (0.7, 1.9)	1.7 (1.1, 2.3)	1.63 (0.25-2)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.07 (0.5-2)
$t_{1/2}$ (h)	25.4 (22.0, 28.9)	27.0 (21.3, 32.8)	1.13 (0.50-1.80)	22.7 (19.7, 25.8)	25.4 (21.7, 29.0)	1.13 (0.82-1.37)
$AUC_{0-\infty}$ (ng*h/mL)	16968 (15233, 18701)	18166 (15705, 20628)	1.07 (0.87-1.54)	15851 (12686, 19016)	14756 (11768, 17745)	0.93 (0.78-1.03)
CL (mL*kg/h)	5.0 (4.6, 5.4)	4.7 (4.1, 5.3)	0.95 (0.65-1.13)	5.6 (4.7, 6.4)	6.0 (4.9, 7.1)	1.08 (0.97-1.28)
The S/R ratios of $AUC_{0-\infty}$	0.51 (0.47, 0.54)	0.43 (0.40, 0.46)††	0.82 (0.76-0.88)	0.37 (0.31, 0.43)***	0.38 (0.31, 0.44)	1.05 (0.98-1.12)
***S*-7-hydroxywarfarin**						
C_{max} (ng/mL)	69.8 (61.7, 77.8)	72.0 (62.8, 81.2)	1.03 (0.91-1.18)	68.1 (63.1, 73.1)	67.6 (63.0, 72.2)	1.00 (0.83-1.08)
t_{max} (h)	18.0 (13.0, 23.0)	26.0 (19.7, 32.3)	2.35 (1.0-12.0)	24.0 (16.7, 27.5)	18.9 (9.1, 28.6)	0.74 (0.3-1.5)
$t_{1/2}$ (h)	28.8 (19.3, 38.2)	25.2 (20.5, 30.0)	1.07 (0.33-2.14)	22.1 (16.7, 27.4)	24.6 (16.3, 33.0)	1.24 (0.39-2.41)
$AUC_{0-\infty}$ (ng*h/mL)	2584 (1997, 3171)	2695 (2101, 3289)	1.06 (0.87-1.21)	2471 (1982, 2959)	2429 (2065, 2792)	1.00 (0.85-1.13)
The metabolic ratio	0.15 (0.12, 0.19)	0.16 (0.12, 0.19)	1.04 (0.89-1.11)	0.17 (0.11, 0.24)	0.18 (0.12, 0.24)	1.03 (0.97-1.22)

AUC, area under plasma concentration-time curve; C_{max}, peak concentration; t_{max}, time to C_{max}; $t_{1/2}$, elimination half-life; CL, apparent oral clearance. The S/R ratios of AUC; $AUC_{0-\infty}$ *S*-warfarin / $AUC_{0-\infty}$ *R*-warfarin. The metabolic ratio; $AUC_{0-\infty}$ of *S*-7-hydroxywarfarin / $AUC_{0-\infty}$ of *S*-warfarin.
$^{*}P$ <0.05,$^{**}P$ <0.01, $^{***}P$ <0.001, between hmEMs and PMs., †P <0.05,††P <0.01, between control and omeprazole phase. Data are shown as mean and 95% confidence interval ; t_{max} and fold change data are shown as a median wich a range.

Table 1. The summary of pharmacokinetics of warfarin enantiomers

5. Pharmacodynamics of warfarin

No significant difference was found between hmEMs and PMs in either the PT-INR AUC_{0-120} or the PT-INR max during the placebo phase, and the omeprazole treatment did not affect these parameters in both hmEMs and PMs (Uno T et al., 2008).

6. The effect of CYP2C19 genotypes on the pharmacokinetics

Previous studies in patients with different CYP2C19 genotypes reported not to affect plasma *R*-warfarin concentrations at the steady state in clinical studies, in which the concentrations were evaluated at a one sampling point (Obayashi K et al., 2006; Scordo MG et al., 2002; Takahashi et al., 1998). However, two of the reports (Obayashi K et al., 2006; Scordo MG et al., 2002) observed that the *S*/*R* ratio based on steady-state concentrations in PMs was smaller than that in hmEMs. The third study (Takahashi et al., 1998) compared PMs with EMs which included both hmEMs and heterozygous EMs with one mutated CYP2C19 allele. Therefore, the present study was designed to evaluate the elimination phase of warfarin and examine the effect of the CYP2C19 genotype on the pharmacokinetics of warfarin enantiomers. Although the pharmacokinetics was measured after a single administration in this study, our results indicated that the plasma concentrations and $t_{1/2}$ of *R*-warfarin in PMs were markedly higher compared with those of the corresponding *R*-enantiomer in hmEMs. In addition, the $AUC_{0-\infty}$ *S*/*R* ratio in PMs decreased significantly more than that in hmEMs, thereby showing that the

pharmacokinetics of *R*-warfarin may be significantly affected by CYP2C19 polymorphism. In contrast, no difference was found in any pharmacokinetic parameters of *S*-warfarin between the hmEMs and the PMs. Consequently, these findings suggest that CYP2C19 activity is an important determinant of *R*-warfarin pharmacokinetics.

We also demonstrated that the reported interaction of *R*-warfarin with omeprazole was found only in the hmEMs of CYP2C19. In previous pharmacokinetic studies (Sutfin T et al., 1989; Unge P et al., 1992), omeprazole has been reported to cause a minor but significant increase in *R*-warfarin plasma concentrations [9.5% (Unge P et al., 1992) and 12% (Sutfin T et al., 1989)]. In our present study, although the pharmacokinetics of warfarin enantiomers of the PMs were not affected by the omeprazole treatment, mean *R*-warfarin $AUC_{0-\infty}$ and $t_{1/2}$ of the hmEMs increased after the omeprazole treatment to the levels comparable to those of the PMs. Mean *R*-warfarin $AUC_{0-\infty}$ of our hmEMs showed an 18 % increase, and the increase was greater than that of the previous studies (Sutfin T et al., 1989; Unge P et al., 1992), probably due to recruiting the same genotype in the present study. Omeprazole is known to be an inhibitor of some CYP enzymes including CYP2C9 and 2C19 (Ko JW et al., 1997; Li XQ et al., 2004). CYP2C9 is known to be responsible for the biotransformation from *S*-warfarin to *S*-7-hydroxywarfarin **(**Kaminsky LS and Zhang ZY, 1997**)**, and the ratio of *S*-7-hydroxywarfarin AUC to *S*-warfarin AUC would reflect the *in vivo* activity of CYP2C9. Previous report suggested that the clearance of omeprazole is markedly reduced and plasma concentrations of omeprazole in CYP2C19 PMs are much more elevated than those in CYP2C19 EMs (Sohn DR et al., 1992). Increased plasma concentrations of omeprazole in CYP2C19 PMs might affect the pharmacokinetics of warfarin *S*-enantiomer, a substrate of CYP2C9 **(**Kaminsky LS and Zhang ZY, 1997**)**, as well as its *R*-enantiomer, compared to those in CYP2C19 EMs. In this study, the inhibitory effect of omeprazole was noted only in the hmEMs of CYP2C19 despite higher omeprazole concentrations in the PMs, and the $AUC_{0-\infty}$ ratio of *S*-7-hydroxywarfarin to *S*-warfarin was relatively constant between the placebo and the omeprazole phases, suggesting that the 7-day administration of omeprazole 20 mg once daily would affect the CYP2C19 activity solely.

7. The effect of CYP2C19 genotypes on the pharmacodynamics

Interestingly, no significant difference was found in PT-INR between the hmEMs and PMs in both the control and the omeprazole phases even though the CYP2C19 genotypes affected the *R*-warfarin pharmacokinetic parameters. However, these findings are not surprising because the anticoagulant effect of *S*-enantiomer is 3-5 times more potent than that of *R*-enantiomer (Takahashi H and Echizen H, 2001), and a concentration rises of *R*-enantiomer was seemed to have little influence on the anticoagulant effect of warfarin. These results therefore suggest that altered pharmacokinetics of *R*-warfarin may play a minor role in determining the average clinical doses of warfarin. Moreover, these results also imply that inhibition of the *in vivo* CYP2C19 activity by the co-administration of a CYP2C19 inhibitor, such as omeprazole, lansoprazole or fluvoxamine (Hemeryck A and Belpaire FM, 2002; Ko JW et al., 1997; Li XQ et al., 2004), may scarcely modify the anticoagulant effects of warfarin. Recently, Rieder et al. (2005) have shown that there is an effect of the VKORC1 on dose requirement. Furthermore, Obayashi et al. (2006) reported that the genotyping of the vitamin K epooxide reductase complex subunit 1 gene (VKORC1) may be more predictive of the anticoagulant effect than genotyping of CYPs, which reflects the warfarin plasma

concentrations. Therefore, these studies suggest that VKORC1 activity may be an important determinant of the pharmacodynamics of warfarin in Japanese patients.

8. Conclusion

These results indicate that CYP2C19 activity is important in the pharmacokinetics of *R*-warfarin because the pharmacokinetics of warfarin enantiomers were different between the CYP2C19 genotypes and the omeprazole affected the *R*-warfarin pharmacokinetics of CYP2C19 in only hmEMs. However, these affects are not translated into any significant effect in the pharmacodynamics of warfarin.

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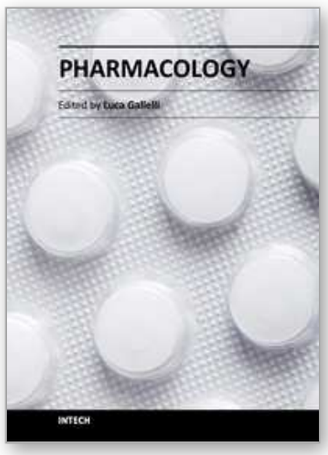

Pharmacology
Edited by Dr. Luca Gallelli

ISBN 978-953-51-0222-9
Hard cover, 720 pages
Publisher InTech
Published online 14, March, 2012
Published in print edition March, 2012

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Yumiko Akamine and Tsukasa Uno (2012). Warfarin Enantiomers Pharmacokinetics by CYP2C19, Pharmacology, Dr. Luca Gallelli (Ed.), ISBN: 978-953-51-0222-9, InTech, Available from: http://www.intechopen.com/books/pharmacology/the-effect-of-cyp2c19-genotypes-on-the-pharmacokinetics-of-warfarin-enantiomers

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