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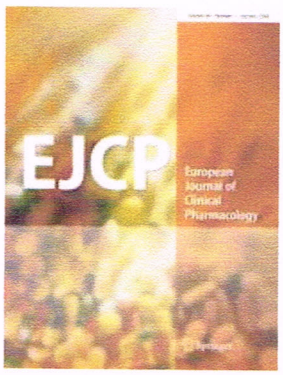

European Journal of Clinical Pharmacology

Coordinating Editor: R. Dahlqvist

ISSN: 0031-6970 (print version)
ISSN: 1432-1041 (electronic version)

Journal no. 228

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ABSTRACTED/INDEXED IN

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European Journal of Clinical Pharmacology
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Volume 69, Issue 3, March 2013

ISSN: 0031-6970 (Print) 1432-1041 (Online)
From Volume 1 (1968) to Volume 2 (1969), this journal was published as Pharmacologia Clinica.

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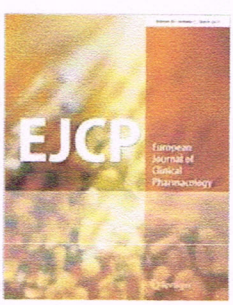

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Eur J Clin Pharmacol
DOI 10.1007/s00228-012-1356-9

PHARMACOGENETICS

Responsiveness to low-dose warfarin associated with genetic variants of *VKORC1*, *CYP2C9*, *CYP2C19*, and *CYP4F2* in an Indonesian population

T. Rusdiana · T. Araki · T. Nakamura · A. Subarnas · K. Yamamoto

Received: 7 February 2012 / Accepted: 11 July 2012

Abstract
Purpose The aim of this study was to assess the pharmacokinetics and pharmacodynamics of warfarin associated with genetic polymorphisms in *VKORC1*, *CYP2C9*, *CYP2C19*, and *CYP4F2* in Indonesian patients treated with low-dose warfarin.
Methods Genotyping of *VKORC1*, *CYP2C9*, *CYP2C19*, and *CYP4F2* was carried out in 103 patients treated with a daily dose of 1–2 mg warfarin, 89 of whom were treated with a fixed daily dose of warfarin (1 mg). The plasma concentrations of *S*- and *R*-warfarin and *S*- and *R*-7-hydroxywarfarin were used as pharmacokinetic indices, while prothrombin time expressed as the international normalized ratio (PT-INR) was used as a pharmacodynamic index.
Results In patients treated with a fixed daily dose of warfarin (1 mg), a higher PT-INR was associated with *VKORC1*-1639 AA [median 1.35; interquartile range (IQR) 1.21–1.50] than with the GA (1.18; IQR 1.12–1.32; $p<0.01$) and GG (1.02; IQR = 1.02–1.06; $p<0.01$) polymorphisms, and with *CYP2C9**1/*3 (1.63; IQR 1.45–1.85) compared to *1/*1 (1.23; IQR 1.13–1.43; $p<0.05$). The *S*-warfarin concentration was significantly higher in patients with *CYP2C9**1/*3 than in those with *1/*1 ($p<0.05$). With low-dose warfarin administration, there was no significant difference in the concentrations of warfarin metabolites among any of the genotype variants. The genotype variations of *CYP2C19* and *CYP4F2* were not significantly associated with the PT-INR.
Conclusion For low-dose warfarin treatment, the *VKORC1*-1639 G>A and *CYP2C9* genotype variations affected the pharmacokinetics and pharmacodynamics of warfarin, while we could not find significant effects of *CYP4F2* or *CYP2C19* genotype variations on warfarin (metabolite) concentrations or PT-INR.

Keywords Warfarin · Pharmacogenetics · *VKORC1* · *CYP2C9* · *CYP4F2*

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Introduction

Warfarin (WF) is used as an oral anticoagulant drug for the treatment and prevention of thromboembolic disorders [1]. Bleeding is one of the serious adverse reactions in anticoagulant therapy, and it still remains a risk factor during long-term therapy with low-dose WF [2, 3]. Due to the large individual variability in WF response, drug therapy with WF requires frequent and regular monitoring by measurement of the prothrombin time expressed as the international

Published online: 02 August 2012