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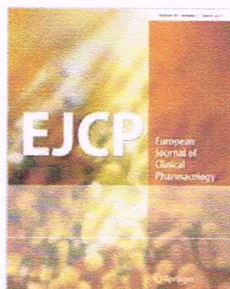
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Responsiveness to low-dose warfarin associated with genetic variants of *VKORC1*, *CYP2C9*, *CYP2C19*, and *CYP4F2* in an Indonesian population

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

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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-hydroxy-warfarin 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.

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

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