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A model analysis for dose–response relationship of warfarin in Japanese children: An introduction of the SIZE parameter

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ABSTRACT

The objective of the present study was to develop an optimal equation for the pediatric dose–response relationship of warfarin using a size parameter with an exponent of body weight (SIZE) which has been proposed for scaling drug clearance. Twenty patients with stable anticoagulation by warfarin were enrolled in the present study. During a mean follow-up period of 7.36 years, 857 data points were obtained. The average patient age and body weight were 8.49 years and 24.5 kg, respectively. The relative response index to warfarin with PT-INR values normalized by daily-dose per *SIZE* showed fewer systematic changes than those per body weight. The anticoagulant effect of warfarin in patients with the *VKORC1 1173CT* or *1173CC* genotype was 47.3% of that with the *1173TT* genotype. Concomitant use of bosentan attenuated the anticoagulant effect of warfarin to 84.1%. In conclusion, the SIZE parameter appeared to be an effective way to describe the pediatric dose–response relationship of warfarin, and consequently, a longitudinal follow-up study design with multiple measurements was useful to detect changes within individual subjects.

1. Introduction

Antithrombotic therapy is required for the prevention and treatment of thromboembolic complications in pediatric patients with heart disease [1]. In recent years, several novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban and apixaban have been approved for clinical use, and these drugs have advantages and disadvantages compared to warfarin [2]. Warfarin is, however, still preferably prescribed for children who have arrhythmia, cardiomyopathy, coronary artery disease, or congenital heart disease because the clinical effectiveness of the drug has been well established [3]. On the other hand, careful adjustment of the dose based on the prothrombin time-international normalized ratio (PT-INR) is essential because of the narrow therapeutic index and large individual variability in the relationship between the warfarin dose and its anticoagulant effect [4].

The role of genetic polymorphisms in *CYP2C9*, the enzyme largely responsible for the metabolism of *S*-warfarin, with respect to interindividual variability in the pharmacokinetics of warfarin has been extensively studied [5,6]. However, it only partly explains the great interindividual variability in the maintenance dose of warfarin among Japanese because the allele frequency of *CYP2C9*3*, leading to an impairment in the enzymatic activity of CYP2C9, is only 2.1% in Japanese [5]. Subsequently, genetic polymorphisms of the vitamin K epoxide reductase complex 1 (*VKORC1*) were found to be responsible for the large interindividual, and even interethnic, variability observed in the response to warfarin [7]. A common single nucleotide polymorphism (SNP) of *VKORC1* (*1173C > T* in intron 1) is one of the polymorphic alleles which produces an enzyme with an Asp^{38}/Tyr^{38} amino acid substitution, and the frequency of the mutant *1173T* allele is reported to be 89.1% among Japanese [6]. Obayashi et al. [4] reported that the warfarin dose in Japanese patients (mean age, 25.2 years; range, 20–52) with the *VKORC1 1173TT* genotype was 64.3% of that with the *1173CT* or *1173CC* genotype. Kosaki et al. [3] reported that the warfarin dose in Japanese patients (median, 22 years; range, 12–34) with the *VKORC1 1173TT* genotype was 68.0% of that with the *1173CT* genotype.

We previously reported that the *VKORC1* genotype and age were major factors affecting the relationship between the weight-normalized warfarin dose and the therapeutic PT-INR value in 48 Japanese pediatric patients (mean age, 6.6 years; range,

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0.42–19.25) [8]. The model for predicting the PT-INR values was as follows (Eq. (1));

$$PT\text{-}INR = 1.26 + 6.70 \cdot DD/WT \cdot (1 + 0.105(Age - 6.6)) \cdot 0.523^{VKORC1} \quad (1)$$

where *DD* is the daily-dose in mg of warfarin, *WT* is the body weight in kg of each subject, and *Age* is the age in years of each subject. *VKORC1* is zero for patients with the *VKORC1 1173TT* genotype, and one for patients with the *1173CT* or *1173CC* genotype. That is, the anticoagulant effect of warfarin in patients with the *VKORC1 1173CT* or *1173CC* genotype was 52.3% of that with the *1173TT* genotype, and the anticoagulant effect of the drug increased by 10.5% per year in young pediatric patients. Because of a limit on the number of data sampling points (n = 142), our earlier study modeled the effect of developmental changes on the response to warfarin as a linear function of age for simplicity [8]. However, there is a significant difference in body development and/or maturation in pediatric patients, and true body size in some patients is likely to be poorly-matched with age [9]. It is therefore important to clarify the developmental changes from childhood to adulthood.

Takahashi et al. [10] has reported developmental changes in the pharmacokinetics of warfarin enantiomers for pharmacologically more active *S*-warfarin in Japanese children. They found that body weight-normalized unbound oral clearance values for *S*-warfarin were elevated particularly during early childhood in pediatric patients as compared with adult patients, and tended to decrease linearly toward the adult value. In contrast, no differences were observed in the liver weight-normalized unbound oral clearance for *S*-warfarin between prepubertal and adult groups. They proposed that liver weight may be a better parameter than body weight for estimating warfarin doses in children; however, liver weight is much less commonly used than body weight in clinical practice [9]. Instead, size parameter (SIZE) plays a significant role in determining pediatric pharmacokinetic parameter estimates and consequently drug doses for young children [9]. A size parameter using an exponent of weight now has been proposed for scaling drug elimination clearance [9,11].

The main purpose of the present study was to develop an optimal equation for the pediatric dose–response relationship of warfarin by using SIZE. Moreover, the relative impact of other possible covariates on the *SIZE*-normalized PT-INR values was also evaluated by multiple regression analysis. Because pediatric patients with heart disease are physiologically heterogenic, a large population would be required for standard systematic analysis. In the present study, however, to solve the problem of a small cohort study, we conducted a longitudinal follow-up study on 20 Japanese pediatric patients with stable anticoagulation by warfarin.

2. Materials and methods

2.1. Patient inclusion criteria

A retrospective longitudinal follow-up study was conducted in 20 Japanese pediatric patients (13 boys and 7 girls). These patients had been treated with oral administration of warfarin for at least 3 years at Toyama University Hospital and had participated in our previous study [8]. The dosage of warfarin was adjusted on the basis of clinical grounds. To compensate for the lack of data due to the small number of patients, we extracted data from medical records over the period between February 2003 and January 2015. Information concerning anticoagulant therapy was collected from the medical records, including demographics, the corresponding day for each PT-INR measurement, indication for warfarin use, concomitant medications, and other medical diagnoses. When patients received a stable warfarin dose for at least 2 weeks, their data was eligible for analysis except when the PT-INR value was unstable and/or unexpectedly exceeded the therapeutic range.

2.2. Genotyping of CYP2C9, VKORC1 and CYP4F2 (rs2108622; 1347 C > T)

Genotypes for *CYP2C9* and *VKORC1* were determined in our previous study [8]. In short, *CYP2C9* genotypes were determined using the polymerase chain reaction-retention fragment length polymorphism (PCR-RFLP) method and the *VKORC1 1173 C > T* variant was determined by direct sequencing [8]. *CYP4F2* polymorphism (rs2108622; *1347 C > T*) was determined using the PCR-RFLP method as described elsewhere [12]. That is, the amplified PCR products were digested with *Pvu* II (TaKaRa, Shiga, Japan), and analyzed on Nusieve GTG agarose gel (Cambrex Bio Science Rockland, Inc., ME, USA) [12]. The patients and/or parents gave written informed consent to participate in the present study, which was approved by the ethics committee of the University of Toyama (#EG21-6).

2.3. Analysis of the dose–response relationship of warfarin

To understand the dose–response relationship of warfarin as rationally as possible, PT-INR values observed were described as a sum of the intrinsic PT-INR value without anticoagulation and increase in the PT-INR value associated with warfarin dose.

The intrinsic PT-INR value in the *i*th individual ($PT\text{-}INR_{base,i}$) was modeled using the following equation;

$$PT\text{-}INR_{base,i} = \theta_1 \cdot \exp(\eta_{1i}) \quad (2)$$

where θ_1 is the predicted population mean of the baseline of PT-INR without anticoagulation and η_{1i} is a random variable with a mean zero and variance of ω_1^2. Note that the baseline parameter (θ_1) for PT-INR was likely to be almost 1.0.

The response to warfarin in the *i*th individual ($PT\text{-}INR_i$) was modeled using the following equation;

$$PT\text{-}INR_i = \theta_1 \cdot \exp(\eta_{1i}) + \theta_2 \cdot DD/SIZE_i \cdot \exp(\eta_{2i}) \quad (3)$$

$$SIZE_i = 24.5 \cdot (WT_i/24.5)^{\theta_3} \quad (4)$$

where θ_2 and θ_3 are the model parameters to be estimated, $SIZE_i$ is the hypothetical body size, WT_i is the individual body weight in kg and η_{2i} is a random variable with a mean zero and variance of ω_2^2. Modeling body size in this way allows the data to determine the optimal power function of weight [9,11]. Note that when $\theta_3 = 1$, $SIZE_i$ is simply linearly proportional to weight, and when $\theta_3 = 0$, $SIZE_i$ is independent of weight [9,11]. Initially, when the residual variances were freely estimated, the NONMEM could not provide reasonable θ_1 and θ_2 values separately from the data set. Therefore, the ω_1^2 value was fixed empirically as 0.04 in the present analysis.

Finally, the *j*th observed PT-INR value in the *i*th patient ($PT\text{-}INR_{ij}$) was assumed to be randomly and exponentially distributed from the predicted value ($PT\text{-}INR_{ij}^*$);

$$PT\text{-}INR_{ij} = PT\text{-}INR_{ij}^* \cdot \exp(\varepsilon_{ij}) \quad (5)$$

where ε_{ij} is a random variable that describes intraindividual variability with a mean of zero and covariance of σ^2.

Table 2 summarizes the 5 models for analyzing the possible covariates of the therapeutic PT-INR value. First, PT-INR was