Journal of Cardiology 65 (2015) 178–184

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Effect of impaired renal function on the maintenance dose of warfarin in Japanese patients

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ARTICLE INFO

Article history:
Received 27 March 2014
Received in revised form 22 July 2014
Accepted 10 August 2014
Available online 30 October 2014

Keywords:
Renal impairment
Non-renal elimination
Dose–effect relationship
Warfarin

ABSTRACT

Background: Chronic kidney disease (CKD) alters dose–effect relationship not only of drugs eliminated by the kidney but also of some drugs metabolized by the liver and not renally excreted. It is not known whether impaired renal function alters dose–effect relationship of warfarin in Asian patients. It is also unknown whether the maintenance dose of warfarin can be predicted more accurately by incorporating renal function in Asians.

Methods: This was a cross-sectional study of patients receiving constant doses of warfarin who had PT-INR within 1.5–3.0 for 3 months or longer.

Results: In a total of 137 participants, the estimated creatinine clearance (eCrCl) was 62.5 ± 25.5 [ml/min] and the warfarin dose was 3.21 ± 1.46 [mg/day] (both mean ± standard deviation). There was a significant correlation between warfarin dose and eCrCl ($p < 0.0001$, $r^2 = 0.23$). In a stepwise linear regression with the maintenance dose of warfarin as the dependent variable, eCrCl as well as age, body weight, intra-individual average prothrombin time/international normalized ratio (PT-INR), and genotype of *VKORC1* −1639 G>A polymorphism were chosen as independent variables. The coefficient of determination (r^2) of this formula was 0.47. A regression equation with all the same explanatory variables except for eCrCl had an r^2 of 0.41.

Conclusions: The maintenance warfarin dose was positively correlated with kidney function as represented by eCrCl in Japanese patients. Incorporating eCrCl improved accuracy of predicting warfarin maintenance dose in this population.

Introduction

Impaired renal function alters the dose–effect relationship not only for drugs that are excreted by the kidney, but also for some drugs that are metabolized primarily by the liver and not renally excreted [1–4]. Warfarin is one such drug that is eliminated through hepatic metabolism and not directly excreted by the kidney [5–8]. Recent studies reported that patients with impaired renal function had lower maintenance doses of warfarin than those with normal renal function in cohorts which consisted primarily of African and European Americans [9,10]. In Asian patients, however, the effect that decreased kidney function has on the maintenance dose of warfarin remains unclear. It is also unknown whether the maintenance dose of warfarin can be predicted more accurately by including renal function along with conventional demographic and genetic variables in Asians.

In this cross-sectional study in Japanese patients, we examined: [1] whether the maintenance dose of warfarin has a correlation with renal function that is independent from conventional demographic and genetic variables; and [2] whether the maintenance dose of warfarin can be predicted more accurately by including renal function along with conventional demographic and clinical variables.

Materials and methods

Patients

This study was approved by the Ethics Committee of Yokohama City University. Patients who were receiving anticoagulation therapy with warfarin were recruited at Yokohama City University

DOI of commentary article: http://dx.doi.org/10.1016/j.jjcc.2014.10.001
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http://dx.doi.org/10.1016/j.jjcc.2014.08.008
0914-5087/

Hospital. Only Japanese patients who were receiving a constant dose of warfarin for 3 months or longer and had a prothrombin time/international normalized ratio (PT-INR) of 1.5–3.0 on at least three consecutive visits during the same period were included. Patients who had either liver dysfunction, serum aminotransferase levels at least twice the upper limit of normal, or who were receiving chronic renal replacement therapy (e.g., hemodialysis) were excluded. Patients were also excluded if they had started receiving warfarin within the previous three months, if accurate information on their prescribed medication was not available, or if their compliance with medical treatment was poor. Written informed consent was obtained from each patient after the individual had received a detailed explanation of the study objectives and protocol, presented by a single investigator using a printed document. Clinical information was gathered by reviewing the patients' medical records and by personal interviews, conducted by a single investigator according to a questionnaire consisting of closed questions. All prescribed medication was recorded for each patient. Body surface area (BSA) was calculated using the formula proposed by Dubois and Dubois [11]. Body mass index (BMI) was calculated by the following formula: BMI = body weight (in kg)/height (in m) squared. Serum creatinine concentration (Cre), blood urea nitrogen (BUN), serum albumin, and PT-INR were measured using conventional techniques.

Estimation of renal function and classification of patients based on these estimates

Estimated creatinine clearance (eCrCl) was used as an estimate of kidney function of the patients based on clinical information [12]. Measured body weight, not ideal or adjusted body weight, was used for calculating eCrCl as BMI of the study subjects distributed around the normal range (Table 1).

In addition, we categorized the patients into three groups based on their estimated glomerular filtration rate (eGFR) using nomenclature presented in clinical practice guidelines for the evaluation and management of chronic kidney disease (CKD) [13,14]. An equation designed to estimate the glomerular filtration rate (GFR) in Japanese subjects was used [15]. Estimated GFR $\geq$60 ml/min/1.73 m^2 was categorized as categories G1/G2; eGFR of $\geq$30 to $<$60 ml/min/1.73 m^2 as categories G3a/G3b; and eGFR $<$30 ml/min/1.73 m^2 as categories G4/G5.

Genotyping

Genomic DNA was obtained from peripheral blood mononuclear cells using standard methods. Two single nucleotide polymorphisms (SNPs) (*VKORC1* −1639 G>A or rs9923231 or *VKORC1* *2 and *CYP2C9* 1075 A>C or rs1057910 or *CYP2C9* *3) were genotyped using TaqMan® Drug Metabolism Genotyping Assays (Applied Biosystems®, Foster City, CA, USA). Allele-specific probes were labeled with the fluorescent dyes FAM and VIC. The polymerase chain reaction (PCR) was carried out in a total reaction volume of 25 μl, containing 50 ng genomic DNA as template, 1.25 μl of TaqMan® Drug Metabolism Genotyping Assay, and 12.5 μl of TaqMan® Genotyping Master Mix. The amplification protocol used was initial denaturation at 95 °C for 10 min, followed by 50 cycles of denaturation at 92 °C for 15 s and annealing/extension at 60 °C for 90 s. After the PCR, the genotype of each sample was determined according to the allelic-specific fluorescence, using Sequence Detection Software Version 1.3.1 (Applied Biosystems®).

Statistical analyses

The assumption of the Hardy–Weinberg equilibrium was tested using the chi-square test of independence. Unpaired Student's *t*-test and analysis of variance (ANOVA) were used to compare mean doses of warfarin among patients grouped according to genotypes and other categorical variables. For post hoc comparison between all pairs of means, the Tukey HSD method was used. Possible correlations of numerical variables with the warfarin dose were examined by linear regression analysis. The significance level (α) for all statistical tests was set at $p < 0.05$. Statistical analysis was performed with JMP® 10 (SAS Institute Inc., Cary, NC, USA).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

Patients

There were 137 patients who fulfilled the conditions of the protocol and gave informed consent to participate in the study, including 32 females (23.4%). The average age of the patients was 70.0 ± 9.1 years and the average dose of warfarin was 3.21 ± 1.46 mg/day (Table 1).

Kidney function and other laboratory measurements

In the entire cohort, the average of eCrCl and eGFR were 62.5 ± 25.5 ml/min and 63.1 ± 21.6 ml/min/1.73 m^2, respectively (Table 1, Supplementary Fig. 1).

The numbers and characteristics of the patients with each category of eGFR are summarized in Table 1. Seventy-seven patients had an eGFR of 60 ml/min/1.73 m^2 or higher and were classified as in eGFR categories G1/G2, among whom 11 had an eGFR of 90 ml/min/1.73 m^2 or higher (eGFR category G1). Fifty-one patients had an eGFR of 30 ml/min/1.73 m^2 or higher but less than 60 ml/min/1.73 m^2 and were classified as in eGFR categories G3a/G3b. Nine patients had an eGFR of less than 30 ml/min/1.73 m^2 and were classified as in eGFR categories G4/G5.

Genotypes

Frequencies of genotypes and alleles are summarized in Supplementary Table 1. As for *VKORC1* −1639 G>A polymorphism, 24 patients (17.5%) had genotype GA and none had GG. As for *CYP2C9* 1075 A>C, only three (2.2%) patients had AC, and all of the rest had AA. One patient (0.73%) was heterozygous both for *VKORC1* −1639 G>A and *CYP2C9* 1075 A>C polymorphisms. Allele G of *VKORC1* −1639 G>A polymorphism and C of *CYP2C9* 1075 A>C had frequencies of 0.088 and 0.011, respectively. No deviation from the Hardy–Weinberg equilibrium was observed.

Genotypes and warfarin dose

We compared the warfarin doses in groups of patients with different genotypes of *VKORC1* −1639 G>A and *CYP2C9* 1075 C>A polymorphisms. Patients heterozygous for *VKORC1* −1639 G>A polymorphism had a significantly higher warfarin dose than those homozygous for the A allele (Supplementary Table 2 and Supplementary Fig. 2a). In both groups of patients with and without the G allele of *VKORC1* G>A polymorphism, patients with the C allele of *CYP2C9* 1075 A>C had a lower warfarin dose than those without this allele, though these patients were few in number and these differences were not statistically significant (Supplementary Table 2 and Supplementary Fig. 2b).