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Original Article

Warfarin dosage adjustment strategy in Chinese population

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Abstract: Background: Blood anticoagulation after heart valve replacement is a recognized difficulty all over the world. In this study, we identified the effect of amiodarone on the function of warfarin and confirmed the countermeasure by concluding the genotype distribution of vitamin K epoxide reductase complex 1 (VKORC1) and cytochrome P450 2C9 (CYP2C9) of the patient to predict the security dose of warfarin. Methods: Studying on the VKORC1 (-1639G>A) and CYP2C9 genotype of 271 cases on heart valve replacement in the First Affiliated Hospital of Soochow University from Jan. 2012 to Jan. 2014. Warfarin's multivariable regression equation was taken to calculate their warfarin dosage. In the study, 80 of them were selected and divided into 4 groups according to their different warfarin dosage and their usage of amiodaron. The differences of INR values at the 5th, 8th, 11th, 14th days of operation were analyzed. Results: Among the 80 cases, VKORC1 (-1639G>A) AA types accounted for 90%, and AG types accounted for another 10%, while GG types were not found. In addition that, all of the patients (100%) had CYP2C9*1/*1 type, and CYP2C9*1/*3 had not appeared. There was significant difference in INR values between the groups who used amiodarone or not. The pharmacogenetic equation was accurate in the predicting of the warfarin dosage, so that satisfied anticoagulation efficacy had been achieved in 2 weeks after surgery. Conclusion: It is necessary for the patients to do the warfarin pharmacogenetic test to get the suitable dose before heart valve replacement. Amiodarone can enhance the anticoagulant efficacy of warfarin, so the dosages of warfarin should be reduced properly because of the medicine combination, and INR values must be monitored more frequently to make the anticoagulant process secure and efficient.

Keywords: Heart valve replacement surgery, anticoagulation, pharmacogenomic testing, warfarin, amiodarone

Introduction

Heart valve replacement (including artificial metal valve replacement and artificial biological valve replacement) is commonly used in the treatment of heart valve diseases in recent years. After valve replacement, thrombus will appear soon because of the blood clotting, due to the change of hemodynamics or foreign body stimulation. This phenomenon will change the blood flow pattern and make the new valve ineffective, even endanger patients' lives if the embolism is formed in these pivotal organs. To avoid these adverse outcomes, anticoagulation is particularly important after cardiac valve surgery. Warfarin, one kind of coumarin anticoagulant drug, has been identified as an important role for anticoagulation both domestic and abroad currently [1-4]. In clinical application, frequent monitoring of prothrombin time (PT) and international normalized ratio (INR) is necessary to modify the warfarin oral dose, so that these indexes can be controlled in an ideal and security range [5]. Our medical team thinks that the INRs of various valve replacements should be achieved in these extents: the aortic valve replacement (AVR) is 1.8-2.0; the mitral valve replacement (MVR) is 1.8-2.5, tricuspid valve replacement (TVR) is 2.5-3.0. This is consistent with the guide which was announced by The American College of Chest Physicians (ACCP) in 2008 [6, 7], also its safety and efficacy in minimizing hemorrhage and infarction has been proved.

Moreover, there are some disadvantages about warfarin, such as the narrowness of the safe range, the variety of influence factors, the indi-

Table 1. Characteristics of the 4 groups' populations

Variable	Group A	Group B	Group C	Group D
Cases number*	20	20	20	20
Warfarin dose#	1.25	1.25	2.5	2.5
Combined with amiodarone	No	Yes	No	Yes
MVR*	12	11	10	10
AVR*	4	5	4	5
MVR + AVR*	4	2	5	3
TVR*	0	1	0	1
MVR + TVR*	0	1	1	1

Total n = 80. MVR: Mitral valve replacement; AVR: Aortic valve replacement; TVR: Tricuspid valve replacement. *means the number of cases; #means the unit was milligram.

vidual differences of every patient, thus the efficient dose is not easy to regulate [8, 9]. It has been proposed that, the genetic variations in the function receptor (Vitamin K Epoxide Reductase Complex 1, VKORC1) and the main metabolic enzymes (Cytochrome P450 2C9, CYP2C9) of warfarin, play an important role in the diversity of warfarin doses in different nationalities and individuals, and these two factors influence the efficient dose [10-12]. After years of exploration and practice about the gene polymorphism of VKORC1 and CYP2C9 by the cooperation of our department and the department of pharmacy of our hospital, we have structured the multiple linear regression equation about the warfarin dose aim at Chinese population [13] (**Formula 1**). VKORC1 genotype, CYP2C9 genotype, age and weight have been regarded as the covariates of the equation, so that the rational warfarin's maintenance dose can be achieved easily.

Formula 1. The Calculation Method of Warfarin Dose

$$D = 6.22 - 0.011 (Age) + 0.017 (Weight) + 0.775 (CYP2C9) - 3.397 (VKORC1\text{-}x1) - 4.803 (VKOR1\text{-}x2)$$

Age, input age in years; Weight, input weight in kilograms; CYP2C9 genotype, input 1 for *1/*3, while input 0 for *1/*1; VKORC1 genotype, input 0 in VKORC1-x1 and input 1 in VKORC1-x2 for AA, input 1 in VKORC1-x1 and 0 in VKORC1-x2 for AG, input 0 in VKORC1-x1 and VKORC1-x2 for GG. The y variable is the warfarin dose (D) in milligram.

In addition, drugs interaction is another important factor which influences the stability of warfarin dose. Amiodarone, one kind of antiarrhythmic drugs, which is famous for its efficiency and security in the therapy of tachyarrhythmia, especially in atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardia, can decrease the overquick heart rate in a relatively shorter time [14, 15]. In those heart valve replacement patients who are combined with atrial fibrillation, warfarin is usually associated with amiodarone, and it is reported that amiodarone will make certain impact on the anticoagulation of warfarin. Therefore, how to adjust the appropriate warfarin dose to achieve an optimum result when combined use of amiodarone is need to be discussed in clinical treatment.

Patients and methods

Patients

All the patients who had undergone heart valve replacement surgery and taken warfarin in our department from Jan. 2012 to Jan. 2014, a total of 271 cases, were selected, and the informed consents in accordance with the Declaration of Helsinki had been subscribe by all. Among them, combined with tachyarrhythmia (mainly included atrial fibrillation and/or atrial flutter) were 85 cases so that they had been treated with amiodarone, while another 186 cases had not. Preoperatively, every patient had a blood examination for warfarin drug gene (VKORC1 and CYP2C9) detection routinely. Put one patient's information into the formula, the warfarin maintenance dose had been achieved, thus we can start the warfarin therapy postoperatively without dose adjustment.

Eliminated redundant cases according to the following conditions: the cases had undergone one of the operations: atrial septal defect repair, ventricular septal defect repair, patent ductus arteriosus ligation, coronary artery bypass graft, cardiac tumor resection, bentall operation; the cases whose warfarin dose had been adjusted because of excess or deficiency for anticoagulation in the initial two weeks (due to the accurate prediction of the warfarin dose, there were only 58 cases, accounted for 21.4% of the total number, had been eliminated); the cases who had taken other medicines which

Table 2. Characteristics of patients' information

Groups	AGE/Years	HEIGHT/cm	WEIGHT/kg
Group A	54.6±9.7	168.3±5.2	71.6±8.8
Group B	55.1±10.9	169.7±4.9	69.6±8.9
Group C	52.2±10.2	168.8±4.7	70.4±7.9
Group D	54.2±10.8	167.9±5.4	68.4±9.1
P value*	*P* > 0.05	*P* > 0.05	*P* > 0.05
P value#	*P* > 0.05	*P* > 0.05	*P* > 0.05

*Means the comparison groups were group A and group B; #means the comparison groups were group C and group D.

Table 3. Characteristics of genotypes distribution

Groups	VKORC1 (-1639G>A) Genotype (n)			CYP2C9 Genotype (n)	
	AA[a)]	AG[a)]	GG[a)]	*1/*1[b)]	*1/*3[b)]
Group A	18	2	0	20	0
Group B	17	3	0	20	0
Group C	18	2	0	20	0
Group D	19	1	0	20	0
Total	72	8	0	80	0
Proportion	0.9	0.1	0	1.0	0

[a)]the three subtypes of VKORC1 genotype. [b)]the two subtypes of CYP2C9 genotype; there were no CYP2C9*1/*3 genotype had been found.

had been definitely confirmed would change the anticoagulant effect of warfarin. Then there were 128 cases remained. According to the warfarin dose (1.25 mg/d and 2.5 mg/d were chosen) and whether amiodarone was combined with, we selected 80 cases and divided them into 4 groups randomly, 20 cases in each group. The valve operation methods of cases were slightly different in every group (**Table 1**), in addition that the age, height, weight had no significant difference between group A and group B as well as group C and group D (**Table 2**), and the warfarin drug gene distribution was roughly same (**Table 3**).

Echocardiography and ECG examination had been performed and the valvular diseases were identified in all patients before the operations, therefore the indications for surgeries were unambiguous. Radiofrequency ablation were operated simultaneously with the surgeries for these patients, whose ECGs showed atrial fibrillation or atrial flutter as well as the echocardiography revealed that the left atrial diameter > 40 mm. Followed-up each patient ranged from 1-13 months after discharge, no one was died among those 80 cases. No fault about prosthetic valve function had been found by echocardiography postoperatively, and serious arrhythmia, low cardiac output syndrome, cerebral apoplexy, paravalvular leakage, infective endocarditis was also not happened.

Surgery methods

All of the surgeries were supported by general anesthesia and extracorporeal circulation, and supine position was been chosen. The majority of patients were through median sternotomy for surgeries, while parts of the mitral valve replacement patients (33 cases) were through right chest incision into the chest. Mechanical valves were used for the patients younger than 60 years old; on the contrary the older were replaced by bio-valves.

Postoperative treatment

In perioperative period, all of the patients were transferred into ICU for transition. Warfarin therapy began from the second day after the surgery. An initial dose of 1.25 mg/day was taken to group A and group B, while the group C and group D with 2.5 mg/day. The usage method of amiodarone for group B and group D was: after the patient returned to the ICU, took amiodarone 18 mg-90 mg/h through the central vein according to the patient's heart rate, and orated amiodarone 200 mg three times a day, then stopped amiodarone intravenous used when the heart rate was reduced and stable. After a regular usage of amiodarone for 7 days, we adjusted the dose to 200 mg twice a day for a week, and then changed to 200 mg once a day at the third week after the surgery, maintained for 3 months-6 months. After that, it would be decided whether to continue on the basis of the patient's heart rate.

Statistical methods

Discrete variables were expressed as numbers and proportion, and all the continuous variables were presented as mean ± standard deviation. Student *t*-test was carried out for the comparisons of the ages, heights, weights and time-dependent INR values between group A

Table 4. Comparisons of time-dependent INR values between group A and group B ($\bar{x}$ ± SD)

Groups	5 days	8 days	11 days	14 days
Group A	1.418±0.412	1.745±0.424	2.049±0.448	2.401±0.417
Group B	1.782±0.509	2.218±0.441	2.401±0.417	2.445±0.424
P value*	0.0261	0.0021	0.0212	0.0335

*Means the comparison groups were group A and group B.

Table 5. Comparisons of time-dependent INR values between group C and group D ($\bar{x}$ ± SD)

Groups	5 days	8 days	11 days	14 days
Group C	1.509±0.323	2.009±0.417	2.136±0.365	2.244±0.379
Group D	1.802±0.363	2.391±0.387	2.424±0.390	2.481±0.402
P value*	0.0156	0.0071	0.0312	0.0923

*Means the comparison groups were group C and group D.

and group B as well as group C and group D. Statistical significance was concluded when $P < 0.05$. All the data analyses were performed with the SPSS version 14.0 statistical software (SPSS Science, Chicago, IL, USA).

Results

Venous blood had been collected for INR value measurements at the 5th, 8th, 11th, 14th days postoperatively, thus we calculated the average value and standard deviation ($\bar{x}$ ± SD) for each group. Afterwards, we compared the divergences of the time-dependent INR values between group A and group B as well as group C and group D (**Tables 4**, **5**).

As **Tables 4**, **5** shown, there were statistical significances in INR values between group A and group B as a result of whether had taken amiodarone. It was similar to group C and group D, but only one pair of INR values which belonged to the 14th days was exceptive (It could be attributed to the dose decrease of amiodarone). The statistical significances suggested that the anticoagulation of warfarin would been strengthened by amiodarone, just liked a synergistic effect. Another discovery was that, although the INR values in group B and group D were higher than in group A and group C respectively (compared at the same warfarin doses), all of the INR values were almost security because of the accurate predictions of warfarin doses. On the other hand, to prevent patients from hemorrhage, the warfarin dose is necessary to be reduced appropriately in consideration of the effect of amiodarone.

Discussion

Currently, warfarin is the most commonly and classical prescribed anticoagulant, and there is no substitute exists yet. As a kind of coumarin anticoagulation, warfarin is a mixture of S-warfarin and R-warfarin, while the S-warfarin is more potent fivefold than the latter one [16, 17]. And their metabolisms are catalyzed by CYP2C9 and CYP1A2, two kinds of cytochrome P450 isoenzymes, respectively. Warfarin, as a kind of antagonist against vitamin K, inhibits the vitamin K epoxide reductase (VKOR) in liver, and it leads to vitamin K cycle blocked. Therefore the vitamin K-dependent clotting factors (FII, FVII, FIX and FX) are limited to generate due to the vitamin K absence, so that the extrinsic coagulation process is stopped [18, 19]. The vitamin K epoxide reductase complex 1, which is an activator for VKOR, has been identified as a target for warfarin's function [20, 21]. But warfarin is invalid to these mature clotting factors, so the anticoagulation begins when they are exhausted. Slowness and long half-life (20-60 h, mean 40 h) are considered as the main characteristics of this anticoagulant [22].

When the steady-anticoagulation after surgery has been achieved, every patient's individual warfarin dose is nearly discrepant. As several genetic studies has shown that, the polymorphism of VKORC1 gene and CYP2C9*3 gene which described as a principle hereditary factor, plays an important role in the metabolism and dose modification of warfarin [5, 23]. And it is reported that, the mutation of -1639 locus in the VKORC1 gene promoter region is a significant reason [19, 24]. AA is the most common one in the 3 kinds of -1639 locus' genotypes in Asian populations, while the other two (AG and GG) are rare. The Han population in China is almost similar to this, but in the western countries, AG and GG genotypes are more common [8, 12, 13, 25, 26]. On the other hand, there are a variety of mutants for CYP2C9 gene. Among

them, the mutation rate of CYP2C9*1/*1 is higher than others, which can reduce the activity of CYP2C9 enzyme, inhibit the metabolism of warfarin, thus the anticoagulant effect will be enhance indirectly [13, 27, 28]. Therefore, the polymorphisms of VKORC1 gene and CYP2C9 gene is able to change the pharmacokinetic and metabolism characteristic of warfarin, so that the effect of anticoagulant will be influenced. Through the detection of VKORC1 and CYP2C9 genotypes with other information of a patient, warfarin dose can be predicted by the formula previously mentioned. As we researched, it makes a typical significance in the decrease of adverse reactions, maybe also in the development of anticoagulation.

When combined with other medication, the blood concentration of warfarin is usually unstable [28, 29]. Amiodarone and its metabolites (mainly is desethylamiodarone) can weaken the eliminate function of warfarin in liver through the inhibition of the activities of CYP2C9 and CYP1A2 (Cytochrome P450 1A2), so that some warfarin's translating processes, such as R- warfarin transforming to R-1-S warfarin alcohol and R- and S-warfarin oxidizing to some phenolic products, especially S-warfarin becoming to S-7- hydroxyl warfarin, are partially blocked [30]. Finally, all of these lead to the concentration increase of S-warfarin in blood. As a word, amiodarone can decrease the clearance function of warfarin, thereby enhance anticoagulant effect and hemorrhage risk [31].

In conclusion, it is necessary to do pharmacogenetic test for warfarin-related genotypes (VKORC1 [-1639g>A] and CYP2C9) to forecast the suitable warfarin dose for each patient before the heart valve replacement, thus the steady-anticoagulation can be achieved sooner. We also realized that amiodarone is a serious factor in the anticoagulative treatment besides the age, height, weight because of its enhancement to warfarin. With amiodarone therapy, base on the calculated dose which get from the pharmacogenetic test, the warfarin oral dose should be reduced appropriately (we think that it is feasible to reduce 0.625 mg-1.25 mg), and decreasing the interval time of INR value tests in the initial anticoagulation is also considered as essential. We proposed that to do the tests daily until the anticoagulation is steady, and then the further consultation can be delayed. Indeed, although the pharmacogenetic test is willing to give confidence to our clinicians, the individual differences of patients cannot be ignored. Pay attention to the anticoagulation monitoring and the adjustment of warfarin dose when it is necessary, in this way it is likely to avoid the warfarin's adverse reactions.

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Disclosure of conflict of interest

None.

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