PERSONALIZED ADJUSTMENT OF WARFARIN DOSAGE REQUIREMENTS FOR PATIENTS WITH WARFARIN RESISTANCE: THE GENOTYPE IS NOT THE WHOLE STORY

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CASE REPORT

HIGHLIGHTS

- Approved by US FDA in 1954, warfarin is generally recognized as a first-line or gold-standard medicine used to reduce the risk of thrombosis-related diseases or to prevent the formation of thrombosis, such as atrial fibrillation, heart attack, stroke, rheumatic heart disease (in particular after artificial valve replacement), deep vein thrombosis, and pulmonary embolism, with a cost-effective expectation better than the novel or other anticoagulants.
- There is a wide inter-individual or -ethnic variation in warfarin dose requirements to achieve a target INR value (2–3), with extreme response defined as resistant or sensitive phenotype in clinical settings.
- Adjustment of warfarin dosage for patient care is the art of fine tune due to its narrow therapeutic window.
- There are known and unknown causes that could affect the metabolism of and response to warfarin in humans, such as genetic variation, drug-drug or drug-food interactions, adherence, knowledge, and more.
- The genotype cannot be considered as the key player in the whole show about the optimal use of warfarin in clinical practice.
- In addition to its potent anticoagulation, warfarin may prevent some (if not all) cancer through its inhibition of vitamin K–associated tyrosine kinase activity,

ABSTRACT

The extreme response of patients to warfarin is defined as resistant or sensitive, which leads to thrombosis or bleeding complications as a result. Although warfarin resistance results from many known and unknown factors, its major causes include poor compliance (taking warfarin and monitoring INR irregularly), concomitant medication (increasing warfarin clearance), warfarin-food interactions (increasing warfarin dose requirements), genetic variability (enhancing VKOR activity), and lack of knowledge of anticoagulation therapy. From this case report formatted as SOAP, increasing dose of warfarin, reinforcing education of patients, and long-term follow-up for anticoagulation are useful strategies to improve warfarin therapy. The two lessons may be learnt from this case report, one is that DNA is not the whole story, and the other is that some over-the-counter and traditional Chinese medicine should not be taken with warfarin concomitantly.

KEY WORDS *clinical pharmacist; dosage adjustment; genotype; personalized medicine; warfarin resistance*

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INTRODUCTION

Warfarin is a most frequently prescribed oral anticoagulant for patient care, characterized by a narrow therapeutic window, marked inter-individual or inter-ethnic variation in its dosage requirements, and pronounced susceptibility to some diseases and concomitant use of certain drugs or vitamin K-rich food. In clinical practice, it is commonly encountered that bleeding complications occur due to excessive anticoagulation or that thrombosis forms due to insufficient anticoagulation [1]. To reduce or even avoid such risk, prothrombin time (PT) and international normalized ratio (also known as INR) are regularly monitored to adjust daily dosage requirements of warfarin for patients who are taking that medicine. Warfarin resistance is defined as over 5-fold higher than recommended dosage of warfarin to achieve a target INR value in some patients unable to extend PT and INR according to the approved labelling of warfarin [2]. Clinical research studies have documented that a small fraction of the Chinese population would achieve a target INR value only when they take a warfarin dosage of greater than 6 mg per day [3,4], suggesting that warfarin resistance is reasonably diagnosed for Chinese patients if a mean warfarin dose exceeds 6 mg per day.

It is well known that there are marked genetic polymorphisms in the genes that encode drug-metabolizing enzymes, drug transporters, and drug targets responsible for the metabolism, transport and anticoagulation of warfarin. Of them, genetic polymorphisms of VKORC1 (the target of warfarin) and CYP2C9 (a P450 enzyme) alone or in combination with age, body surface area, concomitant medication, and diseases, can affect maintenance dose of warfarin, explaining approximately 56% of total variation of warfarin dosage [5].

In this case report, 2 patients with warfarin resistance were genotyped, their INR values were monitored, and dosing algorithms of warfarin were made individually by well-trained clinical pharmacists (i.e., specialists of anticoagulant drug therapy), with knowledge of warfarin discussed. The major health recording of a patient was formatted as SOAP (see below) [6], which is convenient for the information exchange between pharmacists and physicians.

CASE-1

Subjective data

Female, 24 years old, no history of cigarette smoking and alcohol drinking, and no recording of essential hypertension and diabetes. Diagnosed with rheumatic heart disease, accompanied with mitral stenosis and insufficiency, aortic insufficiency, pulmonary artery hypertension, and NYHA (cardiac function) class III at 4 months before admission for mitral and aortic valve replacement. After discharge, long-term use of warfarin (5 mg/day) plus dipyridamole (when needed) was required for persistent anticoagulation, with a stable INR of 1.2 measured. Frequently taking some traditional Chinese medicine (TCM) concomitantly with the anticoagulants, with an INR of 1.1 measured after concomitantly taking Korean ginseng (20g, q.d.), and of 3.7 after taking complex acetaminophen-containing flu medicine and oral liquid of Gan Cao (*Glycyrrhiza uralensis Fisch*) (10 ml, tid.) for 3 days. This time, patient was admitted because of 4 months after cardiac valve replacement and 20-day shortness of breath.

Objective data

T: 36.7 ^{o}C; P: 130 bpm; HR: 130 bpm; R: 21 bpm; BP: 104/70 mmHg. Cardiac color ultrasound indicated the presence of dysfunction of mechanistic mitral valve (which was unable to open). For this, mechanistic mitral valve replacement and tricuspid valvuloplasty were performed, with mitral thrombosis seen. Starting with the 2nd day after surgery, warfarin (5 mg/day) was taken, with 15.1 of PT and 1.21 of INR monitored at the 3rd day after dosing of warfarin. Clinical pharmacists recommended that genotype be performed, and results indicated that the patient harbors *CYP2C9*1/*1* and *VKORC1 -1639G/G*.

Assessment

i. High risk of thrombosis and low risk of bleeding (OBRI) scored as 0, suggesting a very low risk of bleeding.
ii. Good adherence: A stable INR of 1.2 after discharge of the first surgery. Re-admission for thrombosis was due to insufficient anticoagulation.
iii. According to the genotype of this patient and the prediction model of warfarin dosage [7], warfarin dose would be 7.3 mg/day if the patient achieved a target INR of 2.5. This patient was diagnosed as inherited warfarin resistance after further exclusion of the potential causes of acquired resistance.
iv. The patient had knowledge of anticoagulation therapy, with knowledge of warfarin scored as 95.

Plan

i. Continue to increase warfarin dose until a target INR value is achieved by monitoring INR regularly.
ii. Strengthen education of knowledge of drug- or herb-warfarin interactions.
iii. Reinforce education of the management of warfarin use if at gestation.
iv. Lifelong follow-up is required for patients through the online anticoagulation clinic (OAC) [8] (see Figure 1), which is managed by well-trained clinical pharmacists.

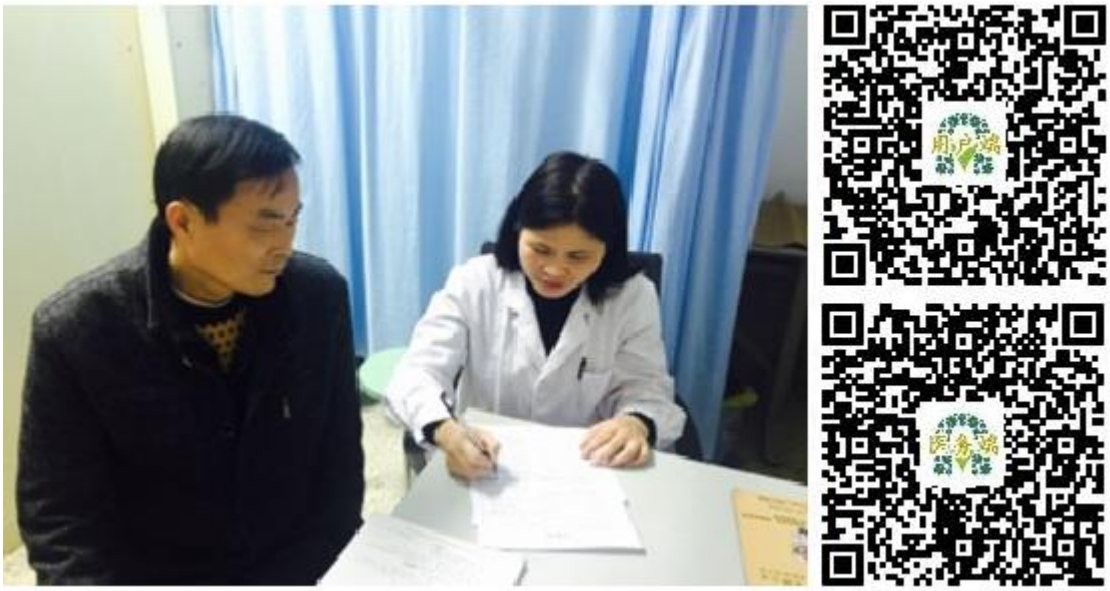

Figure 1. Hospital anticoagulation clinic (HAC, left), and online anticoagulation clinic (OAC, right)

CASE-2

Subjective data

Male, 56 years old, 10-year hypertension, 30-year history of cigarette smoking (5 cigarettes/day), not drinking alcohol, no history of taking TCM, and mitral valve replacement performed three years ago. Long-term use of warfarin of 7.5 mg/day plus dipyridamole (when needed) for persistent anticoagulation, with a stable INR of 1.3 – 1.4 measured. No recording of bleeding due to excessive anticoagulation or of thrombosis due to insufficient anticoagulation. Neither regularly monitoring INR nor visiting his primary care physician (PCP) to adjust warfarin dosage due to residing in the rural area, and forgetting to take warfarin sometimes. The drugs taking currently: amlodipine (5 mg, q.d.) and warfarin (4.5 mg/day). His PCP recommended that he visit OAC for follow-up.

Objective data

T: 36.0 °C; P: 66 bpm; BP: 136/92 mmHg; INR: 1.32 at admission; genotyping: *CYP2C9*1/*1*, and *VKORC1 -1639G/A*.

Assessment

i. High risk of thrombosis; low bleeding risk (OBRI) scored as 0.
ii. According to his genotype and the prediction model of warfarin dosage [7], warfarin dose would be 7.5 mg/day if he achieved a target INR of 2.5. This patient was diagnosed as inherited warfarin resistance after further exclusion of the potential causes of acquired resistance.
iii. Poor compliance of taking medicine.
iv. The patient had insufficient knowledge of anticoagulation therapy, with knowledge of warfarin scored as 35.

Plan

i. Continue to increase warfarin dose until a target INR value is achieved by monitoring INR regularly.
ii. Suggest that the patient give up cigarette smoking.
iii. Strengthen education of knowledge of optimal use of warfarin, with the major focus on WWHM (What is warfarin? Why do I want to take warfarin? How to take warfarin correctly? And how to monitor the efficacy and safety of warfarin?).
iv. Reinforce education of the adherence of taking medicine. The time of administration can be reminded by alarm clock, or calendar. And use of 7-day pillbox and knife (for

cutting a pill) is recommended.

v. Lifelong follow-up is required for patients through the OAC [8].

DISCUSSION

In clinical practice, warfarin resistance is classified as inherited vs. acquired [9,10]. Above-mentioned 2 cases were diagnosed as inherited warfarin resistance, and their warfarin doses required to achieve target INR exceeded 6.0 mg/day (10.5 for case 1, and 9.75 for case 2), both of which exceeded the warfarin doses recommended by the prediction model of warfarin dosage [7], indicating that there would be a marked difference in the predicted and required doses of warfarin when this prediction model is used for the Chinese patients. Although genotyping of *CYP2C9* and *VKORC1* was used for the prediction of warfarin dosage, other genotypes of multiple relevant genes and their clinical significance were not taken into account. Therefore, a prospective, multicenter, randomized controlled clinical trial (RCT) of genotype-guided warfarin dosage requirements in a large-scale Chinese population is needed to establish a dose prediction model that would fit Chinese patients more perfectly.

For these 2 cases, they were carriers of *CYP2C9*1/*1*, and of *VKORC1-1639G* (G/G for case 1, and G/A for case 2), both of which are associated with increased warfarin dose requirements [11,12]. These results are consistent with the findings reported in the Chinese patients described elsewhere [4], in which all 5 cases with warfarin resistance were carriers of *CYP2C9*1/*1*, and of *VKORC1-1639G* (G/G for 3 cases, and G/A for 2 cases). In terms of the fact that the loss-of-function variant allele *CYP2C9*2* is almost absent and *CYP2C9*3* occurs rarely in the Chinese population [13], and that clinical testing of *CYP2C9* and *VKORC1* variant alleles is not covered in the health insurance, only *VKORC1 -1639G/A* genetic testing is considered for the cases with highly suspected inherited warfarin resistance. In addition to genotyping of *CYP2C9* and *VKORC1*, clinical significant variants present in other genes [14–16], such as *CYP4F2, ORM1, NQO1, CYP1A1, STX1B, DNMT3A* and more, may be involved.

The major causes that result in acquired warfarin resistance [10,17] may include: 1) poor adherence; 2) excessive intake of vitamin K-rich food or supplements; 3) impaired absorption of warfarin due to malabsorption (such as gastroenteritis, celiac disease, chronic pancreatitis, and short bowel syndrome); 4) increased clearance and metabolism of warfarin; 5) drug-drug interactions; and 6) hypothyroidism. For this, a set of detailed strategies for its management have been proposed [17]. For example, 1) systematic assessment of potential drug-drug or drug-food interactions associated with warfarin; 2) adherence of each patient; 3) systematic assessment of malabsorption of warfarin; 4) clinical testing of thyroid function (T3 and T4); 5) clinical testing of coagulation factor activity. In this case report, for the case 1, some OTC (such as acetaminophen-containing flu medicine) and TCM (such as Gan Cao) should be avoided to take with warfarin concomitantly, because acetaminophen would lead to increased INR values, or even bleeding [18,19], and also because Can Cao could increase warfarin clearance through activation of pregnane X receptor [20], when patients take these drugs and warfarin concurrently.

In summary, patients with warfarin resistance are required to increase doses of warfarin or to switch to the other anticoagulants to achieve a target INR value according to all known factors that could affect maintenance doses of warfarin, including, but not limited to, the genotypes. Desired anticoagulation largely depends upon genotype testing, taking warfarin regularly, monitoring INR closely, good adherence, and long-term follow-up for anticoagulation.

CONCLUSSIONS AND PERSPECTIVES

There is big variation in warfarin dose requirements among individual patients or across diverse ethnic groups to achieve a target INR value, with extreme response defined as sensitive or resistant phenotype in clinical practice. There are well-characterized factors and unknown causes that could affect the metabolism of and response to warfarin in humans, such as age, gender, body surface area, genomic or epigenetic variability, disease status (intestine, liver, kidney, thyroid, or coagulation system), drug–drug or drug–food interactions, adherence, knowledge, and more, in which genetic variation or genotype cannot be used to describe the whole story about precision medicine of warfarin for patient care. Therefore, further basic and clinical research studies will be still needed in the future.

CONFLICT OF INTEREST

The authors declare no competing interests.

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FINANCIAL DISCLOSURE

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AUTHORSHIP CONTRIBUTIONS

Drs. Zhang, Li, and Cao presented the case reports in Chinese and provided Figure 1 and part of references cited. Dr. Xie drafted, revised, and finalized the whole manuscript in English. All authors critically reviewed and approved the final version of the manuscript for publication.

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