• CASE REPORT •

Exposure to Non-Therapeutic INR in a High Risk Cardiovascular Patient: Potential Hazard Reduction with Genotype-guided Warfarin (Coumadin®) Dosing

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A case to illustrate the utility of genetic screening in warfarin (*Coumadin®*) management is reported. A 45 year-old woman of Puerto Rican ancestry was admitted to the emergency room twice within one month with chest pain. She was diagnosed with congestive heart failure, which was stabilized both times. At her second release, warfarin therapy was initiated at 5 mg/day to prevent thrombus formation and was lowered to 3.75 mg/day at day 7 by her primary physician. International Normalized Ratio (INR) test results in the follow-up period at days 1, 7, and 10 of warfarin therapy were 4.5, 6.5, and 7.3, respectively—far in excess of the therapeutic range, despite the lower dosage in effect from day 7 onward. The patient achieved target INR over the next 43 days after downward adjustment of the dose to a dose of 1.5 mg/day by trial and error. DNA-typing specific for the *CYP2C9*2,*3,*4,*5,*6* alleles and seven variants in the *VKORC1* gene, including the *VKORC1*-1639 G>A polymorphism, revealed the presence of combinatorial *CYP2C9*2/*3* and *VKORC1*-1639 G/A genotypes in this patient. Entering the patient's demographic and genotype status data into independent algorithms available in the public domain to predict effective warfarin dose yielded predicted doses which ranged from 1.5 to 1.8 mg/day. Notably, the prediction of 1.5 mg/day, which was generated by the online resource www.warfarindosing.org, coincided with the patient's actual effective warfarin dose. We conclude that the rapid rise in INR observed upon the initiation of warfarin therapy and the final effective warfarin dose of 1.5 mg/day, are attributable in some part to the presence of two minor alleles in *CYP2C9*, which together significantly reduce warfarin metabolism. Warfarin genotyping can therefore inform the clinician of the predicted effective warfarin dose. The results highlight the potential for warfarin genetic testing to improve patient care. [*P R Health Sci J 2010;4:402-408*]

Key words: Warfarin (Coumadin®), Pharmacogenetics, Genotyping, INR, Minor alleles, CYP2C9, VKORC1, Dosing algorithm, Personalized Medicine

In 2008, nearly 23 million warfarin (Coumadin®) prescriptions were written in the United States (1). Data from IMS Health™ and National Sales Perspective™(2005) reveal that 2 million individuals initiate warfarin therapy in the United States every year to prevent blood clots, heart attacks and strokes (2). Warfarin is the second most common drug, after insulin, implicated in emergency room visits for adverse drug events (3). According to the U.S. Food and Drug Administration (FDA), hemorrhage during warfarin therapy is a leading cause of death in Western countries and related adverse events account for 1 in 10 hospital admissions. Such events generate a mean hospital

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stay of 6 days and healthcare costs of $16,000 per admission per year (4), resulting in poor clinical outcomes and over 1 billion dollars in health care services (2).

Despite over 50 years of clinical experience with warfarin, notable challenges persist when determining the optimal and safest dosage, which must be individualized for each patient (5). Warfarin is notoriously difficult to administer due to the highly variable optimal dose and multiple factors that influence dosage, including: patient age, body mass, gender, nutritional factors such as vitamin K intake, concurrent medications, indications, co-morbidities, and genetic variations (5). Also, warfarin has a very narrow therapeutic index making it all the more difficult to establish the correct dose (5). To assist in the management of warfarin dosing, physicians use a rate of change for blood coagulation as measured by the International Normalized Ratio (INR) value, which also has its limitations. These factors contribute to the need for frequent follow-up visits for INR tests and reassessment of the patient dosing regimen. Incorrect dosing especially during the induction phase (approximately the first 30-90 days of treatment) carries 10 times greater risk of severe bleeding (6).

In January 2010, FDA revised the warfarin label to include pharmacogenetics dosing recommendations based on gene polymorphisms (7). The main role of pharmacogenetics in warfarin therapy management is to provide the DNA-based information that can be used to achieve the patient's effective dose and target INR in a shorter period of time. Up to 45% of the variability in the effective warfarin dose depends on variants in two highly polymorphic genes, cytochrome P450 (*CYP2C9*) and vitamin K epoxide reductase complex subunit 1 (*VKORC1*) (8-12). *CYP2C9* polymorphisms include *2 and *3, which are associated with decrease in cytochrome p450 enzyme activity to approximately 12-70% and 5% of the normal level, respectively (6, 13-16). These polymorphisms lead to subsequent warfarin accumulation. Warfarin inhibits vitamin K epoxide reductase (VKOR), the enzyme responsible for activating an essential cofactor of clotting factors II, VII, IX and X (5). The *VKORC1* -1639G>A polymorphism in the promoter region of the gene results in reduced enzymatic activity. A patient with one or more polymorphisms in either or both of these genes is at risk of supra-therapeutic warfarin dosing, increasing the risk of bleeding. This case presentation provides an example of the importance and utility of pharmacogenetic testing in the development of successful therapeutic regimens.

Here we describe a patient with a rapid increase in INR upon the initiation of warfarin therapy and a sustained elevation in INR despite conventional dose, the elevation of which, in response to the typical 5mg starting dose, is consistent with her genotype status: namely, the metabolic loss of function and decreased warfarin clearance anticipated with *CYP2C9 *2/*3*, and the decreased sites of drug action due to the presence of the -1639 G>A polymorphism.

Case Report

A 45 year-old Puerto Rican female with a past medical history of congestive heart failure, hypertension, bronchial asthma, lupus, and substance abuse, was admitted to the emergency room with an acute onset of shortness of breath. The patient had a history of tobacco use and addiction to cocaine and heroin in the past. At the time of the admission she was taking only methadone and furosemide (*Lasix®*, Sanofi Aventis US), with evidence of non-compliance regarding the latter. The patient denied nausea, vomiting, and fever at the time of admission.

Her diagnosis was congestive heart failure (CHF) exacerbation as a result of furosemide (*Lasix®*, Sanofi Aventis US) non-compliance. The cardiac examination was unrevealing. Her laboratory studies revealed a brain natriuretic peptide (BNP) level of 1,511ng/L which implies severe CHF, a creatine kinase (CK) of 66U/L, and troponin levels of less than 0.01ng/mL. Her chest x-ray indicated her heart was enlarged and the patient had diffuse pulmonary edema. The second set of cardiac enzymes revealed a CK of 1,531ng/L, CKMB of 3.2ng/mL, and CKMB index of 0.2. An echocardiogram showed a left ventricle that was markedly dilated and profoundly hypokinetic. The left ventricular ejection fraction was 10% to 15%, markedly decreased. PET scan showed anterior and lateral perfusion abnormalities and regional wall motion abnormalities. Computer tomography angiography was recommended; however, IV access was not obtained due to patient's refusal of IV. Due to the patient's low ejection fraction, it was considered that she was at an increased risk of a thrombus formation. She was started on heparin therapy; however, the heparin was discontinued because of chest pain. The patient did not receive aspirin due to self-reported allergy to this medication. Her discharge medications included lisinopril 10mg per os daily; carvedilol (*Coreg®*, GSK) 6.25 mg per os twice a day; fluticasone propionate/salmeterol xinafoate (*Advair® Diskus* 250/50, GSK) inhaled twice a day; furosemide (*Lasix®*, Sanofi Aventis US) 40 mg *per os* twice a day; methadone hydrochloride 75 mg *per os* daily; and albuterol sulfate as needed for asthma exacerbation.

A month after this visit the patient returned to the emergency room with the same complaints and similar clinical findings. The physical examination revealed irregular heart beats. The patient's PT and PTT were 23.3 and 55 sec., respectively. Cardiac enzymes were negative. BNP was elevated at 1,500ng/L and her chest x-ray showed mild pulmonary edema. The patient was discharged and prescribed warfarin at the standard dose of 5 mg/day (*per os*) for prevention of thrombus formation. Consecutive INR values of 4.46, 6.53, and 7.34 were measured on days 1, 7, and 10 of therapy, which demonstrated an incremental pattern (Figure 1). The baseline INR value for this patient was 1.21 (Table 1). In healthy people, the INR is by definition 1.0. For this patient the INR therapeutic range is between 2.0 and 3.0, based on the diagnosis of congestive heart failure. Warfarin dosage was

changed four times in this patient during the course of 43 days. There were 7 INR assessments made before the patient reached target (Table 1). Six of the seven INRs exceeded target level, peaking at 7.34, suggesting a supra-therapeutic level of warfarin dosage, and exposing her to a higher risk of bleeding. Fortunately in this case, no minor or major life-threatening bleeding episodes were reported and dosage was eventually stabilized at 1.5 mg/day, the lowest dose prescribed, at the time of achievement of target INR. In this patient, the initial warfarin dose of 5 mg/day resulted in successively higher INRs all of which exceeded the target range (Figure 1). At the initiation of therapy the dose was the highest dose given to the patient.

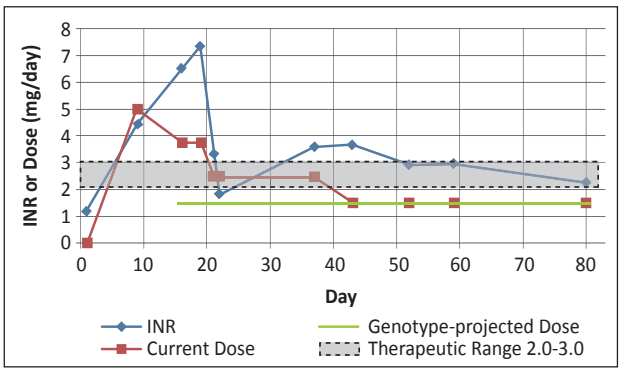

Figure 1. Serial INR results and drug dose, during first 80 days of warfarin therapy, showing the peak INR level at day 19 of warfarin therapy and the stabilization of INR beginning at day 52 The effective warfarin dose of 1.5 mg/day, first administered at day 43, was predicted (green line) by a warfarin algorithm (18).

Table 1. Warfarin Doses and INR Responses

Day	INR	Current Dose (mg/day)
1	1.21	0
9	4.46*	5
16	6.53*	5/2.5 alt (3.75)
19	7.34*	5/2.5 alt
21	3.34*	2.5
22	1.84	2.5
37	3.62*	2.5
43	3.69*	2/1 alt (1.5)
52	2.93§	2/1 alt
59	2.99§	2/1 alt
80	2.27§	2/1 alt

Therapeutic Range 2.0-3.0 *Above therapeutic range §Target achieved

After almost three years on warfarin therapy, this patient underwent genotype testing as a volunteer participant in an IRB-approved research study conducted at Hartford Hospital-affiliated Brownstone anticoagulation clinic to investigate the frequency distribution of up to twelve common minor alleles in *CYP2C9* and *VKORC1* genes (5, 8) in the Puerto Rican population [i.e., five minor alleles in *CYP2C9* (**2, *3, *4, *5,* and **6*) and seven minor alleles in *VKORC1* (including -1639 G>A]. She signed an informed consent form approved by the Hartford Hospital Institutional Review Board. The HILOMet WARFARIN DNA-typing system (8) was used to run the test at the Laboratory of Personalized Health (LPH, Genomas Inc.), a CLIA-certified lab that is also licensed by the Connecticut Department of Health (CL-0644). DNA testing to infer patient's metabolic capacity and sensitivity to warfarin revealed this patient is a carrier of three major variants in these two warfarin-related genes: i.e., *CYP2C9* *2 and *3 and the *VKORC1*-1639 G/A polymorphisms.

Discussion

The target INR for patients diagnosed with heart failure is a range of 2.0-3.0. The recommended starting dose of warfarin is 5 mg/day. Many non-genetic factors, such as body size, sex, dietary change, and drug interaction, can contribute to an elevation in INR. Our patient denied significant dietary changes that would have altered Vitamin K intake. Furthermore, no pharmacokinetic or pharmacodynamic factors associated with the warfarin response such as drug-drug or drug-food interactions were found. Other factors to take into consideration are the medical condition of the patient and whether the patient complies with the drug regimen as prescribed. CHF exacerbation can increase the INR value due to an increase in hepatic congestion and decreased warfarin catabolism. However the patient's BNP was unaltered suggesting no change in CHF status. Also the non-compliance to furosemide therapy that was mentioned in the patient's history can put the patient at risk of future exacerbations and increase in INR values. It is conceivable but not likely that noncompliance to furosemide therapy contributed to the patient's elevated INR, because here the rapid rise in INR coincided with the onset of warfarin therapy. During the treatment course with warfarin, no drugs that interfere with *CYP2C9* function were prescribed and there is no evidence of a change in diet that could have altered the intake of Vitamin K. The status of the *CYP2C9* gene is consistent with decreased metabolic function and a high likelihood of warfarin accumulation. For these reasons, genetic polymorphisms in *CYP2C9* and *VKORC1* are the most likely explanations for the elevated INR, resulting from a supra-therapeutic warfarin dose.

Such unintended over-anticoagulation puts the patient at high risk for bleeding events. Severe bleeding complications do occur with warfarin therapy and are more likely during induction phase and with supra-therapeutic doses (17). According to a meta-analysis of 33 studies, major and fatal bleeding events occur at rates of 7.2 and 1.3 per 100 patient years, respectively (18). Even though our patient did not suffer any major bleeding event, she had some high risk factors for bleeding, which included: excessive anticoagulation (INR>4.0), highly variable INRs,

hypertension, serious heart disease and genetic polymorphisms suggested significantly decreased enzyme activity (19). One randomized trial of 211 patients, found that 32 patients (15% of all patients) with INR values between 4.1-8.0 experienced a major bleeding event (20). It is important to note that the first three INR values ranged between 4.1 and 8.0 when a standard dosing initiation procedure was followed. Patients with more than four dose modifications within one year had approximately 25% more bleeding events than patients with less dose adjustments. Our patient's warfarin dose was changed four times during the course of 43 days, exposing her to a higher risk of bleeding. Reynolds et al. found that 83% of reported bleeding events occurred when patient INRs were above 3.0 (6). With each 1-point rise in the INR above 3.0, the risk of bleeding events increases by 42% (21). Our case report patient evidenced a total of six INRs above 3.0, the highest being 7.34. Patients at high risk of bleeding may need more frequent INR monitoring, which not only prolongs the dose adjustment period but also increases the health care spending.

The INR test has limitations with respect to clinical relevance especially in the initiation phase of warfarin therapy. There is a lag-time between the suppression of the synthesis or activation of vitamin K-dependent clotting factors by ingested warfarin and the increase in the INR6. This is due to differences in the biological half-life of active vitamin K-dependent clotting factors involved in coagulation, the reserve of these proteins when warfarin therapy is initiated, and the time needed for warfarin to accumulate to a sufficient therapeutic concentration (6). Factors that can promote an increase in INR value include 1) the use of concurrent medications that alter the metabolic activity of *CYP2C9*, 2) sudden reduction in vitamin K ingestion, and 3) polymorphisms in *VKORC1* or *CYP2C9*.

Pharmacogenetic Analysis

DNA-typing of the *CYP2C9* and *VKORC1* genes was performed at 12 variable sites, 5 SNPs in *CYP2C9* and 7 SNPs in *VKORC1*. The assay employed PCR to amplify selectively these two genes without co-amplifying pseudo-genes or other closely related sequences. The PCR-derived target DNA with 2 universally-tagged allele-specific primers, whose 3' ends define the corresponding alleles, were then used for running multiplexed Allele Specific Primer Extension (ASPE) reactions. A thermophilic DNA polymerase was used for primer extension and biotin-dCTP label incorporation. Following ASPE, tagged, extended products labeled with biotin were captured by their tag complements (anti-tags), which had been chemically coupled to spectrally addressable polystyrene microspheres. A fluorescent reporter molecule (streptavidin-phycoerythrin) was used to detect incorporated biotin. The fluorescent reporter signals generated for each bead population was measured on the Luminex xMAP™ platform (Luminex® Corp., Austin TX). Wild-types were assigned as a result of the absence of other SNPs.

Combinatorial genotyping analysis revealed *CYP2C9*2/*3* and *VKORC1*–1639 G/A genotypes, which classifies this patient as a carrier of three loss-of-function polymorphisms. Patients with **1* homozygous alleles are considered wild type and have a normal and fully functional *CYP2C9* enzyme (5). A *CYP2C9*2* allele variation produces a base pair exchange of cytosine to thymine (430 C>T) resulting in a Arg144Cys amino acid substitution reducing enzymatic activity (5, 17). A *3 variant (1075 A>C) causes an amino acid change at position 359 resulting in a null enzyme. For *VKORC1*, the transition from G to A at position -1639 in the promoter region leads to an altered transcription and, therefore, decreased amount of the enzyme with a subsequent higher patient's sensitivity to warfarin5. The *CYP2C9* and *VKORC1*-1639 statuses by themselves accounts for approximately 15-20% and 20-25% of warfarin dose, respectively (10-11, 16, 22-23).

In Caucasian populations, the *CYP2C9* polymorphisms are associated with 1.4-fold increased risk of excessive anticoagulation and a two- to three- fold increased risk of bleeding during warfarin induction phase specifically (16-17, 24-27). A recent study in African-Americans demonstrated an increased risk of hemorrhage during long-term therapy in patients with *CYP2C9* minor variants (28). Even though our patient is neither Caucasian nor African-American, it is important to mention that her Puerto Rican ancestry background includes an admixture of Caucasian, African and Amerindian (Taino) heritage (29). The combinatorial genotype prevalence in Puerto Rican population for carriers of both the *CYP2C9* and *VKORC1* polymorphisms, as in our case report patient, is reported to be between 16%-18% (8, 30). Furthermore, nearly 5% of Puerto Rican population carried three polymorphisms (8). Duconge et al. showed that the predicted warfarin dose reduction (using 5mg/day as standard dose) for Puerto Rican patients having combinatorial *CYP2C9* and *VKORC1* genotypes ranged from 1.6 to 3.7mg daily (30). The reduction in effective warfarin dose for carriers of three polymorphisms compared with non-carriers is in the range of 34-47% (31). Patients with polymorphisms in *VKORC1* and *CYP2C9* are at high risk of over-anticoagulation compared to patients with 1 or no polymorphism (32).

Recent papers have published DNA-guided algorithms to predict effective warfarin dose (9-10, 14, 22, 31, 33-34). Also, computer based algorithms such as *Couma Care®*, *Coag Clinic™*, *INR star*, and *www.warfarindosing.org* are available to guide clinicians in the incorporation of genotyping results relative to warfarin prescription. If any of these recently developed algorithms were employed, the patient's dosage might have been altered. Since genotyping analysis was performed three years after the patient started warfarin therapy, as part of a research study, it was not used to predict the patient therapeutic dose. We calculated the effective dose based on algorithms that incorporate gene status and compared the results with the actual effective dose of the patient. We tried

different algorithms to calculate the predicted warfarin dose for our patient, including: Perini et al. model (34) for Brazilian patients; Sconce et al. model (10); Zhu et al. model (9); and *warfarindosing.org* (Table 2). The warfarin dose calculated by the website *warfarindosing.org* (http://www.warfarindosing.org/Source/Home.aspx) was 1.5 mg/day, which agrees precisely with the dose given when the patient reached target. In retrospect, had the dosage been reduced during the first few days of therapy, it is reasonable to expect the treatment course to have been altered.

Table 2. Predictions based on published DNA-guided warfarin dosing algorithms

Algorithms	Predicted Warfarin Dose (mg/day)
Perini et al.	1.8
Zhu et al.	1.3
Sconce et al.	1.3
warfarindosing.org	1.5

In August 2007, the FDA announced a warfarin label change recommending but not requiring testing for *VKORC1* and *CYP2C9* gene variants in patients receiving warfarin therapy (35). These tests are done in pharmacogenetic laboratories with an average turnaround time of four days, but 1 day turnaround time for warfarin genotyping is feasible (36). The necessity of a 1 day turn-around time is unclear since warfarin algorithms have focused on maintenance dose, rather than initiation dose (35). The impact of genetic variants on effective dose is well-known but the impact on the initiation dose or adjustment of initial dose has been given less attention (37). Schwarz et al (17) have shown that the *CYP2C9* genotype is a significant predictor of time to first INR>4. Preliminary observations in our clinical practice indicate that double carriers of *CYP2C9**2* and *3 compared to *2/*2 and non-carriers (unpublished data), increase INR quickly upon initiation of warfarin therapy. If this finding is confirmed, early knowledge of genetic testing results may expand prescribing options to include the early adjustment of the initial dose of 5 mg/day to a lesser dose, or initiation with a smaller dose.

Cost of Genetic Testing

Genetic testing for the presence of the most common *VKORC1* and *CYP2C9* minor alleles currently ranges in cost from $200 to $450, averaging $350 per test (2), while INR test costs an average of $50. For the case report patient six INR tests were ordered and performed before reaching target INR for a total approximately cost of $300. In addition to the INR cost it is important to add the cost of the laboratory personnel conducting the tests and the clinician making the dose adjustments. Estimates on cost savings suffer from a lack of hard data. If DNA typing were to be performed before warfarin is prescribed, one analysis estimated that 85,000 serious bleeding events and 17,000 strokes could be avoided annually in the US, saving over US $1.1 billion in health care (2). In contrast, another estimate based on genotype testing at the initiation of warfarin therapy, suggests lesser but still worthwhile cost savings, assuming the turn-around time for results is reduced to one day (38). Based on current estimates, the cost of warfarin per quality-adjusted life year is greater than $170,000, a number far too large to institute across the board. A more acceptable number for practical application is $50,000, which would require halving of the genotype costs and a return of results within 24 hours. In order to obtain this acceptable number, the utility would have to be in those with a very high risk for hemorrhage, like the patient in this case report, given the average annual estimate for warfarin-related intracranial bleeding being approximately 0.1%. Both public health improvement and significant reduction in the health care costs can be accomplished if clinicians can effectively incorporate pharmacogenetic into therapeutic management. The avoidance of adverse events for warfarin therapy such as bleeding, may soon justify the cost of genotyping, particularly in patients at high risk of bleeding complications.

Conclusion

Patients with polymorphisms in *CYP2C9* and/or *VKORC1* are more prone to develop supra-therapeutic levels of warfarin and usually require a prolonged dose adjustment period. The excess of anticoagulant can result in adverse events such as bleeding or hemorrhages. To improve patient's outcomes and reduce bleeding events we recommend genotyping for patients at high risk for bleeding.

Resumen

Se reporta un caso que ilustra la utilidad del cernimiento genético en el manejo clínico de warfarina (*Coumadin®*). Una mujer puertorriqueña de 45 años de edad fue admitida a una sala de emergencias dos veces en un mismo mes con dolor de pecho. Ella fue diagnosticada con un fallo cardiaco congestivo, el cual fue estabilizado en ambas ocasiones. En su segunda visita, se inició un tratamiento con warfarina en dosis diaria de 5 mg, para prevenir la formación de trombos, que luego del séptimo día se redujo por su médico primario a 3.75 mg diarios. Los resultados de sus pruebas de INR en los días 1, 7 y 10 fueron 4.5, 6.5 y 7.3, respectivamente. Estos valores estaban muy por encima del rango terapéutico, independientemente de la reducción en la dosis a partir del séptimo día. La paciente alcanzó el INR requerido después de 43 días de ajustes de la dosis de warfarina, con reducciones diaria hasta los 1.5 mg, mediante tanteo y error. Una prueba de ADN específica para los alelos *CYP2C9*2,*3,*4,*5,*6*

y otras siete variantes del gen *VKORC1*, incluyendo *VKORC1*-1639 G>A, revelaron la presencia en esta paciente de una combinación de variantes alélicas en ambos genes que determinan el genotipo *CYP2C9*2/*3* y *VKORC1*-1639 G/A. La dosis efectiva de warfarina para esta paciente fue estimada en el rango de 1.5 - 1.8 mg diarios, mediante un algoritmo farmacogenético de dominio público (www.warfarindosing.org), utilizando la información demográfica y el genotipo de la paciente. Interesantemente, la dosis diaria de 1.5 mg estimada por el algoritmo coincidió con la verdadera dosis efectiva de warfarina para esta paciente. Podemos concluir que el rápido incremento de los valores de INR en esta paciente, observados durante la fase de iniciación, así como la baja dosis efectiva de 1.5 mg al día, son atribuibles en parte a la presencia de dos variantes en el gen *CYP2C9*, lo cual reduce significativamente su capacidad para metabolizar la warfarina. Esta prueba genética para warfarina puede entonces informar mejor al médico sobre la dosis más efectiva en el paciente. Estos resultados resaltan el potencial de la prueba genética de warfarina para mejorar el cuidado al paciente.

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