

Effect of patient-specific factors on weekly warfarin dose

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Abstract

Objective: To determine the influence of various patient-specific factors, use of concomitant medications, and weekly vitamin K intake on total weekly warfarin maintenance dose (TWD).

Methods: Information collected, via retrospective chart review, included TWD, general demographics, vitamin K consumption, target INR range, use of alcohol, tobacco, and cytochrome P450 (CYP)-inducing medications, and concomitant medications and diseases.

Results: The majority of patients ($n = 131$) were Caucasian (71%), with more females (55%) than males. Use of CYP-inducing medications resulted in the largest correlation coefficient ($r = 0.30$). The sample was divided into high warfarin dose ($TWD \geq 50$ mg) and low warfarin dose ($TWD \leq 25$ mg) patient populations to discern areas where the two populations differed. Age and amiodarone use were the only statistically significant differences between the two groups, with high dose patients tending to be younger and to use less amiodarone. Age and CYP-inducing medications were found to be the only statistically significant predictors of TWD in the regression analysis. The TWD was 2.4 mg less for each additional decade of patient age. The coefficient on CYP-inducing medications indicates that the concomitant use of a CYP inducer is associated with an increase in TWD of 17.2 additional milligrams, adjusting for all other variables in the model.

Conclusion: We found concomitant use of CYP inducer, age, height, and ethnicity to have the greatest influence on TWD. Positive relationships were found between TWD and the use of CYP450 inducer, height, and African American ethnicity. Although it did appear that women required a lower TWD than men, this factor contributed mildly. Further studies with a greater sample size may more precisely predict the effect of patient-specific factors on TWD, thus uncovering additional relationships.

Keywords: anticoagulation, survey, vitamin K, warfarin, CYP450 inducers

Introduction

Warfarin therapy is widely used for the prevention of thromboembolic events for a variety of medical conditions. The dosing of warfarin is patient-specific. Although there are several methods to initiate warfarin therapy, most clinicians elect to begin with empiric doses of 5 mg daily, and titrate as needed to achieve a therapeutic international normalized ratio (INR) (Harrison et al 1997; Crowther et al 1999; Ansell et al 2004). Experience shows that within a cohort, patients may require as little as 0.5 mg up to as much as 20 mg or greater of warfarin daily to maintain a target INR. This large variability in warfarin dose may be explained, to some extent, by concomitant medications, gender, nutritional status, liver disease, alcohol consumption, diarrhea, hyperthyroidism, fever, chronic heart failure (CHF), and more recently, ethnicity.

For over a decade, evidence has indicated that elderly patients require smaller total weekly warfarin maintenance doses (TWD) compared with younger counterparts (Gurwitz et al 1992; James et al 1992; Absher et al 2002; Ansell et al 2004; Singla and Morrill 2005). Several studies have also suggested that women require lower warfarin doses than do men

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(Absher et al 2002). More recently, evidence has shown that patients of African American descent require larger doses of warfarin to maintain therapeutic INRs (Blann et al 1999; Absher et al 2002; Dang et al 2005; Rieder et al 2005). However, little evidence is available concerning the impact of other factors, such as body mass index (BMI) and vitamin K intake.

Objective

The purpose of this investigation is to determine the influence of various patient-specific factors, use of concomitant medications, and weekly vitamin K intake on TWD in the population of patients at our internal medicine clinic. Clearly defined effects of patient factors on warfarin dose may better facilitate achievement of therapeutic INRs following initiation of warfarin therapy.

Methods

This research was approved by the hospital's institutional review board through the exempt process, thus consent was not required for patients.

Study location and population

This study was conducted within a university-based internal medicine clinic. All adult patients (18 to 100 years old) who were using warfarin therapy and were followed by clinical pharmacists for anticoagulation management and education were eligible. Additionally, to further reduce confounders, only those patients with stable TWD for three consecutive months were included. Patients who were deemed as noncompliant with warfarin therapy were excluded. Noncompliance was defined, per patient report, as missing greater than one dose for two consecutive months, as documented in their electronic medical record (EMR). Patients with target INR ranges of 2 to 3 or 2.5 to 3.5 were included, while patients with target INR ranges outside of these values were excluded.

Data collection took place via retrospective chart review. Information collected included age, gender, ethnicity, weight, height, vitamin K consumption, date of warfarin initiation, indication, target INR range (either 2.0 to 3.0 or 2.5 to 3.5) and TWD. Body mass index (BMI) was calculated via weight and height. Patients' weekly dietary vitamin K content was quantified just prior to their anticoagulation appointment using a 2-page survey. The presence of various health conditions was also collected, such as heart failure and thyroid disorders. Use of alcohol, tobacco, amiodarone, aspirin, a multivitamin, and cytochrome P450 (CYP) inducers were also identified. Those medications identified as CYP inducers for the purpose of this study included the following:

carbamazepine, phenobarbital, phenytoin, primidone, rifampin, ritonavir, and St. John's Wort.

Statistical analysis

Descriptive statistics were calculated for the entire sample and then separately for high and low warfarin dose patients, using a two sample t-test to detect statistically significant differences between the two groups. High dose was considered to be greater than or equal to 50 mg of TWD, while low dose was considered as less than or equal to 25 mg. We also examined individual Pearson correlation statistics for meaningful associations between each of the patient specific variables and TWD. Finally, we analyzed an ordinary least squares regression of the combined factors in predicting warfarin dose.

Results

A total of 170 patients were provided pharmaceutical care for anticoagulation within the internal medicine clinic. Due to warfarin noncompliance or unstable weekly warfarin dose, 36 patients were excluded. An additional three patients were excluded for having target INR ranges other than 2.0–3.0 or 2.5–3.5. A total of 131 patients were analyzed.

Baseline demographics showed those analyzed for the study to range in age from 23 to 98 years (mean age 67 years). The majority was Caucasian (71%), followed by African American (29%), with more females (55%) than males. Descriptive statistics for the sample are summarized in Tables 1 and 2, including indications for warfarin therapy and weekly vitamin K intake for 77 patients.

The mean weight, height, and BMI were 83.9 kg, 172 cm, and 28.4 kg/m², respectively. The most common indications for warfarin use were atrial fibrillation (n = 69, 50%), deep vein thrombosis (DVT) (n = 32, 23%), pulmonary embolism (PE) (n = 16, 21%), cerebral vascular accident (CVA) or transient ischemic attack (TIA) (n = 20, 15%), and valve replacement (n = 13, 9%). The majority of patients had INR target ranges of 2.0 to 3.0 (n = 115 out of 131, or 87.8%). Concomitant medication use and presence of CHF and thyroid disorders are also presented in Table 1.

Simple pairwise correlation statistics between each of the variables and TWD are presented in Table 3. The concomitant use of CYP-inducing medications resulted in the largest correlation coefficient (r = 0.30). The difference in mean TWD between patient groups who did and did not use CYP inducers was found to be statistically significant using a paired t-test (p < 0.001).

Table 1 Descriptive statistics for the sample of 131 patients

Continuous variables	Mean value	Standard deviation
TWD (mg/week)	36.61	16.03
Age (years)	66.91	13.06
Weight (kg)	83.91	20.91
Height (cm)	172	10.3
BMI (kg/m ²)	28.39	6.34
Vitamin K consumption (mcg/week) ^{***}	1764.93	1745.91
Ethnicity	Percentage	
Caucasian	71.0%	
African American	29%	
Dichotomous variables	Percentage	
Female	55.0%	
Amiodarone use	12.1%	
Aspirin use	36.6%	
Tobacco use	9.9%	
Alcohol use	22.1%	
CYP inducer	7.7%	
Multivitamin use ^{**}	21.5%	
History of CHF	16.8%	
History of Hypothyroidism	14.6%	
LFT 3× ULN [*]	1.6%	
Target INR 2.5–3.5	12.9%	

Notes: *Data only available for 129 patients; **Data only available for 130 patients; *** Data only available for 77 patients.

When the low (≤ 25 mg TWD, $n = 24$) versus high (≥ 50 mg TWD, $n = 105$) TWD patient groups were analyzed to discern areas where the two populations differed, age and CYP were the only statistically significant differences. Those patients within the high dose group tended to be younger and to use CYP-inducing medications (see Table 4).

We compared those patients consuming >3000 mcg of vitamin K per week with those consuming <250 mcg of vitamin K per week and found no difference in the TWD. The mean TWD for the lower consumption was 35.8 mg ($n = 17$), the mean for the higher consumption was 37.3 mg ($n = 14$), and a two sample t-test with equal variances concluded no difference ($p = 0.83$).

Table 2 Descriptive statistics – Indications for warfarin therapy ($n = 131$)

Indications	Mean value
History of atrial fibrillation	49.6%
History of deep vein thrombosis	24.5%
History of pulmonary embolism	12.2%
Prosthetic valve	10.8%
Other indication for warfarin therapy	21.6%

Table 3 Pearson correlation coefficients between TWD and patient specific variables

Variable	Correlation coefficient
Demographics	
Age	-0.241**
BMI	0.076
Caucasian	-0.109
Female	-0.050
Medication use	
Amiodarone	-0.066
Aspirin	-0.019
CYP inducer	0.300**
Multivitamin	-0.084
LFT 3× ULN	0.042
Comorbidities	
CHF	-0.095
Hypothyroidism	-0.112
Prior embolism	0.108
Other patient characteristics	
Target INR 2.5–3.5	0.068
Vitamin K consumption	0.026
Tobacco use	-0.004
Alcohol use	0.108

Notes: **Statistically significant at the 1% level.

Finally, we analyzed an ordinary least squares regression of the combined factors in predicting warfarin dose (see Table 5). Because the regression is restricted to patients with no missing data, the resulting sample size was 130. Variables with many missing observations, such as vitamin K consumption, were excluded from this stage of the analysis to preserve sample size and increase the chances of obtaining statistically significant results.

Age and CYP-inducing medications were again found to be the only statistically significant predictors (at the 5% and 1% levels of significance, respectively) of TWD. The regression coefficient on age quantifies the inverse association with dose requirements, while controlling for all other variables included in the regression. It indicates that the TWD is 2.4 mg less for each additional decade of patient age. The coefficient on CYP inducers indicates that the concomitant use of a CYP inducer is associated with an additional 17.2 mg of warfarin a week, while controlling for patient demographics (age, BMI, race, gender), medications (amiodarone and aspirin), comorbidities (CHF, hypothyroidism, and a history of prior thromboembolic event), and tobacco or alcohol use.

Discussion

Our analysis included patients with target INRs of 2–3 and 2.5–3.5. The correlation coefficient of 0.07 indicated

Table 4 Comparison of high and low warfarin dose patient populations

Variable	Low (≤ 25 mg) warfarin dose (n = 35)	High (≥ 50 mg) warfarin dose (n = 26)	P-value from a two sample t-test or chi-squared test
Demographics			
Average TWD	19.4 mg	60.7 mg	<0.0001**
Age	72.3	61.6	0.001**
BMI	27.1	29.3	>0.10
Caucasian (%)	0.77	0.62	>0.10
Female (%)	0.63	0.50	>0.10
Medication use			
Amiodarone (%)	0.08	0.09	>0.10
Aspirin (%)	0.37	0.35	>0.10
CYP Inducers (%)	0.0	0.15	0.016*
Multivitamin (%)	0.26	0.23	>0.10
LFT 3 \times ULN (%)	0.03	0.04	>0.10
Comorbidities			
CHF (%)	0.20	0.17	>0.10
Hypothyroidism (%)	0.23	0.12	>0.10
Prior Embolism (%)	0.43	0.50	>0.10
Other patient characteristics			
Target INR 2.5–3.5 (%)	0.11	0.19	>0.10
Vitamin K consumption	1881.5	2040.4	>0.10
Tobacco use (%)	0.11	0.04	>0.10
Alcohol use (%)	0.17	0.27	>0.10

Notes: *Statistically significant at the 5% level; **Statistically significant at the 1% level.

that target INR had a relatively low influence on TWD in our sample. It was therefore decided to include both target populations in an effort to increase power. To check for potential bias resulting from this decision, we reran each of the analyses on the larger subgroup with INR targets of 2–3 and found that statistical significance and directions of correlations were unchanged.

As expected, this investigation suggests that one of the strongest and statistically significant patient-specific factors that affect TWD is the concomitant use of CYP-inducing medications. The predominately active warfarin isomer (S) is metabolized through CYP450 2C9, while the less active isomer (R) is a substrate of the 1A2, 2C19, and 3A4 isoenzymes. Addition of medications that induce the metabolism of these enzymes would thus increase plasma warfarin concentrations, and thus decrease the TWD need. The concomitant use of CYP inducers resulted in the largest correlation coefficient ($r = 0.30$). The difference in mean TWD between patient groups that did and did not use CYP-inducing medications were found to be statistically significant using a t-test ($p < 0.001$). Because a simple correlation is not adjusted for other patient-specific characteristics, the relationship may be confounded. To address this issue, we conducted a regression analysis which indicates

that the concomitant use of a CYP inducer is associated with 17.2 additional milligrams of warfarin per week, adjusting for all other variables in the model. In this investigation, the most

Table 5 Ordinary least squares regression of weekly warfarin dose explained by patient specific variables (n = 130)

Variable	Coefficient	Standard error
Demographics		
Age	-0.24	0.12*
BMI	0.026	0.233
Caucasian	-2.75	3.42
Female	-2.55	3.08
Medication use		
Amiodarone	-3.35	6.60
Aspirin	-1.62	2.86
CYP inducer	17.19	5.41**
Comorbidities		
CHF	-2.66	3.78
Hypothyroidism	-1.99	4.22
Prior embolism	-0.36	3.01
Other patient characteristics		
Tobacco use	-5.17	4.74
Alcohol use	3.32	3.46

Notes: R-squared = 0.1676; Adjusted R-squared = 0.0822; *Statistically significant at the 5% level; **Statistically significant at the 1% level.

commonly used CYP-inducing medications were phenytoin, phenobarbital, and primidone; therefore, when initiating warfarin therapy in a patient who currently uses one of these inducers, the clinician should consider empirically initiating therapy at a higher dose.

Age was also a statistically significant predictor of TWD, with a regression correlation coefficient of -0.24 . This inverse association indicates that a TWD of 2.4 fewer milligrams are prescribed for each additional decade of patient age, adjusting for all other variables in the regression analysis. Similar data have been published by Garcia and colleagues (2005) who found that as patients age the TWD declined by 0.4 mg per year of life. Age was also found to be significantly different between the high and low warfarin dose groups, with high dose patients tending to be younger (see Table 4). Patients in the low and high categories of warfarin use averaged 72 and 62 years of age, respectively. These findings confirm previously published literature; warfarin dose for maintenance therapy is inversely proportional to age (Gurwitz et al 1992; James et al 1992; Absher et al 2002; Singla and Morrill 2005; Garcia et al 2005; Merli 2005).

A very weak correlation existed between gender and TWD. Although not statistically significant, the regression analysis quantified this difference with female patients requiring a 2.55 mg lower TWD when compared with males. This finding is similar compared with previous studies which showed that women require an average of 4.5 mg less of warfarin per week (Ansell et al 2004; Garcia et al 2005). Conversely, several published articles cite gender to be an important factor in predicting warfarin dose (Oates et al 1998; Absher et al 2002). Regardless of the effect gender plays in warfarin dosing, studies are consistent in reporting lower doses required for women compared with men.

We found a weak correlation between ethnicity and TWD ($r = -0.11$), with African American patients requiring greater TWD than Caucasian patients. Overall African Americans required approximately 2.75 mg more per week to maintain a therapeutic INR than did Caucasians, controlling for all other variables in the regression. Although not statistically significant, this finding agrees with previous study results (Blann et al 1999; Absher et al 2002; Dang et al 2005).

Similarly, we found only a weak correlation between BMI and TWD ($r = 0.08$). Adjusting for all other variables in the regression, we found that the small positive association remained, though it was not statistically significant. Several other studies found no relationship between BMI or body weight and warfarin dose (Gurwitz et al 1992; Oates et al 1998; Blann et al 1999). Sconce and colleagues, however, found that height has greater

predictive value of warfarin dose than does body weight or BMI (Sconce et al 2005), while Singla and colleagues found that BMI influences TWD equally to gender ($r^2 = 5.3$, $p = 0.001$) (Singla and Morrill 2005). It is currently not clear how much of an effect, if any, BMI plays upon TWD.

Although there have been various case reports of the affect of tobacco (Evans and Lewis 2005), alcohol (Havrda et al 2005), and aspirin use (Wittkowsky et al 2004) on warfarin metabolism and INR, this study did not show a profound effect of these products on TWD.

Unfortunately, alcohol use was not stratified into frequency, volume, or type consumed. Patients were simply asked if they used alcohol. Alcohol use has opposing effects on warfarin metabolism depending on whether it is consumed on a chronic, binge, or occasional basis (Ansell et al 2004). Individuals who chronically ingest alcohol experience increased warfarin clearance through induction of CYP450 isoenzymes, which results in larger TWD requirements. Conversely, binge drinking inhibits the hepatic metabolism of warfarin, thus smaller amount TWD are needed. Likewise, tobacco use was not clearly established. Again, patients were simply asked if they used tobacco; the study was not designed to assess amount, frequency, or tobacco products used. Better assessment of these variables of alcohol and tobacco consumed may have produced a more predictive value on TWD.

Of the 77 patients who completed the vitamin K survey, the average weekly intake did not prove to have a profound influence on TWD. As patients assessed their average weekly vitamin K intake just prior to their anticoagulation appointment, rather than concurrently, the retrospective completion of surveys could be subject to recall bias.

Interestingly, the adjusted R-squared value was also low, even for cross-sectional data. It indicates that the regression model as a whole only explains 8% of the variation in TWD. Both the low adjusted R-squared and the small number of statistically significant variables may be attributed to the relatively small sample size. Other recent literature have suggested similar findings (Singla and Morrill 2005). This may indicate that other variables, not analyzed in this study, may provide greater contributions to the determination of TWD. Sconce and colleagues (2005) suggest that genetics, specifically CYP 2C9 and VKORC1 genetic polymorphisms, may contribute up to 55% of TWD variations.

Limitations

There are limitations inherent in this study. All information collected was via retrospective chart review. Furthermore,

alcohol and tobacco use were not quantified at each visit. Because height was not documented on every patient, BMI was unable to be calculated for each subject. Lastly, the relatively small sample size means that this study may not have been adequately powered to detect a statistically significant difference between patient-specific factors, if a true difference did exist.

Conclusion

In summary, from a retrospective chart review of 131 patients with therapeutic INRs, we found factors having the greatest influence on TWD to include the concomitant use of CYP-inducing medications and age. Positive relationships between TWD and the following factors exist: use of CYP450 inducer, younger age, taller height, and African American ethnicity. Although it did appear that women required a smaller TWD than did men, we found that gender contributed only mildly. Further studies with a greater samples size in this area may more precisely predict the effect of patient-specific factors on the TWD. This information may help decrease consequences of supratherapeutic INRs while facilitating the achievement of therapeutic levels. In turn, this may result in decreased time of concomitant injectable anticoagulant use and/or hospitalizations which could ultimately decrease healthcare costs.

Disclosure

This information was presented in part at the University Health System Consortium on December 3, 2005 in Las Vegas, NA. Whitley HP, Brzezinski W, Fermo JD. Effect of patient-specific factors on weekly warfarin dose. Proceedings from the University Health System Consortium. 2005; December: 107. The authors have no financial information to disclose.

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