Time Trend in Outpatient Warfarin Therapy Based on International Normalization Ratio

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Abstract

Introduction- The anticoagulation activity of warfarin is monitored by the prothrombin time (PT) using the international normalization ratio (INR). Factors such as genetic polymorphism and ethnic differences can cause an unpredictable dose response. In our study, the primary end point was time in days to therapeutic INR in the Iranian race. The secondary end point was time in days to stable dose for our patients, and the third end point was determination of stable dose related to sex and age distribution of our patients.

Method- The anticoagulation clinic records of patients taking warfarin during an index period were retrospectively reviewed. INR measurements were performed on citrated venous blood samples. Under-anticoagulation was defined as any out of range INR<1.8 and over-anticoagulation as INR >3.4.

Result- Stable warfarin dose was achieved in only 5% of the patients by day 14, 55% by day 21, 85% by day 28, and >95% by day 35. The mean stable dose showed an inverse relation with the day 5 INR. However, about 12% of the patients required a final stable dose of < 2.5 mg. No patients suffered any hemorrhagic or thrombosis episodes during the first month of warfarin therapy. After the first month, hemorrhagic complications such as gum bleeding, hematuria, and bloody stool were seen in about 5.5%; however, hospitalization due to hemorrhagic cardiovascular accident was less than 0.7% and thrombosis events were less than 2%. We conclude that warfarin dose during the second and third weeks was highly predictive of the patients' "stable dose", which is different from the time to reach the therapeutic INR level ***(Iranian Heart Journal 2008; 9 (3):37- 41).***

Key words*:* warfarin ■ stable dose ■ therapeutic dose ■ international normalization ratio ■ prothrombin time

Warfarin is the most commonly used oral anticoagulant and is a narrow therapeutic index agent.

A small change in the systemic concentration of the drug may lead to significant changes in pharmacodynamic response.

Careful clinical management is required to balance the risk of bleeding (over-anticoagulation) against the risk of thrombosis (under- anticoagulation).[1]

The anticoagulation activity of warfarin is monitored by the prothrombin time (PT) using the international normalization ratio (INR). For most warfarin indications, the target INR is 2-3,[2] which requires frequent patient visits to physician's office and laboratories.[3] For example, the use of warfarin with a range INR of 2-3 is recommended in the prevention of stroke for non-valvular patients, in particular those older than 75 years.[4]

Received Aug. 23, 2007; Accepted for publication May 2, 2008.

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The aim of anticoagulant treatment is to reach an optimal INR level in which the risk of thrombosis as well as bleeding is minimal.[5]

Variability of drug response among individuals is a well-recognized problem that may result in either under- or over-treatment of patients receiving similar drug concentrations.[4] Warfarin use is complicated by an unpredictable dose-response that depends on factors such as demographics, diet, drugs, genetic polymorphism, and ethnic differences.[1,6]

The ability to provide more precise dosage reductions of warfarin based on the warfarin nomogram[7-8] may be of clinical importance in light of current recommendations for higher intensity and maintenance of higher INR values.[9-13] In our study, the primary end point was time in days to therapeutic INR in the Iranian race. The secondary end point was time in days to stable dose for our patients, and the third end point was the determination of stable dose related to sex and age distribution of our patients. A final end point was the number of INR measurements greater than 3.4 as over-treatment and INR lesser than 1.8 as under-treatment, respectively and incidence of thromboembolism and major bleeding episodes.

Methods

The anticoagulation clinic records of patients taking warfarin during an index period were retrospectively reviewed. Patients 20 years of age and older were eligible if they had been receiving warfarin for at least 3 months and required anticoagulation for at least 6 months to a target INR of 2-3.

Between November 2005 and September 2006, 200 patients (148 men and 52 women, age range 30-85 years) were started on the anticoagulation protocol, which was issued by consultant cardiologists, hematologists, and nurses in a university-affiliated warfarin clinic, all experienced in warfarin dosing. Forty-two percent of the patients were aged 70 or over. The median age of the men was 65 years, while that of the women was 78 years. All the patients were assessed by the clinic physicians for their ability to take warfarin safely and to observe dosing instructions.

Indications were atrial fibrillation associated with ischemic heart disease, valve disease, impaired left ventricular function, congestive cardiac failure, and age >75 years. Other indications were deep vein thrombosis, pulmonary emboli, and post-mitral valve replacement/aortic valve replacement patients.

Exclusion criteria were the presence of a known hypercoagulability disorder, mental incompetence, inability to follow INR controlling, and patients concurrently taking statins, antibiotics, or other drugs known to increase warfarin level.

Data extracted from the medical records for each patient included demographic characteristics, indication for warfarin therapy, and duration of therapy during the index period.

For the purpose of this investigation, under-anticoagulation was defined as any out of range INR less than 1.8 and over-anticoagulation defined as any out of range INR greater than 3.4. These definitions were chosen to represent INR values likely to be associated with clinically significant outcomes.

At each clinic visit, the patients were assessed for bleeding complications and thromboembolic events that might have occurred since the last visit. Bleeding events were considered major if they resulted in hospitalization.

The results on all the patients who correctly followed the protocol were analyzed to determine the time taken to achieve a therapeutic INR. The results were analyzed to determine end points of our study by SPSS software.

Results

All the patients were started on warfarin by their physician and first seen in the clinic on day 7. Each patient was prescribed 5mg

warfarin tablet for the first dose and had an arranged clinical visit with an INR test on days 1 and 5. All the patients had a day 1 INR performed, and this was 1.5 or less in all the cases. The dose for the second week was then selected according to the day 5 INR.

About 86% of the patients followed the protocol correctly, and the data from these patients are presented. In 8 patients, the protocol was followed incorrectly by the clinic staff: four patients had the wrong dose and interval, one patient was given the wrong interval to the next clinic visit, and in three patients the other dose was prescribed. Three percent of the patients started interacting drugs during the first two weeks and 2% of patients developed other medical problems unrelated to their anticoagulation.

It is obvious that the therapeutic INR was not attained in the first week; only 16% of the patients had an INR >1.8 by day 5, 84% by day 14, and 98% by day 21 (Fig. 1). Meanwhile, only 2% of the patients took more than three weeks to achieve an INR of 1.8.

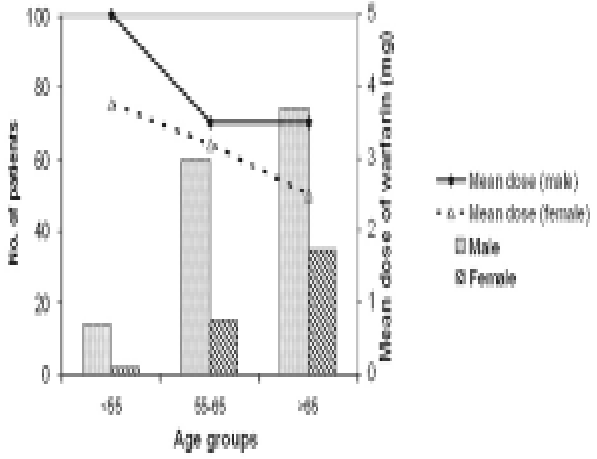

Fig. 1. Age and sex distribution of mean warfarin dose.

We defined the warfarin dose as "stable" when the patient was within the target range for two weeks on the same dose of warfarin. With regard to this definition, stable dose was achieved in only 5% by day 14, 55% by day 21, 85% by day 28, and >95% of the patients by day 35 (Fig. 1). The mean stable dose showed an inverse relation with the day 5 INR.

Fig. 2 demonstrates that in the patients younger than 55 years, the final stable dose was 5 mg (men) and 4 mg (women); in the patients between 55 and 65 years, the final stable dose was 3.5 mg (men) and 3 mg (women); and the patients over 65 years had a final stable dose of 3.5 mg (men) and 2.5 mg (women, Fig. 2).

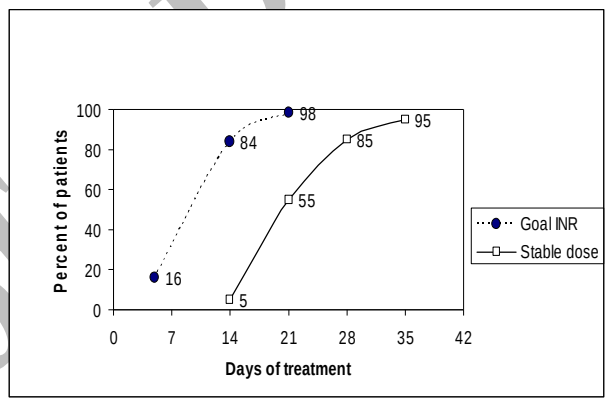

Fig. 2. Comparison of time (days) to achieve therapeutic INR level with stable dose of warfarin.

12% of the patients required a final maintenance dose of <2.5 mg. It seems that age and sex are associated with a trend in anticoagulant dose; however, this was insufficient to define dosing subgroups. In our study, about 25% of the patients had INR more than 3.4 and about 10% below 1.8.

No patients suffered any hemorrhagic or thrombosis episodes during the first month of warfarin therapy. After the first month, hemorrhagic complications such as gum bleeding, hematuria, and bloody stool were seen in about 5.5%, but hospitalization due to hemorrhagic CVA was less than 0.7% and thrombosis events were less than 2%.

Discussion

Unfortunately, many health care professionals have little or no experience with oral

anticoagulants.[12] The potential danger of having inexperienced professionals guiding oral anticoagulant therapy is enhanced by the fact that oral anticoagulants have a narrow therapeutic window; individual patients may require much larger or smaller doses.

Out of range INR is encountered frequently during warfarin therapy as a result of changes in numerous factors. Despite extensive evaluation of potential causes of over- and under-anticoagulation, a specific cause commonly cannot be determined.[11]

According to Janes et al., it seems that the patients' age and sex is not sufficiently related to warfarin requirements to provide useful predictive information.[13] However, in our study, it appeared that age and sex were associated with a trend in anticoagulant dose. Be that as it may, this was insufficient to define dosing subgroups.

Inter-ethnic differences may have profound implications for the efficacy and safety of warfarin. Ethnic differences, environmental factors, and genetic variants affect pharmacokinetic features such as bioavailability, binding, and volume of distribution, as well as hepatic and renal metabolism, which may result in some patients being more susceptible to serious or life-threatening adverse events. For example, Gage et al. reported 16% of their patients would have been overdosed if they had been prescribed the empirical dose of 5mg/day,[14] but in our study 25% of the patients were overdosed (INR>3.4, P<0.05). For these reasons, this study suggests frequent INR testing may permit standard warfarin monitoring across diverse geographical regions and facilitate analysis of ethnic variation among subpopulations.

Finally, our study demonstrates the difference between the day to therapeutic INR and the day to achieve stable dose, and we would, therefore, suggest that sufficient attention be paid to this point in the management of warfarin therapy. In our opinion, all patients with warfarin therapy, due to the long half - life of the drug, should be followed at least for 2 weeks intermittently after reaching therapeutic INR, and warfarin doses during the second and third weeks are highly predictive of the patients' stable dose.

Conflict of Interest

No conflicts of interest have been claimed by the authors.

References

1. El Rouby S, Mestres CA, LaDuca FM, Robert A. Racial and ethnic differences in warfarin response . J Heart Dis 2004; 13: 15-21.
2. Baker RI, Coughlin PB, Gallus AS, Barford BS. Warfarin reversal: consensus guidelines, on behalf of the Australian Society of Thrombosis and Haemostasis. Med J Aust 2004; 181: 492-7.
3. Yang DT, Robetorye RS, Rodgers GM. Home prothrombin time monitoring: a literature analysis. Am J Hematol 2004; 77: 177-86.
4. Perret-Guillaume C, Wahl DG. Low-dose warfarin in atrial fibrillation leads to more thromboembolic events without reducing major bleeding when compared to adjusted-dose: a meta analysis. Throm Haemost 2004; 91: 394-402.
5. Odegaard KJ. Self-management in anticoagulation: a meta-analysis. Tidsskr Nor Laegeforen 2004; 124: 2900-3.
6. Blann A, Barford D. Ethnic background is a determinant of average warfarin dose required to maintain the INR between 3.0 and 4.5. J Thromb Haemost 2004; 2: 525-6.
7. Kovacs MJ, Anderson DA, Wells PS. Prospective assessment of a nomogram for the initiation of oral anticoagulation therapy for outpatient treatment of venous thromboembolism. Ann Pharmacother 2001; 35: 589-617.
8. Kovacs MJ, Cruickshank M, Wells PS, Davis F, Hennry J. Randomized assessment of a warfarin nomogram for initial oral anticoagulation after venous thromboembolic disease. Clin Pharm 1991; 10: 923-7.
9. Dalere GM, Coleman RW, Lum BL. Warfarin

adjustment. Haemostasis 1998; 28: 62-9.

10. Kovacs MJ, Rodger M, Anderson DR. Comparsion of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial. Clin Lab Haematol 2003; 25: 127-30.

11. Wittkowsky AK, Devine EB. Frequency and causes of over-anticoagulation and under-anticoagulation in patients treated with warfarin. Pharmacotherapy 2004; 24: 1311-6.

12. Crowther MA. Oral anticoagulant initiation: rationale for the use of warfarin dosing nomogram. Semin Vasc Med 2003; 3: 255-60.

13. Janes S, Challis R, Fisher F. Safe introduction of warfarin for thrombotic prophylaxis in atrial fibrillation requiring only a weekly INR. Clin Lab Haem 2004; 26: 43-7.

14. Gage BF, Eby C, Milligan PE, Banet GA. Use of pharmacogenetics and clinical factors to predict the maintenance dose of warfarin. Thromb Haemost 2004; 91: 87-94.