Optimal Understanding of Warfarin: Beyond the Nomogram

Randolph E. Regal, BS, PharmD, and Vanna Tsui, PharmD

Abstract

To help prescribers of warfarin reach the therapeutic International Normalized Ratio as quickly and safely as possible, dosing nomograms for this medication have been established in institutions throughout the U.S. However, even when warfarin is administered using a well-designed nomogram, it is helpful to understand some of the pharmacokinetic and pharmacodynamic idiosyncrasies inherent to this agent with its narrow therapeutic window.

This article discusses (1) the plasma half-lives of both warfarin and the clotting proteins that it inhibits; (2) warfarin’s paradoxical procoagulant effect early in therapy; (3) the ways in which age, diseases, drugs, and nutritional conditions affect the patient’s response to warfarin acutely and chronically; and (4) the benefits and the risks of loading-dose regimens.

Introduction

For the past few decades in the U.S., warfarin has become the oral anticoagulant of choice for treating or preventing thromboembolic events and for procedures associated with a substantial risk of thromboembolism. Despite the widespread prescribing of this medication, clinicians remain uncertain about how to best manage warfarin dosing. Over the years, many institutions have developed nomograms to assist clinicians in bringing International Normalized Ratios (INRs) into the “therapeutic” range. Indeed, these guidelines often provide a “safer harbor” in which to navigate, but by no means do they guarantee a successful “docking” to the target INR in the shortest possible time. In addition, despite our best efforts to minimize bleeding risks with long-term use, the occurrence of serious hemorrhagic events cannot be totally avoided; approximately 20% of these events result in fatalities. Even when warfarin dosing has been carefully performed and patients have been closely monitored in anticoagulation clinics, the incidence of major hemorrhage may still approach 3% per year in patients aged 60 years and older.

Because of the long plasma half-lives of both warfarin isomers and three of the four clotting proteins whose hepatic synthesis warfarin inhibits, the INR manifestations of a given dose—or a cluster of doses—may be delayed by several days. Therefore, it is little wonder why it can be such a challenge to adjust a dose on a daily basis with hopes of making a “smooth landing” into that relatively narrow therapeutic window a few days later. Of course, warfarin may interact unpredictably with a plethora of different medications by both pharmacokinetic and pharmacodynamic mechanisms.

Finally, a patient’s disposition of warfarin may be affected by acute dietary changes and by common exacerbations of acute disease states such as congestive heart failure, biliary obstruction, and infection. Chronic diseases such as cirrhosis and malabsorption syndromes also alter a host’s response to warfarin.

To help elucidate why certain patients fall outside the population norms, thereby leading to warfarin dosing nomogram “failures,” we will discuss the complicated pharmacokinetics and pharmacodynamics of this oral anticoagulant—beyond the nomogram.

Pharmacokinetics and Pharmacodynamics

Vitamin K is contained in the phylloquinones in many green vegetables. It is also produced by bacteria from substrates within the intestinal tract and subsequently recycled enterohepatically as absorbable menaquinones. As vitamin K is absorbed from the intestine, it is stored in the liver for the production of clotting factors and anti-clotting proteins. Administration of warfarin blocks the oxidation of vitamin K
between the third and eighth days of therapy. The most commonly cited risk factors are a high initial warfarin dose, obesity, and female sex. Although sometimes referred to as the “purple toe syndrome,” the red painful plaques, hemorrhagic blisters, or necrotic scars are often found in such fatty areas as the breasts, hips, and buttocks. The syndrome affects only about one in 10,000 patients receiving warfarin, but it exacts a high mortality rate if it is not treated promptly. Treatment consists of vitamin K reversal, heparin anticoagulation, and monoclonal antibody–purified protein C concentrate. Surgical debridement may also be necessary.11,15–17

During the first two to three days of warfarin therapy, it should be remembered that a rapid increase in INR reflects only a reduction of the shorter half-life of factors VII and IX, whereas clinically significant reductions of factors X and II have yet to occur. Because factor II (prothrombin) has the longest half-life (Figure 2), the optimal potential of warfarin to inhibit the expansion and development of the clot is determined after the final clearance of factor II. This delayed effect on adequately depleting activated factor II is the principal reason why the overlap of heparin therapy with warfarin must be at least four to five days if patients are in the throes of an acute thromboembolic event, even when a target therapeutic INR is attained earlier than this time. Of course, this overlap is not required in patients with chronic atrial fibrillation who have not within the liver (Figure 1). Ultimately, warfarin elicits its therapeutic effect by limiting the activation of vitamin K–dependent clotting proteins that are synthesized and secreted by the liver.

Numerous compounds are involved in the complicated clotting cascade. The anticoagulant effect of warfarin is attained by blocking the activation of the intrinsic clotting factors VII, IX, X, and II. However, warfarin also has a simultaneous procoagulant effect, caused by blocking the activation of two endogenous anticoagulants, protein C and protein S. Over time, warfarin therapy results in reduced amounts of all of these factors in the circulation.6,11,14

As shown in Table 1, relative to all factors other than factor VII, protein C has a very short half-life. Therefore, protein C is depleted quickly after the initiation of warfarin therapy. Because both proteins C and S are anticoagulants, a rapid depletion of these proteins leads to a transient hypercoagulable state in the first one to two days of warfarin therapy. Therefore, by causing rapid and precipitous declines in circulating protein C, the use of high loading doses may actually potentiate this phenomenon.

Indeed, one possible sign of this transient hypercoagulable state is sometimes manifested as an ischemia-related skin necrosis reaction. Caused by thrombosis of venules or capillaries within the subcutaneous fat, this phenomenon is usually apparent between the third and eighth days of therapy. The most commonly cited risk factors are a high initial warfarin dose, obesity, and female sex. Although sometimes referred to as the “purple toe syndrome,” the red painful plaques, hemorrhagic blisters, or necrotic scars are often found in such fatty areas as the breasts, hips, and buttocks. The syndrome affects only about one in 10,000 patients receiving warfarin, but it exacts a high mortality rate if it is not treated promptly. Treatment consists of vitamin K reversal, heparin anticoagulation, and monoclonal antibody–purified protein C concentrate. Surgical debridement may also be necessary.11,15–17

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### Table 1 Vitamin K–Dependent Clotting Factors

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
<th>Half-Life</th>
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<tr>
<td>Protein C</td>
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<td>8 hours</td>
</tr>
<tr>
<td>Protein S</td>
<td>Anticoagulant</td>
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<td>Factor VII</td>
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<tr>
<td>Factor II</td>
<td>Procoagulant</td>
<td>50 hours</td>
</tr>
</tbody>
</table>

Figure 1 Warfarin and the vitamin K cycle. (Reproduced with permission from Hirsch J, Dalen J, Anderson DR, et al. Chest 2001;119[1 Suppl]:8S–12S.6)

Figure 2 Changes in clotting factor concentrations upon initiation of warfarin. INR = International Normalized Ratio; Pro = prothrombin. (Reproduced with permission from Katzung BG, ed. Basic and Clinical Pharmacology, 8th ed. New York: McGraw-Hill; 2001:571.35)
shown any evidence of an acute thromboembolic event.

Next, we need to consider the half-life of warfarin itself. Warfarin’s S and R isomers are metabolized hepatically by cytochrome P-450 (CYP450). The S-enantiomer has a half-life of about one to two days; the R-enantiomer’s half-life is approximately 1.5 to four days (Figure 3).6

The S-enantiomer exhibits two to five times more anticoagulant activity than the R form. CYP = cytochrome; INH = isoniazid; TMP/SMX = trimethoprim/sulfamethoxazole; T1/2 = half-life.

Wynne et al.18 noted that as a person’s age increases, liver volume decreases, thus leading to a reduction in warfarin dosing requirements. Hodges et al.19 found that the availability of vitamin K in elderly patients was less than that seen in younger patients. Not surprisingly, to tie it all together, Shepherd et al.20 found that the rate of clotting factor synthesis was lower in older patients than in their younger counterparts. Therefore, when dosing warfarin for elderly patients, clinicians should anticipate lower initiation and maintenance dose requirements than for younger people. They should also be especially vigilant in looking for exaggerated responses to dosing changes and for an increased sensitivity to drug interactions.

Other issues that might be overlooked include acute changes in a patient’s condition or diet. Even subacute changes in vitamin K intake can make a significant difference in the response to warfarin.9,10,21 Of course, because of consequential reductions in procoagulant synthesis or turnover, parenchymal
liver damage and acute biliary obstruction also potentiate warfarin’s effects.22 Passive hepatic congestion caused by exacerbations of congestive heart failure also reduce warfarin clearance, although alleviating the heart failure with diuretics can reverse this process.12

Hypermetabolic events such as hyperthyroidism and fever are thought to potentiate warfarin by increasing the catabolism of clotting proteins.12,23,24 Conversely, interferons or other inflammatory mediators released during sepsis may down-regulate various CYP450 isozymes, thereby slowing the metabolism of warfarin and potentiating a supratherapeutic response.25

Drug Interactions

When patients are taking warfarin along with other medications, it is always prudent to identify and monitor them for possible pharmacokinetic and pharmacodynamic drug–drug interactions. Many reviews have covered the importance and character of these interactions.6–8 Some of the medications that have the potential to increase or decrease the effects of warfarin as a result of metabolic inhibition are shown in Figure 3.

In addition to the previously mentioned effect of interferon or other inflammatory cytokines seen with infections and the many pharmacokinetic interactions with other medications, there are at least two other types of warfarin–antibiotic interactions. Certain broad-spectrum cephalosporins contain the N-methylthiotetrazole side chain, a moiety that chemically opposes vitamin K by inhibiting hepatic vitamin K epoxide reductase.12 Of these agents, however, only cefotetan disodium (Cefotan®, AstraZeneca) still remains in common use. In the absence of concomitant warfarin, clinically significant hypoprothrombinemia with cefotetan is usually seen only when renal dosing is not implemented and when patients have some degree of debility or malnutrition.26 Of course, the onset is gradual, and the problem is easily reversed or prevented with the use of vitamin K supplementation.27,28

Through yet another mechanism of warfarin potentiation, broad-spectrum antibiotics of virtually any class may eradicate intestinal microbes that synthesize absorbable menaquinones within the intestinal tract. Menaquinones are vitamin K precursors that are usually reabsorbed in the ileum and thus provide an endogenous source of vitamin K.29 When the stores of vitamin K are depleted, even in the absence of coexisting warfarin therapy, hypoprothrombinemia may gradually appear.

In one study,20 a 58-year-old patient who had been stabilized with long-term warfarin therapy, with INR ranges of 2 to 3, showed an otherwise unexplainable increase in the INR to 6.2 along with hematuria 2½ weeks after a seven-day course of amoxicillin/clavulanate potassium (Augmentin®, GlaxoSmithKline) for an ear infection. This case appears to be a good example of the occasional clinical significance of this type of drug interaction.

Loading Doses

Among the current controversies regarding warfarin is the issue of dosing in the first few days, or the “loading phase” of therapy. Over the last 10 to 20 years, clinicians have moved away from the loading doses of 10 to 50 mg in favor of less aggressive “front-loading.”

Harrison et al.31 compared the effects of single loading doses of warfarin 5 mg and 10 mg in a randomized clinical trial. They examined the time to reduction in levels of factor II and X, as well as protein C, as indicators of both efficacy and safety. They also measured the time needed to reach therapeutic INR values (2 to 3). Their results showed a significantly greater number of patients in the 10-mg group with supratherapeutic INRs. Levels of factor II and factor X gradually decreased with no significant difference between the two groups, but factor VII and protein C levels decreased quickly and were much lower in the 10-mg group at 36 and 60 hours. These findings suggested that despite the faster attainment of a therapeutic INR, the use of a 10-mg loading dose was not recommended.

In a trial by Crowther et al.,32 the primary endpoint was the proportion of patients with therapeutic INR values for two consecutive days and whose INRs did not exceed 3.0. Patients received either a 5-mg or a 10-mg dose of warfarin for the first day, after which an algorithm was used to adjust the dosing. More patients receiving 5 mg were able to reach their target INRs than patients receiving 10 mg. In addition, more patients in the 10-mg group reached supratherapeutic levels.

In a study that reached the opposite conclusions of the previous two, Kovacs et al.33 compared a single 10-mg initiation-dose nomogram with a 5-mg nomogram in a randomized, controlled clinical trial; they found the loading dose to be of some benefit. The primary endpoint was the number of days needed to achieve a therapeutic INR. Patients in the 10-mg group achieved therapeutic INRs 1.4 days earlier than patients in the 5-mg group (P < .001). By the “magic” fifth day, 83% of patients receiving 10 mg had achieved a therapeutic INR, in contrast to only 46% of the patients receiving 5 mg (P < .001). There were no significant differences in recurrent thromboembolic events, in major bleeding, in 90-day survival, or in the number of INRs above 5 in the two groups.

One plausible explanation for the more favorable loading dose results in the Kovacs study was that the subject population consisted entirely of outpatients. Outpatients are generally healthier and younger and are taking fewer medications than their inpatient counterparts. In fact, in a previous study, Kovacs et al.34 concluded that hospitalized patients were generally more sensitive to warfarin than outpatients. Therefore, inpatients might be less in need of the higher loading dose in order to attain the most efficient anticoagulant regimen.

Thus, from the composite of these three studies, the ability of front-loading regimens to help attain target INRs more safely and efficiently appears to be inconsistent at best; larger, well-designed studies are still needed to further clarify this issue. At present, perhaps higher “initiation doses” would work better when patients are younger, healthier, and relatively free of acute illnesses, as is the case in many outpatient clinics. Of course, the one major drawback of more dramatic forms of loading doses is the fear of inducing the aforementioned necrotic skin reaction from an acute protein C deficiency. In reality, however, these necrotic reactions have been observed most commonly in patients who received much larger loading doses than 10 mg.
On the other hand, for the treatment of active thromboembolic events, the proper front-loading regimen may still have the potential to more consistently attain the desired target INR by the fourth or fifth day instead of a few days later. Given the average daily cost of enoxaparin of at least $15 to $20 per day for prophylaxis and $50 to $100 per day for treatment, a high-volume service or institution that could reduce its enoxaparin–warfarin overlap period, by even a day or two per case, might be able to markedly reduce its annual pharmaceutical costs.

Conclusion

Clinicians must consider a plethora of factors when administering warfarin. Despite the many reasonably successful studies that have used “nomograms” to initiate and manage warfarin therapy, questions remain as to how to best titrate the agent to obtain a therapeutic INR quickly and safely. Despite the many reasonably successful studies that have used “nomograms” to initiate and manage warfarin therapy, questions remain as to how to best titrate the agent to obtain a therapeutic INR quickly and safely. More research is needed to clarify which types of “front-loading” regimens, if any, can be used to foster the appropriate use of warfarin is especially challenging in the geriatric population. Indeed, both underdosing and overdosing may lead to increased morbidity and mortality, longer hospital stays, and increased health care costs. Of course, the intensity of anticoagulation and the duration of treatment should be tailored according to the indication of treatment and to the presence or absence of both acute and chronic illnesses.

Doses should be initiated and adjustments should be made with an adequate understanding of warfarin’s mechanism of action, its pharmacokinetics, and its proclivities for drug–drug interactions. More research is needed to clarify which types of “front-loading” regimens, if any, can be used to foster the most rapid, consistent, and safe titration to a therapeutic INR.

References


Disclosure

Drs. Regal and Tsui have indicated no relationships to disclose.
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#### Multiple Choice
Select the one correct answer.

1. **All of the following statements are true regarding warfarin except:**
   a. Warfarin is the oral anticoagulant of choice for the treatment and prevention of thromboembolic diseases.
   b. Warfarin is the oral anticoagulant of choice for the treatment and prevention of thromboembolic diseases.
   c. Clinicians are uncertain about the management of warfarin dosing for their patients.
   d. Warfarin possesses a long plasma half-life.

2. **The following statements regarding the International Normalized ratio (INR) are true except:**
   a. Many institutions have developed nomograms that assist in achieving therapeutic INRs.
   b. These nomograms guarantee achievement of target INRs for all patients.
   c. Warfarin is associated with a bleeding risk and serious hemorrhagic events, with 20% of the cases being fatal.
   d. Patients 60 years of age and older are most likely to be at risk for increased INRs and a 3% chance of major hemorrhage.

3. **All of the following statements are true regarding the use of warfarin except:**
   a. Because of its long half-life, warfarin shows a delayed effect.
   b. Warfarin has been documented to interact with numerous medications.
   c. Therapeutic levels of warfarin are not affected by dietary changes.
   d. Exacerbations from congestive heart failure and infection cause changes in the plasma levels of warfarin.

4. **Which of the following is incorrect concerning warfarin?**
   a. Its anticoagulant effect is attained by blocking the activation of intrinsic clotting factors.
   b. Warfarin blocks oxidation of vitamin K within the liver.
   c. Warfarin’s procoagulant effect is the result of blocked activation of proteins C and S.
   d. High loading doses of warfarin can overcome the hypercoagulable state that occurs in the first few days of warfarin therapy.

5. **Which of the following is incorrect concerning the first few days of warfarin therapy?**
   a. A possible sign of a transient hypercoagulable state might be a skin necrosis reaction.
   b. Purple toe syndrome affects approximately 25% of patients taking warfarin.
   c. Obesity and female sex are risk factors of the skin necrosis reaction.
   d. Treatment of skin necrosis reaction includes vitamin K reversal and heparin anticoagulation.

6. **According to published literature, which of the following is correct concerning warfarin?**
   a. An increase in the warfarin dose may be required as age increases because of increased liver mass.
   b. Higher initiation doses should be used in elderly patients owing to their increase in clotting factor production.
   c. An increase in vitamin K may decrease the INR.
   d. Patients with congestive heart failure require increased warfarin dosages.

7. **Which of the following does not contribute to an increase in warfarin’s anticoagulant effect?**
   a. hypermetabolic status
   b. parenchymal liver damage
   c. vitamin K consumption
   d. interferons released during sepsis

8. **According to Figure 3, which of the following is not a drug that inhibits both the metabolic pathways of the S-enantiomers and the R-enantiomers of warfarin?**
   a. amiodarone
   b. INH
   c. zafirlukast
   d. omeprazole

9. **According to the article, which statement is true?**
   a. The ability of “front-loading” regimens to help attain a target INR more safely and efficiently appears to be inconsistent at best.
   b. Higher “initiation doses” would work better in settings where patients are younger and healthier.
   c. For the treatment of active thromboembolic events, the front-loading regimen might be more likely to foster the attainment of the desired target INR by the fourth to fifth days instead of a few days later.
   d. all of the above.

10. **According to the article, when setting warfarin dosages, clinicians need to consider all of the following factors except:**
    a. the patient’s age.
    b. presence of an acute illness.
    c. drug–drug interactions.
    d. socioeconomic status.
CE Registration and Evaluation Form

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Submission deadline: October 31, 2005
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1. a □ b □ c □ d □ 6. a □ b □ c □ d □
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Rate the extent to which:

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<th>Very High</th>
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<th>Low</th>
<th>Very Low</th>
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1. Objectives of this activity were met
2. You were satisfied with the overall quality of this activity
3. Content was relevant to your practice needs
4. Participation in this activity changed your knowledge/attitudes
5. You will make a change in your practice as a result of participation in this activity
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8. Adequate time was available for Q&A
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   □ I will immediately implement the information into my practice.
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    □ Discuss with industry representative(s) □ Participate in another educational activity
    □ Other _________________________ □ None

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