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Review Article

The role of warfarin in anticoagulation therapy: Current insight's and clinical perspectives

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ABSTRACT

Warfarin, a widely used oral anticoagulant and vitamin K antagonist, plays a critical role in the prevention and treatment of venous thrombosis and thromboembolic complications. This review explores the pharmacological properties, pharmacokinetics, pharmacodynamics, therapeutic monitoring, and drug-food interactions of warfarin. By inhibiting vitamin K-dependent clotting factors, warfarin induces a controlled anticoagulation state. However, its narrow therapeutic index presents challenges in achieving and maintaining optimal dosing. Regular monitoring of the International Normalized Ratio (INR) is essential to ensure efficacy while minimizing risks. Warfarin's pharmacokinetics, characterized by its racemic mixture and metabolism, contribute to its sensitivity to drug-drug and drug-food interactions. These interactions often necessitate personalized dosing and close monitoring. This review emphasizes evidence-based strategies for warfarin management, including the application of nomogram, computer-assisted dosing systems, and protocols for handling adverse events. It underscores the importance of balancing therapeutic benefits with safety to optimize outcomes for patients undergoing warfarin therapy.

1. Introduction

Warfarin is an oral anticoagulant of vitamin K antagonist used for the prevention, treatment and extension of venous thrombosis and treatment of the thromboembolic complications.[1] It is most frequently used to control and prevent thromboembolic disorders. The doses are recommended in such a manner that avoids both hemorrhagic complications and suppresses thrombosis.

To attain maximum efficacy it's mandatory to know the signs and symptoms of bleeding, the diet impact, potential drug interactions and actions to taken just in case if a dose is missed.[2] The initiating and efficacy of warfarin therapy International Normalized Ratio (INR).[3]

2. Applications

2.1. Pharmacology

Warfarin is a Vitamin K antagonist which acts upon the clotting factors II, VII, IX and X. which also acts upon the anticoagulant proteins C, S, and Z. The synthesis of both mentioned clotting factors and anticoagulant proteins require Vitamin K. Therefore, vitamin K antagonism or vitamin k deficiency decreases the rate of production of clotting factors and anticoagulant proteins, hence creating an anticoagulation state. Without the carboxylation of certain glutamic acid residues, these factors and proteins are biologically inactive. The process of carboxylation needs low level of vitamin K as a cofactor which occurs primarily in the liver.[4] Inter conversion of vitamin K and its vitamin K 2, 3 epoxide is inhibited by warfarin, the γ-carboxylation of glutamate residues on the N-terminal regions of the

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coagulation proteins gets modulated and the coagulation cascade gets interrupted.[5] Warfarin in therapeutic dose reduces by approximately 30 to 50 percent in production of functional vitamin K–dependent clotting factors and there is 10 to 40 percent decrease in the carboxylation of secreted clotting factors. Therefore, the coagulation system becomes functionally deficient.[6]

2.2. Pharmacokinetics

Warfarin is essentially completely absorbed after oral administration with the peak concentration occurring between 2 and 6 hours.[7,8] Maximum concentrations are observed between 0.3 and 4 hours for a primary peak and 1 to 8 hours for a secondary peak.[9] Warfarin has a racemic mixture of R- and S-enantiomers. A 99 percent of warfarin is bound to albumin.[10] Two enantiomers have similar volume of distribution with an average of 0.15 l/kg for each enantiomer and racemic mixture have 0.11 to 0.18 l/kg which is similar to that of albumin.[11,12] Stereo selective and Regio selective metabolism of warfarin occurs in the endoplasmic reticulum present in liver parenchyma by cytochrome p450 hepatic microsomal enzymes.[13–15]

The changes in elimination half-lives of an estimated average of 29 hours (range 18 to 52 hours) for S-warfarin compared with an average of 45 hours (range 20 to 70 hours) for R-warfarin affects the rate of clearance.[12,16,17] After the formation, elimination of hepatic metabolites is excreted by urinary and stool.[18]

2.3. Pharmacodynamics

The clearance of clotting factors from the systemic circulation determines the anticoagulant effect of warfarin after the first dose of administration, which is based upon the half-lives. Typically, the International Normalized Ratio (INR) was measured 24 to 36 hours after administering the first dose to evaluate the treatment's efficacy. Increase in the INR may not be noted for 24 to 36 hours after administration of the first dose as warfarin has a long half-life, and maximum anticoagulant effect may not be achieved for 72 to 96 hours.[19]

Early changes in INR are unreliable as factor VII being with the shortest half-life of six hours cannot solely predict the efficiency of the treatment given.[4]

Anti-thrombotic effect of warfarin is not observed until the fifth day of therapy as the half-life of prothrombin is 50 hours and influences the clearance.[19]

The anti-coagulation and antithrombotic effect depends upon the loading dose and clearance of specific clotting factors.[20]

S-warfarin has 2.7 to 3.8 times potency than that of R-warfarin.[17,21] Greater accumulation of vitamin K 2, 3-epoxide by S-warfarin, indicates a larger degree of vitamin K epoxide reductase inhibition when compared with R-warfarin.[22] A linear relationship was observed between total plasma warfarin concentrations and prothrombin time ratio but there was no similarity in the warfarin concentration required to reach a specific response in patients.[23] In addition, it was observed that, dose required to attain a specific therapeutic response and in the plasma concentrations of warfarin associated with that dose.[24]Henceforth, thus, individualizing of dosing should take into consideration with prothrombin monitoring time.

2.4. Monitoring

The International Normalized Ratio (INR) is calculated by dividing the patient's prothrombin time by the mean of the normal prothrombin.[25,26] Warfarin being narrow therapeutic index drug, dose requirement varies among some individuals with requirement of 1- 20mg/day to obtain therapeutic INR values.[27] Tapering of therapy was determined based on the individual's INR response, which was often monitored over several weeks. To minimize the risk of adverse reactions, this process was conducted under close surveillance.[28,29] The PT gives the time in seconds taken by the patient's plasma to clot and activation of the coagulation pathway and deficiencies of clotting factors within the coagulation pathways result in prolongation of the PT. The mathematical expression for the calculation of INR is represented as INR = (patient PT/MNPT)ISI ,PT is the patient's Prothrombin time and MNPT is the mean Prothrombin time.PT reagents are more sensitive to inhibition of factor VII within the pathway and less sensitive to inhibition within the pathway (factors V, X, and II and fibrinogen).[30]

2.5. Warfarin Therapy

An average of 2 weeks is seen for the steady state achievement with INR response.[31,32] The contributing factors for the delay are long half-life of warfarin, time taken to clear clotting factors and establishment of correct daily dose.

In patients starting warfarin without any demographic or clinical information for seeks the steady-state dose with an expectation of given INR.[33] The mean steady-state dose is 4 to 5 mg per day,[34] but warfarin doses range from 0.5 to more than 50 mg per day.[35–38]

First dose of 5mg is compared with 10 mg dose using a nomogram for adjusting subsequent doses.[39] Patients who received initial 5 mg dose were likely to attain therapeutic INR on days 3,4 after therapy initiation and 5 days showed less likely for excessive INR.[40,41] The second dose is calculated on the basis of nomogram,[31–41] experienced clinicians[42–44]and computer programs.[45–48] Furthermore the INR after 15 to 24 hours after first dose of administration can be included in the dose calculation. There is computer software for the accurate dose calculation

such as White and colleagues had compared traditional empirical dosing performed by medical house staff[47] even Vadher and colleagues used Bayesian forecasting.[48] Program resulted shortened time for a stable therapeutic dose and hospital stay, and reduced number of patients who had a supratherapeutic INR.

Studies show that INR of a patient varies from time to time.[49–51] There are various reasons regarding for the development for the change in time to time such as measurement error with standard deviation of 0.2 sec,[52] a dose change recommended on difference of two consecutive INR values of desired range (e.g.: 2.0-3.0)[53] or even when two consecutive INR values are more than 0.3 above or below the target value.[54]The Confined policies can be harmful if health becomes burden and the patients are without outcome.[55] In a study conducted by Vadher and colleagues conducted a study in warfarin dosing , where the doctors changed the warfarin dose for those falling in the range of below 1.8 and or greater than about 3.4.[56]

For a steady-state dosage adjustment can be done based on a formula[57] clinical experience and nomogram.[48,53,58,59]Experienced physicians prescribe commonly; suggest a change in 5% to 20% of the total weekly dose for moderate INR.[57,60,61]

For second trial,[62] system usage was related with INR control that was similar to dosing prescribed by practitioners.

Two randomized trials were conducted upon computer-based decision-support system DAWN AC. Puller and colleagues' trial,[63] used this system and increased the percentage of time that INR values were therapeutic.

For a patient who has INR value s more than 0.2 below or more than 0.4 above from the expected range, the causes of change in the INR range are investigated and dose calculation is recommended. The reasons include non-adherence to dosing regimen,[64] laboratory errors, diet,[65] changed health condition and Drug interactions.Inspite intervention producing poor results should be rechecked within 2 weeks with INR reports. The change dose depend is proportional to the value of the INR and patient response to previous dose modifications. Usually, dose modifications should be 5% to 20% range.[53,61,66,67] One third change in weekly dose can end up in abnormal INR.[68]

Patients with INR non-compliance are mostly observed in lack of physician, males, younger individuals and non-whites.[69] College of American Pathologists suggest physicians to check INR 4 times during first week of warfarin therapy and gradually decrease the dose based upon INR stability.[70]

The Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy has released recommendation for the management of non-therapeutic INR.[71]

INR less than 5 without significant bleeding: omit a dose or lower dose, frequently monitoring should be done and resume therapy at a lower dose only, when the INR has fallen into the therapeutic range.

INR 5 to less than 9 with no bleeding: one to two successive doses should be omitted; more frequent monitoring should be done. Late resume the therapy at a lower dos or it is advised to omit a dose. Following an administration of vitamin K1 (1 mg–2.5 mg) orally, which should result in a decline of the INR in 24 hours.

INR greater than 9 without significant bleeding: Withhold warfarin and administer vitamin K1 in the range 5 mg–10 mg orally, which should show a decrease of the INR within 12 to 24 hours. The INR can be monitored closely and additional vitamin K1 can be given as necessary. Warfarin can be resumed at a lower dose when the INR reaches therapeutic levels.

Serious bleeding and elevated INR patient: Suggestion are to withhold warfarin and give vitamin K1 10 mg dose by slow intravenous infusion along with prothrombin complex concentrate, fresh frozen plasma or recombinant factor VIIa, depending on the need of the situation.

Elevated INRs and with serious bleeding: warfarin should be withheld and prothrombin complex concentrate or recombinant factor VIIa, and vitamin K1 of 10mg should be given by slow intravenous infusion .

2.6. Drug interaction

Warfarin has interactions with both drugs and food which has clinical importance. Hence it is essential to be cautious while recommending warfarin.

The following are the pathways in which the action of warfarin can be either hindered or modified.

2.7. Interference with warfarin metabolism

Warfarin being a racemic mixture has isomeric forms of S-warfarin and R-warfarin. S-warfarin is more biologically active than R-warfarin. The former is metabolized by cytochrome P450 (CYP) isoenzyme 2C9 whereas, the later is by various hepatic enzymes (CYP 3A4, CYP 1A2 and CYP 2C19).[72] Drugs that induce CYP 2C9 activity (e.g., revamping) inhibit the action. There is scenario when the enzyme is inhibited and thereby the warfarin action is potentiated e.g., amiodarone, co-trimoxazole, metronidazole and fluvoxamine) with respect to s-warfarin. Therefore, R-warfarin has less effects on anticoagulation control.

2.8. Interference with platelet function

Antiplatelet (e.g. Clopidogrel and acetylsalicylic acid) have an impaired effect on the production of platelets and hence causing major risk of hemorrhage in patients under warfarin treatment. In addition, anti-depressants specifically

Serotonin reuptake inhibitors inhibits platelet aggregation by depletion of platelet serotonin levels resulting bleeding risk.[73]

2.9. Interruption of the vitamin K cycle

The phenomenon is mostly observed by acetaminophen which yields a highly reactive metabolite N-acetyl (p)-benzo quinonimine. This metabolite inhibits vitamin k dependent carboxylase which plays a vital role in the vitamin k cycle.[74]

2.10. Gastrointestinal mucosal injury

This interaction is observed in Nonsteroidal anti-inflammatory drugs gastrointestinal erosions on accordance with dose and duration. Although international normalized ratio remains normal, the risk of bleeding cannot be neglected in patients whose prescriptions indicates the use of warfarin along with NSAIDs. The revealed erosions are asymptomatic in suggested patients.[75]

2.11. Reduced synthesis of vitamin K by intestinal flora

Intestinal micro flora synthesis vitamin k2 which has influence on the hypoprothrombinemia response. On usage of antibiotics, the gut flora balance undergoes changes resulting in altered effects of warfarin.[76]

There was a criterion established to determine warfarin drug and food interactions, which was based on the answers obtained from these certain questions.

Questions used for assessing are:

1. (a) Was the timing pharmacologically plausible?
   (b) Did results from the international normalized ratio, prothrombin time, or thrombo test support the contention?
   (c) Were other potential factors affecting warfarin pharmacokinetics or pharmacodynamics ruled out?
   (d) Was there other objective evidence?
   (e) Presence of dose-response relation shown for the interacting drug?
   (f) Was the patient re challenged and, if so, occurrence of similar result?
   (g) Did the same thing happen on previous exposure to the drug?

The classification is done, on the level of evidence collected. Which is as follows:

1. (Highly probable): A, B, and C, plus any one or more of D to G
2. (Probable): A, B, plus one or more of C to G
3. (Possible): A plus one or more of B to G
4. (Doubtful): Any combination of B to G or An alone

2.12. Inhibition

2.12.1. Class I

Anti-infectives: Griseofulvin,[77] Nafcillin,[78] And Ribavirin,[79] Rifampin[80] Cardio-vascular drugs: Cholestyramine[81]

Analgesics, Anti-inflammatories and Immunologics: Mesalamine[82]

CNS drugs: Barbiturates[83], Carbamazepine[84]

2.12.2. Class II

Anti-infectives and GI drugs: Dicloxacillin,[85] Ritonavir,[86] Sucralfate[87]

Cardio-vascular drugs: Bosentan[88]

Analgesics, Anti-inflammatories and Immunologics: Azathioprine[89]

CNS drugs: Chlordiazepoxide[90]

2.12.3. Class III

Anti-infectives: Terbinafine[91]

Cardio-vascular drugs: Telmisartan[92]

Analgesics, Anti-inflammatories and Immunologics: Sulfasalazine[93]

2.12.4. Class IV

Anti-infectives: Cloxacillin,[94] Nafcillin/dicloxacillin,[95] Teicoplanin[96]Cardio-vascular drugs: Furosemide[97]
Analgesics, Anti-inflammatories and Immunologics: -

CNS drugs: Propofol[98]
Warfarin has found interactions with food. Thus, it is important to educate patients about their diet modification in order to achieve effective therapy and preventing risks associated.

Potentiation[99]

Class I: Fish oil, Papaya
Class II: Grapefruit juice
Class III: Cranberry juice

Inhibition

Class I: High vitamin K content foods, AvocadoClass II: Soy milkClass III: Sushi containing seaweedClass IV: Green Tea

3. Conclusion

Warfarin had long been a cornerstone in the management of thromboembolic conditions, proving highly effective in preventing and treating venous thrombosis. Despite its benefits, its narrow therapeutic window, the necessity for individualized dosing, and the risk of numerous drug and food interactions made its management challenging. To ensure therapeutic effectiveness and minimize bleeding risks, regular monitoring of the International Normalized Ratio (INR) was crucial. While advancements in clinical decision-support tools and personalized medicine enhanced

warfarin therapy, challenges persisted, particularly in maintaining stable INR levels among diverse patient populations. Although future anticoagulation therapies were expected to rely more on novel agents with fewer interactions, warfarin's proven track record and cost-effectiveness continued to make it a mainstay in clinical practice. Continued education for both healthcare providers and patients was essential to optimize outcomes and reduce associated risks.

4. Conflict of Interest

The authors declare no conflict of Interest.

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None.

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