



Warfarin-drug interactions are often encountered in the care of older adults. Interactions may be classified as pharmacokinetic, resulting in changes in serum warfarin concentrations, or pharmacodynamic, resulting in changes in hemostasis or platelet function. Knowledge of these mechanisms of warfarin-drug interactions may help identify warfarin interactions, facilitate prescribing decisions, and assist with appropriate monitoring.

Key words: warfarin, drug interactions, anticoagulants, cytochrome P-450 enzyme system, older adults

Warfarin-Drug Interactions among Older Adults

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Introduction

There is good evidence supporting the use of warfarin for a variety of indications, including the prevention of stroke in patients with atrial fibrillation.^{1,2} Despite this compelling evidence, warfarin is underutilized, especially among older adults.³ A commonly cited explanation for the underuse of warfarin is the increased risk of bleeding.^{4,5} Risk factors for bleeding include anticoagulation intensity, increasing age, and drug interactions (Table 1). This article will review the significance and etiology of various drug interactions on the efficacy and safety of warfarin therapy, including practical recommendations to address these interactions, with a focus on older adults.

Types of Drug Interactions

Drug interactions may be categorized as either pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions are based on alterations to absorption, distribution, metabolism, and elimination, which all change the effective serum concentration of warfarin. Pharmacodynamic interactions do not affect serum warfarin levels, but either counteract or enhance the pharmacologic effect at its site of action, causing changes in hemostasis or platelet function. These interactions can occur when an interacting medication is either initiated or discontinued.

Pharmacokinetic Interactions

The most common manifestation of pharmacokinetic interactions with war-

farin involves the inhibition or induction of its metabolism. Attention should be paid to the relative importance of the warfarin cytochrome P450 (CYP) metabolic pathways. Warfarin is a racemic mixture of its R-isomer (less potent) and S-isomer (more potent).⁶ S-warfarin is metabolized primarily by the CYP 2C9 isoenzyme whereas R-warfarin is metabolized by CYP 1A2 and 3A4. Depending on the dominant isoenzyme inhibited by the interacting drug, the effect on warfarin may or may not be clinically significant. Consequently, drugs that impact CYP 2C9 metabolism can be expected to have a disproportionate effect on the INR (International Normalized Ratio) compared with other mechanisms.

There are numerous agents, such as metronidazole, trimethoprim/sulfamethoxazole (TMP/SMX), and amiodarone, that are commonly prescribed to older individuals that inhibit the CYP 2C9 pathway. These medications, when used in conjunction with warfarin have significant effects on the INR and bleeding risk. In addition, while warfarin clearance is not affected by renal dysfunction, serum levels of interacting drugs (such as ciprofloxacin or TMP/SMX) may increase with renal dysfunction, enhancing the interaction.

The onset and duration of the drug interaction is dependent on serum concentrations of the interacting drug. For example, a drug with a long half-life will have a delayed-onset warfarin interaction while steady state levels are achieved. This interaction will persist

Table 1: Risk Factors for Bleeding with Warfarin Therapy

| | |
|---------------------------|---|
| Older age | Prior stroke or ICH |
| Female sex | Bleeding lesions or disorders |
| Diabetes mellitus | Concomitant drug use (NSAIDs, antiplatelets, antibiotics) |
| Malignancy | Unstable INR control |
| Hypertension | INR >3.0 |
| Liver disease | Pretreatment INR >1.2 |
| Renal impairment | Previous hemorrhage with warfarin in therapeutic range |
| Anemia | |
| Poor adherence to therapy | |

Source: Adapted from Gage BF, et al., 2006²⁶; van Walraven C, et al., 2002²⁷; Hirsh J, et al., 2003⁶; Hylek EM, et al., 1994²⁸; and Horton JD, et al., 1999.²⁹

well after the discontinuation of the drug due to its prolonged elimination phase. Table 2 highlights some of the more common pharmacokinetic interactions.

Pharmacodynamic Interactions

Pharmacodynamic interactions with warfarin, while not as numerous as pharmacokinetic interactions, may also influence the efficacy and safety of warfarin therapy. The most common type of pharmacodynamic warfarin interaction is the concomitant use of antiplatelet agents (Table 3) including prescription and non-prescription nonsteroidal anti-inflammatory drugs (NSAIDs)^{7,8} and clopidogrel. These antiplatelet agents can increase bleeding risk without increasing the INR. Acetyl salicylic acid (ASA) added to warfarin therapy increases the risk of bleeding compared to warfarin alone and produces a twofold risk of intracranial hemorrhage (~1.5% per year).⁹ Celecoxib (a COX-2 selective NSAID) may lack an inhibitory effect on platelet function¹⁰ and may not potentiate the anticoagulant effect.¹¹ However, the risk of gastrointestinal injury is not completely eliminated.¹² Numerous herbal/natural products may also have antiplatelet effects, but these interactions are less predictable and the evidence for them is less well-established. Examples of natural substances and foods reported to potentiate the bleeding

risk when combined with warfarin include garlic, ginkgo, coenzyme Q, dan-shen, Devil’s claw, dong quai, ginseng,

vitamin E, and papaya. Green tea and St. John’s wort may result in the converse effect.¹³

In contrast to those described above, other forms of pharmacodynamic interactions (outlined in Table 3) can affect the INR. The onset of pharmacodynamic interactions is variable. Nonsteroidal anti-inflammatory drugs and other antiplatelet agents will have a rapid onset while effects on clotting factors or vitamin K absorption will be delayed. The duration of effect is typically associated with the half-life of the interacting medication except where the effect is irreversible such as COX enzyme inhibition with ASA.

Special Consideration for Older Adults

Although the risk of bleeding increases with age, the overall benefits of warfarin also increase. In fact, as age increases, the

Table 2: Common Pharmacokinetic Interactions and Proposed Mechanisms

| INR Elevation | *INR Depression |
|-------------------------|-------------------------|
| Amiodarone (2C9) | Rifampin (2C9) |
| Ciprofloxacin (1A2/3A4) | Secobarbital (2C9) |
| TMP/SMX (2C9) | Carbamazepine (2C9) |
| Metronidazole (2C9/3A4) | Phenytoin (2C9) |
| Fluconazole (2C9/3A4) | Phenobarbital (2C9) |
| Fluvastatin (2C9) | Primidone (2C9) |
| Fluvoxamine (2C9) | St John’s wort (2C9) |
| Isoniazid (2C9) | Cigarette smoking (1A2) |
| Lovastatin (2C9) | Charbroiled food (1A2) |
| Phenylbutazone (2C9) | |
| Sertraline (2C9) | |
| Gemfibrozil (2C9) | |
| Ethanol (1A2) | |
| Clarithromycin (3A4) | |
| Erythromycin (3A4) | |
| Voriconazole (3A4) | |

*mechanism for all agents listed, thought to be due to liver enzyme induction

Source: Adapted from Holbrook AM, et al., 2005³⁰; Badyal DK, et al., 2004³¹; Stading JA, et al., 2007.³²

Table 3: Common Pharmacodynamic Interactions and Proposed Mechanisms

| Pharmacodynamic interactions | Mechanism |
|---------------------------------------|--|
| ASA/NSAIDs | Antiplatelet, gastrointestinal injury |
| Clopidogrel/Ticlopidine | Antiplatelet |
| Tramadol | INR elevation (unclear mechanism) ³³ |
| Levothyroxine | Increased catabolism of clotting factors |
| Vitamin K-containing food/supplements | INR depression (circumvent warfarin mechanism of action) |

overall benefits increase disproportionately. The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study provided further evidence that the benefit of anticoagulation over antiplatelet therapy in preventing strokes was greater than the perceived harm of increased bleeding, even among individuals over 75 years of age.¹⁴ Given this net clinical benefit with warfarin, older adults should be treated with warfarin with the appropriate management of bleeding risk.

Although maintaining therapeutic INRs is effective in reducing bleeding complications, this may be more difficult among older individuals due to a variety of factors. Older adults are more sensitive to warfarin due to lower body weight, reductions in liver and renal function, and low dietary vitamin K intake.^{15,16} Drug interactions causing small variations in serum warfarin levels may have more profound effects on anticoagulation for older individuals, who are also more likely to experience drug interactions due to polypharmacy.^{17–20}

Management of Warfarin Interactions

The most important step in managing potential drug interactions with warfarin is to recognize that adding, stopping, or changing the dose of any drug may affect the patient's response to warfarin. A thorough medication history is required to identify current and recently discontinued prescription and nonprescription medications, dietary supplements and herbal/alternative treatments.

Identifying pharmacokinetic interactions involves recognizing the major mechanisms of warfarin metabolism (CYP 2C9/1A2/3A4) including stereospecific interactions with the more potent S-warfarin isomer (CYP 2C9). Various drug databases can provide information about cytochrome P450 inhibitors.^{21–23} Major interactions should be avoided, especially for short duration therapies, and replaced with alternative drug selection whenever possible. If a major interaction that results in an increased INR cannot be avoided, one may generally consider a 25–50% reduction of the dose of warfarin for the duration of treatment and a few days after the interacting drug is discontinued.^{24,25} If the interacting drug is maintained for an extended peri-

od of time, a new warfarin dosage must be titrated based on INR measurements. For less profound pharmacokinetic interactions, additional INR monitoring is usually indicated to determine the effect of the interaction on anticoagulation. Any warfarin dose modification as a result of a drug interaction necessitates increased frequency of INR monitoring.

Medications with pharmacodynamic interactions such as platelet inhibition should be identified separately, recognizing that risk of bleeding may increase independent of changes in INR. In all cases of potential drug interactions, a systematic assessment of bleeding complications should be performed.

The importance of patient education cannot be overstated. The patient must have an appreciation of the potential for adverse consequences due to other medications or alternative therapies used with warfarin. The physician, in collaboration with other health providers such as nurses and pharmacists, can offer reminders of the signs of bleeding, emphasize vigilance in disclosing the usage of nonprescription remedies, promote diligence in medication adherence, and encourage adherence to regular INR monitoring.

Conclusion

Warfarin continues to play a significant

Key Points

Although the risk of bleeding increases with age, the overall benefits of warfarin also increase. In fact, as age increases, the overall benefits increase disproportionately.


The most important step in managing potential drug interactions with warfarin is to recognize that adding, stopping, or changing the dose of any drug may affect the patient's response to warfarin.

Identify warfarin-drug interactions as pharmacokinetic and/or pharmacodynamic in nature when starting or stopping pharmacotherapy. Thorough medication histories are essential.

Avoid prescribing medications with major interactions (such as ciprofloxacin, metronidazole, or TMP/SMX) with warfarin. Choose another drug or therapy if possible.

Increase INR monitoring frequency with onset of drug interactions, and especially, after warfarin dose adjustments.

Educate the patient and enlist the aid of other healthcare professionals to facilitate the safe use of warfarin.

role in the prevention and treatment of thromboembolic disease among older adults. The appropriate management of drug interactions can enhance the efficacy and safety of warfarin therapy. 

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