REVIEW

Interactions of Warfarin with Drugs and Food

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■ *Purpose:* To evaluate the quality of studies about drugs and food interactions with warfarin and their clinical relevance.

■ *Data Sources:* MEDLINE and TOXLINE databases from 1966 to October 1993 using the Medical Subject Headings warfarin, drug interactions, and English only.

■ *Study Selection:* All articles reporting original data on drug and food interactions with warfarin.

■ *Data Extraction:* Each report, rated independently by at least two investigators (using causality assessment), received a summary score indicating the level of assurance (level 1 = highly probable, level 2 = probable, level 3 = possible, and level 4 = doubtful) that a clinically important interaction had or had not occurred. Inter-rater agreement was assessed using a weighted kappa statistic.

■ *Results:* Of 793 retrieved citations, 120 contained original reports on 186 interactions. The weighted kappa statistic was 0.67, representing substantial agreement. Of 86 different drugs and foods appraised, 43 had level 1 evidence. Of these, 26 drugs and foods did interact with warfarin. Warfarin's anticoagulant effect was potentiated by 6 antibiotics (cotrimoxazole, erythromycin, fluconazole, isoniazid, metronidazole, and miconazole); 5 cardiac drugs (amiodarone, clofibrate, propafenone, propranolol, and sulfinpyrazone); phenylbutazone; piroxicam; alcohol (only with concomitant liver disease); cimetidine; and omeprazole. Three patients had a hemorrhage at the time of a potentiating interaction (caused by alcohol, isoniazid, and phenylbutazone). Warfarin's anticoagulant effect was inhibited by 3 antibiotics (griseofulvin, rifampin, and nafcillin); 3 drugs active on the central nervous system (barbiturates, carbamazepine, and chlordiazepoxide); cholestyramine; sucralfate; foods high in vitamin K; and large amounts of avocado.

■ *Conclusions:* Many drugs and foods interact with warfarin, including antibiotics, drugs affecting the central nervous system, and cardiac medications. Many of these drug interactions increase warfarin's anticoagulant effect.

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Warfarin is the most widely used oral anticoagulant drug in North America, in part because of its relatively predictable onset and duration of action and its excellent bioavailability (1–3). Warfarin, a racemic compound with a more potent S enantiomer and a less potent R enantiomer, achieves its anticoagulant effect by inhibiting the activation of vitamin K–dependent clotting factors. Oral anticoagulants are effective in the prevention and treatment of deep venous thrombosis and also in the prevention of thromboembolic events in patients with atrial fibrillation (4–8), prosthetic heart valves (9–12), and indwelling central venous catheters (13), as well as in patients who have had myocardial infarction (14–20). Despite excellent evidence (21) for its clinical value, warfarin may be underused because of the inconvenience of monitoring and the concern about potential complications, primarily bleeding (22–24). The risk for complications may be increased when concomitant drug therapy is required (25, 26). The potential for warfarin to interact with other drugs, resulting in changes in its anticoagulant effect, is widely recognized among health professionals and informed patients.

Many published reviews (3, 27–35) and extensive lists in standard medical textbooks (110 interacting drugs listed in the United States Pharmacopeia Dispensing Information [USP DI]) (36) attest to the widely held belief that drug interactions with warfarin are common and potentially harmful. However, reports on drug interactions are replete with small case series, single case reports, and extrapolation of in vitro or animal data. This evidence, when judged by the usual evaluative scales for therapy, is of lower quality (21, 37, 38). Given that expensive clinical trial resources are unlikely to be used to address the fine points of therapy such as drug interactions, it is essential to evaluate the quality of these studies.

Thus, we evaluated the quality of reports about drug and food interactions with warfarin. We prospectively applied explicit, reproducible criteria for determining the strength of inferred causation. We recognized that a "yes, did cause" or a "no, did not cause" conclusion might not be possible and used an estimate of the probability of causation (level of evidence) by adapting previously described principles of causality assessment (39–42).

Methods

Relevant studies were identified by searching the MEDLINE and TOXLINE databases from 1966 to the end of October 1993

Drug	
Generic Name	**Brand Name**
Warfarin	Coumadin

using the Medical Subject Headings warfarin, drug interactions, and English only. Articles were considered eligible for evaluation if they contained original data about drug and food interactions with warfarin in humans. Bibliographies were also checked for additional pertinent studies. Reports on drugs not available in the United States or Canada were excluded.

Eligible studies were evaluated independently by two authors according to three main categories: participants, description of interaction, and level of evidence.

Participants

We separated reports into those describing 1) patients who received the interacting drug during usual warfarin therapy and 2) healthy volunteers or patients prospectively entered into an experiment while receiving warfarin.

Description of Interaction

We noted the drug or food affected by the interaction, the type of interaction (potentiation, inhibition, or no effect), and the proposed or documented mechanism of interaction.

Level of Evidence (Assurance)

Each article was evaluated, with "yes" or "no" responses given according to seven criteria previously approved by a panel of experts in the fields of thromboembolism, clinical pharmacology, and clinical epidemiology (Appendix 1).

Responses to four criteria (A to D) required additional guidelines in order to be specific to the evaluation of drug interactions with warfarin. To meet criterion A, for patient-based studies, before the potentially interactive substance was started, the warfarin dose and intensity of anticoagulation must have been stable. Further, the potentially interacting substance had to be used in usual doses for enough time to attain a substantial plasma level. For volunteer-based studies, participants had to have received warfarin alone and with the interacting drug for similar periods. For criterion B, in patient-based studies, the coagulation variable had to be outside the therapeutic range, whereas for volunteer studies, a change of at least 20% in coagulation variables was required.

To satisfy criterion C, we required some indication that medical conditions, especially liver disease, as well as other drug therapy and diet (notably dietary vitamin K intake) were constant. However, for healthy volunteers we assumed that these confounders were absent, even if not explicitly stated. For criterion D, other objective evidence refers to changes in plasma levels of warfarin or of vitamin K–dependent factors II, VII, IX, or X.

The level of evidence (assurance) that a drug or food interaction with warfarin could occur was then determined as outlined in Appendix 1. Level 1 evidence obtained from patient-based and volunteer-based reports was considered definitive evidence of an interaction. Inter-rater agreement was assessed using a weighted kappa statistic (43). Wherever reported, we considered data from individual participants rather than relying on summary results. If individual data were not available, the summary statistics were used. If several studies assessed the same drug, the interaction supported by the highest level of evidence was considered the final warfarin interaction. If a study in volunteers showed a different type of interaction than did a study with the same level of evidence in a patient-based report, the latter was considered to be the final warfarin interaction.

Level 1 studies were further reviewed with regard to the severity of effect of the interaction. Two thresholds were established: The first was clinically evident hemorrhage or thrombosis and the second was a doubling or halving (for inhibition) of coagulation measurements. Articles were also appraised for any description of the mechanism of interaction. Pharmacokinetic data suggesting altered drug clearance or changes in pharmacodynamic data, such as clotting factor or vitamin K levels, were considered adequate evidence. Because warfarin is a racemic compound, we classified the interaction as 1) being stereoselective if a differential change was noted in enantiomer concentrations, 2) being nonstereoselective if both enantiomers changed substantially but by a similar proportion, or 3) affecting clearance by an unknown mechanism if only plasma warfarin levels without its enantiomers were measured.

Results

Of 793 citations retrieved, 120 contained original data on 186 interactions. The weighted kappa statistic for the level of evidence evaluation was 0.67, representing substantial agreement (43). Disagreement about the scores of 38 articles was resolved by repeat review and discussion until a consensus was reached. Forty-three of 86 different drug and food interactions appraised were judged highly probable (level 1 evidence): Sixteen had a potentiating effect, 10 had an inhibiting effect, and 17 had no effect. These drugs were classified into the following six categories: antibiotics, anti-inflammatory agents or analgesics, cardiac drugs, gastrointestinal drugs, drugs active on the central nervous system, and miscellaneous drugs or foods (Table 1). The reported interactions for another 18 drugs were judged probable (level 2 evidence): 14 potentiating, 1 inhibiting, and 3 with no effect.

Of the remaining 25 interacting medications, 16 were considered possible (level 3 evidence) and 9 were doubtful (level 4 evidence). All reports described interactions leading to some effect on warfarin therapy (as opposed to altering the effect of the other drug). Our summary of results listing the type of interaction by level of evidence according to drug categories is presented in Appendix 2.

Drugs Potentiating the Effect of Warfarin

Many antibiotics are reported to potentiate the effect of warfarin. The evidence was considered highly probable (level 1) for cotrimoxazole, erythromycin, isoniazid, fluconazole, miconazole, and metronidazole (44–50) and was probable (level 2) for ciprofloxacin, itraconazole, and tetracycline (51–58). The evidence was much weaker for six other antibiotics (59–63). Several cardiac drugs had highly probable evidence (64–73) that they potentiated the effect of warfarin: These included amiodarone, clofibrate, propafenone, propranolol, and sulfinpyrazone. Sulfinpyrazone's effect was biphasic, which means that an initial potentiation of the warfarin anticoagulant effect was noted, followed by inhibition of the effect. Quinidine, simvastatin, and acetylsalicylic acid had probable evidence that they potentiated warfarin (74–76). Possible and doubtful evidence were reported for five other drugs (77–81).

Among the anti-inflammatory or analgesic drugs, phenylbutazone, piroxicam, acetylsalicylic acid, acetaminophen, and dextropropoxyphene had highly probable or probable evidence (74, 82–89). The other medications with highly probable or probable evidence were cimetidine, omeprazole, alcohol (only if concomitant liver disease was present), chloral hydrate, disulfiram, phenytoin (late effect of inhibition), tamoxifen, anabolic steroids, and influenza vaccines (74, 90–105).

Drugs Inhibiting the Effect of Warfarin

Fewer drugs inhibited the effect of warfarin, but the proportion with level 1 evidence was higher. Highly probable evidence was reported for nafcillin, rifampin, griseo-

Table 1. Level 1 Evidence of Drug and Food Interactions with Warfarin*

Interaction	Antibiotics	Cardiac	Anti-Inflammatory	Central Nervous System	Gastrointestinal	Miscellaneous
Potentiation	cotrimoxazole (8), erythromycin (8), fluconazole (6), isoniazid (1), metronidazole (8), miconazole (6)	amiodarone (28), clofibrate (8), propafenone (8), propranolol (12), sulfinpyrazone† (13)	phenylbutazone† (14), piroxicam (1)	alcohol (with liver disease) (1)	cimetidine‡ (50), omeprazole (19)	
Inhibition	griseofulvin† (2), nafcillin (1), rifampin (31)	cholestyramine (27)		barbiturates (12), carbamazepine (3), chlordiazepoxide (1)	sucralfate (1)	High vitamin K content foods/enteral feeds (5), large amounts of avocado (2)
No effect	enoxacin (5)	atenolol (6), bumetanide (10), felodipine (2), metoprolol (6), moricizine (1)	diflunisal (5), ketorolac (10), naproxen (5)	alcohol (15), fluoxetine (3), nitrazepam (3)	antacids (6), famotidine (8), nizatidine (7), psyllium (6), ranitidine§ (14)	

* Numbers in parentheses are numbers of patients, volunteers, or both.
† Supporting level 1 evidence (see Appendix 1 for criteria) from patients and volunteers.
‡ In a small number of volunteers, an inhibitory drug interaction occurred.
§ Level 2 evidence of potentiation in patients.

fulvin, cholestyramine, barbiturates, carbamazepine, chlordiazepoxide, sucralfate, high vitamin K content in enteral feeds or in the diet, and large amounts of avocado (97, 106–119). Probable evidence was reported with dicloxacillin (120). The reported interactions of four other drugs in addition to the consumption of large amounts of broccoli were considered possible evidence (121–126).

Drugs with No Effect on Warfarin

Highly probable evidence indicated that several cardiac and gastrointestinal drugs did not interact with warfarin. These drugs included atenolol, bumetanide, felodipine, metoprolol, moricizine, antacids, famotidine, nizatidine, psyllium, and ranitidine (69, 90, 108, 127–132). Seven other drugs also had highly probable evidence that they did not interact with warfarin: enoxacin, diflunisal, ketorolac, naproxen, alcohol, nitrazepam, and fluoxetine (97, 133–139). In addition, probable evidence was noted for ketoconazole, ibuprofen, and ketoprofen (140–142). It is possible that diltiazem, tobacco, and vancomycin do interact with warfarin because the evidence for no interaction was doubtful (level 4 evidence) (62, 143–145).

Definitive Interactions

Only three drugs—phenylbutazone, sulfinpyrazone, and griseofulvin—had definitive evidence of an interaction with warfarin according to our criteria (level 1 evidence from patients and volunteers). Phenylbutazone and sulfinpyrazone resulted in potentiation of warfarin effect, whereas griseofulvin resulted in inhibition of warfarin effect.

Sample Sizes

Our conclusions for many drug and food interactions were based on very small numbers of patients. There were 17 patient-based reports with level 1 evidence, of which 13 reported an interaction in only 1 patient, whereas the other 4 reports each involved 2 or 3 patients. Because volunteer studies can be planned and organized prospectively, sample size numbers tend to be larger. However, of 36 studies for which level 1 volunteer evidence was abstracted, only 13 studies contributed data on 10 or more participants.

Patient- Compared with Volunteer-based Reports

Patient-related evidence tends to confirm potentiation or inhibition, whereas volunteer-derived evidence is more heavily weighted toward no effect; only one patient-based report described no effect. The summary conclusions shown in Table 1 obscure the interindividual variability of data from patients and volunteers. For example, sucralfate inhibited the warfarin anticoagulant effect in one patient (115) but had no effect on five volunteers (116). Because our preset policy was that patient-based conclusions took precedence, sucralfate appears in Table 1 under inhibition. The volunteer data for cimetidine (74, 90–94), felodipine (129), and propranolol (69, 70) include all three types of interaction—potentiation, inhibition, and no effect. As previously described, the higher level of evidence was accepted.

Severity and Mechanism of Interaction

Despite all the level 1 interactions reported, only three patients had a hemorrhagic complication. These occurred

Table 2. Studies Providing a Mechanism of Interaction with Warfarin

Mechanism of Action	Drug (Reference)
Clearance by unknown mechanism	carbamazepine (107), cholestyramine (109), dextropropoxyphene (88), etretinate (123), nafcillin (112, 147, 148)
Nonstereoselective clearance	amiodarone (64, 66), barbiturates (106, 149), erythromycin (45, 150), fluconazole (46), phenylbutazone (83, 84), rifampin (114)
Stereoselective clearance on R enantiomer	cimetidine (90, 97, 151), omeprazole (96)
Stereoselective clearance on S enantiomer	cotrimoxazole (44), sulfinpyrazone (72, 73)
Stereoselective clearance on S and R enantiomers	miconazole (50)
Antiplatelet effect	aspirin (152)
Coagulation factor related	clofibrate (67)
Vitamin K pathway	High vitamin K content in foods and enteral feeds (117)

with alcohol (in a patient with liver disease), isoniazid, and phenylbutazone. No reports indicated that thrombosis occurred because of inhibition of warfarin's anticoagulant effect. Only one interaction doubled the coagulation measurements (for sulfinpyrazone), and one interaction halved the measurements (for carbamazepine).

A mechanism for the interaction with warfarin was not investigated in most reports but was well supported for 19 substances (Table 2). Many of these mechanisms involved alterations in the elimination of warfarin, reflected in measurements of clearance.

Discussion

Our review shows that the anticoagulant effect of warfarin therapy can be affected by concomitant administration of 26 drugs and foods (level 1 studies indicating that potentiation or inhibition is highly probable) (Table 1). Potentiation occurred with 6 antibiotics, 5 cardiac drugs, and other assorted drugs. Inhibition occurred with 3 antibiotics, 3 drugs active on the central nervous system, and other drugs and foods. Conversely, the evidence did not support an important interaction with 5 cardiac drugs, 5 gastrointestinal drugs, and 7 other drugs. The evidence was less conclusive for the other 43 drugs or foods reviewed.

Although only three patients in these reports had a clinically evident hemorrhage as a result of an interaction potentiating warfarin's effect, this should not be misinterpreted as evidence against the clinical relevance of interactions. It is well documented that intensity of anticoagulation correlates directly with incidence of hemorrhage (146). Thus, all of the observed potentiation interactions, because they resulted in important increases in the international normalized ratio (INR) for warfarin or equivalent measures, could be viewed as exposing patients to increased risk for hemorrhage. In many instances, particularly in volunteer studies, hemorrhage was probably avoided by close monitoring of coagulation status, rapid withdrawal of the interacting drug, adjustment of the dose of warfarin, or administration of vitamin K.

The criteria used to produce the level of evidence (assurance) of an interaction were designed using three main objectives. First, we chose to concentrate on interactions measurable through assays monitoring the anticoagulant effect of warfarin. Obviously, those substances that affect platelet function (for example, aspirin and other nonsteroidal anti-inflammatory drugs) or the coagulation process (for example, heparin) have the potential to increase the risk for bleeding apart from any possible effect on warfarin, but we chose not to evaluate these types of interactions. Second, we attempted to incorporate the general rules used in assessment for causation. Causality assessment is an inherently subjective process, and no gold standard exists. The application of standard guidelines ensures reliability in our evaluation of levels of evidence (assurance). Third, because of the nature of the studies, we adapted previously validated methods for evaluating case reports of adverse effects of medicines (41) to deal with drug-interaction papers specific for warfarin.

Clinicians must be aware of several fundamental requirements when evaluating causation in clinical practice.

1. Warfarin must be at a stable dose, with a stable level of anticoagulation before initiating the potentially interactive drug. Causation is difficult to assess in 20% to 25% of patients who never achieve anticoagulant stability (27).

2. The potentially interacting drug should have been given time to attain a substantial plasma level and must have been used in doses typical for clinical practice; otherwise, a conclusion of no effect may have no clinical relevance. For example, the report concluding no effect from a single 120-mg dose of diltiazem is unlikely to provide assurance that daily administration of diltiazem would also have no effect.

3. A substantial change must occur in coagulation measurements (international normalized ratio, prothrombin time, thrombotest), that is, a change requiring an alteration in warfarin dose. Even in the event of a hemorrhagic complication, if this is not accompanied by an alteration in warfarin-dependent coagulation measurements, one could not be sure that an interaction with warfarin was responsible.

4. Other potential causes that alter coagulation measurements must be ruled out. These would include increases in dietary vitamin K (which can antagonize the anticoagulant effect of warfarin), hepatic dysfunction (which decreases synthesis of vitamin K–dependent clotting factors [for example, alcohol potentiates only in the presence of liver disease]), and hypermetabolic states including fever and hyperthyroidism (which may accelerate the clearance of vitamin K–dependent clotting factors [2]).

If additional proof of an interaction is required (our level 1 evidence), then other objective evidence (including plasma warfarin levels or plasma levels of factors II, VII,

Appendix 1. Criteria for Establishing a Drug or Food Interaction with Warfarin

Level of Evidence	Criteria Required
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 A alone

A. Was the timing pharmacologically plausible?
B. Did results from the international normalized ratio, prothrombin time, or thrombotest support the contention?
C. Were other potential factors affecting warfarin pharmacokinetics or pharmacodynamics ruled out?
D. Was there other objective evidence (such as warfarin blood levels)?
E. Was a dose-response relation shown for the interacting drug?
F. Was the patient rechallenged and, if so, did a similar response occur?
G. Did the same thing happen on previous exposure to the drug?

IX, and X) should be obtained to rule out laboratory error in the measurement of coagulation variables and to help confirm that the outcome was mediated through warfarin. A drug rechallenge also provides objective evidence and could be done if this is more feasible than obtaining plasma warfarin levels or coagulation factor levels.

In evaluating the studies, we distinguished between studies in volunteers and those in patients. Publication bias, as predicted, was a major determinant of the type of interaction reported in patients. Only one study reported the absence of interaction in a patient group. In contrast, most reports in volunteers described the absence of an interaction. Reports of interactions between warfarin and other substances in patients may arise from thousands of exposures and identify uncommon interactions that would not be detectable in the typically small volunteer study. In other words, data derived from healthy volunteers only may not be applicable to patients if no interaction is shown. Therefore, when the level of evidence was the same in studies of patients and volunteers but the interaction differed, as occurred with sucralfate, the patient-based evidence took priority to produce the most conservative conclusion. Alternatively, if level 1 evidence with the same type of interaction was derived from studies in patients and volunteers, this was considered definitive evidence of interaction. This occurred for only three medications—phenylbutazone, sulfinpyrazone, and griseofulvin. None of these is commonly prescribed in Canada or the United States.

Some cautions are appropriate:

1. Absence of proof does not mean proof of absence. Many drugs currently in use have not been evaluated for their potential to interact with warfarin and should not be presumed to have no effect on warfarin pharmacokinetics or pharmacodynamics. Therefore, concomitant use of unevaluated drugs still requires close monitoring of anticoagulant effect.

2. Level 2 to 4 evidence for a drug interaction does not imply that a drug interaction cannot or does not occur; it merely indicates that adequate evidence for an interaction has yet to be reported.

3. Most patient-based studies are case reports and thus lack control or comparison groups. As a consequence, it is impossible to totally rule out confounding factors (153), even when specifically attempted in the report. Thus, even our level 1 evidence may still be less valid than evidence that could be derived from randomized controlled clinical trials assessing warfarin interactions.

4. It is difficult to extrapolate from case reports to the general population. Thus, predicting incidence, prevalence, and severity of an interaction is problematic. We

Appendix 2. Drug and Food Interactions with Warfarin by Level of Supporting Evidence and Type of Interaction*

Level of Evidence	Potentiation	Inhibition	No Effect
1	alcohol (if concomitant liver disease), amiodarone, cimetidine†, clofibrate, cotrimoxazole, erythromycin, fluconazole, isoniazid (600 mg daily), metronidazole, miconazole, omeprazole, phenylbutazone‡, piroxicam, propafenone, propranolol, sulfinpyrazone‡	barbiturates, carbamazepine, chlordiazepoxide, cholestyramine, griseofulvin‡, nafcillin, rifampin, sucralfate, high vitamin K content foods and enteral feeds, large amounts of avocado	alcohol, antacids, atenolol, bumetanide, diflunisal, enoxacin, famotidine, felodipine, fluoxetine, ketorolac, metoprolol, moricizine, naproxen, nitrazepam, nizatidine, psyllium, ranitidine§
2	acetaminophen, anabolic steroids, aspirin, chloral hydrate, ciprofloxacin, dextropropoxyphene, disulfiram, itraconazole, quinidine, phenytoin, simvastatin, tamoxifen, tetracycline, influenza vaccine	dicloxacillin	ibuprofen, ketoconazole, ketoprofen
3	disopyramide, 5-fluorouracil, ifosphamide, lovastatin, metolazone, nalidixic acid, norfloxacin, ofloxacin, topical salicylates, sulindac, tolmetin	azathioprine, cyclosporine, etretinate, trazodone	
4	cefamandole, cefazolin, gemfibrozil, heparin, indomethacin, sulfisoxazole		diltiazem, tobacco, vancomycin

* References available on request.
† In a small number of volunteers, an inhibitory drug interaction occurred.
‡ Supporting level 1 evidence from patients and volunteers.
§ Level 2 evidence of potentiation in patients.

observed a wide variation in severity of interaction, from minor changes in coagulation variables to hemorrhage. Fortunately, clinically serious outcomes were uncommon. However, given that under-reporting or selective reporting of interactions in patients occurs, the probability of a serious outcome from an interaction is unknown. Similarly, it is difficult to determine which patients are at risk for an adverse outcome. Given the results of other investigations (26), it is likely that those patients with comorbid conditions or advanced age will be more susceptible when a drug interaction occurs.

Although much rarer than one would expect from the volume of studies, many high-quality reports of drug interactions with warfarin exist, most describing potentiation of anticoagulation. However, drugs that appear highly probable to interact with warfarin are not absolutely contraindicated. Instead, patients and clinicians must be aware of the possibility of interactions and of individual variability in the response to interactions to concomitantly prescribed medications and to dietary changes. For patients receiving warfarin, when concomitant drug therapy is initiated or discontinued, the potential for adverse effects on anticoagulation should be considered, and intensified monitoring of the patient's anticoagulation status is recommended.

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