Journal of Thrombosis and Thrombolysis 12(1), 67–71, 2001.

Drug Interactions Update: Drugs, Herbs, and Oral Anticoagulation

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Abstract. **Management of warfarin drug interactions is often complicated by lack of information regarding interactions with new drugs and with herbal medicinals. The pharmaceutical industry has increased both the number and quality of drug interaction studies prior to marketing new agents. Interactions may still occur in patients, however, despite negative premarketing studies in healthy volunteers. The clinical significance and intensity of warfarin interactions with prescription drugs (e.g., celecoxib, proton pump inhibitors, and selective serotonin reuptake inhibitors) can often be predicted on the basis of known metabolic characteristics of the drugs and warfarin enantiomers. Drug interactions with herbal medicinals are much more difficult to characterize and predict because of the lack of federal regulations regarding safety, efficacy, and manufacturing standards. Published case reports of interactions between warfarin and even the most widely used herbal medicinals are limited. Practitioners are encouraged to report such interactions through the FDA MedWatch program.**

Key Words. **warfarin, anticoagulation, drug interactions, herbal medicinals**

Introduction

Managing interactions of warfarin with prescription and common non-prescription agents is an ongoing challenge for health care practitioners because of limited information regarding the effect of new drug compounds and herbal medicinals on the pharmacokinetics and pharmacodynamics of warfarin. The pharmaceutical industry has intensified its efforts to identify potential drug interactions during the pre-clinical phase of drug development. Improvements in premarketing analysis of drug interactions were demonstrated in a recent survey of drug-drug interaction studies conducted for new drug entities approved during the time periods 1987 to 1991 (Period 1) and 1992 to 1997 (Period 2) [1]. During Period 1, 32 of 98 (33%) new drug entities approved by the FDA included 117 drug interaction studies (1.2 studies per new drug entity). During Period 2, 106 of 193 (55%) new drug entities approved by the FDA included 540 drug interaction studies (2.8 studies per new drug entity). Evaluations of interactions of new products with warfarin were among the most common studies, accounting for 7.7% of all drug interaction studies during Period 1 and 6.1% of studies during Period 2.

In addition to improvements in the search for potential drug interactions, this survey identified improvements in the quality of drug interaction studies. While 70% of studies in both periods were conducted in healthy male volunteers rather than in patients, multiple-dose/steady-state dosing regimens and crossover and fixed-sequence designs increased substantially during Period 2 compared to Period 1. Among all interaction studies conducted, 14% demonstrated a clinically relevant pharmacokinetic change in the new drug entity or the interacting drug, resulting in the development of a cautionary statement (1%) or in recommendations for additional monitoring (1%), dosing adjustments (8%), or contraindication to concurrent use (4%). Overall the results of this survey suggest increasing attention to the recognition of potential interactions between drugs likely to be used concomitantly.

Despite these improvements, potential interactions that appear unlikely in studies conducted in healthy volunteers may indeed occur when patients are treated with the offending agents. While drug interaction studies effectively describe the pharmacokinetic characteristics of certain interactions, the use of healthy volunteers limits the characterization of pharmacodynamic response. Case reports in patients overcome this disadvantage, but are limited by selective reporting and underreporting of events.

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Despite negative pre-marketing drug interaction studies, post-marketing drug interaction cases may be reported, as was the case with celecoxib.

Warfarin Interactions with Newer Prescription Drugs

The selective cyclooxygenase-2 inhibitor, celecoxib, was initially thought to be a preferred non-steroidal antiiflammatory drug (NSAID) for use by patients taking concomitant warfarin because of its limited effects on platelet aggregation and the presumed reduction in bleeding complications compared with other NSAIDs when used in conjunction with warfarin. The celecoxib-warfarin interaction was investigated prior to marketing in an open-label, multi-dose, placebo-controlled randomized study in 24 healthy volunteers [2]. In Phase I, subjects received warfarin alone for 8 days, dosed at 10 mg qd for 2 days, followed by 1 to 5 mg/day to reach a target prothrombin time ratio (PTR) of 1.2 to 1.7. In Phase 2, warfarin was continued for an additional 7 days, and subjects were randomized to concomitant oral celecoxib 200 mg bid or placebo. No clinically or statistically significant differences in steady state area under the curve (AUC) or maximal serum concentrations (Cmax) of S- and R-warfarin enantiomers were observed; and PTR values were the same in subjects who received celecoxib as in those who received placebo.

When celecoxib was released in December 1998, no interaction with warfarin was expected based on the results of this study; however, post-marketing case reports revealed a clinically significant drug interaction between celecoxib and warfarin. For example, a 77 year-old female previously taking stable doses of warfarin developed hemoptysis associated with an elevated INR after initiation of celecoxib 200 mg/day [3]. In a second reported case, the INR increased significantly in an 88 year-old female taking warfarin after initiation of celecoxib 200 mg qd [4]. It was necessary to reduce this patient's warfarin dose by 25% to maintain a therapeutic INR during concomitant warfarin-celecoxib therapy.

The possibility of a significant warfarin-celecoxib interaction might have been anticipated despite negative findings in a pre-marketing study. The metabolism of drugs (substrates) that are metabolized by a specific isozyme can be directly induced or inhibited by other drugs, resulting in clinically significant interactions. A drug that is metabolized by a specific isozyme may compete for metabolism with other drugs metabolized by the same enzyme [5]. Celecoxib is metabolized by CYP2C9, the hepatic microsomal enzyme that is the primary metabolic pathway for S-warfarin, the more potent of the two warfarin enantiomers (Fig. 1). The metabolism of the drug with the weaker affinity for the enzyme (S-warfarin) is inhibited by the drug with the stronger affinity (celecoxib). A clinically significant interaction would be anticipated in this case since it involves a primary metabolic pathway of the more potent enantiomer.

A less significant interaction would be anticipated if a minor metabolic pathway of the less potent enantiomer of warfarin were competitively inhibited. A recent example of this type of interaction involves warfarin and the proton pump inhibitors (PPI). Two drug interaction studies concluded that omeprazole may interact with warfarin, but without clinically significant results. A randomized crossover trial in 21 healthy males age 20–36 years noted a 12% increase in R-warfarin levels, and an 11% change in Trombotest results in patients taking concurrent warfarin and omeprazole compared with warfarin alone [6]. Similarly, a randomized crossover trial in 28 patients taking warfarin found that concurrent omeprazole increased R-warfarin levels by 9.5% and changed Trombotest results by 8% [7].

All four available PPIs are metabolized by CYP 2C19, a very minor contributor to the metabolism of the less potent R-warfarin. Thus, warfarin-PPI interactions might be expected to occur with a limited but consistent frequency and intensity for all agents. Warfarin-drug interaction studies have been positive for omeprazole, but negative for lansoprazole and pantoprazole and not reported for rabeprazole [8]. Despite their similar metabolic pathways, differences in the frequency and intensity of PPI-warfarin drug interactions may occur because of possible differential affinity among the PPIs compared with warfarin for CYP2C19. In addition, the genetic expression of CYP2C19 can influence the resultant contribution of CYP2C19 to R-warfarin metabolism. Consequently, some patients who receive this drug combination may experience significant

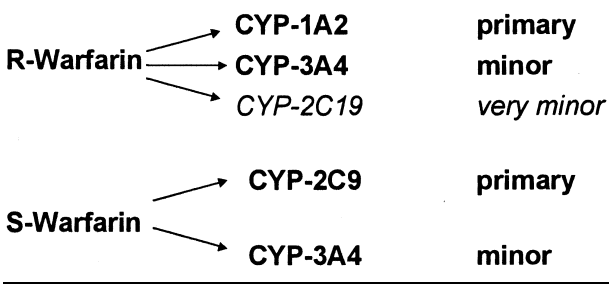

Fig. 1. *Warfarin hepatic metabolism by mixed function oxidases.*

elevations in INR and resultant bleeding complications [9].

The likelihood of an interaction can be predicted by knowing which isozymes are primarily responsible for metabolism of the drugs involved, the relative contribution of these isozymes to the total metabolism of the drugs, and the relative affinity of these drugs for the isozymes. Selective serotonin reuptake inhibitors (SSRIs) represent a drug class in which differences in metabolic characteristics and metabolizing enzyme induction/inhibition properties result in a differential risk of interaction with warfarin (Table 1) [10]. Fluvoxamine, a substrate for CYP1A2 and a recognized inhibitor of CYP1A2, CYP3A4, and CYP2C9 should be considered the most likely of the SSRIs to interact with warfarin. The risk of warfarin interaction with fluoxetine (an inhibitor of CYP3A4 and CYP2C19) and paroxetine (an inhibitor of CYP1A2) is considered moderate. Sertraline, a substrate for CYP3A4, likely has a lower interaction risk. The lowest risk is likely with citalopram, a substrate for CYP2C19.

Several valuable lessons can be learned from recent experiences with these three relatively new drugs and drug classes. Practitioners should not assume that an interaction will not occur simply because it has not been reported. Rather, it is important to consider the metabolic characteristics of all new drugs and their potential for interactions with warfarin, and to increase the frequency of monitoring whenever potentially interacting drugs are added to a stable warfarin regimen. Finally, current drug therapies should be evaluated at each anticoagulation visit, regardless of the INR result.

Warfarin Interactions with Herbal Medicinal Products

Evaluating and managing warfarin interactions with herbal products is also a distinct challenge for health care practitioners. A recent survey found that herbal products account for $5.1 billion in annual sales and that use of these products has risen dramatically since the early 1990s [11]. Nearly 50% of Americans have used dietary supplements to treat a variety of illnesses, and up to 20% report regular use of these products. However, 60% of patients do not report the use of alternative therapies to their health care providers.

Herbal products are regulated by the 1994 Dietary Supplement Health and Education Act [12]. The purpose of this legislation, however, is to protect consumer access to non-drug products. Unlike drug products, dietary supplements are not tested for safety and efficacy prior to marketing. In addition, manufacturers of dietary supplements are not required to follow good manufacturing practices [13]. These products may therefore include varying doses of the active ingredient, unlisted ingredients, and potential contaminants. Labeling may not represent actual tablet contents, as was the case in two studies of commercially available ginseng products [14,15]. These studies found that the active ingredients, ginsenosides, were absent in 42% and 12% of products tested, and that the ginsenoside content in the remaining products varied from 0.1 to 0.7% in 17 products tested in one study and from 1.9 to 9% in 40 products tested in the other study.

Published case reports, although very limited in the medical literature, account for most of the available information on herbal medicinal-drug interactions. For example, a 47 year-old male previously stable on warfarin experienced a significant reversal in anticoagulant effect when he started using ginseng [16]. The INR returned to the therapeutic range when he discontinued ginseng. Health care practitioners cannot assume a similar response in other patients, however, because of the wide variability in tablet contents among commercially available ginseng products. In addition, the chemical composition and pharmacology of ginsenosides may be affected by the method of deriving the plant extract, the age of the root at the time of harvesting, the location where the plant was grown, the season in which it was harvested, and the method of drying [17]. The mechanism for this interaction is unknown.

The mechanisms of other interactions between herbal products and warfarin are more clearly defined. Both *dan shen* (*Salvia*) and *dong quai* (*Angelica*) have been reported to elevate the INR [18]. These compounds contain coumarin deriva-

Table 1. *Warfarin Interactions with Selective Seretonin Reuptake Inhibitors*

SSRI	Substrate	Inhibition	Warfarin interaction general risk
Fluvoxamine	CYP1A2	CYP 1A2;CYP 3A4;CYP 2C9	Highest
Fluoxetine	–	CYP 3A4;CYP 2C19	Moderate
Paroxetine	–	CYP 1A2	Moderate
Sertraline	CYP 3A4	–	Low
Citalopram	CYP 2C19	–	Lowest

tives, as do a number of other plant extracts for which interactions are possible but have not yet been reported (Table 2). Coenzyme Q contains ubidecarenone, a compound related to vitamin K. Three cases of significant reduction in INR values have been reported in patients previously taking stable doses of warfarin in whom coenzyme Q was added [19].

Other compounds may interact with warfarin by increasing the risk of bleeding without interfering with the anticoagulant effect of warfarin. Garlic and ginkgo both inhibit platelet aggregation, and bleeding complications have been reported in patients who have used these compounds with and without concurrent warfarin [20]. Other herbal products, including extracts from cassio, clove, feverfew, ginger, onion, and turmeric may cause a similar interaction, although no cases have been reported. Similarly, bleeding complications may result from use of meadowsweet, poplar, and willowbark, as these compounds contain salicylate derivatives which may interfere with platelet aggregation. Papain has been reported to increase the INR [21]. St John's Wort was reported to reduce the INR in 7 elderly patients taking warfarin [21]. Recent evidence suggests that St John's Wort may in fact act as an inducer of CYP3A4, a minor metabolic pathway for both R-warfarin and S-warfarin [22].

Conclusion

Practitioners managing patients taking warfarin are faced with several challenges regarding herbal product-drug interactions.

It is imperative to determine patients' actual use of herbal medicinals by taking drug histories throughout the course of warfarin therapy. In order to assure that patients report use of these products, however, it is important to remain nonjudgmental and to establish rapport with patients so that they can feel comfortable reporting accurate information. When providing patient education, the risks and benefits of herbal products must be presented in the context of potential interactions with warfarin. If patients are adamant about using herbal products despite potential risks, practitioners should emphasize that "natural" does not necessarily mean "safe" and should counsel patients to avoid multi-ingredient products.

Table 2. *Warfarin Interactions with Herbal Products*

Mechanism of interaction with warfarin	Resulting interaction	Documented reports	Potential interactions
Unknown	Decreased INR	Ginseng, St John's Wort	–
Unknown	Increased INR	Papain	–
Contain vitamin K derivatives	Decreased INR	Coenzyme Q	–
Contain coumarin derivatives	Increased INR	Dan shen *(salvia)* Dong quai *(Angelica)*	Alfalfa Anise Arnica Artemesia Celery Chamomile Fenugreek Horse chestnut Licorice Parsley Passionflower Prickly ash Quassia Red clover Sweet woodruff Tonka beans
Inhibition of platelet aggregation	Increased risk of bleeding	Garlic, Ginkgo	Cassio Clove Feverfew Ginger Onion Turmeric
Contain salicylate derivatives	Increased risk of bleeding	–	Meadowsweet Poplar Willow bark

Table 3. *Resources for Herbal Product Drug Interactions with Warfarin*

	Website
Information on dietary supplements	
The Natural Pharmacist	www.tnp.com
The Pharmacist's Letter	www.naturalpharmacist.com
National Institutes of Health	http://dietary-supplements.info.nih.gov
Reporting adverse events	
Special Nutritionals Adverse Event Monitoring System	http://vm.cfsan.fda.gov
MEDWATCH Reporting	www.fda.gov/medwatch

Several on-line resources are available to answer practitioner questions about herbal products (Table 3). In addition, the FDA MedWatch program, contacted directly or through the Center for Food Safety and Applied Nutrition, can be used to report adverse effects associated with herbal medicinals, including drug interactions.

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