The Interface

WARFARIN AND ANTIDEPRESSANTS: Happiness without Hemorrhaging

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

ABSTRACT

Warfarin, a commonly prescribed anticoagulant, has a very narrow therapeutic index. Because a multitude of drugs may potentially alter warfarin levels, primarily through the cytochrome P-450 isoenzyme system, in this edition of The Interface, we explore drug interactions between warfarin and the antidepressants. According to the available data, sertraline and citalopram appear to be the safest antidepressants to use in patients on warfarin, whereas fluvoxamine and fluoxetine pose the highest potential risks. The remaining antidepressants appear to lie somewhere in between, with most having little empirical data to guide the practitioner other than the *potential* interactions of these drugs and warfarin in the cytochrome P-450 isoenzyme system.

KEY WORDS

warfarin, antidepressant, SSRI, SNRI, tricyclics, drug-drug interaction

INTRODUCTION

Warfarin (Coumadin™, Jantoven™) is an oral coumarin anticoagulant that is used to prevent and treat various thromboembolic disorders (e.g., deep venous thrombosis, pulmonary embolism, prophylaxis against coronary artery thrombosis following acute myocardial infarction, prophylaxis against cardioembolic stroke in patients with atrial fibrillation).[1] Because of its clinical indications, warfarin tends to be used in older populations. According to the US Food and Drug Administration (FDA), approximately two million people in the US are annually prescribed warfarin, indicating that it is a widespread medication.[2] Because warfarin has a narrow therapeutic index, in this edition of The Interface, we describe the potential for drug interactions between warfarin and the antidepressant drugs.

CLINICAL PHARMACOLOGY OF WARFARIN

Warfarin was initially approved by the Food and Drug Administration in 1954 as an anticoagulant and has been medically available for over 60 years.[1] In terms of its mechanism of action, warfarin effectively produces anticoagulation by impeding vitamin K metabolism,

which is necessary for the synthesis of several hepatic clotting factors. The drug consists of a racemic mixture of S-warfarin and R-warfarin.[1] While both isomers are clinically active, the S-isomer is 3 to 5 times more potent than the R-isomer.[1,3]

POTENTIAL FOR DRUG INTERACTIONS: PROTEIN BINDING

From the perspective of potential drug interactions with the antidepressants, two theoretical possibilities must be considered. First, because warfarin is highly protein bound, coadministered drugs that are also highly protein bound could hypothetically displace warfarin from its binding sites, thereby increasing serum levels and enhancing anticoagulation. However, according to Sayal et al,[3] there is little clinical evidence that this pharmacodynamic scenario genuinely contributes to meaningful drug interactions with warfarin.

POTENTIAL FOR DRUG INTERACTIONS: CYTOCHROME P-450 ISOENZYME SYSTEM

A second possibility for potential drug interactions relates to the hepatic cytochrome P-450 isoenzyme system. The biological function of this system, which is composed of a myriad of various isoenzymes, is to oxidize and prepare compounds for elimination from the body.[4] While more than 40 hepatic isoenzymes have been identified, the majority play minor roles in the metabolism of most compounds. In accordance with this observation, according to Cozza and Armstrong,[4] only six isoenzymes (1A2, 3A4, 2C9, 2C19, 2D6, 2E1) account for the metabolic clearance of more than 90 percent of all drugs.

When exposed to a specific drug, individual cytochrome P-450 isoenzymes may be 1) unaffected and perform their oxidative function as designated, 2) induced and hastened in their metabolic activity, or 3) inhibited and slowed in their metabolic activity. When an isoenzyme undergoes induction, then coadministered drugs that utilize the isoenzyme will undergo an increase in their rate of elimination. When an isoenzyme undergoes inhibition, then coadministered drugs that utilize the isoenzyme will experience a decrease in their rate of elimination. (Antidepressants may be inhibitors of isoenzymes, but we are not aware of any that cause induction of isoenzymes.)

To return to our discussion about the pharmacokinetics of warfarin, the S-isomer (the more potent of the two) is metabolized by the 2C9 isoenzyme whereas the R-isomer is metabolized by the 1A2 isoenzyme (major route) as well as the 2C19 and 3A4 isoenzymes (minor routes).[3] Because the 2C9 isoenzyme relates to the metabolism of the more potent isomer, this is likely to be the primary isoenzyme of interaction relevance, followed by the 1A2 isoenzyme.

ANTIDEPRESSANTS AND THEIR INFLUENCES ON THE CYTOCHROME P-450 ISOENZYMES

Because potential drug interactions via the cytochrome P-450 isoenzyme system are clinically relevant to warfarin, we next examine the potential influences of antidepressants on specific isoenzymes. The inhibition potentials on the cytochrome P-450 isoenzymes by nontricyclic antidepressants, according to Preskorn, Borges-Gonzalez, and Flockhart[5] and Cozza and Armstrong,[4] are shown in Table 1.[5] (Note that the table also includes the interaction risk according to Lexi-Comp Online[6] and Clinical Psychopharmacology.[1])

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Selective serotonin reuptake inhibitors (SSRIs) are extremely popular in clinical practice because of their clinical tolerability and broad efficacy. As we examine the cytochrome P-450 isoenzyme data for SSRIs, note that each potentially inhibits a different collection of isoenzymes. Again, the isoenzymes of relevance for warfarin metabolism are the 2C9 and the 1A2.

Fluvoxamine, fluoxetine. According to the data in Table 1, both fluvoxamine and fluoxetine appear to harbor the highest potential risk for inhibiting warfarin metabolism. According to Sayal et al,[3] this mirrors the conclusion of *in-vitro* studies with SSRIs, which indicate that fluvoxamine exhibits the highest potential for the inhibition of warfarin through the 2C9 isoenzyme, followed by fluoxetine.[7] In this regard, Hemeryck et al[8] found, via *in-vitro* examination, that fluvoxamine markedly inhibited the metabolism of warfarin, and there is a case report of a warfarin/fluvoxamine interaction.[9] In addition, case reports support the theoretical and *in-vitro* risks of prescribing fluoxetine[10–13] to patients who are taking warfarin, although a study by Ford et al[14] found no significant changes in prothrombin times in participants taking fluoxetine 20mg per day for three weeks.

Paroxetine. Bannister et al[15] examined the coadministration of paroxetine and warfarin in human subjects and noted mild yet

TABLE 1. NONTRICYCLIC ANTIDEPRESSANTS AND THEIR RISKS OF INTERACTION WITH WARFARIN

Antidepressant	Potential Inhibition Effects on Cytochrome P-450 Isoenzymes*					Risk of Warfarin Interaction According to Lexi-Comp Online[6]	Risk of Warfarin Interaction from Clinical Psychopharmacology[1]
	1A2	2C9/10	2C19	2D6	3A3/4		
SSRIs							
Sertraline	--	--	--	+	--	C = monitor therapy	May ↑ PT(not clinically significance)
Citalopram/ Escitalopram	--	--	--	++	--	C = monitor therapy	May ↑ PT (not clinically significant)
Paroxetine	--	--	--	+++	--	C = monitor therapy	May ↑ bleeding
Fluvoxamine	+++	+++	+++	--	++	C = monitor therapy	May ↑ INR
Fluoxetine	--	++	++	+++	+	C = monitor therapy	Avoid with warfarin
SNRIs							
Venlafaxine	--	--	--	--	--	No listing	May ↑ INR/PT
Duloxetine	--	--	--	++	--	D = consider therapy modification	--
Other							
Bupropion	unknown	unknown	unknown	+++	unknown	No listing	May ↑ INR/PT
Mirtazapine	unknown	unknown	unknown	unknown	unknown	No listing	--

*All data from Preskorn et al[5] except for data for mirtazapine, which is from Cozza et al[4]

KEY: -- = no effect; + = mild effect; ++ = moderate effect; +++ = substantial effect

NOTE: Gray shaded areas under specific cytochrome P-450 isoenzymes represent the major routes of warfarin metabolism; INR = international normalized ratio; PT = prothrombin time; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

clinically significant bleeding in 5 of 27 subjects after several days of combined treatment. They cautiously concluded that, "an increased bleeding tendency [may occur with] the coadministration of paroxetine and warfarin."

Sertraline, citalopram. As for the remaining SSRIs, Apseloff et al[16] examined the potential interaction between warfarin and sertraline. Although prothrombin times were increased after 22 days of sertraline exposure, the change was not deemed clinically meaningful. Similar findings have been reported with citalopram.[17,18] Therefore, among the SSRIs, both sertraline and citalopram appear to be the safest to prescribe in patients who are taking warfarin.

Summary of the SSRIs. From a conservative perspective, the SSRIs least likely to cause drug interactions with warfarin appear to be sertraline and citalopram. Paroxetine appears to have low-to-moderate risk, whereas fluvoxamine and fluoxetine are most likely to increase or enhance the effects of warfarin.

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS

Venlafaxine. Venlafaxine is a mixed action antidepressant that has pronounced serotonergic effects at lower doses, noradrenergic effects at moderate doses, and dopaminergic effects at high doses. According to Sayal et al,[3] venlafaxine does not appear to have any inhibition effect on the relevant cytochrome P-450 isoenzymes that are related to warfarin metabolism and "can be assumed" to have a low risk with coadministration. However, warfarin enhancement has been reported when venlafaxine was added to established warfarin therapy.[1]

Desvenlafaxine. Desvenlafaxine is the active metabolite of venlafaxine. Therefore, it is reasonable to assume that its metabolic effects on the cytochrome P-450 isoenzymes are subsumed by venlafaxine and to tentatively conclude a low risk of interaction between desvenlafaxine and warfarin, as well.

Duloxetine. Duloxetine is also an inhibitor of serotonin and norepinephrine.[1] Like venlafaxine, duloxetine does not appear to affect the cytochrome P-450 isoenzymes relevant to the metabolism of warfarin. Therefore, there should theoretically be minimal risk. However, there is at least one case report of duloxetine decreasing the effects of warfarin[19] and a second case report of this antidepressant increasing the effects of warfarin.[20] Being a relatively new antidepressant, only continued observation will reveal if duloxetine is potentially problematic or not when added to warfarin.

OTHER ANTIDEPRESSANTS

Mirtazapine. Mirtazapine has effects on both serotonin and norepinephrine, but is not a genuine reuptake inhibitor.[1] According to Spina et al,[21] mirtazapine has "minimal inhibitory effects" on the major cytochrome P-450 isoenzymes and therefore is suspected to have a low risk for drug interactions. Like Sayal et al,[3] we were unable to find any published data on interactions between mirtazapine and warfarin, although caution is advised.

Bupropion. Bupropion inhibits the reuptake of dopamine and norepinephrine. Although we could locate no empirical data, according to Clinical Pharmacology, "Altered PT and/or INR [international normalized ratio]…was observed when bupropion was coadministered with warfarin during clinical trials and post-marketing experience."[1]

TRICYCLIC ANTIDEPRESSANTS

While tricyclic antidepressants (TCAs) have been available for prescription for nearly 60 years, their use has been curtailed because of newer and safer antidepressants. In addition, the use of TCAs in cardiac patients is fraught with potential complications because of their antimuscarinic and quinidine-like properties.[3] While studies with regard to warfarin interactions are limited, Loomis and Racz[22] examined the effects of amitriptyline and nortriptyline in rats. These investigators noted a dose-dependent increase in prothrombin time, which correlated with increases in the plasma half-life of warfarin. Nortriptyline produced greater effects on warfarin metabolism than amitriptyline.

Pond et al[23] explored in human beings the effects of warfarin metabolism when coadministered with either amitriptyline or nortriptyline. These investigators found no alteration in the plasma half-life of warfarin following chronic treatment with the antidepressant dosages used in this study. In drawing conclusions from these two studies, it appears that TCAs have the potential to increase warfarin effects, but perhaps not at the usual doses prescribed.

CAVEATS

While the preceding conclusions are proposed as general guides, they are not absolute in nature. All patients taking warfarin who begin treatment with an antidepressant need to have regular INRs to observe for any interaction. Note that the risk of antidepressant

interactions may be most relevant for individuals already taking warfarin (i.e., the warfarin dose and effects have already been established); if antidepressant-induced inhibition occurs, the effects of warfarin will be enhanced. For those already on antidepressants, the addition of warfarin and potential inhibition effects will be accounted for in the early stages of titration of the anticoagulant.

CONCLUSIONS

Clearly, there is limited empirical data on the possible drug interactions between warfarin and the antidepressants. In addition, much of the available data consists of either *in-vitro* studies or sporadic case reports. In examining the overall available information, it appears that both sertraline and citalopram have minimal effects on the cytochrome P-450 isoenzymes that are chiefly responsible for the metabolism of warfarin and both have reasonable empirical studies that implicate safety. Therefore, at the present time, sertraline and citalopram appear to be the safest antidepressants to prescribe with warfarin.

In contrast, the antidepressants with the most convincing risks with warfarin are fluvoxamine and fluoxetine. Ironically, among the newer antidepressants, the SSRIs offer both the safest as well as the riskiest antidepressant options.

The remaining antidepressants genuinely warrant further investigation, although several may pose minimal risk given their potential effects on the cytochrome P-450 isoenzyme system.

Regardless of the available data and their possible implications, patients who are prescribed warfarin and an antidepressant warrant careful monitoring of their coagulation status. Clearly, we clinicians want to offer the best benefit (happiness) with the lowest risk (avoidance of hemorrhage).

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