

Antimicrobial Drug Interactions and Warfarin

DRUG CLASS	EFFECT ON WARFARIN/ MECHANISM	RECOMMENDATION/ COMMENTS
Azole antifungals Fluconazole (<i>Diflucan</i>) Itraconazole (<i>Sporanox</i>) Ketoconazole (<i>Nizoral</i>) Miconazole (<i>Monistat</i>) Posaconazole (<i>Noxafil</i> [U.S.], <i>Posanol</i> [Canada]) Voriconazole (<i>Vfend</i>)	<u>Increased response</u> due to inhibition of warfarin metabolism. ^{1,2}	<ul style="list-style-type: none"> •Increased INR also reported with intravaginal and topical miconazole.^{2-4,19} INR can be increased significantly with single doses of fluconazole.²³ •Dose-related interaction, but can be seen with lower doses. •Monitor INR when therapy started, stopped, or dose changed.^{a,b,c} Some clinicians consider empirically lowering the warfarin dose by about 25%.²⁵
Cephalosporins	Second- and third-generation cephalosporins might <u>increase the effect</u> of warfarin by inhibiting the production of vitamin K-dependent clotting factors and other mechanisms. ^{5,6,20}	<ul style="list-style-type: none"> •Oral cephalosporins such as cefaclor, cefixime, cefpodoxime, cefuroxime have generally not been shown to interact with warfarin.^{2,21} •Avoid use of cefotetan. It can increase INR directly.⁶ •Consider monitoring INR when therapy started or stopped.^{a,b,c}
Fluoroquinolones Ciprofloxacin (<i>Cipro</i>) Gemifloxacin (<i>Factive</i>) Levofloxacin (<i>Levaquin</i>) Moxifloxacin (<i>Avelox</i>) Norfloxacin (<i>Noroxin</i>) Ofloxacin (<i>Floxin</i>)	<u>Increased response</u> possibly due to inhibition of warfarin metabolism, displacement of warfarin from protein binding sites, or disruption of intestinal flora that contribute to vitamin K synthesis. ⁷	<ul style="list-style-type: none"> •Increase in INR is typically seen within first week of quinolone therapy.⁷ •Monitor INR when any fluoroquinolone started or stopped.^{a,b,c}
Griseofulvin (<i>Fulvicin</i> , etc)	<u>Decreased response</u> possibly due to induced hepatic metabolism. ⁸	<ul style="list-style-type: none"> •Effect on warfarin is gradual. Maximum effect might not be seen for several weeks or more. •Monitor INR when therapy started, stopped, or dose changed. Continue to monitor until INR stable.^{a,b,c}
Isoniazid	<u>Increased response</u> possibly due to inhibition of warfarin metabolism. ⁹	<ul style="list-style-type: none"> •Slow INH acetylators are at greatest risk.⁹ •Monitor INR when therapy started, stopped, or dose changed.^{a,b,c}

More . . .

DRUG CLASS	EFFECT ON WARFARIN/ MECHANISM	RECOMMENDATION/ COMMENTS
Macrolides Azithromycin (<i>Zithromax</i>) Clarithromycin (<i>Biaxin</i>) Erythromycin	Macrolides can <u>increase the effect</u> of warfarin through inhibition of hepatic metabolism of warfarin. ² (Azithromycin affects warfarin by an unknown mechanism.)	<ul style="list-style-type: none"> •Increased INR reported with all macrolides. Strongest evidence with erythromycin.² Increased INR reported with ophthalmic erythromycin.²¹ •Monitor INR when any macrolide is started or stopped.^{a,b,c}
Metronidazole (<i>Flagyl</i>)	<u>Increased response</u> caused by inhibition of metabolism of warfarin. ⁵	<ul style="list-style-type: none"> •Avoid use if possible. Metronidazole can dramatically increase INR.²⁵ Topical preparations are less of a problem due to minimal systemic absorption. •If used, monitor INR closely when therapy started or stopped.^{a,b,c} Some clinicians consider empirically lowering the warfarin dose by 25% to 40%.²⁵
Penicillins	High doses of IV penicillins <u>increase the risk</u> of warfarin-associated bleeding by inhibiting platelet function. ⁵ Oral amoxicillin and amoxicillin/clavulanic acid may increase the risk of bleeding with warfarin. ^{22,24} Exception: <u>Decreased response</u> seen with dicloxacillin and nafcillin possibly due to enhanced metabolism of warfarin. ¹⁰	<ul style="list-style-type: none"> •Oral penicillin G or V and ampicillin do not appear to interact with warfarin.² •Monitor INR several days after start of dicloxacillin or nafcillin, and again after treatment ends. Effects might persist for weeks after dicloxacillin or nafcillin is discontinued.^{10,11} • For high-dose IV penicillins and amoxicillin or amoxicillin/clavulanic acid, monitor INR when therapy started or stopped.^{a,b,c}
Rifampin (<i>Rifadin</i>) Rifabutin (<i>Mycobutin</i>)	<u>Decreased response</u> due to increased hepatic clearance of warfarin. ⁵	<ul style="list-style-type: none"> •Avoid use if possible. •Effect usually seen within one to three weeks after starting rifampin.^{12,24} •If used, monitor INR closely for at least two weeks when therapy is started, stopped, or dose is changed.¹² Some clinicians consider empirically increasing the dose of warfarin by 25% to 50%.²⁵ •It can take more than a month after rifampin is stopped for warfarin metabolism to normalize.²⁷ Check INR at least weekly until stable.²⁵

DRUG CLASS	EFFECT ON WARFARIN/ MECHANISM	RECOMMENDATION/ COMMENTS
Sulfonamides Sulfamethoxazole, Sulfisoxazole, etc.	<u>Increased effect</u> resulting from reduced warfarin clearance, displacement of warfarin from protein binding sites, alterations in gut flora. ^{5,13}	<ul style="list-style-type: none"> •Increased INR reported with TMP/SMX, sulfamethoxazole, sulfisoxazole.² (Including with 3-day courses of TMP/SMX for acute cystitis.)¹⁸ •Avoid use if possible. A case study showed a more than three-fold increase in INR after six days of concomitant therapy with TMP/SMX.¹³ Increased risk of bleeding may be especially significant in the elderly.²⁶ •If used, monitor INR when therapy is started or stopped.^{a,b,c} Some clinicians consider empirically lowering the warfarin dose by 25% to 40%.²⁵
Telithromycin (<i>Ketek</i>)	<u>Increased effect</u> likely due to reduced hepatic metabolism of warfarin. ¹⁴	<ul style="list-style-type: none"> •Monitor INR closely when telithromycin is started or stopped. A case report noted an increase in INR over the first five days of concomitant therapy.¹⁴
Tetracyclines Doxycycline Minocycline Tetracycline	<u>Increased response</u> due to unknown mechanisms. ¹⁵	<ul style="list-style-type: none"> •Increased INR seen with doxycycline and tetracycline.^{2,15} •Monitor INR when therapy with any tetracycline is started or stopped.^{a,b,c}

a. Potentiation or reduction of warfarin effect following inhibition or induction of metabolism can take several days.^{16,25,26} Sensitivity of patients to drug interactions can vary in terms of magnitude of response, time of onset, and duration of interaction's effect.¹⁷ Some clinicians recommend checking INR about five days after start of interacting drug, and then adjusting warfarin dose as needed.

b. Prolonged fever can increase sensitivity to warfarin by enhancing the breakdown of vitamin K-dependent clotting factors.^{16,17}

c. Factors that increase the risk of bleeding in warfarin patients include advanced age, history of GI bleeding, hypertension, cerebrovascular disease, severe heart disease, concurrent use of interacting drugs, alcohol abuse, liver disease, and renal insufficiency.¹⁶

Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Project Leader in preparation of this PL Detail-Document: Stacy A. Hester, R.Ph., BCPS, Assistant Editor

References

1. Purkins L, Wood N, Kleinermans D, Nichols D. Voriconazole potentiates warfarin-induced prothrombin time prolongation. *Br J Clin Pharmacol* 2003;56 Suppl 1:24-9.
2. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005;165:1095-106.
3. Devaraj A, O'Beirne JP, Veasey R, Dunk AA. Interaction between warfarin and topical miconazole cream. *BMJ* 2002;325:77.
4. Thirion DJ, Zanetti LA. Potentiation of warfarin's hypoprothrombinemic effect with miconazole vaginal suppositories. *Pharmacotherapy* 2000;20:98-9.
5. Ansell J, Hirsh H, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 Suppl):160S-98S.
6. Pai MP, Momary KM, Rodvold KA. Antibiotic drug interactions. *Med Clin North Am* 2006;90:1223-55.
7. Carroll DN, Carroll DG. Interactions between warfarin and three commonly prescribed fluoroquinolones. *Ann Pharmacother* 2008;42:680-5.
8. Wells PS, Holbrook AM, Crowther NR, Hirsh J. Interactions of warfarin with drugs and food. *Ann Intern Med* 1994;121:676-83.
9. Self TH, Chrisman CR, Baciewicz AM, Bronze MS. Isoniazid drug and food interactions. *Am J Med Sci* 1999;31:304-11.
10. Kim KY, Frey RJ, Epplen K, Foruhari F. Interaction between warfarin and nafcillin: case report and review of the literature. *Pharmacotherapy* 2007;27:1467-70.
11. Mailloux AT, Gidal BE, Sorkness CA. Potential interaction between warfarin and dicloxacillin. *Ann Pharmacother* 1996;30:1402-7.
12. Kim KY, Epplen K, Foruhari F, Alexandropoulos H. Update on the interaction of rifampin and warfarin. *Prog Cardiovasc Nurs* 2007;22:97-100.
13. Weinberg AD, Altman JS, Pals JK. Quality improvement case study: warfarin sodium interactions. *J Am Med Dir Assoc* 2006;7:315-8.
14. Kolilekas L, Anagnostopoulos GK, Lampaditis I, Eleftheriadis I. Potential interaction between telithromycin and warfarin. *Ann Pharmacother* 2004;38:1424-7.
15. Tetracyclines [last updated January 12, 2010]. Baxter K (ed), Stockley's Drug Interactions. [online] London: Pharmaceutical Press
<http://www.medicinescomplete.com/>. (Accessed July 19, 2012).
16. Witt DM, Tillman DJ. Thrombosis. Module I Cardiovascular. Pharmacotherapy Self-Assessment Program, 4th edition. Kansas City, MO: American College of Clinical Pharmacy.
17. Wittkowsky AK. Thrombosis. Applied Therapeutics. The Clinical Use of Drugs. 6th ed. Vancouver, WA: Applied Therapeutics, Inc.
18. Greenlaw CW. Drug interaction between cotrimoxazole and warfarin. *Am J Hosp Pharm* 1979;36:1155-6.
19. Kovac M, Mitic G, Kovac Z. Miconazole and nystatin used as topical antifungal drugs interact equally strongly with warfarin. *J Clin Pharm Ther* 2012;37:45-8.
20. Bohm NM, Crosby B. Hemarthrosis in a patient on warfarin receiving ceftaroline: a case report and brief review of cephalosporin interactions with warfarin. *Ann Pharmacother* 2012;doi:10.1345/aph.1Q771.
21. Parker DL, Hoffmann TK, Tucker MA, et al. Elevated International Normalized Ratio associated with concurrent use of ophthalmic erythromycin and warfarin. *Am J Health Syst Pharm* 2010;67:38-41.
22. Zhang Q, Simoneau G, Verstuyft C, et al. Amoxicillin/clavulanic acid-warfarin drug interaction: a randomized controlled trial. *Br J Clin Pharmacol* 2011;71:232-6.
23. Turrentine MA. Single-dose fluconazole for vulvovaginal candidiasis: impact on prothrombin time in women taking warfarin. *Obstet Gynecol* 2006;107(2 Pt 1):310-3.
24. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 Suppl):e152S-84S.
25. Bungard TJ, Yakiwchuk E, Foisy M, Brocklebank C. Drug interactions involving warfarin: practice tool and practical management tips. *CPJ/RPC* 2011;144:21-34.
26. Schelleman H, Bilker WB, Brensinger CM, et al. Warfarin-fluoroquinolones, sulfonamides, or azole antifungals interactions and the risk of hospitalization for gastrointestinal bleeding. *Clin Pharmacol Ther* 2008;84:581-8.
27. Krajewski KC. Inability to achieve a therapeutic INR value while on concurrent warfarin and rifampin. *J Clin Pharmacol* 2010;50:710-3.

Cite this document as follows: *PL Detail-Documents, Antimicrobial Drug Interactions and Warfarin. Pharmacist's Letter/Prescriber's Letter. August 2012.*



Evidence and Recommendations You Can Trust...



3120 West March Lane, P.O. Box 8190, Stockton, CA 95208 ~ TEL (209) 472-2240 ~ FAX (209) 472-2249
Copyright © 2012 by Therapeutic Research Center

Subscribers to the *Letter* can get *PL Detail-Documents*, like this one, on any topic covered in any issue by going to www.pharmacistsletter.com, www.prescribersletter.com, or www.pharmacytechniciansletter.com