Antimicrobial Drug Interactions and Warfarin

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| Azole antifungals | **Increased response due to inhibition of warfarin metabolism.**<sup>1,2</sup>                | • Increased INR also reported with intravaginal and topical miconazole. INR can be increased significantly with single doses of fluconazole.  
• Dose-related interaction, but can be seen with lower doses.  
• Monitor INR when therapy started, stopped, or dose changed.  
Some clinicians consider empirically lowering the warfarin dose by about 25%.<sup>25</sup> |
| Cephalosporins   | Second- and third-generation cephalosporins might increase the effect of warfarin by inhibiting the production of vitamin K-dependent clotting factors and other mechanisms.<sup>5,6,20</sup> | • Oral cephalosporins such as cefaclor, cefixime, cefpodoxime, cefuroxime have generally not been shown to interact with warfarin.<sup>2,21</sup>  
• **Avoid use of** cefotetan. It can increase INR directly.<sup>6</sup>  
• Consider monitoring INR when therapy started or stopped.<sup>a,b,c</sup> |
| Fluoroquinolones | **Increased response 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.**<sup>7</sup> | • Increase in INR is typically seen within first week of quinolone therapy.<sup>7</sup>  
• Monitor INR when any fluoroquinolone started or stopped.<sup>a,b,c</sup> |
| Griseofulvin     | **Decreased response possibly due to induced hepatic metabolism.**<sup>8</sup>                 | • 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.<sup>a,b,c</sup> |
| Isoniazid        | **Increased response possibly due to inhibition of warfarin metabolism.**<sup>9</sup>          | • Slow INH acetylators are at greatest risk.<sup>9</sup>  
• Monitor INR when therapy started, stopped, or dose changed.<sup>a,b,c</sup> |
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| Macrolides | Erythromycin | Increased INR reported with all macrolides. Strongest evidence with erythromycin. Increased INR reported with ophthalmic erythromycin. Monitor INR when any macrolide is started or stopped.²,³,⁴,⁵  
Azithromycin (Zithromax)  
Clarithromycin (Biaxin) |  
Macrolides can increase the effect of warfarin through inhibition of hepatic metabolism of warfarin.² (Azithromycin affects warfarin by an unknown mechanism.) |
| Metronidazole | Increased response caused by inhibition of metabolism of warfarin.⁵ | Avoid use if possible. Metronidazole can dramatically increase INR.⁶  
Topical preparations are less of a problem due to minimal systemic absorption.  
If used, monitor INR closely when therapy started or stopped.²,³,⁴ Some clinicians consider empirically lowering the warfarin dose by 25% to 40%.⁵ |
| Penicillins | High doses of IV penicillins increase the risk 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 | 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.²,³,⁴,⁵ |
| Rifampin | Decreased response due to increased hepatic clearance of warfarin.⁵ | 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 |
| (Rifadin) |  
Rifabutin (Mycobutin) |  
Exception: Decreased response seen with dicloxacillin and nafcillin possibly due to enhanced metabolism of warfarin.¹⁰ |
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| Sulfonylamides   | Increased effect resulting from reduced warfarin clearance, displacement of warfarin from protein binding sites, alterations in gut flora.⁵,¹³ | • Increased INR reported with TMP/SMX, sulfamethoxazole, sulfisoxazole.⁷ (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.⁵  
Some clinicians consider empirically lowering the warfarin dose by 25% to 40%.²⁵ |
| Telithromycin (Ketek) | Increased effect likely due to reduced hepatic metabolism of warfarin.¹⁴ | • 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    | Increased response due to unknown mechanisms.¹⁵                                              | • Increased INR seen with doxycycline and tetracycline.²,¹⁵  
• Monitor INR when therapy with any tetracycline is started or stopped.⁴,²⁶,³⁴ |

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

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References


