



Enhanced Warfarin Response and Antibiotics

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Warfarin has been reported to interact with more than 100 drugs, including many antibiotics. Warfarin is a racemic mixture of S- and R-warfarin enantiomers. S-warfarin is considered to have several times more anticoagulant activity than R-warfarin. S-warfarin is primarily metabolized by CYP2C9, whereas R-warfarin is metabolized by CYP1A2, CYP2C19, and CYP3A4. Thus, one would expect that drugs inhibiting CYP2C9, and therefore S-warfarin metabolism, would increase the concentration of warfarin and enhance its anticoagulant effect (Table).

Other antibiotics have been reported to increase warfarin response. Some—such as moxalactam, cefoperazone, cefamandole, cefotetan, and cefmetazole—appear to inhibit the formation of clotting factors and indirectly increase the effect of warfarin. As with the antibiotics that are inhibitors of CYP2C9, there may be a reasonable mechanism for these purported inter-

actions. For the majority of antibiotics associated with warfarin interactions, however, there is no obvious mechanism for the interaction.

Positive interaction reports usually come in the form of case reports from infected patients, whereas controlled, prospective trials with healthy subjects fail to demonstrate any interaction. Unfortunately, authors of case reports often fail to consider all the potential variables known to influence warfarin response. In addition to enzyme inhibition, case reports typically accuse the antibiotic of displacing warfarin from protein binding or impairing vitamin K production by gastrointestinal (GI) flora as the mechanism responsible for the interaction.

Recently, protein-binding displacement of warfarin by the antibiotic has become less commonly invoked as a mechanism. More authors understand that protein-binding displacement rarely will result in a change in the concentration of unbound drug and thus will not alter its pharmacologic response. Protein displacement will result in an increased percentage of unbound drug, but increased warfarin clearance, as more unbound drug becomes available to enzymes, prevents an increased concentration of unbound drug. Thus, any increase in warfarin effect usually is transient and of little clinical relevance.

Antibiotic-impaired production of vitamin K by the inhibition of GI flora is a possible mechanism. It would be unlikely, however, to alter the response to warfarin in patients eating a normal diet. The typical diet contains approximately 300 to 500 mcg/d of vitamin K. It has been estimated that a chronic change of about 250 mcg/d would be required to alter the response to warfarin.¹ Yet, it is possible that, during periods of low dietary vitamin K intake, GI flora could become more important as a source of vitamin K.

It is important to note that most of the antibiotics reported to alter warfarin response do so only in patients with infections (case reports) and often have no discernible effect when tested in healthy subjects. Infected patients may eat fewer leafy green vegetables. Antibiotic therapy, particularly if it is long term, could reduce GI flora vitamin K production and lead to increased warfarin effect.

Another potential mechanism rarely considered in case reports is the effect on warfarin metabolism of the infection and the immune response to that infection. It has been established that stimulation of the immune system by infection or inflammation can inhibit the activity of several drug-metabolizing enzymes, including CYP2C9.^{2,3} Cytokines, such as tumor necrosis factor and interleukins, can down-regulate cytochrome P-450 enzymes, thereby decreasing enzyme activity. The administration of influenza vaccine has been associated with an increased warfarin effect.⁴ Vaccinations have been associated with reduced theophylline and carbamazepine metabolism.

For antibiotics that are not CYP2C9 inhibitors, the enhanced anticoagulant effect observed during anti-infective therapy may be due to a combination of mechanisms. A patient with an infection will have a stimulated cytokine response, inhibiting the normal ability to metabolize warfarin. With the addition of a reduced vitamin K supply from appetite suppression, and perhaps some antibiotic-induced suppression of GI flora vitamin K production, it is conceivable that a preinfection dose of warfarin could become excessive. By considering the known effects of infection on vitamin K intake and warfarin metabolism, most cases of antibiotic warfarin interactions can be explained without invoking mechanisms of enzyme inhibition or protein-binding displacement. 

Table

Anti-Infective Agents Known to Inhibit CYP2C9

Sulfamethoxazole/trimethoprim
Chloramphenicol
Delavirdine (Rescriptor)
Efavirenz (Sustiva)
Fluconazole (Diflucan)
Isoniazid (INH)
Metronidazole (Flagyl)
Miconazole (Monistat)
Sulfamethizole (Urobiotic)
Sulfamethoxazole (Bactrim, Septra)
Voriconazole (Vfend)

Adapted from Hansten PD, Horn JR. The Top 100 Drug Interactions: A Guide to Patient Management. Edmonds, Wash: H&H Publications; 2004:157-169.