

More Evidence of a Warfarin–Antibiotic Interaction

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Several years ago, this column reviewed the topic of drug interactions between antibiotics and warfarin.¹ We discussed the role of antibiotics that inhibit the metabolism of warfarin, primarily inhibitors of the cytochrome P (CYP) 450 enzyme CYP2C9, such as fluconazole (Diflucan) and sulfamethoxazole/trimethoprim (Bactrim). These antibiotics can predictably inhibit warfarin clearance and cause hypoprothrombinemia. In addition, many other antibiotics have been noted in case reports to be associated with elevated international normalized ratio (INR) values in patients taking warfarin.

In our previous review, we summarized data showing that the infection itself can affect warfarin metabolism leading to higher INR values. The mechanism appears to be via stimulation of the immune system, resulting in secretion of proinflammatory cytokines, such as tumor necrosis factor and interleukin. This intrinsic inhibition of warfarin metabolism combined with dietary changes (reduced vitamin K intake) often associated with bacterial or viral infections may account for the reported increases in INR noted in the antibiotic–warfarin case reports.

Recently, the FDA approved label revisions for azithromycin (Zithromax), warning of a potential interaction with warfarin.² The FDA notice reported that a study of 22 healthy patients administered a 5-day course of azithromycin found no change in prothrombin time. The label also notes that azithromycin

did not alter sulfamethoxazole (primarily metabolized by CYP2C9) plasma concentrations. Others have reported a lack of effect of azithromycin on INRs in patients stabilized on warfarin.^{3,4}

The FDA also cites postmarketing case reports of elevated INRs in patients receiving azithromycin and warfarin, however. Indeed, several case reports have been published of a purported interaction between azithromycin and warfarin.⁵⁻⁷ These case reports were reviewed, and the issue of infection-induced changes in warfarin discussed in a brief review.⁸ More recent reviews also have found azithromycin to be devoid of any appreciable effects on cytochrome P450 enzymes.⁹ Although it appears that the data demonstrating inhibition of warfarin metabolism by inflammatory mediators present during infective processes are not reaching a wide audience, no direct data exist supporting the effect of infection on INRs.

Perhaps all antibiotics should carry a warning in their labels of the potential for enhanced warfarin effect.

Designing a study to show the effect of infection on patients taking warfarin would seem to require a group of infected patients not treated with antibiotics. Fortunately, an alternative study design was developed comparing gastrointestinal (GI) bleeding episodes in warfarin users.¹⁰ The association between GI bleeding and exposure to ciprofloxacin, levofloxacin, gatifloxacin, sulfamethoxazole/trimethoprim, or fluconazole versus no exposure or the use of cephalexin was estimated. Cephalexin is not expected to alter warfarin metabolism.

The study found that exposure to all of the antibiotics was associated with a higher risk to develop GI bleeding. When the risk was adjusted for confounders, however—including using cephalexin as a reference group to adjust for the presence of infection—the only antibiotics that showed a significant effect were fluconazole and sulfamethoxazole/trimethoprim. These 2 antibiotics are known inhibitors of CYP2C9 and would be expected to increase the risk of bleeding episodes.

It appears that patients stabilized on warfarin are at increased risk to develop hypoprothrombinemia and perhaps a bleeding episode if they develop an infection or other disease precipitating an inflammatory response. The label for azithromycin notes that, “The FDA advises that prothrombin times be carefully monitored in patients receiving azithromycin with oral anticoagulants.” This would appear to be an appropriate caution. The statement that azithromycin may potentiate the effects of oral anticoagulants seems at odds with the evidence, however.

Practitioners monitoring patients taking warfarin need to be aware of the potential for infection or other sources of inflammation to inhibit the metabolism of warfarin. The magnitude of this inhibition will probably vary based on the etiology of the inflammatory response and each patient’s immune reactivity. Even a modest inhibition in warfarin metabolism might lead to a considerable risk of bleeding, if accompanied by a change in diet with reduced vitamin K intake. Perhaps all antibiotics should carry a warning in their labels of the potential for enhanced warfarin effect. This would appear, in most cases, to be a disease–drug interaction rather than a drug–drug interaction. ■