ALTERNATIVE VIEWPOINTS

Azithromycin-Warfarin Interaction: Are We Fishing with a Red Herring?

Gregory Eschenauer, Pharm.D., Curtis D. Collins, Pharm.D., M.S., and Randolph E. Regal, Pharm.D.

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We appreciate the contribution of Drs. Shrader and her colleagues for their case report that observed an increase in warfarin's therapeutic effect when a patient began receiving azithromycin.[1] The authors addressed two key factors that they felt had changed from when warfarin activity was relatively stable (international normalized ratios [INRs] ranging from 1.75–3.03 during the previous 3 mo) to when the INR increased dramatically to 8.32. The first factor was the addition of azithromycin for treatment of an upper respiratory tract infection; the second was a decline in cigarette smoking from 1 pack/day to 1 pack every 3 days. We feel that there may have been one other factor that could have accounted for, or at least contributed to, the increase in INR. Specifically, the infectious process itself may have had an effect on the functioning of the hepatic isoenzymes that are responsible for warfarin's biotransformation.

Several researchers have documented a decrease in hepatic cytochrome P450 (CYP) isoenzyme activity in relation to various types of infections. A review article examined the available literature concerning the effects of inflammation and infection on drug metabolism through CYP isoenzymes.[2] It is now understood that infection and inflammation may have varying effects on concentrations of drugs that are metabolized hepatically by these isoenzymes. For example, it is known that influenza virus infection can cause an elevation in the plasma concentration of theophylline, sometimes leading to toxic levels.[2–4] In addition, decreased antipyrine clearance was observed in 14 patients when they developed fever and pneumonia (likely secondary to a bacterial infection) compared with when they were healthy.[5] Based on the historic utility of antipyrine as a determinant of hepatic CYP activity, this study served as an important progenitor for future research.

Currently, it is believed that the substances released during inflammation and infection elicit a downregulation of CYP isoenzymes. Whereas production of cytokines such as interleukins, glucocorticoids, and tumor necrosis factors is implicit in all cases of infection, specific responses may depend on the type of biologic process. For example, lipopolysaccharide production in gram-negative bacterial infections has been shown to cause decreased concentrations of CYP enzymes, and this effect is accompanied by reduced drug clearance.[2, 6] In addition, interferon production has been implicated as a likely factor in viral infections. The decrease in CYP enzyme activity has often been accompanied by a decrease in messenger RNA in the liver, suggesting that inflammation and infection may somehow result in a selective decrease in gene expression.[2–4]

Unfortunately, we could not find any published literature that directly investigated the effects of infection on warfarin disposition. In addition, most of the evidence available on this subject

From the Department of Pharmacy Services, University of Michigan Health System, Ann Arbor, Michigan (all authors).

Address correspondence to Gregory Eschenauer, Pharm.D., Department of Pharmacy Services, University of Michigan Health System, 1500 East Medical Center Drive, UH B2D301, Box 0008, Ann Arbor, MI 48109-0008; e-mail: gregorye@med.umich.edu.

dealt with animals, not in vivo human data. As such, more research is necessary to elucidate the specific effects of infection and inflammation on drug metabolism in humans in the clinical setting.

Hypoprothrombinemic interactions between warfarin and numerous antiinfectives are well documented, clinically evident, and involve several different mechanisms. In their review, Dr. Shrader and colleagues described warfarin-antibiotic interactions involving altered intestinal flora, hepatic enzyme inhibition, and competition for protein binding.[1] In addition, there is evidence that a fourth type of interaction involving methylthiotetrazole side-chain–containing cephalosporins such as cefotetan may also be clinically relevant in some settings.[7]

Finally, we wish to discuss another mechanism of warfarin potentiation interaction, whereby inflammatory cytokines themselves may be the culprits in slowing the metabolism of the anticoagulant. This could be the very mechanism that has led to increased INRs with warfarin in patients taking levofloxacin, an antibiotic that, like azithromycin, has not been found to alter the function of CYP isoenzymes in in vitro studies. Indeed, whereas case reports have implied that a levofloxacin-warfarin interaction may exist,[8, 9] one pharmacokinetic study done in young healthy volunteers showed no pharmacokinetic interaction between levofloxacin and warfarin.[10] Of course, just as was done with research on the ciprofloxacin-warfarin interaction,[11] more studies should be conducted on older, more debilitated patients to better determine the nature and significance of the levofloxacin-warfarin interaction in clinical practice. Now the same appears to be true with azithromycin's effect on warfarin.

Dr. Shrader and colleagues[1] stated that their case was the first documented report of an interaction between azithromycin and warfarin with very little chance of other confounders being present. We offer another consideration for clinicians: some antibiotics may play the role of "red herrings" in the "what caused potentiation of warfarin?" game. However, just as the authors recommended routine monitoring of prothrombin time and INR when patients are receiving concomitant azithromycin and warfarin, we feel that any patient receiving warfarin should be monitored more closely whenever an infection is identified, regardless of the antibiotic(s) chosen to treat that infection.

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Authors' Reply

The comments provided by Dr. Eschenauer and his colleagues in response to our case report[1] describing a potential interaction between azithromycin and warfarin are interesting. We do agree that it is unfortunate that no literature can be found that directly investigates the effects of infection on warfarin disposition. The hypothesis suggesting that an infectious process may alter the anticoagulant response warrants further investigation. Perhaps one does need to be mindful of the hepatic cytochrome P450 isoenzyme activity in response to the infectious process. As we concluded in our case report, patients prescribed azithromycin should receive close monitoring of the anticoagulant response.

Sarah P. Shrader, Pharm.D.
Joli D. Fermo, Pharm.D.