

Warfarin & Antibiotic Drug-Drug Interactions

Background

Warfarin (Coumadin), a coumarin derivative, inhibits clotting by interfering with production of the biologically active vitamin K-dependent clotting factors. The vitamin-K dependent clotting factors include factors II, VI, IX, and X. These factors normally undergo a carboxylation reaction to be converted into their activated forms. Warfarin inhibits this carboxylation reaction, and the reduction in amount and activity of these factors results in the anticoagulant response. Warfarin also interferes with production of Protein C and Protein S, which are the body's natural anticoagulants. Warfarin is metabolized by different enzymes. Therefore, medications that either induce, inhibit, or are substrates of these enzymes have the potential to cause significant elevation or decrease in the INR.

Drug-Drug Interaction

A large number of drugs are introduced every year, and new interactions between medications are increasingly reported. Therefore, managing potential drug interactions is a challenge for physicians with patients on warfarin therapy.

Drug-drug interactions with warfarin can be classified as either pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions may involve changes in the absorption, protein binding, and/or the hepatic metabolism of warfarin. One of the most common Macrolide antibiotics is Erythromycin. Erythromycin inhibits the metabolism and subsequent clearance of warfarin from the body. Pharmacodynamic interactions alter the risk of bleeding or clotting by either effect on platelet aggregation or vitamin K catabolism. Broad-spectrum antibiotics can suppress production of vitamin K by the gut flora, increasing the response to warfarin.

It is also suggested that correlations of the INR's between different systems during antibiotic therapy may show unusual/unexpected results that should be taken into consideration. This is because different thromboplastins are sensitive to different levels of the vitamin K dependent coagulation factors. A reagent that is very sensitive to Factor VII levels may give a different INR result than another that is less sensitive if the level of that factor in the patient sample has dropped significantly due to some of these pharmacokinetic or pharmacodynamic interactions.

In Table 1 below, a few common antibiotics have been grouped in three categories based on their effect on PT/INR and warfarin metabolism. For a more complete list of antibiotics and their effect on warfarin, please refer to the warfarin package insert.

Three groups of antibiotics and their interference with Warfarin:

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Table 1:

| Group 1 | Group 2 | Group 3 |
|--|---|---|
| <ul style="list-style-type: none"> • TMP/SMZ (co-trimoxazole) • metronidazole • erythromycin clarithromycin (less likely, less effect than erythromycin) • ciprofloxacin, enoxacin • "azoles" fluconazole (multi-dose and doses greater than or equal to 200mg/day), itraconazole, ketoconazole | <ul style="list-style-type: none"> • 3rd generation cephalosporins e.g. Fortaz®, Suprax® • 2nd generation cephalosporins e.g. Mefoxin®, Cefotan® • Flouroquinolones (levofloxacin, gatifloxacin) other than ciprofloxacin, enoxacin, azithromycin (7,8) • broad spectrum penicillins e.g. piperacillin • combination br. spec. penicillins e.g. Zosyn®, Unasyn®, Augmentin® • clindamycin | <ul style="list-style-type: none"> • 1st generation ceph's e.g. Ancef®, Keflex® • penicillin, amoxicillin, ampicillin, dicloxacillin, etc. • tetracyclines • nitrofurantoin |

Group 1: Those antibiotics that interfere with warfarin via its pharmacokinetic pathway e.g. metabolism/elimination. This group of antibiotics is very likely to produce an alteration in INR e.g. greater than 75% of the time, and unless specified otherwise, you may likely see increases in INRs from e.g. 3.0 to e.g. > 4.0 to 7.5.

Group 2: Antibiotics, that due to their broad spectrum, may likely produce a noticeable effect in the INR (increase, yet smaller than the first group mentioned above) due to their potential reduction in gut flora-producing vitamin K. This effect may be more significant if the patient has relatively poor nutritional habits and may be mildly-moderately deficient in vitamin K already. This effect may take a few days to "show itself".

Group 3: Narrow spectrum antibiotics with less chance to interfere with warfarin.

Recommendation

Because the effect of the antibiotic is temporary (unless prescribed long-term), there is no need to make a "permanent" change in warfarin's dosage. Physicians should take the antibiotic effect into consideration. More frequent monitoring of INRs may be considered while patients are on antibiotics. It is suggested that INRs be obtained prior to starting antibiotics and periodically during concurrent therapy.

When comparing lab results with INRatio results from a patient on antibiotics the potential difference in coagulation factor sensitivity should be taken into account if unusual or unexpected differences are observed.

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