Disaster: Failing to Consider the Time Course of Drug Interactions

John R. Horn, PharmD, FCCP, and Philip D. Hansten, PharmD

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references if any, visit www.hanstenandhorn.com.

Several years ago, a 75-year-old man who was stabilized on warfarin for atrial fibrillation was started on fluconazole 800 mg daily for 1 week, then 400 mg daily for 3 weeks.[1] Two days later he was discharged from the hospital, and the physicians—who knew about the drug interaction between warfarin and fluconazole—told the patient to have his international normalized ratio (INR) checked 1 week after discharge. They apparently were unaware that a substantial increase in warfarin effect could occur after a few days on fluconazole.

One week after finishing the fluconazole, the patient came back to the emergency department with back pain; his INR was now 40. He subsequently developed severe leg weakness as well as bladder and bowel incontinence. Magnetic resonance imaging showed an epidural hematoma, which resulted in a prolonged hospital stay with extensive physical therapy. At discharge, he could not walk without assistance, and he required catheterization for his neurogenic bladder.

What Can Be Learned from This Case?

The primary lesson is that simply knowing that a patient is taking interacting drugs is not sufficient to prevent serious adverse outcomes. If the interacting drug combination is deemed necessary, as it was in this case, one must be prepared to manage the interaction to minimize the risk of an adverse event. Effective management usually includes assessment of the likely time course of the drug interaction, so that the patient can be monitored at the appropriate times.

When a CYP2C9 inhibitor such as fluconazole is given to a patient who is stabilized on warfarin—which has a long half-life—the INR usually increases gradually over 7 to 10 days.[2] This situation does not mean, however, that one can wait 7 to 10 days to monitor the INR, because an excessive INR can occur in just a few days, thus putting the patient at risk.

Of course, the patient's INR at the time the fluconazole is started also can be important. For example, if the patient is underdosed with warfarin and has a subtherapeutic INR, he or she could actually benefit from the fluconazole. On the other hand, if the patient has a borderline high INR prior to starting the fluconazole, he or she may become overanticoagulated more rapidly and to a greater extent than one might expect.

How Can One Predict the Time Course of Drug Interactions?

Look at the Literature

For many drug interactions, there are enough case reports and pharmacokinetic studies to predict the likely time course of drug interactions. It is known, for example, that giving a CYP3A4 inhibitor such as verapamil to a patient on carbamazepine usually results in clinical carbamazepine toxicity within a few days. On the other hand, a patient stabilized on lithium who starts taking an angiotensin-converting enzyme inhibitor often develops lithium toxicity only weeks later.

Use Pharmacokinetic Principles

If the literature does not have adequate information on time course, one can sometimes estimate the time course using simple pharmacokinetic principles. We will assume that one knows that theophylline has a half-life of about 8 hours in adult nonsmokers, and a particular CYP1A2 inhibitor approximately doubles the theophylline half-life. Because it takes about 4 half-lives to achieve steady state, multiplying the new prolonged half-life of 16 hours times 4 gives a new steady state at about 2 to 3 days.

Consider the Mechanism of the Interaction

Knowing the mechanism of the interaction can provide important insights into the time course.

Gastrointestinal absorption. If one drug binds with another in the gastrointestinal tract, it is just like decreasing the dose of the affected (object) drug. Thus, reduced therapeutic effect can be seen fairly quickly, especially if the absorption of the object drug is markedly affected.

Enzyme induction. Increased object drug metabolism due to enzyme induction tends to be fairly gradual and can take up to a week or more for maximal effect.

Enzyme inhibition. As already mentioned, the time course of enzyme inhibition reactions depends largely on the half-life of the object drug, although other factors also can be involved.

Pharmacodynamic interactions. Depending on the type of pharmacodynamic interaction, the effects can be observed almost instantly, or they may take many weeks. PT

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