Controversial Drug Interactions

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It was the early 1970s on the surgery floor of a university hospital in California, and one of us (Dr. Hansten) was watching as an eminent cardiac surgeon—red-faced, with eyes bulging—tore a piece of paper from a patient's chart, crumpled it up, and threw it on the floor. What had infuriated him was a drug interaction notice provided by a computer program devised by a fellow professor at the medical school.

The interaction in question was between warfarin and acetaminophen, and the limited data available at the time suggested that giving moderate doses of acetaminophen for 2 weeks might somewhat increase the anticoagulant response to warfarin. But studies showing no interaction had also been published, so the interaction was controversial. And now—40 years after this squabble—the acetaminophen-warfarin interaction is still subject to debate. Indeed, another review of the interaction was just published in the June 2011 issue of *Pharmacotherapy*.[1]

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EXAMPLES OF CONTROVERSIAL INTERACTIONS

Almost all drug interactions have at least some areas of controversy, but some have more than others. We have discussed many of these interactions in previous columns.

Acetaminophen + Warfarin. This interaction has been controversial from the very first reports in the 1960s, and almost every possible outcome on warfarin anticoagulation has been reported: no effect, small to moderate effects, and major effects with bleeding. The variability results primarily from different study design: different dose and duration of acetaminophen, patients vs healthy subjects, retrospective vs prospective, number of subjects, and so on. Too often studies failed to account for the many other factors that can affect warfarin response, such as fever, acute illness, dietary factors, thyroid function, other medications, and the like. Newer evidence also suggests that genetics may play a role in the outcome. So even after 4 decades, the best we can do is advise patients on warfarin to minimize their acetaminophen intake (eg, no more than 2 g daily for a few days).

Tamoxifen + CYP2D6 Inhibitors. Overall, the evidence suggests that cytochrome P450 (CYP) 2D6 activity is important for converting tamoxifen to its active metabolite, and that breast cancer patients lacking CYP2D6 or taking potent CYP2D6 inhibitors have higher rates of cancer recurrence. A recent epidemiologic study failed to find this association, and the authors concluded that CYP2D6 activity is unimportant in patients receiving tamoxifen.[2] The study, however, has several design flaws, and it is premature to ignore this drug interaction until this negative study has been thoroughly critiqued. A single epidemiologic study virtually never yields the final answer on any subject. So until the dust settles, it would be prudent for patients on tamoxifen to avoid potent CYP2D6 inhibitors.

Clopidogrel + Proton Pump Inhibitors. This purported interaction has received more press recently than the sex scandals of politicians…well, almost. The data do suggest that some proton pump inhibitors (PPIs) inhibit the antiplatelet activity of clopidogrel in at least some patients, but the question is what this means clinically. One must also consider the potentially beneficial effect of the PPI in reducing the risk of gastrointestinal (GI) bleeding. Until this interaction is better defined, weigh the benefit of PPIs in patients at risk of GI bleeding. To (possibly) reduce the risk of interaction, give the PPI before breakfast and the clopidogrel at bedtime, and avoid omeprazole or esomeprazole.

Oral Contraceptives + Antibiotics. As we discussed in our March 2010 column, the evidence to support this interaction is not convincing. But the negative studies are also poorly done, and—given potential legal liability (which may change if there are changes in product labeling) and the possibility that the interaction actually *does* occur in certain predisposed patients—one should probably continue to warn patients to use alternative contraception during antibiotics, and for 1 cycle after the antibiotic is discontinued.

SUMMARY

For many drug interactions conflicting published reports result in controversy on clinical importance or raise doubts as to whether the interaction even exists. But while the experts duke it out, practitioners in the real world still have to make decisions about how to handle the interactions in specific patients. Although each interaction is unique, in general it is best to err on the side of caution until the clear preponderance of evidence shows that the purported interaction is not clinically important. ***PT***

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