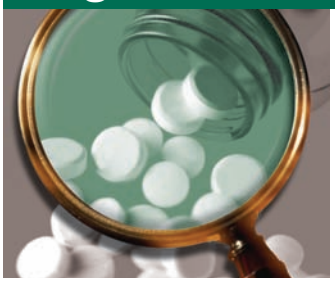

# Dealing with the Drug Interaction Skeptic

John R. Horn, PharmD, FCCP, and Philip 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.*

For Dr. Hansten, it was not his best moment as a pharmacist. It was the late 1960s, and he had just started his first job as a staff pharmacist/drug information specialist at a hospital in Berkeley, Calif. The drug order that came down in the pneumatic tube said, "Tetracycline 250 mg po every 6 hours. Give 2 oz Maalox with each dose of tetracycline." Not many drug interactions were well-documented in the 1960s, but this was certainly one of them. The young pharmacist called the physician on the phone and explained in his most tactful manner that the antacid would reduce the bioavailability of the tetracycline to nearly zero. The physician was an older man, and his response was something like, "Well sonny, I've been giving tetracycline together with antacids for quite a while now, and I have not seen any problems. So, just fill the orders exactly the way I wrote them." The physician slammed the phone down before the pharmacist could respond, and that was that.

Crestfallen that he had failed in his very first attempt to inform a physician about a drug interaction, the young pharmacist immediately sought consolation from his pharmacist colleagues who were standing nearby. They knew what had happened, however, because they had previously tried to get this physician to change these same orders. With the wisdom that comes with experience, the colleagues pointed out that it might be better that the physician gives his tetracycline with antacids, because his use of tetracycline was almost always prophylactic in patients who did not really need it.

The second author learned something important from that unpleasant experience, however—namely, that casual clinical experience often is misleading in the assessment of whether a drug interaction is potentially clinically important. Essentially, this physician had been using placebo tetracycline, but—because the patients did not need the tetracycline in the first place—he never noticed.

*Prescribers' difficulty in correctly identifying adverse drug interactions in the clinical setting makes life more difficult for pharmacists.*

Prescribers' difficulty in correctly identifying adverse drug interactions in the clinical setting makes life more difficult for pharmacists, because it can make the prescriber skeptical about the clinical importance of many drug interactions. What pharmacist—upon informing a prescriber about a drug interaction in one of his or her patients—has not heard, "I use that combination together all the time, and I don't see any problems"?

What are some of the factors that persuade clinicians to underestimate the clinical importance of drug interactions?

## Interactions Involving Inhibition of Drug Effect

As the tetracycline–antacid example showed, inhibition of drug effect is often overlooked. Even when the patient truly needs the affected drug, reduced drug effect may be interpreted as simply normal variation in drug requirements or worsening of the disease state requiring increased dose. Moreover, many drugs are given without any objective measure of drug response, and, in such cases, reduced drug effects easily pass undetected.

## Interactions with Rare AEs

Some drug interactions rarely cause serious adverse events (AEs), and thus the individual clinician is unlikely to observe the AE. For example, if a drug interaction causes a serious AE only once in 1000 times that the combination is given, one would have to observe 3000 patients on the combination to have a 95% chance of observing the AE. Those odds presume that the clinician correctly identifies every adverse interaction when it occurs—a clearly improbable assumption.

## Interactions That Mimic Normal Adverse Drug Effects

When the manifestation of an adverse drug interaction is simply an extension of the pharmacodynamic effect of the affected drug, an interaction may be overlooked. For example, when a patient on a benzodiazepine becomes excessively sedated due to a drug interaction, the effect may be written off as just a side effect and the dosage reduced.

## Interactions in Complex Patients

In complex patients who have multiple diseases and many drugs being started and stopped, it may be particularly difficult to identify adverse drug interactions. For example, many drugs, diseases, and foods affect the international normalized ratio (INR) in

*continued on page 49*

**Table 5**

**Hormones**

| Drug | Description | First Approval | Previous Indication(s) | New Indication |
|---|---|---|---|---|
| Medroxyprogesterone acetate (Depo-subQ Provera 104; Pfizer) | A lower-dose, subcutaneous formulation of Depo Provera (medroxy progesterone acetate) | 2004 | Prevention of pregnancy in women of childbearing potential | Management of pain associated with endometriosis |

cated for the treatment of patients with chronic hepatitis B who are either hepatitis-B-envelope-antigen–positive or –negative.[12,13] The presence of the envelope antigen is a marker of active viral replication.

### Rheumatologic Drugs

Two existing agents received additional indications for rheumatologic conditions in 2005 (Table 4). Based on the results of 2 trials,[14,15] celecoxib (Celebrex; Pfizer) is now indicated for the relief of signs and symptoms of ankylosing spondylitis, a type of arthritis that affects the spine and sacroiliac joints.

Infliximab (Remicade; Centocor) is a monoclonal antibody that specifically binds to and blocks the action of tumor necrosis factor alpha (a substance involved in the inflammatory processes of the body). Its indication has been expanded to include the treatment of patients with active psoriatic arthritis, based on efficacy in a clinical trial.[16]

### Hormones

Depo-subQ Provera 104 (medroxyprogesterone acetate, Pfizer) is a lower dose, subcutaneous formulation of Depo Provera providing 104 mg/0.65 mL. The dose was chosen after determining that 100 mg was the lowest dose that effectively suppresses ovulation at 91 days. A study enrolling 274 patients demonstrated efficacy in the management of pain associated with endometriosis[17] (Table 5). PT

*For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. A. Stahl, Pharmacy Times, 241 Forsgate Drive, Jamesburg, NJ 08831; or send an e-mail request to: astahl@ascendmedia.com.*

## Drug Interactions: Insights and Observations

*continued from page 20*

patients on warfarin, and patients with acute illness—especially infections—can have wide swings in their INR. Sorting out the effect of drug interactions in such patients is problematic.

### Interactions Lost to Follow-up

Ambulatory patients who manifest adverse drug interactions may simply stop one or both medications on their own without ever informing their prescriber. In such cases, the prescriber has no chance of understanding what went wrong. Anyone who has elderly relatives knows that the more obstinate elderly are prone to making decisions about their drug therapy without informing their health care provider.

### Recommendations

- Make sure that you only call prescribers about *real* drug interactions. Not all drug interaction alerts represent clinically important drug interactions, and prescribers may be correct in being skeptical because the drug interaction is bogus.
- Even when the drug interaction is real, it is natural for prescribers to be skeptical. Before discussing a drug interaction with prescribers, plan your response if you get the "I don't see it in my practice" line.
- Before discussing drug interactions with prescribers, try to get a rough idea, if possible, of how often the interaction produces AEs. If AEs from the interaction are indeed rare, prescribers may better understand why they have not seen them.
- Be ready to offer management options to prescribers. They are likely to be more responsive if they see a rational way to get around the interaction and reduce the risk to the patient. PT