The Parachute Principle of Drug Interactions

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In an article published in the December 20, 2003, issue of the *British Medical Journal*, Gordon Smith and Jill Pell pointed out that no double-blind randomized controlled trials have been completed on the efficacy of the parachute in preventing death from the "gravitational challenge" of jumping out of an airplane. They suggest that the benefit of parachutes in such situations is purely anecdotal; it is based merely on common sense instead of scientific investigation, and thus it cannot be trusted to be true.

Although their article was tongue-in-cheek, it raises an important issue in the evaluation of drug interactions—namely, the extent to which one can use *informed* common sense and reason to make clinical decisions about drug interactions in the absence of actual scientific studies. Put another way, are inferences about the danger of specific drug interactions justified based on the known interactive properties of the 2 drugs in the absence of published studies involving the 2 drugs used concurrently?

When drug interactions first became the object of intense study in the mid 1960s and the 1970s, we knew only that some drugs were "enzyme inhibitors" and some were "enzyme inducers," with little information on the specific enzymes involved. It was therefore often mysterious why a particular enzyme inhibitor reduced the metabolism of one drug and not another. Inferences and generalizations were problematic during this time, because the patterns were obscured by our ignorance of CYP450 isozymes and membrane transport proteins such as P-glycoprotein.

As the mechanisms of drug interactions began to be understood in the 1980s and the 1990s, it became possible to predict that certain drug pairs would interact even before the interactions were studied. Old habits die hard, however, and even to this day some people continue to insist that the only reality regarding drug interactions comes from actual clinical studies of the 2 drugs. This is knowledge trumping wisdom.

This focus on the published drug interaction literature to the exclusion of common sense has also been reinforced by calls for making all drug-therapy decisions based on "evidenced-based medicine." But "evidenced-based" does not apply to the drug–drug interaction literature, where perhaps 90% of the reports are in the form of pharmacokinetic studies in healthy subjects and isolated case reports. Controlled outcome studies of drug interactions are rare, and we are usually forced to make clinical decisions about drug interactions with less information than we would like.

Inferences, therefore, must be made based on what we know about the interactive properties of drugs. For example, the metabolism of carbamazepine is known to be highly sensitive to inhibition by CYP3A4 inhibitors. So if a new drug comes on the market that is known to inhibit CYP3A4, we know that it is highly likely that it will cause carbamazepine toxicity even in the absence of actual studies. If someone drives a Buick off a high cliff into the ocean and dies instantly, we do not have to have someone else drive a Chevrolet off the same cliff to see if it will also be lethal. Inferences are justified from known data.

Similarly, we know that P-glycoprotein inhibitors are likely to increase serum digoxin levels; enzyme inducers are likely to reduce verapamil levels; CYP2C9 inhibitors are likely to increase warfarin levels; CYP1A2 inhibitors are likely to increase tizanidine levels; and indirect-acting sympathomimetics are likely to result in a hypertensive crisis in patients on nonselective monoamine oxidase inhibitors. Many patients have been harmed by predictable (but unstudied) drug interactions such as these. Thus, to minimize the risk to the patient, we must assume that these interactions will occur and act accordingly. Even for those rare occasions when subsequent study proves that the 2 drugs do not interact, we still have acted appropriately, given the data we had at the time.

Summary

The "parachute principle" of drug interactions says that we have reached a point where—for many drugs with well-known interactive properties—it is possible to predict other drugs with which they are likely to interact. To demand actual clinical studies before taking action is like asking for controlled studies of the efficacy of parachutes before recommending that parachutes be used by people jumping out of airplanes. In the absence of data, *informed* common sense may be our only defense against an adverse outcome. PT