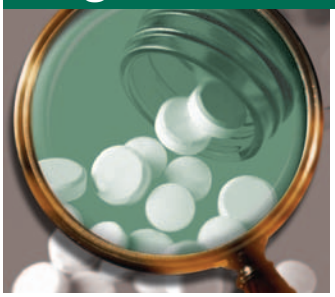

Predicting Drug Interactions Outcomes—Do We Do Better Than Meteorologists?

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"Prediction is very difficult. Especially if it's about the future." This sounds like something Yogi Berra might have said, but it was actually the Danish physicist, Niels Bohr. Prediction is indeed difficult, especially when one is trying to predict the clinical outcome of drug–drug interactions in individual patients.

The deluge of information on drug–drug interactions in the past decade—particularly in the area of cytochrome P450 isozymes and more recently ATP [adenosine triphosphate]-Binding Cassette (ABC) transporters—has demystified much of the seemingly inconsistent behavior of interacting drugs. We now can often predict which drugs are likely to interact with other drugs. Even in vitro studies of drug interactions are now providing useful data in assessing the interactive properties of drugs.

But these remarkable advances in our understanding of drug interaction mechanisms raise the question: How useful is this information for predicting the *clinical* outcome in a patient who begins taking a particular interacting drug combination? The answer is, "Not very." This quandary—lack of predictability in clinical outcome—has proven to be a particularly sticky point in making clinical decisions about drug interactions. We can, of course, often predict that the serum concentration of a drug will be affected by another drug. Clarithromycin, for example, is very likely to increase serum digoxin concentrations.[1] What we have trouble predicting is, for example, of 10 people on digoxin who are started on clarithromycin, which of them will develop clinical evidence of digoxin toxicity (and of those, which will be the most severe)?

The Weather

Meteorologists have struggled with this problem for years—as anyone planning a picnic is well aware—and the similarities are striking. Although meteorologists are often taken to task for their less-than-accurate forecasts, they actually do rather well in their predictions, their reputation for bungling being fueled by our selective recall. (We tend to remember their mistakes much more vividly than their correct forecasts, just as it appears to most of us that we almost always select the wrong line at the bank.)

But what about drug interactions? Why is it so difficult to predict the clinical outcome when a patient takes an interacting drug combination? It is true that the clinical outcomes of a few drug interactions are relatively predictable. For example, if a patient stabilized on carbamazepine begins taking a CYP3A4 inhibitor such as erythromycin, a high probability exists that symptoms of carbamazepine toxicity will appear. Similarly, meteorologists are confident about *some* forecasts—on occasion they are willing to call for a 90% chance of rain (not prone to taking unnecessary risks, however, they normally reserve "100% chance" for those times when it is *already* raining).

But for most problems, either meteorological or pharmacological, the systems are so complex—that is, subject to so many variables—that truly reliable predictions of outcome are not possible. Is that likely to change soon? It does not appear likely. While meteorologists are improving their predictions by using better models and bigger computers, they cannot accurately make specific predictions (eg, light rain will begin in downtown Seattle at 9:27 AM tomorrow, lasting until 11:52 AM).

Similarly, we are making progress in identifying factors that affect the clinical outcome of drug interactions—pharmacogenetics, disease states, dose and duration of therapy, diet, dosing schedules, and the like. But accurately predicting the extent to which a particular patient will have an adverse clinical outcome from a drug interaction usually takes far more than simply knowing if the patient has *identifiable* risk factors. Moreover, little doubt exists that some of what we currently "know" about drug interactions will eventually be proved false—and most of the remainder will be found flawed by oversimplification. So we have made a start, but only a rudimentary one—the meteorological equivalent of predicting weather using only the barometric pressure and humidity.

A Complex System

Weather has been used as an example of a chaotic system—completely deterministic, but subject to an astronomical number of variables. A subtle change in one of these variables can lead to a chain reaction with major changes elsewhere in the world—the proverbial butterfly beating its wings in New Delhi, India, causing a blizzard in Chicago, Illinois. Precise prediction of future weather in a particular place requires absolute accuracy in the meas-

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urement of each of these variables—an obviously impossible task.

Predicting drug interaction outcomes is not so unruly, representing a "complex system" rather than a chaotic one—the New Delhi butterfly is unlikely to cause a patient in Chicago to bleed from a warfarin drug interaction. Nevertheless, while it is true that drug interaction outcomes—like the weather—are completely deterministic, we know only a small fraction of the factors affecting the outcome in either case. Since we cannot begin to measure all of these variables—even if we knew what they were—we are stuck with imprecise forecasts of both weather and drug interaction outcomes for the foreseeable future.

Conclusion

Given that predicting the clinical outcome of a drug interaction in a specific patient is so often imprecise, what can we do until better models for prediction are developed?

- Use the information we *do* have. Some risk factors for adverse drug interactions are known, and when they are, we should consider them in making decisions—for example, the increased risk of hyperkalemia in a patient on an angiotensin-converting enzyme inhibitor and potassium-sparing diuretic who is also a diabetic with renal impairment.[2]
- Do not make specific predictions when informing a prescriber about a drug interaction in a patient. Even if the interaction is very likely to occur, it is usually best to point out the large variability in the clinical outcome of drug interactions.
- Do not make hasty decisions based on your own clinical experience. If you see a number of patients receiving a particular pair of interacting drugs without any adverse outcomes, remember the variability in outcome, and do not conclude—based on this information alone—that the drug interaction is not clinically important. 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@mwc.com.