Weighing Benefit and Risk When the Risk Is Uncertain

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In an ideal world, for each drug–drug interaction, we would know how often patients are harmed by the interaction, what factors increase the risk of harm and by how much, and how the risk escalates when the patient has multiple risk factors. Ideally, we also would know how much we reduce the risk to the patient if we use an alternative drug for one of the interacting drugs.

Unfortunately, for the vast majority of drug interactions, we have little information on these questions. Indeed, one of the central problems in managing drug–drug interactions is the lack of epidemiologic information on how often patients are harmed by a particular drug–drug interaction. Most drug–drug interactions are based on isolated case reports and/or pharmacokinetic studies in healthy subjects; thus, we can usually only indirectly assess the risk of the interaction in any particular patient.

So, how do we make decisions when we are alerted to a potentially dangerous drug interaction? Well, we do the best we can with the available information by asking ourselves the following questions.

Are Both Drugs Truly Necessary for This Patient?

This is probably the first question that should be asked. It is not unusual for one (or sometimes both) of the interacting drugs to be of questionable value for the patient. For example, in a patient with Parkinson's disease taking a monoamine oxidase A (MAO-A) inhibitor such as rasagiline or selegiline, how necessary is dextromethorphan if the patient develops a cough? Dextromethorphan generally has only a modest therapeutic benefit for coughs, and, even though the risk of giving dextromethorphan with MAO-A inhibitors is probably low, it would be prudent to avoid the combination.

Is This Patient at Risk?

If one of the drugs cannot be deemed unnecessary, we must then attempt to assess the risk of the interaction to the patient. For a small number of drug interactions, the risk of serious adverse consequences is so high that no patient should receive the combination. These interactions are easy to manage, but they also are rare. For some other interactions, the primary risk factors are known. For example, the concurrent use of an angiotensin-converting enzyme inhibitor and a potassium-sparing diuretic is much more likely to result in life-threatening hyperkalemia in an elderly diabetic with renal impairment. For other interactions, risk factors such as dose and duration of the drugs, pharmacogenetic factors, and underlying diseases can increase or decrease the risk.

For most drug interactions, however, only limited data are available regarding risk factors, and we are left with finding an approximate solution to the problem using the available (insufficient) information. At this point, the process becomes very particular to the patient in question, and we must consider all of the pertinent data on the drug interaction in light of all of the patient information.

What Is the Optimal Management for This Patient?

If the patient is considered to be at sufficient risk to take some sort of action, we must settle on a management plan to minimize the risk. This usually takes the form of one or more of the following:

1. Selecting a noninteracting (or lesser interacting) drug to replace one of the interacting drugs
2. Monitoring for evidence of the interaction (eg, signs, symptoms, laboratory tests), so that it may be detected quickly and appropriate changes made, such as dose adjustments or discontinuation of one or both of the drugs
3. Reducing the risk of an adverse consequence by making prophylactic dosage adjustments, temporarily stopping one of the drugs, or separating doses (in the case of gastrointestinal absorption drug interactions)

Conclusion

For the vast majority of drug–drug interactions, the pharmacist is called upon to make decisions based on less than optimal information. This is simply the state of knowledge in drug interactions today (and for the foreseeable future). Nonetheless, ignoring the interaction is not an option, because some of them do indeed represent a danger to the patient. So we must take the best available information and make the best decision we can. PT