Ignoring Drug Interactions for the Right Reasons

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Since most drug interactions cause adverse outcomes in only a minority of patients who receive the combinations, much attention has been given to identifying factors that may increase the risk in particular patients. For example, although combining an angiotensin-converting enzyme inhibitor with a potassium-sparing diuretic is safe and effective in most patients, severe hyperkalemia appears to be more likely in individuals with risk factors such as diabetes and renal impairment and those also taking a potassium supplement.

What About "Un-Risk" Factors?

What about the opposite of risk factors, that is, those issues that *reduce* the likelihood of adverse outcomes to drug interactions? (For now, let us call these "un-risk" factors.) For most drug interactions, one can identify situations where it is very unlikely that the patient will be at risk. Identifying these factors early in the process can save considerable time, whereas the drug interaction can be quickly disregarded from further consideration.

Dosage of Drugs

Sometimes the dose of one or both drugs is low enough to make the risk of an adverse interaction minimal. For example, a full systemic dose of epinephrine in a patient receiving a noncardioselective beta-adrenergic blocker will predictably produce an acute hypertensive reaction. With the small doses of epinephrine with local anesthetic normally used in routine dental procedures, however, it is very unlikely to affect blood pressure significantly.

Duration of Therapy

In some cases, a drug is not given for a long enough time to cause adverse drug interactions. For example, if a patient on chronic simvastatin takes a CYP3A4 inhibitor for only a few days, the risk of significant muscle damage from the simvastatin is likely to be low.

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Dosing Times

For some interactions—particularly those involving binding in the gastrointestinal tract—the interaction may not occur because the drugs are not given close enough together. A patient taking ciprofloxacin, who is taking an antacid only at bedtime (and several hours after the ciprofloxacin), for example, is not likely to experience a significant reduction in ciprofloxacin bioavailability.

Order of Administration

Sometimes one can ignore an interaction because the sequence of administration of the drugs mitigates the interaction. A patient stabilized on levothyroxine who is then titrated on warfarin is unlikely to have an adverse drug interaction. Insofar as this is the most common sequence in patients receiving this combination, most of the time this interaction poses little risk. In the rare patient who is on warfarin first, however, the addition of levothyroxine or other thyroid replacement is likely to substantially (if gradually) increase the hypoprothrombinemic response to warfarin.

Pharmacogenetics

Some interactions are unlikely to be important in patients with certain pharmacogenetic characteristics. For example, a patient taking a drug that is metabolized by CYP2D6 will not have an interaction if a CYP2D6 inhibitor is added to the regimen. Other interactions may occur only in patients who do *not* have CYP2D6, because other CYP450 pathways are then more susceptible to interactions.

Monitoring

Sometimes adverse outcomes are avoided by careful monitoring of the patient. If a patient on chronic digoxin therapy is started on another drug that inhibits P-glycoprotein—thus increasing the digoxin serum concentrations—careful monitoring of the patient for elevated digoxin levels may allow the combination to be given safely.

Conclusion

Most drug interactions have identifiable factors that mitigate the interaction and render it unlikely to produce adverse consequences. These include the way the drugs are administered—dose, duration, dosing times, sequence—as well as individual factors such as pharmacogenetics and planned monitoring of the patient. Many drug interactions in particular patients can be rightfully ignored by considering these factors, thus saving considerable time for pharmacists and physicians. ■