

Prophylactic Dose Adjustments in Management of Drug Interactions

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When a precipitant drug (the drug causing an interaction) increases or decreases the plasma concentrations of an object drug (the drug affected by the interaction), it might seem logical to prophylactically adjust the dose of the object drug to compensate. Unfortunately, there are some significant pitfalls to this approach, and there are often better ways to minimize the risk of such drug interactions. The major pitfalls are outlined below.

PATIENT VARIABILITY

Perhaps the major problem in making prophylactic dosage adjustments is the fact that it is impossible to predict with any degree of accuracy the magnitude of a drug interaction in a particular individual. It is common for the magnitude of drug interactions to vary by 5- to 10-fold, even among a small group of healthy subjects in a controlled pharmacokinetic study. In the clinical setting, in which patients have various diseases and are taking other medications, the variability is often even greater.

The recent changes in the product labeling for colchicine represent a good example of this problem. The pharmacokinetics of colchicine were studied with and without concurrent administration of various interacting drugs, and the following percentage increases (with ranges in parentheses) were observed on the area under the plasma concentration-time curve (AUC) for colchicine: cyclosporine, 259% (76% to 512%); clarithromycin, 282% (89% to 852%); ketoconazole, 212% (77% to 420%); ritonavir, 296% (54% to 924%); verapamil, 103% (-10% to 217%); diltiazem, 93% (-30% to 339%).

Despite the marked variability in mag-

nitude observed in these studies, the colchicine product information recommends "one size fits all" dosage reductions (usually 50%) to avoid colchicine toxicity. Given that there was a 20-fold difference in the magnitude of the colchicine-ritonavir interaction, for example, it is clear that a 50% reduction in colchicine dose would still expose some people to life-threatening colchicine toxicity. Unfortunately, if one were to reduce the colchicine dose enough to protect the patients who are most sensitive to the interaction, most other patients would be likely to develop subtherapeutic colchicine concentrations.

OBJECT DRUGS WITH SERIOUS TOXICITY

There is also a "Catch-22" aspect of making prophylactic dosage adjustments to avoid adverse drug interactions. If the object drug has relatively low toxicity, such that an increase in its pharmacodynamic effects due to a drug interaction could easily be handled if they occur, it is not necessary to make prophylactic dosage adjustments.

If, on the other hand, the object drug has a narrow therapeutic index and elevated concentrations are potentially dangerous, it is almost always better to avoid the combination than to try to manage the interaction by adjusting doses. So regardless of whether the object drug has low or high toxicity, prophylactic dosage adjustments are not likely to be the best remedy.

MAKING 2 CHANGES AT ONCE

When a prophylactic dosage adjustment in an object drug is made upon starting an interacting precipitant drug, 2 opposing effects on the object drug are made simultaneously. It is important to remember that 1 of these 2 actions will almost always predominate over the other, so (as described above for colchicine) some

patients are likely to become toxic and some subtherapeutic.

Also problematic is the fact that the time course of the 2 opposing effects may differ substantially. For example, if one prophylactically lowers the warfarin dose as soon as a patient starts taking a cytochrome P450 2C9 inhibitor, the patient is likely to develop inadequate warfarin effect before the full effect of the interaction is manifest (usually 1 to 2 weeks). Most drug interactions involving inhibition or induction of metabolism take from a few days up to several weeks before the maximal effects on the object drug are observed, making it difficult to decide when and how much to adjust the doses.

SUMMARY

In the rare case when both the object drug and the precipitant drug are absolutely necessary, and the object drug has serious toxicity, it may be necessary to make prophylactic dosage adjustments. Nonetheless, such adjustments are usually not the optimal method for managing drug interactions. Because it is not possible to predict the magnitude of drug interactions in specific patients, prophylactic dosage adjustments are often too large or too small for a given patient.

Moreover, when the object drug has serious toxicity, it is almost always preferable to avoid the combination rather than try to reduce doses of the object drug to avoid toxicity. Finally, inability to accurately predict the time course of an interaction is likely to result in toxic or subtherapeutic object drug concentrations (sometimes one followed by the other) despite the dosage adjustments. **PT**

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