The Importance of the Order of Drug Administration

John R. Horn, PharmD, FCCP, and Philip D. Hansten, PharmD

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references if any, visit www.hanstenandhorn.com.

One of the features of drug–drug interactions that can cause difficulty for pharmacists and physicians is the wide variation in patient response that can result from the same 2 drugs administered in the same doses. The sequence in which the object and the precipitant drugs are administered will contribute to the relative risk of the interaction to cause patient harm. By considering a basic drug interaction involving a substrate (object drug) of a metabolizing enzyme and either an inhibitor or an inducer (precipitant drug) of that substrate's metabolism, a pharmacist or physician can develop an approximation of what is likely to occur when one of the object or precipitant drugs is added or deleted from the patient's regimen. Based on this estimate, the pharmacist or physician can then decide how to avoid a potential adverse patient outcome.

Adding an Inhibitor to a Patient Taking the Object Drug

This is perhaps the most common scenario associated with an adverse drug interaction outcome. The precipitant drug will reduce the clearance of the object drug, resulting in accumulation of the object drug. If the plasma concentration of the object drug increases beyond its therapeutic range, toxicity is likely to occur. Object drugs with narrow therapeutic ranges, large first-pass metabolism, and the administration of potent inhibitors are all associated with an increased risk of an adverse outcome. The most important risk to the patient is a lack of awareness of the potential interaction on the part of the physician or pharmacist. Appropriate monitoring of object drug plasma concentration or response will minimize the risk to the patient of an adverse outcome. Discontinuation of the precipitant drug (inhibitor) will result in a decline in the object drug's concentration and effect. Patients should be monitored for diminution of therapeutic effect, and the object drug dose should be increased as needed.

Adding an Object Drug to a Patient Taking an Inhibitor

When a new object drug is added to a patient's regimen, it usually is titrated to an end point such as patient response or drug concentration. Even if an interaction is not suspected, with usual monitoring the predetermined end point will be reached and the dose titration will be completed without toxicity. Patients often will be maintained on a lower-than-normal dose of the object drug. Object drug toxicity is a risk when a standard dose of the object drug is administered without adequate monitoring. Stopping the inhibitor may result in a reduction or loss of object drug efficacy.

Object drug:
The drug that is affected by the interaction

Precipitant drug:
The drug that causes the interaction

Adding an Inducer to a Patient Taking the Object Drug

The administration of a drug that induces the metabolism of an object drug will reduce the plasma concentration of that object drug. A reduction or loss of the object drug's therapeutic effect would be the usual outcome. The reduced effect of the object drug will not be observed for several days to weeks, because enzyme induction is a more delayed process than inhibition. A dose increase of the object drug, guided by monitoring of the drug concentration or pharmacodynamic response, will usually compensate for the induction. Toxicity or excessive pharmacologic effect could occur if the object drug was a prodrug and if metabolic conversion to its active metabolite was induced. Discontinuation of the inducer will result in a gradual increase in the plasma concentration of the object drug. Careful monitoring and dose adjustments will avoid the development of toxicity.

Adding an Object Drug to a Patient Taking an Inducer

A patient with induced metabolism caused by the precipitant drug will require higher-than-normal doses of the object drug to obtain therapeutic response. Thus, the prescriber will usually find that the dose titration of the object drug requires more time and larger doses to reach the intended end point. If standard doses of the object drug are administered without adequate monitoring, a subtherapeutic response is likely to transpire. If the object drug is inactive and requires metabolism to produce an effect, the presence of an inducer may increase the risk of toxicity and the need for patient monitoring. If the inducer drug is discontinued, the object drug will slowly accumulate in the patient and may result in an adverse event.

These 4 basic scenarios are useful for predicting what outcome may result from the administration of an interacting pair of drugs. The order that the object drug and the precipitant drug are added or removed from the patient's regimen will markedly influence the potential for toxicity to occur and the specific monitoring approaches that should be considered. Only after considering what effect the order of drug administration has on a potential drug interaction should one develop a plan for patient monitoring. PT