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Evaluation of Drug Interaction Reports: Drug Dosing

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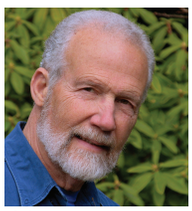

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When evaluating a published report of a potential drug–drug interaction, it is important to consider the variables that are likely to affect the magnitude of the interaction. Perhaps most fundamental to understand is the dosing regimen used in the study or case report.

The dosing regimen of the object and precipitant drug can influence the potential for the interaction to produce a clinically significant change in patient response. Dosing regimens encompass several variables, such as route of administration, size of dose, frequency of dosing, separation of doses of object and precipitant drugs, and attainment of steady-state plasma concentrations.

Effect of Object Drug Dosing

The dose of the object drug, combined with its systemic clearance, will determine where on the concentration-response/toxicity curve the patient is prior to the addition of the precipitant drug. A patient with a high object drug concentration who receives a clearance inhibitor is more likely to experience an adverse effect compared with a patient with a low, preinteraction object drug concentration. Similarly, administration of a single dose of an object drug will not provide the same insight into the risk of the interaction as the presence of a steady-state object drug concentration. If the pharmacologically active compound of the object drug is a metabolite, the metabolite's steady state should be achieved both before and after precipitant drug administration. In case reports, it is important that a stable dose of the object drug has been administered prior to administration of the precipitant drug so that steady-state concentration is achieved.

The route of administration has been recognized as an important variable for drug interactions. An obvious example is the absence of first-pass metabolism when an object drug is administered intravenously. This accounts for the typically smaller magnitude of response for interactions when the object drug is administered intravenously compared with oral dosing. With few exceptions (eg, topical steroids), topically applied object drugs have limited systemic activity and are usually minimally affected by precipitant drugs.

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Effect of Precipitant Drug Dosing

In general, the higher the dose (concentration) of the precipitant drug, the greater is the magnitude of the effect on the object drug. Cimetidine is well known for its dose-dependent enzyme inhibition, which increases as the daily cimetidine dose increases from 400 mg to 2400 mg.[1-3] Differences in the concentration of the precipitant drug probably account for a large amount of the interpatient variability observed with drug interactions.

For precipitant drugs that act by inhibiting the elimination of the object drug, maximum inhibition is unlikely to occur until steady-state concentrations of the precipitant drug are achieved. This will require repetitive dosing for 4 to 5 half-lives of the precipitant drug. If steady-state concentration of the precipitant drug is not achieved, the magnitude of the interaction is likely to be underestimated. Also, if the inhibitor is a metabolite of the precipitant drug, the time to reach maximum inhibition will be prolonged until the metabolite accumulates to steady state. For example, fluoxetine (and its inhibitory metabolite norfluoxetine) required a longer time to produce CYP2D6 inhibition than paroxetine.[4]

If the precipitant acts as an inducer of the object drug's elimination, in addition to achieving steady state of the precipitant drug, additional time is necessary for induction to occur. Depending on the inducer, 7 to 21 days may be required for maximum induction to be achieved.[5-7] The new, postinduction steady-state concentration of the object drug will then be achieved over 4 to 5 half-lives. Since the half-life of the object drug following induction is often shorter than the preinteraction half-life, the new steady state may occur quicker after completion of induction.

Summary

In general, the most reliable drug interaction studies employ repeated dosing to achieve steady state with both the object and precipitant drugs. Doses of the precipitant drug should reflect its usual therapeutic range. Occasionally, the dose of the object drug is reduced prior to the co-administration of the precipitant drug to lessen the risk of toxicity to the subjects, with plasma concentrations adjusted accordingly. Drug interaction studies done with low-dose or non–steady-state protocols may not reflect the true potential of the interaction to alter patient response.

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