# When Is an Interaction Likely to Cause Harm?

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Past columns have discussed various drug interaction properties that need to be considered when assessing a specific patient for the presence of a drug interaction. Once the potential for an interaction is established, the next question is usually: "What is the risk that the interaction will cause an observable change in this patient's response to the object drug?" A few tools can help assess the risk of a potential drug interaction that is caused by inhibition of the object drug's elimination.

## CHANGES IN DRUG CLEARANCE VS PLASMA CONCENTRATIONS

The first thing to consider is how much change in the plasma concentration of the object drug is likely to occur. Often the magnitude of a drug interaction will be described as an average change in area under the concentration time curve (AUC) or drug clearance (Cl). If the dosage interval and bioavailability are kept constant, the AUC and average steady-state plasma concentration (Css) will be determined by the dose of drug and its clearance. The AUC and Css indicate the total exposure to a drug and are usually related to the drug's response. An increase in Cl will decrease AUC and a decrease in Cl increases AUC. If a study determines that the mean AUC of the object drug is increased by 50%, that value will approximate the mean change in the average plasma concentration and the patient's exposure to the drug.

If a study reports that the mean clearance of the object drug is decreased by 50%, this indicates that the mean AUC will increase by 100% or will double in value. The relationship between change in clearance and AUC is shown in the Table.

As can be seen from the Table, a decrease in the clearance of a drug produces a larger relative change in the AUC. A decrease in clearance ≥25% produces at least a 33% increase in the plasma concentration of the object drug. For most drugs that have linear kinetics, a 25% decrease in clearance is equivalent to increasing the dose of the object drug by 33%, because dose changes will produce equivalent changes in AUC.

## ASSESSING THE RISK ASSOCIATED WITH A CHANGE IN CL

Once the mean change in the concentration of the object drug is determined, one needs to consider how that degree of change relates to the usual therapeutic range of the drug. For many drugs, a change in dose of 30% to 50% will produce a change in response. For this reason, a decrease in clearance exceeding 25% to 35% is often used as an indication that a patient may experience an adverse outcome from the interaction.

If the object drug has a wide therapeutic dosage range that does not cause toxicity (ie, diazepam), larger changes in clearance may be well tolerated. Of course, patient-specific factors, such as concurrent diseases or drugs, must be considered when assessing the risk to a patient of a potential drug interaction. It is important to keep in mind that the usual interpatient variation in the magnitude of a drug interaction can be 5- to 6-fold under controlled study conditions.

By doing some simple calculations based on the reported magnitude of an interaction, it is possible to make an estimate about the potential risk to a patient. Based on the degree of risk and the benefit of administering the drugs, appropriate management options can then be selected. *PT*

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**Table**

| RELATIONSHIP BETWEEN CHANGE IN CL AND AUC OF OBJECT DRUG | | | |
|---|---|---|---|
| Decrease in Cl (%) | Increase in AUC (%) | Increase in Cl (%) | Decrease in AUC (%) |
| 10 | 11 | 10 | 9 |
| 20 | 25 | 20 | 17 |
| 25 | 33 | 25 | 20 |
| 30 | 43 | 30 | 23 |
| 50 | 100 | 50 | 33 |
| 75 | 300 | 75 | 43 |
| 90 | 900 | 90 | 47 |
| | | 100 | 50 |
| | | 200 | 67 |
| | | 400 | 80 |

AUC = area under the concentration time curve; Cl = drug clearance.