

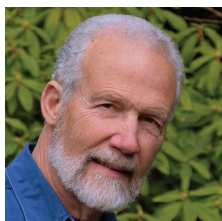
Drug Interaction Mechanisms

Inhibition of CYP450 Metabolism

BY JOHN R. HORN, PHARM.D, FCCP, AND PHILIP D. HANSTEN, PHARM.D



JOHN R. HORN, PHARM.D, FCCP



PHILIP D. HANSTEN, PHARM.D

AUTHOR BIO

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, visit hanstenandhorn.com.

WE HAVE OFTEN DESCRIBED DRUG-DRUG INTERACTIONS that are caused by the precipitant drug inhibiting the CYP450 enzyme responsible for the metabolism of the object drug. Although the outcome of these interactions is similar—an increase in the plasma concentration of the object drug—different mechanisms describe the potential inhibitory action of the precipitant drug on the object drug. These are commonly referred to as reversible inhibition and nonreversible inhibition, and the 2 processes differ in their characteristics. Understanding the differences is useful when considering the time course of the onset and offset of inhibitory drug interactions.

REVERSIBLE INHIBITION

Reversible inhibition is perhaps the most common mechanism of drug-drug interactions. Reversible inhibition implies that the effect of the precipitant drug on the enzyme metabolizing the object drug is the result of mutually exclusive competition between the precipitant drug and the object drug for binding to the enzyme. This competition is a function of the concentration of the 2 drugs at the enzyme and their respective affinities for the enzyme-binding site. Although any 2 drugs that have the same metabolic (enzyme) pathway can display competitive inhibition, the interaction only becomes an issue when the concentration and the binding affinity of one drug is high enough to block access to the enzyme by the other drug.

Competitive inhibition fails to occur when 2 drugs that are substrates for the same enzyme are coadministered when there is sufficient enzyme to accommodate both drugs. Competitive inhibition is observed when the plasma concentration (and/or binding affinity) of one drug is much greater than that of the second drug. In this case, the drug with a higher concentration is preferentially bound to the enzyme and is metabolized, while the drug with lower concentration is unable to bind to the enzyme and accumulates in the body.

Reversible inhibition is dependent on the concentration of the precipitant drug. As the concentration of the precipitant drug falls, the object drug is again able to bind to the enzyme, and the interaction

abates. The timing of the onset and offset of the inhibition is dependent on the half-life of the precipitant drug. Because many drugs have relatively short half-lives (<12 hours), the onset and offset will occur over 2 to 4 days of starting or discontinuing the precipitant drug, respectively.

IRREVERSIBLE INHIBITION

In some cases, CYP450 inhibition is irreversible. The formation of a stable complex, between a drug and the metabolizing enzyme, is one mechanism that can result in irreversible inhibition.¹ The inhibitor can be a drug or one of its metabolites. If the complex involves the parent drug, the inhibition onset is rapid, as seen with competitive inhibition, and will maximize as the inhibitor reaches steady-state concentrations. However, if a metabolite of the drug forms the complex, as with erythromycin, maximal inhibition may be delayed for up to several days.² This was observed with the interaction between erythromycin and theophylline when only 1 or 2 doses of erythromycin were administered. For some drugs, such as itraconazole, the parent compound and its metabolites act as irreversible inhibitors. This may partially explain the generally potent effect of itraconazole on CYP3A4 substrates. Other common irreversible inhibitors include clarithromycin, diltiazem, fluoxetine, ritonavir, and verapamil.

An important distinguishing feature of irreversible inhibition is the time required for the inhibition to abate, after the inhibitor is discontinued.³ Unlike competitive inhibition, in which the offset is based on the half-life of the inhibitor, the offset of irreversible inhibition is based on the formation rate of new enzyme. CYP450 enzyme half-life in humans is about 36 hours; thus, 3 to 5 days may be required for enzyme function to return to baseline following the discontinuation of an irreversible inhibitor.

SUMMARY

Cytochrome enzyme inhibition can occur by several mechanisms. The result is an increase in the concentration of the object drug. Irreversible inhibitors may require more time for drug interaction onset and offset than competitive inhibitors, and often result in a greater change in object drug clearance. ♦

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