

Inhibition and Induction of Drug Metabolism (involving Cytochrome P-450)

In the context of metabolism of many drugs (small drug molecules not antibody drugs), it is important to understand that cytochrome P-450 enzymes are susceptible to inhibition or induction by other drugs. Generally, these phenomena are described as drug-drug interactions.

For example, if a patient is administered drug A initially, and then drug B afterward, and drug B is an inhibitor of a cytochrome P-450 enzyme that is important in the clearance of drug A, then the serum level of drug A can increase (Figure 1). Conversely, if a patient is administered drug A initially then drug B afterward, and drug B is an inducer of a cytochrome P-450 enzyme that is important in the clearance of drug A, then the serum level of drug A can decrease.

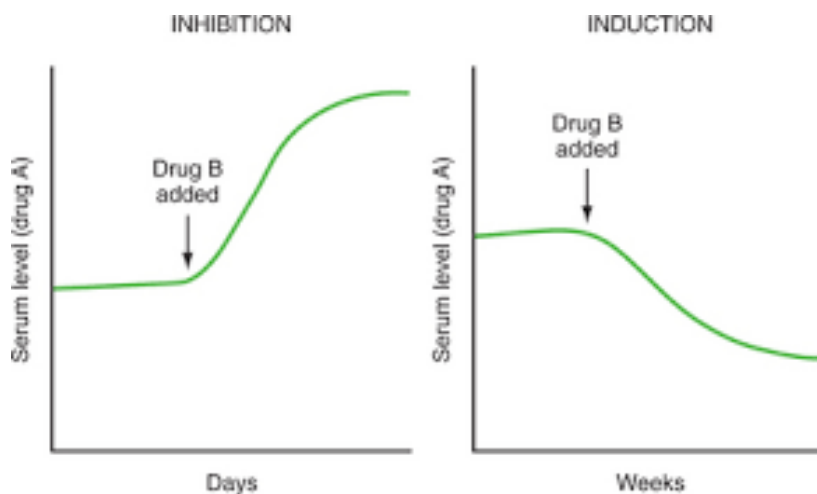


Figure 1. Simple depiction of drug metabolism inhibition of drug A by drug B (left panel), and depiction of drug metabolism induction of drug A by drug B (right panel).

The mechanism of inhibition of a drug metabolism inhibitor on cytochrome P-450 enzymes is most often a result of direct inhibition of the inhibitor drug at or near the active site of cytochrome P-450. The amount of P-450 enzymes typically does not change. The effects can be seen within hours or days. Big effects can lead to overdose and/or drug toxicities.

In contrast, the mechanism of induction of a drug metabolism inducer on cytochrome P-450 enzymes is most often a result of induction of the biosynthesis of the cytochrome P-450 enzymes. The amount/number of P-450 enzymes increases. Measurable increases in both the mRNA and enzyme protein are found. The effects take more time and take several days or weeks. Big effects can lead to loss of drug activity and/or effectiveness.

Occasionally, but not often some large molecule drugs (interleukins, antibodies) can modulate (decrease or increase) the levels of cytochrome P-450 enzymes. This is an area that is not well understood and remains an area of research.