Triple Drug Interactions

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For most drug interactions, we consider only the interaction between 2 drugs. In clinical practice, however, patients are often concurrently taking multiple medications, and sometimes 3 drugs interact with each other in a toxic *ménage à trois*. These "triple" drug interactions are not well studied, but the available data point to some general principles that may be useful in managing such combinations. Of course, drug interactions may involve even more than 3 drugs, but we will limit our discussion to 3.

TRIPLE PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic interactions involving more than 2 drugs have been known for many years, and some of them can result in serious adverse outcomes. An obvious example would be the combined use of 3 or more sedative drugs, resulting in additive sedative effects. With large enough doses, such additive effects can be fatal.

Another example is the use of multiple drugs that can increase serum potassium concentrations, such as ACE inhibitors, potassium sparing diuretics, and potassium supplements. In the predisposed patient (eg, an elderly diabetic with renal impairment), life-threatening hyperkalemia can occur.

TRIPLE PHARMACOKINETIC INTERACTIONS

Unfortunately, many pharmacokinetic interactions involving 3 drugs tend to be more difficult to sort out. Nonetheless, some general patterns have emerged.

Enzyme Inducer + Enzyme Inhibitor. One would expect that if a patient is taking an object drug that is a CYP3A4 substrate, for example, the concurrent use of both a CYP3A4 inducer and a CYP3A4 inhibitor would result in mutual attenuation of the effects of the inducer and inhibitor. But the available evidence suggests that the inducer and inhibitor would seldom cancel each other out exactly, so the plasma concentrations of the object drug are likely to be different than if the drug were given alone. For example, the combined use of a CYP3A4 inducer (St. John's wort) and a CYP3A4 inhibitor (ritonavir) with the CYP3A4 substrate midazolam results in elevated midazolam concentrations.[1] One should be especially alert for adverse outcomes if either just the inducer or just the inhibitor is stopped, since this may result in marked changes in the object drug.

A beneficial outcome from an inducer-inhibitor combination has been reported in a 50-year-old woman on tacrolimus (CYP3A4 substrate) who developed undetectable tacrolimus concentrations after rifampin (CYP3A4 inducer) was started for tuberculosis.[2] The addition of itraconazole (CYP3A4 inhibitor) for fungal prophylaxis resulted in elevation of tacrolimus concentrations to therapeutic levels.

Although triple drug interactions are not well studied, theoretical considerations can often help determine the general direction that the interaction will take.

Multiple Enzyme Inducers. One would expect that a patient taking 2 enzyme inducers would have more enzyme induction than if they were only taking 1 or the other. Available evidence suggests that this is true, but much more clinical study is needed to determine the magnitude of these interactions.

Multiple Enzyme Inhibitors. One would expect that a person taking more than 1 inhibitor for a particular enzyme would manifest some additional inhibitory effects on that enzyme. That is probably true, but little information is available on this point.

More interesting—and probably more clinically significant—is what occurs when a drug has 2 primary pathways for metabolism, and each pathway is inhibited by a drug. For example, the antidiabetic drug repaglinide is metabolized by CYP2C8 and CYP3A4, and both gemfibrozil (CYP2C8 inhibitor) and itraconazole (CYP3A4 inhibitor) individually can increase repaglinide plasma concentrations. But when both inhibitors are given simultaneously with repaglinide, a "one plus one equals three" situation occurs. In 1 study, gemfibrozil produced an 8-fold increase in repaglinide concentrations, while itraconazole produced a small 1.4-fold increase. But when gemfibrozil and itraconazole were given together, repaglinide concentrations increased by almost 20-fold.[3]

A similar effect was seen when oxycodone (metabolized by CYP2D6 and CYP3A4) was given alone and with quinidine (CYP2D6 inhibitor), ketoconazole (CYP3A4 inhibitor), and quinidine + ketoconazole. Giving both inhibitors resulted in oxycodone concentrations that were higher than with either inhibitor alone.[4]

In summary, although triple drug interactions are not well studied, theoretical considerations can often help determine the general direction that the interaction will take. ***PT***

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