Combination Drugs: Difficult to Predict Interaction Outcomes

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Several months ago, this column described *pharmacoenhancement*, the purposeful combination of 2 interacting drugs.[1] (To read the full article, please visit www.pharmacytimes.com/pharmacoenhancement.) The idea of pharmacoenhancement is to use one drug (precipitant drug) to affect the second drug (object drug) in a way that benefits the patient, usually by slowing the elimination of the object drug. Our previous column discussed only the effects of the 2 combined drugs on each other. When drugs with similar or opposing drug interaction properties are coadministered to a patient, however, unpredictable effects on other drugs often occur.

Recently, a review of the drug interactions reported with the combination product tipranavir/ritonavir (Aptivus) noted several interactions with drugs that are substrates for CYP3A4 or p-glycoprotein.[2] Ritonavir is known to be an inhibitor of CYP2D6, CYP3A4, and p-glycoprotein. In addition, ritonavir appears to be an inducer of glucuronidation. Tipranavir inhibits CYP1A2, CYP2C9, CYP2C19, and CYP2D6 and induces CYP3A4 and p-glycoprotein.[3] The combination of ritonavir and tipranavir has been reported to inhibit CYP3A4 and induce p-glycoprotein. The effect of the combination on other cytochromes has not been defined.

The Table lists the effects of ritonavir alone and the combination of ritonavir plus tipranavir on several commonly studied object drugs. For some of the object drugs, the effect of the combination produces a very different result than that of following ritonavir alone. Notice lopinavir, where the difference in the magnitude of effect may be due to the relative dose of ritonavir used in the studies. The effect of ritonavir and the ritonavir/tipranavir combination on zidovudine area under the (plasma concentration-time) curve is similar. The reduction in zidovudine concentrations is most likely due to the induction of zidovudine glucuronidation by ritonavir. The addition of tipranavir to ritonavir probably plays no role in modifying the magnitude of the interaction.

Table

Comparison of Effect of Ritonavir on AUC of Various Object Drugs

Object Drug	Ritonavir	Ritonavir/Tipranavir
Amprenavir	↑ 2- to 4-fold	↓ 44%
Atazanavir	↑ 1.4- to 3.3-fold	↓ 68%
Clarithromycin	↑ 77%	↑ 19%
Digoxin	↑ plasma concentration	↓ 10%
Ethinyl estradiol	↓ 40%	↓ 45%
Lopinavir	↑ 15- to 20-fold	↑ 55%
Rifabutin	↑ 4-fold	↑ 2.9-fold
Saquinavir	↑ 16- to 60-fold	↓ 76%
Zidovudine	↓ 25%	↓ 40%

AUC = area under the (plasma concentration-time) curve.

For several of the object drugs in the table, however, the magnitude of the interactions with ritonavir, compared with ritonavir/tipranavir, are quite dissimilar. Note that the magnitude of the effect of ritonavir alone on amprenavir, atazanavir, lopinavir, and saquinavir is much greater, compared with the effect of the combination product on these same object drugs. Some of these differences may be due to ritonavir dosing disparity. For other drugs, such as amprenavir, the combination product may result in inhibition of more metabolic pathways than occurs with only ritonavir.

One of the major differences between ritonavir alone and its tipranavir combination is the effect on p-glycoprotein. Ritonavir is considered to be an inhibitor of p-glycoprotein, as indicated by its effect on digoxin. Ritonavir/tipranavir is reported to increase p-glycoprotein activity. This may explain the minimal effect on digoxin concentrations reported with the combination, compared with ritonavir alone. P-glycoprotein effect also may partially account for the differences observed on the object drugs saquinavir and amprenavir.

If an object drug has only one elimination pathway, multiple inhibitors of that pathway will not generally lead to a large increase in the magnitude of the interaction. Once a single inhibitor has reduced an enzyme's activity, the addition of a second inhibitor of the same enzyme is not likely to produce much additional inhibition; little enzyme activity is left to inhibit. On the other hand, object drugs that rely on several pathways for elimination can have cumulative inhibition from multiple precipitant drugs that affect different pathways of the object drug's elimination. PT

For a list of references, go to: www.pharmacytimes.com.