

Rx Irony: Drug Interactions for Pharmacoenhancement

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Drug interactions usually are thought of as being a source of adverse drug events. Interactions affecting the metabolism of the object drug often result in elevation of the object drug's plasma concentrations, leading to toxicity. This mechanism, however, can be employed to boost the plasma concentrations of the object drug to achieve or maintain therapeutic concentrations that otherwise would be difficult to accomplish.

For example, initially procainamide was available only as an immediate-release formulation. Because of its short half-life, procainamide required administration every 4 to 6 hours to control arrhythmias. This regimen often led to poor adherence and loss of rhythm control. It was known

that cimetidine reduced the renal clearance of procainamide and could increase the plasma concentrations of both procainamide and its active metabolite.^{1,2} Thus, cimetidine occasionally was used with procainamide to reduce its elimination and prolong its half-life. Patients taking cimetidine and procainamide could reduce the procainamide dosing frequency to every 8 hours.

Pharmacoenhancement also can be used to lower the cost of therapy by reducing the dose of the object drug. Several authors have suggested that cyclosporine cost savings could be obtained by coadministration of diltiazem.^{3,4} Diltiazem reduces cyclosporine clearance by 40% to 70% and enables a similar reduction in the dose of cyclosporine. This reduction leads to direct cost savings on cyclosporine that are greater than the additional cost incurred with the addition of diltiazem.

Most recently, several HIV treatment regimens have utilized pharmacoenhancement to change the pharmacokinetic profile of one or more protease inhibitors.^{5,6} Lopinavir is a protease inhibitor that, when administered alone, has such low bioavailability that it is unable to produce antiviral concentrations in the plasma. By combining lopinavir with a low dose of ritonavir, the bioavailability of lopinavir is increased and the drug is able to achieve antiviral efficacy. The dose of ritonavir is too low to be of value as an antiviral, but it is adequate to inhibit the intestinal and hepatic CYP3A4 metabolism of lopinavir. Ritonavir also may be inhibiting the P-glycoprotein-mediated efflux of lopinavir.


In addition, ritonavir has been used to boost the effects of other protease inhibitors, including saquinavir, indinavir, and amprenavir. Ritonavir increases the area under the plasma concentration time curves, minimum plasma concen-

tration (C_{min}), and half-life. By increasing the C_{min} and half-life, the protease inhibitor can be administered at less frequent intervals and still maintain adequate concentrations to inhibit viral replication. The patient benefits by having fewer pills to take less frequently.

Pharmacoenhancement can be associated with its own risks. The precipitant drug may have to be administered in a dose that not only inhibits the elimination of the object drug, but also may produce its own side effects. When diltiazem is used as an enhancer of cyclosporine, patients may manifest hypotension, bradycardia, or constipation. The enhancer usually is a potent inhibitor and may unintentionally inhibit other object drugs, leading to unwanted adverse effects. If the dose of the enhancer is not carefully adjusted, inadequate or excess increases in object drug concentrations can occur.

Of course, it is very important for the patient to adhere to the prescribed drug regimens for both the object drug and the enhancer drug so that a consistent effect can be maintained. Because of the need for a consistent effect, the use of natural inhibitors of drug elimination, such as grapefruit juice, is discouraged due to the potential lack of consistency in inhibition.

The use of drug interactions for the purpose of pharmacoenhancement is becoming more common, as more is learned about the desirable characteristics of both the enhancer and the object drugs. The enhancer should produce its effects on the object drug with a minimum of its own side effects. If increasing the object drug's concentration is the goal, the object drug should produce added therapeutic benefit but with limited additional toxicity. **P**

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

