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Enzyme Inducer Plus Enzyme Inhibitor: What Will Happen?

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Inhibitor Plus Inducer: Therein Lies the Question

We often get questions from practitioners seeking help with the management of potential drug interactions. A recent inquiry asked what might be the result of the concurrent administration of amiodarone (Cordarone) and bosentan (Tracleer). Because we were unable to find any studies of this interaction, we can start by assessing what we know about the interaction potential of each drug.

What Do We Know?

Bosentan is a substrate of cytochrome P450 (CYP) 3A4 and CYP2C9. It is also known to be an inducer of CYP3A4 and CYP2C9 and may induce other isoenzymes as well. Thus, it would be expected to induce its own metabolism with chronic dosing, and steady-state plasma concentrations have been noted to be reduced to 50% to 60% of single-dose levels.

Amiodarone is a substrate of CYP3A4 and CYP2C8 and an inhibitor of CYP2C9, CYP2D6, CYP3A4, and p-glycoprotein. Based on these assumptions, there are several potential interactions that could occur when amiodarone and bosentan are coadministered:

1. Bosentan could induce amiodarone metabolism via CYP3A4. This could lead to reduced antiarrhythmic efficacy of amiodarone.
2. Amiodarone could inhibit bosentan metabolism via CYP3A4 and/or CYP2C9. Increased bosentan response or side effects may occur. This raises the question of what outcome might be expected when the induction of CYP3A4 (via bosentan) is combined with the inhibition of CYP3A4 (via amiodarone).

Are There Related Data to Consider?

Recently a study was done to examine the effects of ritonavir (a CYP3A4 inhibitor) and St. John's wort (a CYP3A4 inducer) alone and in combination on the metabolism of midazolam.[1] Twelve subjects received single oral doses of midazolam alone and with single doses of St. John's wort 300 mg or ritonavir 300 mg. Midazolam was again administered after St. John's wort 300 mg 3 times a day plus ritonavir 100 mg twice a day were administered for 14 days. A third dose of midazolam was given 2 days after ritonavir and St. John's wort were discontinued.

> During the concurrent administration of St. John's wort and ritonavir, the predominant effect is enzyme inhibition.

The area under the concentration time curve (AUC) of midazolam was unaffected by a single dose of St. John's wort but was increased about 5-fold following single-dose ritonavir. After 14 days of combined St. John's wort and ritonavir, the AUC of midazolam was similar to that seen with ritonavir alone. Two days following the discontinuation of St. John's wort and ritonavir, midazolam AUC was less than 5% of that seen during concurrent St. John's wort and ritonavir and was less than 25% of the midazolam AUC at baseline.

This study demonstrates that during the concurrent administration of St. John's wort and ritonavir, the predominant effect is enzyme inhibition. When both drugs were discontinued, the induction effect of St. John's wort appeared to be present 2 days later, whereas the inhibition of ritonavir had ceased.

In another study of the effect of rifampin on lopinavir-ritonavir combination therapy, increasing the dose of lopinavir-ritonavir by only 2-fold resulted in a more than 6-fold increase in lopinavir levels, indicating that a larger dose of ritonavir produced a greater increase in lopinavir concentration than would have been expected from doubling the lopinavir dose.[2] Ritonavir has also been shown to counteract the enzyme-inducing activity of efavirenz (Sustiva) and etravirine (Intelence).[3,4]

Summary

It would appear that when potent enzyme inhibitors are combined with potent inducers, the inhibition will tend to predominate. Unlike inhibitors where the inhibitory activity often abates when the drug is discontinued, recovery from induction may take several days following the withdrawal of the inducer.

Upon discontinuation of the drugs, be alert for a rapid shift to induction and potential reduction in object drug effect. As always, patient monitoring with appropriate drug dose adjustment is extremely important with these complex interactions.

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