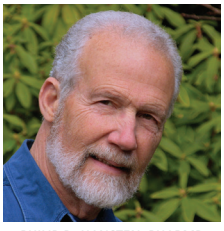
Endothelin Receptor Antagonist Drug Interactions

BY JOHN R. HORN, PHARMD, FCCP, AND PHILIP D. HANSTEN, PHARMD


JOHN R. HORN, PHARMD, FCCP


PHILIP D. HANSTEN, PHARMD

AUTHOR BIOS

John R. Horn, PharmD, FCCP, and **Philip D. Hansten, PharmD,** are both professors of pharmacy at the University of Washington School of Pharmacy in Seattle. For an electronic version of this article, including references, visit hanstenandhorn.com.

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ENDOTHELIN ANTAGONISTS—ambrisentan (Letairis), bosentan (Tracleer), and macitentan (Opsumit)—are indicated to treat pulmonary arterial hypertension. Although these drugs have similar pharmacologic activity, they differ in their potential for their plasma concentrations to be altered by other medications (ONLINE TABLE 1).[1-3] Taking other medications with endothelin antagonists can have various effects (ONLINE TABLE 2).

Ambrisentan

The half-life of ambrisentan is 9 to 15 hours, with its primary metabolism via uridine 5'-diphosphate glucuronosyltransferases (UGTs); CYP450 (CYP) 3A4, CYP2C19, P-glycoprotein (P-gp), and organic anion transporting polypeptides (OATPs) also contribute to its elimination.[1] The mean area under the curve (AUC) of ambrisentan increases about 2-fold with the addition of cyclosporine but is not markedly affected by ketoconazole.[4,5] Both cyclosporine and ketoconazole inhibit CYP3A4 and P-gp, but cyclosporine also inhibits OATPs, perhaps accounting for the greater effect seen with cyclosporine. The importance of OATP in ambrisentan elimination is key in rifampin's effect on ambrisentan pharmacokinetics. Although the steady-state AUC of ambrisentan was minimally changed, during the first 2 days following rifampin plus ambrisentan, the AUC rose nearly 90%. This initial effect is likely because of rifampin inhibition of OATPs that is offset by the enzyme induction of rifampin following several days of coadministration.[6] Clarithromycin has been reported to increase the AUC of ambrisentan by 41%, similar to the effect of ketoconazole.[7] Other inhibitors of CYP3A4 would be expected to produce modest increases in ambrisentan plasma concentrations.

Bosentan

Bosentan is metabolized by CYP3A4, and CYP2C9, and, to a lesser extent, CYP2C19. It is a potent inducer of CYP enzyme activity, including CYP3A4, CYP2C9, and CYP2C19. Thus, bosentan causes autoinduction of its metabolism. With chronic dosing, the AUC of bosentan will be reduced by up to 65% of the value observed following a single dose. The CYP3A4 inhibitors cyclosporine and ketoconazole produce about a doubling of bosentan AUC.[8,9] Rifampin is known to induce CYP3A4 and CYP2C9 but acutely can inhibit OATPs. As was observed with ambrisentan, rifampin produced an 6-fold increase in the AUC of bosentan, but with steady-state rifampin dosing, the net effect was nearly a 60% reduction in bosentan AUC.[10] When a combination of lopinavir and ritonavir was coadministered with bosentan, the steady-state AUC of bosentan increased more than 400%.[11] Bosentan will likely reduce the plasma concentration of other drugs that are metabolized by CYP2C9 or CYP3A4.

Macitentan

Inhibitors of CYP3A4 ketoconazole and cyclosporine increased macitentan's AUC by 2.3-fold and 10%, respectively.[12,13] The administration of the CYP3A4 inducer rifampin led to an 80% decrease in macitentan concentrations.[13] Macitentan may be affected similarly by other CYP3A4 inhibitors and inducers.

CONCLUSION

Drug interaction data are limited for these agents. However, based on the pharmacology of the endothelin receptor inhibitors, it is possible to predict how these agents will interact with other drugs. The relatively greater dependence on CYP3A4 for elimination by bosentan and macitentan compared with ambrisentan appears to make ambrisentan less likely to result in clinically significant interactions with CYP3A4 inhibitors or inducers. UGT inhibitors, such as gemfibrozil (Lopid), may increase ambrisentan concentrations. Pending data, monitor patients for an alerted ambrisentan response. Similarly, patients receiving inhibitors of CYP2C9 (eg, amiodarone, cimetidine, fluconazole, sulfamethoxazole, and voriconazole) should have their response to bosentan monitored. The enzyme induction response to bosentan will likely reduce the response to many other drugs. ◆