Correspondence

Letters to the Editor must not exceed 400 words in length and must be limited to three authors and five references. They should not have tables or figures and should relate solely to an article published in Circulation within the preceding 12 weeks. Authors of letters selected for publication will receive prepublication proofs, and authors of the article cited in the letter will be invited to reply. Replies must be signed by all authors listed in the original publication. Please submit three typewritten, double-spaced copies of the letter to Herbert L. Fred, MD, % the Circulation Editorial Office. Letters will not be returned.

Acute Endothelin A Receptor Blockade in Heart Failure

To the Editor:

We were surprised by the findings of Givertz et al and their interpretation.1 These authors describe the acute (6-hour) hemodynamic effects of 3 doses of the intravenous endothelin (ET) A receptor-selective antagonist sitaxsentan, compared with placebo, in patients with severe chronic heart failure. The patients studied had a strikingly high pulmonary vascular resistance (PVR) and mean pulmonary artery pressure compared with those in similar studies of other ET-1 receptor antagonists.2–4 Sixteen patients received placebo, 8 received sitaxsentan 1.5 mg/kg, 16 received sitaxsentan 3.0 mg/kg, and 8 received sitaxsentan 6.0 mg/kg.

Curiously, the 1.5 mg/kg and 3 mg/kg doses seemed to have greater hemodynamic effects than the 6 mg/kg dose. The peak effect occurred at 2 to 4 hours. Although only the pulmonary vascular effects were statistically significant, there was also an apparent reduction in systemic vascular resistance (SVR) by 19% 2 hours after the 3 mg/kg dose compared with a 34% reduction in PVR at this time after the same dose.

The only other published, placebo-controlled study of this type used the nonselective (ET_{A,B}) ET-1 receptor antagonist bosentan.5 In that study, 24 patients received intravenous placebo or 100 mg of bosentan followed by placebo or 200 mg of bosentan, respectively, 1 hour later. The average reductions in PVR and SVR 2 hours after dosing were 33% and 17%, which are remarkably similar to the findings in the sitaxsentan study (although both SVR and PVR were reduced significantly after bosentan). Consequently, it is hard to support the view that there is a difference in the acute hemodynamic actions of an ET_{A}-selective and a nonselective (ET_{A,B}) ET-1 receptor antagonist. In addition, it seems premature to conclude that sitaxsentan has a selective pulmonary vascular action and has no systemic vascular effects.

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Response

Our study population had substantial decompensation, as evidenced by an elevated pulmonary capillary wedge pressure, low cardiac index, and moderate-to-severe pulmonary hypertension. The finding that the baseline pulmonary vascular resistance (PVR) predicted the magnitude of the decrease in PVR with sitaxsentan may explain the reduced pulmonary vasodilator effect of sitaxsentan in the 6.0 mg/kg (high-dose) group, because baseline PVR tended to be lower in this group. Another potential explanation for the attenuated pulmonary vasodilator effects of sitaxsentan in the 6.0 mg/kg group may be that higher doses of sitaxsentan are less endothelin (ET)-A selective, such that antagonism of vasodilator ET_{B} receptors in the pulmonary circulation counteracts the dilator effects of ET_{A} receptor blockade.

In our study population, we did not observe a reduction in systemic vascular resistance with sitaxsentan (overall treatment P=0.446). Potential explanations for the lack of systemic vasodilator effects are discussed in the original article.2 Further studies will be needed to determine whether these observations are drug-specific or related to ET_{A} versus ET_{B} selectivity, patient population, or other factors.

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