Section Editor:
Myung H. Park, MD
Assistant Professor of Medicine
Director, Pulmonary Vascular Diseases Program
Division of Cardiology
University of Maryland School of Medicine

Michael A. Mathier, MD
Associate Professor of Medicine
Director, Pulmonary Hypertension Program
Director, Cardiovascular Fellowship Program
University of Pittsburgh

Are there any data indicating that medication such as bosentan or Revatio™ (sildenafil citrate) or any other medication helps secondary pulmonary hypertension for a patient with mitral regurgitation, obstructive sleep apnea, and pulmonary artery systolic pressure of 85 mm Hg?

A large volume of clinical data has led to the approval of 3 classes of medications for the treatment of pulmonary arterial hypertension (PAH): prostacyclins (epoprostenol, treprostinil, iloprost), endothelin receptor antagonists (ERAs; bosentan, ambrisentan), and phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil).[1] The World Health Organization (WHO) recognizes 5 types ("Groups") of pulmonary hypertension (PH): Group I, PAH; Group II, pulmonary venous hypertension (PVH); Group III, PH related to hypoxic lung disease; Group IV, chronic thromboembolic PH; and Group V, PH of miscellaneous causes. It is important to recognize that the PAH-specific therapies listed above have only been approved for patients with Group I, PAH. Despite the much greater prevalence of Groups II and III PH, there are very few studies of these therapies in these populations. Furthermore, most of the studies that have been reported show negative or at best neutral effects.

The patient would probably best be described as having "mixed" PH, with elements of PVH (from the mitral regurgitation [MR], assuming it is significant enough to raise the left atrial pressure) and of PH related to hypoxic lung disease (from the obstructive sleep apnea [OSA]). Right heart catheterization would be critical to confirm the presence and severity of PH and to help determine the relative contributions of these factors; the cornerstones of therapy for this patient should in any case be optimal care of the MR and the OSA. For the MR this would include afterload reduction, diuretics, and at least the consideration of surgical repair (although the risk of surgery would undoubtedly be increased by the presence of PH). For the OSA this might include nocturnal positive pressure ventilation, supplemental oxygen, appliance therapy, or surgery.

Address for reprints and other correspondence:
mpark@medicine.umaryland.edu

Even with optimal therapy of the MR and the OSA, however, the patient may have persistent, severe PH. Should PAH-specific therapies be considered in that case? When answering this question, both safety and efficacy must be considered. The use of PAH-specific therapy in patients with PVH may be associated with worsening pulmonary edema and clinical deterioration. This has been reported both for prostacyclins and for ERAs, albeit for the most part in patients with systolic heart failure. In the FIRST (Flolan International Randomized Survival Trial) study, 471 patients with advanced systolic heart failure on standard therapy were randomized to epoprostenol vs placebo. Despite hemodynamic improvement, epoprostenol-treated patients experienced increased mortality.[2] Two large-scale studies of bosentan in patients with left heart failure have been completed. The REACH-1 (Research on Endothelin Antagonists in Chronic Heart Failure) study randomized 370 patients with advanced chronic heart failure (CHF) to bosentan or placebo. This study was terminated early owing to a high rate of transaminase elevation observed in the bosentan arm, likely related to the high doses of the drug used in this study.[3] The ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study randomized more than 1600 CHF patients to standard dose bosentan or placebo. No clinical benefit could be shown in the bosentan arm, but there was an increased risk of CHF exacerbation with active therapy.[4] Interestingly, neither of these studies has been published in full form. Also of interest, both studies enrolled patients with left heart failure regardless of the presence, absence, or degree of PH.

Offsetting these reports to a degree are a number of case series and small studies suggesting that PAH-specific therapies *may* be of value in patients whose PH is "out of proportion" to their underlying heart and/or lung disease. Such reports exist for prostacyclins,[5] ERAs,[6] and PDE5 inhibitors. Perhaps the most encouraging of these is the study of Lewis and colleagues demonstrating the safety and efficacy of sildenafil in patients with PH related to chronic systolic heart failure.[7] In this study sildenafil improved exercise hemodynamics, distance achieved on 6-minute walk test, peak oxygen consumption, and quality of life. Importantly, pulmonary capillary wedge pressure (PCWP) did not increase with sildenafil. Before extrapolating the results of this study to clinical practice, however, it is worth remembering several things: this was a very small study (34 patients) conducted over only 12 weeks. Neither the PH nor the CHF was hemodynamically severe in this study (the mean PA pressure at baseline was only 30 mmHg, the mean PCWP only 18 mmHg); patients were carefully evaluated throughout for evidence of clinical compromise; and, in light of all of this, neither sildenafil nor any other PAH-specific therapy has been approved for use in patients with PH who fall outside of WHO Group I. Larger scale studies are underway that will hopefully answer whether they ever should be. Until then, one must err on the side of caution: if the decision is made to use these therapies in an off-label fashion, it should be done with full disclosure to the patient and with great care in monitoring and responding to any adverse effects.

References

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