PAH Therapies in Men: Often Wondered, Seldom Asked

Section Editor
Myung H. Park, MD

Timothy Williamson, MD, FCCP
Associate Professor of Medicine
Director, Pulmonary Vascular Center
The University of Kansas Medical Center
Kansas City, KS

Note from the Section Editor: Though this issue of *Advances in Pulmonary Hypertension* is dedicated to specific challenges faced by women, we took this opportunity to ask Dr Williamson some of the more common questions asked by men with PAH.

Although some etiologies of PAH affect women disproportionately to men, men are clearly also impacted by this devastating disease and require treatment with PAH-specific therapies. A number of adverse effects related to these treatments are seen in both sexes, but gender-specific adverse effects also exist. Perhaps the 2 most frequently asked questions by male patients with PAH are "1) Is it safe for men taking PAH therapies to become fathers?" and "2) While taking PAH medicines, do I need to worry about prolonged erections (priapism)?"

The abbreviated answer to the first question is that it does appear to be safe for men on PAH medicines to father children, though their ability to do so may be hampered by some treatments. Review of the literature and patient prescribing information for the FDA-approved prostacylins and phosphodiesterase-5 (PDE-5) inhibitors reveal no evidence of mutagenesis for these drugs. While the endothelin receptor antagonist (ERA) class of medications, including bosentan (Tracleer, Actelion Therapeutics) and ambrisentan (Letairis, Gilead) have been shown to be teratogenic in females as a class effect (package insert), similar mutagenic effects have not been demonstrated in sperm. Company information does indicate, however, that sperm counts can be significantly decreased in patients on bosentan, and likely is a class effect of other ERAs as well. Although not an ERA, tadalafil has also been shown in some animal studies to diminish sperm counts,[1] though the clinical significance in humans is not clear. Given the limited data, some men have opted to bank sperm prior to the initiation of an ERA. These potential issues should be discussed with male PAH patients considering having children.

The risk of priapism is confined to PDE-5 inhibitors such as sildenafil (Revatio, Pfizer) and tadalafil (Adcirca, United Therapeutics). Priapism is not seen with prostacyclins or ERAs. Fortunately, the literature and our clinical experience suggest that priapism is a rare event. Indeed, despite wide-spread use of PDE-5 inhibitors in our PH center, we have not seen a single case of this complication. A review of double-blind placebo controlled trials and post-marketing databases (both primarily related to use in erectile dysfunction) suggests priapism occurs with an incidence between 0.1% (in the clinical trials) to 2.5% (in the post-marketing databases).[2] Prescription information for PDE-5 inhibitors cautions against using these drugs in patients with anatomical deformations of the penis (eg, angulation, cavernosal fibrosis, Peyonie's disease) or in patients with co-morbid conditions potentially predisposing to priapism (multiple myeloma, leukemia, sickle cell disease). Interestingly, PDE-5 inhibitors have been used to treat and prevent ischemic priapism, including in patients with sickle cell disease,[3-5] but clearly reflects off-label use. If a patient does experience an erection lasting 4 hours or longer, it is important they seek emergency medical evaluation immediately as untreated priapism may lead to cavernosal fibrosis and permanently impaired erectile function.[4]

In summary, it appears it is safe for patients on PAH therapies to father children, though ERAs and possibly tadalifil may decrease sperm counts, which may make conception more difficult. Priapism is a rare adverse effect associated with PDE-5 inhibitors, and caution should be used when considering these medicines for patients already pre-disposed to priapism.

References

1. Khalaf MA, Abbas MF, El-Fakahany HM. Effects of chronic tadalafil use on the testes and sperm parameters of old albino rats. *Andrologia* 2011. [Epub ahead of print]
2. Giuliano F, Jackson G, Montorsi F, Martin-Morales A, Raillard P. Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the postmarketing safety database. *Int J Clin Pract* 2010;64:240-255.
3. Burnett AL, Bivalacqua TJ, Champion HC, Musicki B. Feasibility of the use of phosphodiesterase type 5 inhibitors in a pharmacologic prevention program for recurrent priapism. *J Sex Med* 2006;3:1077-1084.
4. Crane GM, Bennett NE Jr. Priapism in sickle cell anemia: emerging mechanistic understanding and better preventative strategies. *Anemia* 2011;2011:1-6.
5. Lane A, Devaras R. Potential risks of chronic sildenafil use for priapism in sickle cell disease. *J Sex Med* 2011. [Epub ahead of print]

Correspondence: twillia1@kumc.edu