Antioxidant effects of phosphodiesterase-5 inhibitors

This letter refers to ‘The phosphodiesterase-5 inhibitor vardenafil reduces oxidative stress while reversing pulmonary arterial hypertension’ by Y.-F. Fan et al., Cardiovascular Research (2013) 99, 395–403.

Fan et al. have shown convincing results indicating that the phosphodiesterase-5 (PDE5) inhibitor vardenafil reduces oxidative stress and this effect was associated with attenuation of chronic pulmonary hypertension (PH) in rats and in humans.

We would like to make the point that the results shown by Fan et al. may have underestimated the beneficial effects of PDE5 inhibition in their animal model of PH. This suggestion is based on the fact that they determined biochemical alterations associated with PH in samples from animals that survived the monocrotaline challenge. Since the mortality rate was higher in the control group of monocrotaline-induced PH that received saline (20% mortality rate) when compared with the monocrotaline-induced PH that received vardenafil (5% mortality rate), it is highly probable that their results underestimate the biochemical alterations associated with monocrotaline-induced PH. One could intuitively expect that greater differences between groups would have been found, had the authors studied animals before they died. Moreover, PDE5 inhibition could exert more efficient effects in those animals more severely deprived of endogenous nitric oxide (NO) formation (non-surviving animals), as the decrease in the mortality rate from 20 to 5% suggests. This idea is based on recent evidence suggesting that patients with the lowest levels of endogenous NO have the best responses to the PDE5 inhibitor sildenafil. Whether the same is true in patients with PH remains to be proved.

Another important finding is that the antioxidant effects associated with vardenafil are associated with significant changes in the expression of relevant enzymes involved in the regulation of oxidative stress including endothelial nitric oxide synthase (eNOS) and nicotinamide adenine dinucleotide phosphate oxidase (NOX). While these particular results may explain the effects reported by the authors, the antioxidant and antihypertensive effects of vardenafil may also involve other mechanisms not addressed by the authors. Importantly, we have previously shown that PDE5 inhibition with sildenafil attenuates acutely induced PH and this effect was associated with acute antioxidant effects. It is clear that the rapid (1–2 h) antioxidant effects that we found in our animal models of acute pulmonary embolism are not dependent on more delayed effects of sildenafil on the expression of enzymes involved in the regulation of oxidative stress. While the mechanisms explaining acute antioxidant effects associated with PDE5 inhibition are not clear at this time, they apparently contribute to reduce the increases in pulmonary vascular resistance.

References

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Antioxidant effects of phosphodiesterase-5 inhibitors: reply

We thank Dr. Tanus-Santos for his interest in our study.1 The study by Muniz et al.2 found that erectile dysfunction patients with the lowest levels of endogenous nitric oxide (NO) have the best responses to the phosphodiesterase-5 (PDE5) inhibitor sildenafil. We believe an equivalent situation exists in patients with pulmonary arterial hypertension (PAH). We found impaired NO production in the patients with PAH included in our study, suggesting that these patients are the best candidates to take advantage of the benefits of vardenafil treatment. This may be because vardenafil is a relatively selective pulmonary vasodilator, which exerts its effect on PAH by increasing levels of cyclic guanosine monophosphate (cGMP) and augmenting the NO-cGMP axis.

Monocrotaline (MCT)-induced PAH in rats may not fully represent PAH in humans; however, it is a well-established experimental model that has been extensively used.3 In our study, pathological alterations due to PAH became apparent 7 days after injection and thereafter progressively developed, leading to death ~4 weeks later. Vardenafil treatment not only improved survival, but also reduced the severity of PAH. Similar results were shown in the study by Schermuly et al.,4 the survival rate of the MCT group decreased gradually to 48% at Day 42, but fewer animals died in the MCT-sildenafil group when compared with the MCT group [survival rates: 70% (14/20) vs. 48% (12/25), respectively]. Vardenafil studies involving other animal models of PAH as well as in vivo and in vitro studies of related biochemical pathways that might be involved in PAH would be beneficial.

Tanus-Santos and colleagues reported that sildenafil attenuated acutely induced pulmonary hypertension and had antioxidant effects in animal models of acute pulmonary embolism. Indeed, the acute and chronic effects of PDE5 inhibitors were thought to result solely from their ability to increase cGMP levels preferentially in the pulmonary artery smooth muscle cells, thereby inducing relatively selective pulmonary vasodilation, in addition to antioxidant effects on the vessel wall. However, acute pulmonary
embolism and PAH have different pathologies and physiological effects. PAH is a multifactorial and progressive disease, which is characterized by a sustained increase in pulmonary vascular resistance. The lung tissue from patients with PAH is undergoing oxidative stress, including increased expression of nitrotyrosine and 8-hydroxyguanosine, decreased amounts of superoxide dismutase activity and endothelial NO synthase (eNOS), and increased amounts of a number of arachidonic acid metabolites. These changes cause an imbalance in NO production vs. consumption leading to NO insufficiency, and vardenafil may help to redress the balance by decreasing the continual consumption of NO via nitrotyrosine generation.

Studies of models of PAH have confirmed that sildenafil and tadalafil affect the NO-cGMP axis, but there is emerging evidence that sildenafil and tadalafil also normalize elevated levels of oxidative stress. Vardenafil, a new PDE5 inhibitor, has been shown to have a more potent pharmacodynamic effect than sildenafil in inhibiting PDE5. The elucidation of the exact mechanism by which vardenafil ameliorates PAH requires further investigation.

References

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