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Opinion

Role of Tadalafil in pH

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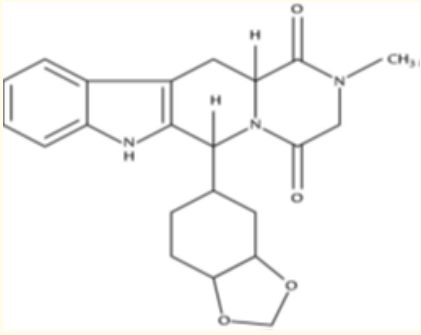
Introduction

Structural changes of the lung parenchyma and functional abnormalities in gas exchange lead to pulmonary hypertension (PH), with subsequent RV remodelling and hypertrophy. Increased pulmonary vascular resistance (PVR) is indispensable in causing RV dysfunction in chronic pulmonary disease. Chronic hypoxemia and the disruption of pulmonary vascular beds through parenchymal loss and fibrosis are the key mechanisms through which chronic lung disease increases PVR. Tadalafil has a longer half-life (t1/2 = 17.5h) and has a greater affinity for PDE-5 when compared with other PDE-5 inhibitors. In addition to vasodilatory and anti-prolif¬erative properties, tadalafil has anti-inflammatory actions and antioxidant effects making it an effec¬tive agent for the treatment of hypobaric hypoxia-induced pulmonary hypertension [1].

Mechanism of Action

Tadalafil acts through the NO-cyclic GMP pathway to increase cGMP, which is the final mediator in the NO-cyclic GMP pathway, and exerts vasodilatory and anti-proliferative effects on pulmonary vascular smooth muscles. In the pulmonary vasculature, cGMP works to activate cGMP-kinase, which results in K^+ channel activation and subsequently the inhibition of Ca^{++} channels, leading to a reduction of intracellular Ca^{++} and finally vasodilation. The PDE-5 isoenzyme specifically is the major cGMP-degrading PDE in the body and is also abundant in the lung tissue [2]. Tadalafil's chemical structure is;



Studies showing role of tadalafil in PH

In a study by Indrajeet., *et al*. [3] tadalafil significantly improved the 6-minute walk distance (336.7 ± 63.0 meters vs. 290.7 ± 54.4 meters, $p < 0.001$), Borg dyspnea score (2.9 ± 1.1 vs. 4.0 ± 1.2, $p < 0.005$), and the Borg fatigue score (2.8 ± 1.13 versus 3.8 ± 1.0, $p < 0.005$).

The quality of life also improved significantly in the tadalafil group (total St George's Respiratory Questionnaires score 44.3 ± 9.0 versus 55.8 ± 12.1, p < 0.0005). Tadalafil also improved resting and peak exercise arterial saturation.

A study in 405 patients with PAH was the first placebo-controlled trial using tadalafil with a favourable safety profile. In a 16-week, randomized, double-blind, placebo-controlled, multicentre, phase III trial in patients with PAH, Galiè., *et al*. [4] reported the effects of tadalafil alone or in combination with bosentan, an endothelin A and B receptor antagonist in the treatment of PAH (PHIRST trial). 405 patients were randomized to placebo, 2.5, 10, 20, or 40 mg of tadalafil daily and followed for 16 weeks. Fifty-three percent of enrolled patients were taking bosentan at the time of enrolment. The primary endpoint was the change from baseline in the 6MWD. Only patients randomized to 40 mg of tadalafil achieved the pre-determined level of statistical significance (P < 0.01) with an improvement in 6MWT of 33m (95% CI, 15 - 50m). Patients not taking bosentan improved by 44m (95% CI, 20 - 69m), and those taking bosentan improved by 23m (95% CI - 2 to 48m).

One another study over a 4-week period on the efficacy and safety of tadalafil compared with placebo in the treatment of PAH, tadalafil was associated with improvements in 6MWD (409.25 ± 40.25 m versus 319.37 ± 42.39 m, p < 0.0001), improvements in Borg Dyspnoea Index (BDI; 4.62 ± 2.56 versus 6.37 ± 2.61, p = 0.021), reduction in pulmonary artery systolic pressure (PASP; 88.75 ± 23.26 mmHg versus 109.5 ± 23.78 mmHg, p < 0.0001), and an improvement in the WHO functional class [5].

A case series of 12 patients with PAH (mean age, 45 years) switched from sildenafil therapy (100 - 150 mg daily) to tadalafil 10 to 20 mg daily was reported by Tay., *et al*. [6] After 3 to 6 months of tadalafil therapy, all patients had improvements in their 6MWD (mean change of 56.73m from baseline), NYHA score (8 patients with NYHA class II vs. 7 in post-sildenafil), and Borg dyspnea index (mean change of 3 points from baseline) compared to patients on sildenafil therapy. Although there was no significant difference reported for the 6-MWD and Borg index, between post-stabilization on sildenafil therapy and post-stabilization on tadalafil treatment (P = 0.98 and P = 0.486, respectively), worth noting was the switch in therapy to tadalafil being motivated by cost and in-convenience of sildenafil therapy.

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