Role of pravastatin in pulmonary hypertension in chronic obstructive pulmonary disease

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ABSTRACT

COPD (chronic obstructive pulmonary disease) is a significant health concern as the fourth leading cause of morbidity and mortality in the U.S.A. Although the prevalence of PH (pulmonary hypertension) in COPD is unknown, its presence is a risk factor for mortality. In this comment, we consider the role of PH in COPD and its pathophysiology, with reference to ET-1 (endothelin-1) and cigarette smoke, as well as exercise and nocturnal hypoxia. We also explore potential mechanisms for the observed improvement in exercise tolerance following 6 months of pravastatin treatment in COPD patients with PH as reported by Lee and co-workers in the present issue of Clinical Science, including possible effects upon ET-1 and Rho kinase, or antioxidant effects, which may be particularly relevant in this group of mainly current smokers.
mortality. There is gathering evidence that blockade of the ET-1 system may also benefit patients with PAH in association with Eisenmenger syndrome, connective tissue disease, HIV and thromboembolic disease.

ET-1 also has potent bronchoconstrictive properties, and has been implicated in the pathogenesis of airways disease. The role of ET-1 in the pathophysiology of COPD remains uncertain and may be related to its effect upon bronchoconstriction or its pro-inflammatory properties. Plasma ET-1 levels are elevated in COPD patients compared with control subjects [16]. Plasma ET-1 increases during acute exacerbations and falls following 1 h of oxygen replacement. Patients with COPD with nocturnal desaturation have higher day and night ET-1 plasma levels [17]. It is possible that ET-1 may contribute to the development of PH in COPD; however, reports of ET-1 levels in PH in COPD have been conflicting, with one study showing no difference in levels among patients without or with PH [18], and another demonstrating increased exhaled and arterial ET-1 levels in patients with PH (with ET-1 levels correlating with echocardiographic systolic PAPs) [19]. There has been one randomized study investigating the effect of bosentan (compared with placebo) on cardiopulmonary haemodynamics during exercise in patients with severe COPD, but importantly with no resting PH [20]. There was no improvement in the 6-min walk test, the primary outcome measure. In addition, there was deterioration in oxygenation and quality of life, with no change in PAP [20].

Statins, HMG-CoA (3-hydroxy-3-methylglutaryl CoA) reductase inhibitors, including pravastatin, block the rate-limiting step in cholesterol synthesis; however, their benefit clearly extends beyond the effect upon lowering cholesterol. Statins have ‘pleiotropic’ effects, including the improvement in endothelial dysfunction, inhibition of vascular smooth muscle proliferation and induction of vascular smooth muscle cell apoptosis. The mechanisms by which these effects occur is uncertain, but appears to be related to the inhibition of synthesis of small GTP-binding proteins required for the activation of RhoA. This, in turn, leads to the reduction in eNOS (endothelial NO synthase) and decreased NO production, and subsequent vasoconstriction. Moreover, RhoA/Rho-kinase signalling plays an important role in the sustained phase of vasoconstriction mediated by ET-1. Although statins prevent and ameliorate PH in animal studies [21], there are no data for their use in the treatment of PH from any cause.

In this context, the study by Lee et al. [22] in the present issue of Clinical Science sets out to test the hypothesis whether statins improve haemodynamics in COPD patients with PH by affecting ET-1 synthesis. This was based on a previous observation that statins inhibit prepro-ET-1 transcription in vitro [23]. A total of 53 patients with stable COPD [FEV1 (forced expiratory volume in 1 s) 56% predicted] and PH (defined as a systolic PAP >35 mmHg by echocardiography) were randomized to receive either pravastatin or placebo in a double-blind manner over a period of 6 months. Exercise capacity, tested using a Naughton stress test treadmill protocol, was significantly improved in the pravastatin-treated group (from 660 to 1006 s; P < 0.0001) while remaining static in the placebo group. Systolic PAP fell significantly from 47 to 40 mmHg, and the Borg dyspnoea index was also improved. There was no change in plasma ET-1 levels measured in the peripheral vein, but a slight decrease in urinary excretion of ET-1. There was a significant correlation between changes in exercise time and levels of ET-1 excreted in the urine. The main conclusion of the authors was that “pravastatin significantly improved exercise tolerance, and decreased PH and dyspnoea during exercise, probably by inhibiting ET-1 synthesis in COPD patients with PH”.

So where does this leave us with the story of COPD, PH and ET-1? The most impressive finding of the study by Lee et al. [22] was the improvement in exercise capacity in patients receiving pravastatin. Was this due to an improvement in PH? Of course, the study was not designed to answer this question. We note a parallel study published by the same authors [24] in which a similar benefit was demonstrated across COPD patients independent of the presence of PH. In addition, given the modest elevation in systolic PAP in patients at the beginning of the study, it is unlikely that PH was the limiting factor and, therefore, that the improvement in PH upon treatment was the reason for improved exercise capacity. The caveat to this statement is that we do not know whether pravastatin (acutely and with time) ameliorates the transient elevation in PAP observed upon exercise, which is a known risk factor for the development of resting PH in COPD [6]. In addition, as the authors note, it is difficult to assess the therapeutic benefit with regard to PH in the absence of the resting, exercise and nocturnal oxygen levels.

What about the role of ET-1? In the study by Lee et al. [22], there was no change in venous plasma ET-1 with treatment. As most ET-1 is produced in the lung, perhaps a better measure would have been trans-pulmonary ET-1 production (i.e. comparisons of central venous and arterial samples). However, a reduction in renal excretion of ET-1 was observed, although, as the authors stated, the magnitude was not enough to explain the change in exercise capacity (R² = 0.22). It is difficult to propose how a reduction in renal excretion of ET-1 would account for the improved exercise capacity. The authors note that urinary ET-1 excretion correlates with global ET-1 levels, and may be more sensitive to changes in overall endogenous ET-1 production than serum ET-1 levels.

However, the beneficial effect of pravastatin is more likely to be independent of ET-1. The authors [22] mention two possible alternative mechanisms in which pravastatin may affect vascular function: oxidative...
stress and the Rho-kinase system. Oxidative stress is increased in COPD, and is obviously important in cigarette-induced vascular injury. Statins may reduce free radical generation. In this cohort of mainly (81 %) current smokers, any antioxidant mechanisms may have been particularly effective. It would be interesting to determine whether a similar benefit is seen in ex- or never-smokers. Statins are also known to effect apoptosis of vascular cells, which may have a longer-term effect on vascular remodelling.

In summary, the most exciting finding from the study by Lee et al. [22] is the beneficial effect of pravastatin on exercise capacity in COPD patients with PH. The exact mechanism of this benefit is uncertain, as is the contribution of PH. The role of ET-1 in PH in association with COPD is also unclear and some doubt has already been cast on the usefulness of ET-1 receptor antagonists in this condition. Clearly, more work needs to be done on the contribution of exercise-induced increases in PH in COPD and the effect of this upon exercise capacity. In addition, we need to study the importance of ET-1 and blocking its action in COPD patients with moderate-to-severe PH, although this appears to be a minority group.

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