

## Losartan and nifedipine therapy in patients with secondary pulmonary hypertension

### *Sekonder pulmoner hipertansiyonu olan hastalarda losartan ve nifedipin*

Pulmonary arterial hypertension (PAH) is a debilitating chronic disease of the small pulmonary arteries that is characterized by vasoconstriction and vascular remodeling (1). Endothelial dysfunction is believed to occur early on in disease pathogenesis, leading to endothelial and smooth muscle cell proliferation and structural changes or remodeling of the pulmonary vascular bed resulting in an increase in pulmonary vascular resistance. PAH is either idiopathic or occurs in association with various conditions such as connective tissue diseases, HIV infection, portal hypertension, chronic hypoxic pulmonary disease, left heart disease, and left-to-right congenital shunts. Although some pathophysiological properties of PAH related to these diseases are similar especially in the terminal phase, mechanisms of increase in pulmonary arterial pressure (PAP) and thereby appropriate treatment are different according to etiology, especially in early phase of the diseases.

It is important to consider that most of studies regarding histopathological properties and proper treatment in PAH have been done in idiopathic PAH. The results of these studies may not be valid for PAH that related to other etiologies. Especially, mechanism of PAH in left heart disease, i.e. systolic/diastolic dysfunction or valvular heart disease, is different from idiopathic PAH. Early increase in PAP is related to increase in pulmonary capillary wedge pressure, and reactive pulmonary arterial vasoconstrictive state without vascular structural changes. This could trigger some mechanisms within the lungs that result in a disproportionate permanent increase in the PAP for later time. Pulmonary arterial structural changes occur in very late phase of the disease. The mechanism of PAH in hypoxemic pulmonary diseases, i.e. chronic obstructive pulmonary disease, is also different.

Among the mechanisms of increase in PAP, the expression of angiotensin converting enzyme has been reported to be increased in pulmonary arteries of PAH patients (2, 3) with a functional predominance at the site of arteriolar remodeling (4). Angiotensin II stimulates hypertrophy of human pulmonary

artery smooth muscle cells in culture (4). It is thus possible that angiotensin II contributes to abnormal pulmonary vascular tone and remodeling in PAH.

In humans, there have been but a few studies on the effects of renin-angiotensin system blockers on PAH; almost all have involved acute administration of angiotensin converting enzyme inhibitors, and different findings have been reported (5-7). A study using losartan in PAH secondary to chronic obstructive pulmonary disease was also in the acute setting and oral dosing with losartan (50 mg) produced a significant reduction in mean PAP and total pulmonary vascular resistance (8). On the contrary, a pilot study to evaluate the effects of losartan on PAP, exercise capacity, quality of life, arterial blood gases and safety did not demonstrate any benefit in patients with cor pulmonale secondary to severe chronic obstructive pulmonary disease (9).

In this issue of Anatolian Journal of Cardiology, Bozbaş et al. presented a study results implying that losartan is non-inferior to nifedipine for reducing PAP and improving exercise capacity in patients with secondary PAH (10). The patients with PAH enrolled in the study were in two very different conditions that lead to increase in PAP by different mechanisms, namely hypoxemic lung disease and left heart diseases. Therefore, it is expected that the effects of losartan and/or nifedipine on PAP may be different between the groups. But, it is not clear that the effects of the drugs were similar between patients with left heart disease and those with hypoxemic lung disease. Beyond the total number of the study group, the number of the patients with hypoxemic lung disease was too low to separately analyze the effect of both drugs on PAP and the other variables in this group. To obtain a clinical implication, the effect of the drugs would be compared separately in each patients group. According to the findings of the study, it is reasonable to say that the effects of losartan and nifedipine on PAP and exercise capacity are similar in a patient group of secondary PAH, majority of which was due to left heart disease. This result may not be valid for other conditions that cause PAH.

When treating the PAH of left-sided heart disease, the first goal is the underlying primary cause. In the context of PAH related to congestive heart failure, one should first look to maximize medical management for the primary condition with consideration being given to diuresis, nitrates, and/or other systemic vasodilators, i.e. renin angiotensin system blockers. Especially in patients who had not previously been given any treatment, at least optimal treatment for heart disease, substantial decrease in PAP can be obtained by only a diuretic (11). More than this may be achieved by an agent that has hemodynamic and neurohormonal effects. In the study by Bozbaş et al., the decrease in PAP with losartan in patients with left heart disease might have also been resulted mostly of its beneficial hemodynamic and neurohormonal effects on left heart disease (10). The findings of the study are not enough to discriminate whether losartan decreases PAP via direct effect on pulmonary arterial tree or indirect effect through left heart disease.

The use of pulmonary vasodilators has also been explored in patients with left heart disease. The Flolan International Randomized Survival Trial (FIRST) of intravenous epoprostenol for heart failure showed no improvement in distance walked, quality of life, or morbid events and a trend to an increased mortality in patients receiving the study drug (12). Bosentan has also been subjected to trial for patients with congestive heart failure with no demonstrable improvement in mortality rate or hospitalizations, and with worsened fluid retention. Sildenafil has also been evaluated in heart failure with reductions in PAP and pulmonary capillary wedge pressure being demonstrated; it therefore appears to have promise in this capacity (13). The last PAH drug mentioned as a potential agent in the context of congestive heart failure was sitaxsentan, which also shows some promise (14).

Calcium channel blockers are primarily advised to patients with idiopathic PAH among groups of patients with PAH. However, it might be harmful in most of patients with idiopathic PAH. The occurrence of life-threatening hemodynamic compromise by acute vasodilator challenge with calcium channel blockers is well documented. In daily practice, calcium channel blockers therapy is still sometimes considered in patients who do not entirely meet current guidelines for use of calcium channel blockers (15). In patients with PAH due to secondary causes, i.e. left heart disease and chronic obstructive pulmonary disease, effects of this group of drugs on symptoms and survival is not certain.

In conclusion, mechanisms for PAH are different according to various etiologic disorders. Therefore, drugs should be tested in these etiologic disorders in separate manner. Renin angiotensin system blockers may have a role for reducing PAP in some forms of the PAH, and take a place in addition to the approved drug classes for PAH.

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