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The Fixed Combination of Aliskiren and Nebivolol in Hypertensive Patients: The Clinical Perspectives

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Abstract

Various antihypertensive treatment regimens, chosen as part of usual care, might distinguish in their clinical efficacy. Pharmacological modeling of high-level activity of the renin-angiotensin system (RAS) in arterial hypertension often makes it possible to effectively monitor patients with elevated blood pressure (BP). The aim of the mini review is summarize knowledge regarding perspectives to use of combined antihypertensive drug contained the direct renin inhibitor (aliskiren) and selective β1-blocker (nebivolol). However, the data regarding co-administration of both drugs are very limited. Recent pre-clinical studies have been shown that concomitant co-administration of aliskiren and nebivolol given in fixed combination did not form any active chemical complexes with novel pharmacological abilities. The clinical data are confirmed a high BP lowering activity of fixed combination of aliskiren and nebivolol associated with desirable level of tolerability and safety. The review is concluded that there is rationale of creating a combined remedy containing aliskiren (150 mg) and nebivolol (5 mg). High BP lowering efficacy, safety and tolerability of aliskiren and nebivolol combined drug in hypertensive patients might emphasize the great potential of its clinical application

Keywords: hypertension, renin-angiotensin system, aliskiren, nebivolol

Hypertension is one of the major risk factor able to promote development and progression of several cardiovascular diseases [1]. Although large long-term clinical trials conducted in the last several decades have identified a number of effective antihypertensive treatments that reduce the risk of future clinical complications, responses to therapy and protection from cardiovascular events vary among individuals [2]. Various antihypertensive treatment regimens, chosen as part of usual care, might distinguish in their clinical efficacy. It is well known that chronic activation of the renin-angiotensin system (RAS) is deeply involved in the pathophysiology of diseases of vasculature, heart, kidneys and others and it plays a crucial role in the development of various cardiovascular (CV) diseases [3]. Pharmacological modeling of high-level activity of RAS in hypertension makes it possible to effectively monitor patients with elevated blood pressure (BP). For this purpose is used angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), and direct renin inhibitors.

One of the important problems of the treatment of patients with hypertension with RAS antagonists is the development of «escape phenomenon», which is associated with attenuation of positive BP lowering effects and limitation of target-organs' damage of the drugs within long-term period [4]. Both ACE inhibitors and ARBs have been shown to reduce target organ damage in organs such as the kidney, brain and heart, and to decrease CV mortality and morbidity in patients with heart failure. However, recent clinical guidelines are not considered rationale to use both drug classes in combination that is result a large body of evidence regarding increased frequencies of terminal kidney injury [5]. In this context, the discovery of novel regime of antihypertensive approaches is attractive.

There are increased interest regarding the combined use of the direct renin inhibitor (aliskiren) and selective β1-blocker (nebivolol) [6, 7]. This combination gives the perspectives of a full control or RAS activity, the sympathetic-adrenal system (SAS) activity, which are considered a clue for improvement of the prognosis in hypertensive patients. The aim of the mini review is summarize knowledge regarding perspectives to use of combined antihypertensive drug contained the direct renin inhibitor (aliskiren) and selective β1-blocker (nebivolol).

Apart from BP lowering effect [6] aliskiren was found to have potentially anti-atherosclerotic in non-diabetic patients with hypertension [7], slightly increase cortical and medullary renal tissue oxygenation in hypertensive patients [8], and exert protective effects on small arteries [9]. However, there was not particularly supported similar approach in hypertensive diabetic patients [10].

In addition to cardioselectivity mediated via β1 receptor blockade, nebivolol stimulates nitric oxide (NO) and thereby improves endothelial function in patients with hypertension when compared with other β1-blockers [11]. While β-blockers are not recommended within the current US guidelines as first-line therapy for treatment of hypertension, in EU nebivolol is recommended [12]. Moreover,

nebivolol has shown comparable efficacy to currently recommended therapies in lowering peripheral blood pressure in adults with hypertension with a very low rate of side effects. Interestingly, that patients with hypertension who switch from the second-generation antihypertensive metoprolol to the third-generation hypertensive nebivolol have significantly lower CV-related healthcare resource utilization (i.e, emergency department and outpatient visits) and lower CV-related medical costs [13].

However, the data regarding co-administration of both drugs are very limited. Recent pre-clinical studies have been shown that concomitant administration of aliskiren and nebivolol given in fixed combination did not form any active chemical complexes with novel pharmacological abilities [14-17]. With the semi-empirical quantum-chemical method PM7, which was optimized for calculations of organic molecules and their complexes and then implemented using the MOPAC-2012 program, we previously assayed energy of intra- and intermolecular interactions between both molecules aliskiren and nebivolol given in fixed combination. We confirmed that reacting aliskiren and nebivolol and their cations does not result in chemical reactions to form covalent bonds, but this reaction ends with the formation of a labile complexes, which are linked by weak intermolecular forces (mainly van der Waals and electrostatic) and easy to dissociate in solution.

Nalotova O.S. (2014) [18] reported that combined therapy of moderate-to-severe hypertension using combination of aliskiren (150 mg/daily) and nebivolol (5 mg/daily) within 8 weeks has associated with being of additional BP lowering effect compaired with using of each drug alone. Therefore, it has confirmed that treatment of hypertensive subjects with aliskiren and nebivolol may relate with improvement of daily BP profile and high tolerability within at least 12 weeks [19]. Thus, there was a rationale in use of fixed combination of both drugs.

In conclusion, the preliminary results indicate that there is rationale of creating a combined remedy containing aliskiren (150 mg) and nebivolol (5 mg). High BP lowering efficacy, safety and tolerability of aliskiren and nebivolol combided drug in hypertensive patients might emphasize the great potential of its clinical application.

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