Tropical Journal of Pharmaceutical Research, April 2009; 8 (2): 181-186

Available online at http://www.tjpr.org

Review Article

Nebivolol might be Beneficial in Osteoporosis Treatment: A Hypothesis

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Abstract

Nebivolol is a β-blocker that is highly selective for β1-adrenergic receptors with vasodilating properties. This property can be attributed to an endothelial release of nitric oxide (NO). It has been reported that nebivolol also reduces intracellular oxidative stress. There are some studies conducted in humans and animal models which have shown that NO is an important regulator of bone metabolism. However, oxidative stress and antioxidant systems may play important roles in the pathogenesis of osteoporosis. In this paper, we hypothesized that nebivolol may have beneficial effects via nitric oxide and antioxidant action in osteoporosis treatment.

***Key Words**: Osteoporosis treatment, Nebivolol, Nitric oxide, Anti-oxidant action*

Received: 20 September 2008 *Revised accepted:* 22 November 2008

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Introduction

There is a balance in the activities of various types of bone cells that is carefully coordinated by several hormones and cytokines termed 'bone remodeling'. Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue leading to increased bone fragility and may result in an increased risk of fracture[1].

Postmenopausal osteoporosis has been described by Fuller Albright[2] as the consequence of impaired bone formation due to oestrogen deficiency. Oestrogen induces endothelial nitric oxide (NO) production[3], and the protective effect of estrogen in bone may be mediated in this way. NO stimulates osteoblast proliferation[4]. There are several drugs that are used for osteoporosis treatment. We think that nebivolol may be a choice in osteoporosis treatment by acting via NO.

Mechanism of Action of Nebivolol and Nitric Oxide

Beta-blockers are one of the drugs of choice for the treatment of hypertension[1], and have been commercially available for nearly fifty years. Recently, several beta-blockers with different mechanisms of action and antihypertensive efficacy have come into use. Beta-blocker mechanisms are very interesting. Reta-blockers are used for hypertension treatment and the basis is the inhibition of renin by beta-blockers, especially at high doses, in the juxtaglomerular apparatus. They also have some central effects because of central inhibition of the sympathetic nervous system[3].

In hypertensive efficacy, beta1-selective agents may be more effective than non-selective beta-blockers. These include some among the third generation betablockers such as labetolol, carvedilol, bucindolol, and nebivolol. Currently, nebivolol is the newest of the beta-blockers with long acting properties; it is also a highly cardioselective beta1-blocker and is different from earlier drugs in the same family. Nebivolol consists of a 1:1 racemic mixture of d- and l-enantiomers, of which D-nebivolol is a highly selective beta1-receptor antagonist. D-nebivolol shows an over 100-fold greater affinity for β1-adrenoreceptors than l-enantiomer[4]. The vasorelaxant action of nebivolol is mediated by not only its main pharmacodynamic property as an adrenergic receptor antagonist, but also through the stimulation of nitric oxide (NO) release from vascular endothelium[5,6]. In particular, the l-form possesses an endothelium-dependent vasorelaxant effect[7]. However,some studies indicate that nebivolol is able to induce a remarkable production of NO in vessels via the dextro-rotatory isomer. NO production is realized through the activation of the endothelial nitric oxide synthase via calcium mobilization[8].

In addition nebivolol has been shown to cause endothelium-dependent vasodilation associated with activation of the L-arginine/nitric oxide (NO) pathway in both hypertensive and normotensive subjects[9,10]. Although the molecular mechanisms that could explain this proposed action of nebivolol on NO release have not been clarified, NO release can be induced by two different intracellular mechanisms. These mechanisms consist of the enzyme endothelial nitric oxide synthase (eNOS) either by its interaction with the Ca2–calmodulin complex[11], or by its calcium-independent phosphorylation[12].

The endothelial effect of nebivolol may result from the activation of different receptors such as β-2 and β-3 adrenoreceptors[9,13-15], oestrogen receptors of plasma membrane[16], 5-hydroxytryptamine 1A receptors[17] as commonly found for other β blockers, and P2Y purinoceptor[6]. In various studies, it has been shown that nebivolol causes vasodilation through endothelial β2 adrenergic receptor–mediated NO production and/or ATP efflux with consequent stimulation of P2Y-purinoceptor–mediated NO release[6,9] nebivolol inhibits NO synthase uncoupling[18].

However, its vasodilating effect depends on soluble guanylyl cyclase inhibitors[19,20].

Besides the vasodilating effect of nebivolol, it has antioxidant activity and its mechanism is due to direct reduction of reactive oxygen species (ROS) that is produced by Nicotinamide adenine dinucleotide phosphate NADPH oxidase system[21]. Moreover, it was reported that nebivolol decreases systemic oxidative stress in young healthy volunteers[22].

Nebivolol is a lipophilic agent and is metabolized in the liver. It is transformed into several active metabolites, essentially via the cytochrome P450 2D6 (CYP2D), an isoform of cytochrome P450 characterized by genetic polymorphism[23]. It was suggested that only some hepatic metabolites, not the parent drug, is reponsible for NO production by activating β2-adrenergic receptors[9]. Epidemiological studies have indicated a higher prevalence of cardiovascular risk factors among African-Americans. In order to understand the basis for this difference, low bioavailability of NO from the endothelium of African-Americans was reported despite much higher levels of endothelium-dependent NO synthase (eNOS)[24]. The observed higher prevalence of cardiovascular risk factors and their complications among African-Americans may be explained by this polymorphism.

Nebivolol is able to induce a significant increase in NO which is the main endogenous mediator of vasorelaxation in conductance (aorta) and in resistance (mesenteric) arteries[8], renal artery[13], rats, bovine aorta and small mesenteric arteries[11,19,25], canine coronary, carotid artery[26] and murine corpus cavernosum[27]. Some studies had shown that nebivolol causes NO-dependent vaso-dilation[5,6,9,11,12]. Moreover, Maffei *et al* have directly observed nebivolol-induced NO production through a NO-specific visualization technique[8]. It was demonstrated that nebivolol exerts an agonist activity on β3 adrenoreceptors to induce sustained NO production through increases in cytosolic calcium concentrations and dephosphorylation of threonine 495 endothelial NO synthase (Thr495-eNOS)[14]. The novel β-blocker nebivolol has been shown to increase synthesis and release of endothelium-dependent NO which plays an important role in the regulation of vascular structure, tone, and function, and endothelial dysfunction which plays an important role in the pathogenesis of hypertension and cardio vascular disease (CVD).

Nitric oxide and Osteoporosis

Nitric oxide (NO), a type of short-lived signaling molecule, plays important roles in several biological processes including bone cell functions. The production of NO from L-arginine is catalyzed by nitric oxide synthase (NOS) that has three isoforms: neuronal (nNOS), inducible (iNOS), and endothelial (eNOS)[28].

Postmenopausal osteoporosis has been described as the consequence of impaired bone formation due to oestrogen deficiency. oestrogen seems to be important in the stimulation of osteoblast proliferation and differentiation via the NO and NOS pathway[29,30,31]. Although, some studies reported that NO is an important regulator of bone metabolism[32-35], the results of these studies are controversial. The studies conducted on the effect of NO on bone cell functions showed that bone cells produce NO in response to various stimuli including oestrogens, pro-inflammatory cytokines, and mechanical stress[33-37] and in this regard, different types of NOS play a role. endothelial NO synthase (ENOS) is the major nitric oxide synthase enzyme expressed in bone by osteoblasts, osteoclasts, and osteocytes, and expressed with estrogen-related receptor alpha (ERRα) in all these bone cells[36]. However, it was suggested that ERRα up-regulates endothelial nitric oxide synthase (eNOS) mRNA and protein expression in bovine pulmonary artery endothelial cells via a DNA site[38].

NO release in osteoblastic cells increases cyclic guanosine monophosphate (cGMP) formation and cGMP signal regulates osteoblastic proliferation and differentiation[39]. Pan et al. showed that phytooestrogen, genistein, stimulates osteoblastic differentiation via NO/cGMP in primary mouse bone marrow-derived mesenchymal stem cell cultures[40]. Resveratrol is a naturally occurring polyphenol that possess estrogenic activity, suggesting that it may possess similar functions as oestrodiol (E2) on NO synthesis and osteoblastic metabolism[29]. Some studies suggested that treatment for 24 hours with E2 causes increased eNOS expression[41,42].

In vitro, NO is produced by osteoblasts and stimulates their proliferation[41]. NO has biphasic effects on bone resorption. Although, low levels of NO production may be essential for normal osteoclast function and maturation, cytokine-induced NO has been found to inhibit proliferation of osteoblasts[43]. It was reported that nitroglycerin ointment was as effective as estrogen in preventing bone loss in women with oophorectomy-induced menopause[44], and taking nitrates increased hip bone mineral density (BMD) in women[45]. Moreover, ovariectomy-induced osteopaenia can be reversed by NO donor nitroglycerin in rats[46,47]. Corticosteroid-induced bone loss was also prevented by NO donor nitroglycerin in male rats[48].

NO inhibits the osteoclasts, thus greatly increasing bone deposition. Vitamin K and magnesium (Mg) also have similar effects[49]. It is fact that oral administration of L-arginine in pharmacological doses stimulates growth hormone and insulin-like growth factor-I responses, and increases nitric oxide synthesis. Since nitric oxide is a potent inhibitor of osteoclastic bone resorption, L-arginine could increase bone mass. Therefore, it is hypothesized that oral supplementation of L-arginine may be a new strategy in the prevention and treatment of osteoporosis[50].

Conclusion

Previous studies have reported that oxidative stress and antioxidant systems play important roles in the development of osteoporosis[51,52]. We also know about the role of NO in the pathogenesis of osteoporosis**.** Nebivolol is able to induce a significant increase in NO which is the main endogenous mediator of vasorelaxation in various tissues. Furthermore, NO may have beneficial effects on osteoporosis. In the light of the available information, we hypothesized that nebivolol may be benefical via nitric oxide in osteoporosis treatment. However clinical studies and investigations are required to confirm this.

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