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Review Article

PHARMACOKINETICS AND PHARMACODYNAMICS OF NEBIVOLOL- A THIRD GENERATION β-BLOCKER

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Abstract: Nebivolol is a newer third generation β-blocker, which is highly selective for the β_1-adrenoceptor. Nebivolol differs chemically from all other β-blockers with a hydroxypropanolamine substructure in that its cardiac antihypertensive activity resides in the *R*-enantiomer at the hydroxy group, whereas all other β-blockers have antihypertensive activity in the *S*-enantiomer and is marketed as d-nebivolol (+SRRR nebivolol) and l-nebivolol (–RSSS nebivolol). The d-enantiomer is responsible for the beta-blocking properties whereas the l-enantiomer induces a vasodilation via a nitric oxide (NO) mechanism. Nebivolol is a unique agent for the management of patients with hypertension, coronary heart disease or congestive heart failure. This paper reviews the Pharmacokinetics, Pharmacodynamics and additional pharmacologic actions of nebivolol.

Key**words:** Nebivolol, β_1-adrenoceptor, Hydroxypropanolamine, Vasodilation, Hypertension, Coronary heart disease

INTRODUCTION

Nebivolol is a third generation β-blocker which is a newer cardioselective beta- blocking agent that is highly selective for the β_1-adrenoceptor. This compound is a dl-racemic mixture. The d-enantiomer is responsible for the beta-blocking properties whereas the l-enantiomer induces a vasodilation via a nitric oxide (NO) mechanism. Nebivolol is an unique agent that appears promising for the management of patients with hypertension, coronary heart disease or congestive heart failure [1]

Nebivolol differs chemically from all other β-blockers with a hydroxypropanolamine substructure in that its cardiac antihypertensive activity resides in the *R*-enantiomer at the hydroxy group, whereas all other β-blockers have antihypertensive activity in the *S*-enantiomer [2]**.** The nebivolol molecule contains four chiral centers and is marketed as d-nebivolol (+SRRR nebivolol) and l-nebivolol (–RSSS nebivolol). Both enantiomers act synergistically with respect to blood pressure reduction: the effect of nebivolol on heart rate is exclusively exerted by d-nebivolol, with these hypotensive effects enhanced by the addition of the l-enantiomer, which in itself does not influence systolic and diastolic blood pressure. Furthermore, this pronounced and lasting blood pressure reduction is roughly equal to the effect of conventional β-blockers in high doses. In certain vascular districts, nebivolol stimulates endothelial nitric oxide (NO) synthesis, thereby increasing the availability of NO in the endothelium, smooth muscle, and platelets and, consequently, producing a sustained vasodilation, with decreases in peripheral resistance and blood pressure. L-nebivolol also increases NO availability under conditions of oxidative stress by the inhibition of endothelial NO synthase (eNOS) uncoupling, thereby reducing NO inactivation. Furthermore, neither nebivolol nor its enantiomers show any intrinsic sympathomimetic activity and undesirable β-blocker effects, such as a decrease in cardiac output, which do not occur or are less pronounced with the combination of d-nebivolol and l-nebivolol [3]**.**

PHARMACOKINETIC PROPERTIES [4]:

Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. This has less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), contribute to β-blocking activity.

Absorption and Distribution

The absolute bioavailability has not been determined.Mean peak plasma nebivolol concentrations occur approximately 1.5 to 4 hours post-dosing in EMs and PMs.

Food does not alter the pharmacokinetics of nebivolol. Under fed conditions, nebivolol glucuronides are slightly reduced. Nebivolol may be administered without regard to meals. The in vitro human plasma protein binding of nebivolol is approximately 98%, mostly to albumin, and is independent of nebivolol concentrations.

Metabolism and Excretion

Nebivolol is predominantly metabolized via direct glucuronidation of parent and to a lesser extent via N-dealkylation and oxidation via cytochrome P450 2D6. Its stereospecific metabolites contribute to the pharmacologic activity.

After a single oral administration of nebivolol, 38% of the dose was recovered in urine and 44% in feces for EMs and 67% in urine and 13% in feces for PMs. Essentially all nebivolol was excreted as multiple oxidative metabolites or their corresponding glucuronide conjugates.

Mechanism of Action

Nebivolol is a novel selective beta-blocker with a much higher affinity for beta-1 adrenergic receptors than for beta-2 adrenergic receptors. Among all the beta-blockers in clinical use today, nebivolol has the highest selectivity for beta-1 receptors [5].

Clinically, nebivolol is administered as a racemic mixture of equal proportions of "d" and "l" isomers. Nebivolol has 4 asymmetric centres, d- isomer refers to (S, R, R, R)-nebivolol and l- isomer to (R, S, S, S)-nebivolol. The enantiomers have unequal potency with regard to β-receptor blocking activity and nitric oxide mediated vasodilation. The combination has greater antihypertensive activity than either enantiomer alone.

Nebivolol binds to the β_1 receptor on cell membrane leading to activation of adenyl cyclase resulting in accumulation secondary messenger cAMP. This cAMP dependant protein kinase coupling of nitric oxide synthase [NOS] increases NO production via L- arginine/ NO pathway. Phosphorylates specific proteins causing modification of action. Nebivolol has an endothelium dependent vasodilatory effect, which is mediated via the L- arginine /NO pathway [6, 7].

Nebivolol induces nitric oxide production via activation of β_3 adrenergic receptors [10]. This activates phospholipase C, which breaks down the membrane phospholipid PIP2 (Phosphotidyl inositol bisphosphate) to IP3 (Inositol triphosphate) and DAG (Diacyl-glycerol) releases calcium from endoplasmic reticulum producing an increase in free cytoplasmic calcium which binds to calmodulin, this calcium-calmodulin complex is responsible for stimulating nitric oxide synthase (NOS),which acts as a catalyst.

L-arginine + O_2 + NADPH NOS ⟶ L-citrulline +NO+NADP

The enzyme consists of two domains the oxygenase domain and the reductase domain. It requires flow of electrons for its function.

NADPH→ Flavin adenine dinucleotide→ Flavin mononucleotide (FMN)

(FMN) →heme →O_2

Binding of calmodulin to NOS has been shown to regulate the catalytic activity by triggering electron flow from FMN to heme, thereby coupling the oxygenase and reductase domains,thus nebivolol prevents NOS uncoupling. Metabolites of the drug cause a significant increase in free calcium content of endothelial NO synthase dependent NO Production. This mechanism leads to effective control of blood pressure by vasodilatation of blood vessels [7, 8].

Other actions produced by nebivolol

It has a protective effect on left ventricular function. It reduces preload, afterload and increases stroke volume. It decreases pre-ejection period and lengthens left ventricular ejection time. Reduces cardiac output and total peripheral resistance when given at the dose of 5mg once daily [9, 10] , Decreases resting heart rate and reduces exercise induced tachycardia [11], Reduces total cholesterol and low density lipoprotein, Nebivolol has benefits for heart failure patient [12]

In addition, nebivolol has no negative effects on chronic obstructive pulmonary disease, erectile function, and glucose and lipid metabolism. It also has an antioxidant, antiproliferative and antithrombotic properties.

PHARMACOLOGICAL ACTIONS

Nebivolol is selective for the beta1-adrenergic receptor in extensive metabolizers (most of the population) and at doses less than or equal to 10 mg (in poor metabolizers and at higher doses nebivolol inhibits both beta1- and beta2-adrenergic receptors). Once-daily dosing of nebivolol significantly reduces systolic blood pressure (SBP) and diastolic blood pressure (DBP) [13, 14, 15 , 16]

At therapeutically relevant doses, nebivolol lacks intrinsic sympathomimetic and membrane-stabilizing activity. Like carvedilol, nebivolol also exhibits vasodilatory effects through activation of the L-arginine/nitric oxide pathway. NO is an intrinsic vasodilator produced in the vascular endothelium; endothelium-derived NO is important in the regulation of large arterial stiffness, which in turn is a major risk factor for cardiovascular disease.Nebivolol enhances nitric oxide bioavailability and improves endothelial function, leading to a reduction in arterial stiffness. Beneficial hemodynamic effects are observed, such as reductions in central aortic blood pressure when arterial stiffness is decreased [17]. Further, data demonstrate nebivolol's antioxidant property, enabling it to decrease markers of oxidative stress. It also modulate the endothelial dysfunction usually seen in hypertension.

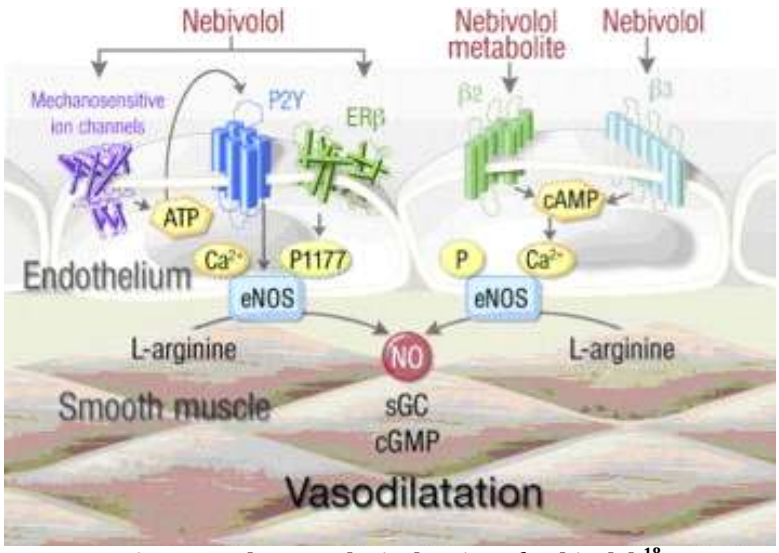

Figure 1: Pharmacological action of nebivolol [18]

Mechanisms Underlying Release of NO in Response to Acute Nebivolol Challenges In renal glomeruli, nebivolol activates mechanosensitive ion channels, which subsequently release adenosine triphosphate (ATP) and stimulate P2Y receptors, causing calcium-dependent eNOS activation. Nebivolol or its metabolite may also activate β_2 (in conduit arteries) (22) or β_3-receptors (in resistance arteries), which also increase intracellular calcium, thereby activating eNOS. cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; ERβ = estrogen receptor beta.

ADDITIONAL ACTION OF NEBIVOLOL

1. **Antioxidant mechanism of Nebivolol.**

   Nebivolol has shown recently to exhibit antioxidant properties [19]. In vitro stimulation of the β_2- receptors on endothelial cells by nebivolol metabolites increased endothelial [ca^{2+}] levels and, accordingly, NOS III activity. Hence the recent review showed that the chronic treatment with nebivolol could normalize vascular superoxide formation as well as endothelial dysfunction in heritable hyperlipidemic rabbits, which is served as a model of hyperlipidemia and early stage atherosclerosis. Nebivolol also exerted this antioxidant effect in vitro when who blood, as well as isolated neutrophils or macrophages, were estimated by a phorbol ester derivative. This indicates that the protective mechanism was mainly based on suppression of the phagocytic NADPH- dependant superoxide formation by either direct inhibition of the enzyme activity or inhibition of its activation by PKC. The antioxidant effect of nebivolol are not stereoselective, because it was mediated by D- as well as L-nebivolol excluding an involvement of the β receptor and pointing toward a free-radical scavenging effect of the molecule itself for these protective effects [20].

2. Nebivolol exhibited gastroprotective effects as evidenced by significant decreases in ulcer index as well as free and total acid output, and pepsin activity in gastric juice in addition to gastric mucosal malondialdehyde concentration, with concomitant increases in gastric juice pH and mucin concentration along with gastric mucosal reduced glutathione and nitric oxide (NO) concentrations [21].

3. Nebivolol inhibits vascular smooth muscle cell proliferation by mechanisms involving nitric oxide but not cyclic GMP [22].

4. It also showed antiepileptic effects in either alone and in combination with lamotrigine against maximal electric shock model [23]

5. It reduces oxidative stress in type 2 diabetics with mild to moderate hypertension [24]

6. Nebivolol appears to be lipid neutral and may even have a positive effect on HDL cholesterol. Despite this it may promote the formation of potentially atherogenic LDL subfractions possibly as a result of reduced antioxidant defences [25].

7. Nebivolol also showed anti-inflammatory effects in human coronary smooth muscle cells [26]

8. Nebivolol Decreased platelet activation. Hence, It might play a role to reduce thrombotic risk in hypertensive patients [27].

9. Nebivolol and zofenopril have protective effects against oxidative damage and apoptosis induced by cerebral ischemia/reperfusion (I/R) [28].

10. The topical nebivolol might helpful for wound healing in diabetic rats against streptozotocin-induced model.

11. Nebivolol is well-tolerated and highly effective in patients with chronic obstructive pulmonary disease in association with arterial hypertension [30].

12. Nebivolol also reduces intracellular oxidative stress. Hence they hypothesized that nebivolol may have

beneficial effects via nitric oxide and antioxidant action in osteoporosis treatment [31].

THERAPEUTIC USES

It is used therapeutically to lower arterial blood pressure in Hypertensive patients, used in the treatment of acute or chronic vascular Hypertension. It is considered as an alternative first line treatment option for patients with uncomplicated mild to moderate essential hypertension and in elderly patients with Congestive Heart Failure. Both morning and evening dosing of nebivolol reduces trough mean blood pressure surge in hypertensive patients[32]

Indication: Oral

Dosage [33]: Hypertension: Adult 5mg daily. Elderly: >65yr: initially 2.5m daily.

Adjunct in the treatment of stable chronic heart failure in patient's ≥70yr: Elderly. Initially 1.25mg once daily. If tolerated, double the dose every 1-2 week up to a maximum of 10mg once daily.

ADVERSE DRUG REACTION [34]:

Peripheral oedema, bradycardia, chest pain, Headache, fatigue, dizziness, insomnia, rash, hypercholesterolaemia, decreased HDL levels. Hyperuricaemia, increased TG levels, increased uric acid levels, diarrhea, nausea, abdominal pain, thrombocytopenia, paraesthesia, weakness, dyspnoea, anaphylaxis

Some side effects can be serious: chest pain, slow heart rate, difficulty breathing, unusual weight gain, and rash, swelling of the hands, feet, ankles, or lower legs

CONTRAINDICATION [35]**:** Nebivolol is contraindicated in patients with Hepatic impairment, sick sinus syndrome, 2nd and 3rd degree heart block (without a pacemaker), and history of asthma, metabolic acidosis, severe peripheral arterial disease, severe bradycardia, cardiogenic shock or decompensated heart failure, untreated phaeochromocytoma. Pregnancy and lactation.

PRECAUTION [35, 36 and 37]

Use with CYP2D6 inhibitors

Nebivolol exposure increases with inhibition of CYP2D6. The dose of nebivolol may need to be reduced.

Impaired Renal Function

Nebivolol should be used with caution in patients with severe renal impairment because of decreased renal clearance. BYSTOLIC has not been studied in patients receiving dialysis.

Impaired Hepatic Function

Nebivolol should be used with caution in patients with moderate hepatic impairment because of decreased metabolism. Since BYSTOLIC has not been studied in patients with severe hepatic impairment, BYSTOLIC is contraindicated in this population.

Risk of Anaphylactic Reactions

While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions. In patients with known or suspected pheochromocytoma, an alpha-blocker should be initiated prior to the use of any β-blocker.

SPECIAL PRECAUTION [37, 38]**:**

Elderly, History of anaphylaxis to various allergens, 1st degree AV block, peripheral arterial disease, Diabetes Mellitus, Compensated heart failure, myasthenia gravis, renal impairment, May mask the hyperthyroidism(eg. tachycardia)

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