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Review Article

Nebivolol - pharmacological aspects

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ABSTRACT

Nebivolol is a beta blocker with a unique function which distinguishes it from other beta blockers. It increases the release of nitric oxide (NO) which produces vasodilatation and thereby improves arterial compliance and reduces peripheral vascular resistance. It also reduces heart rate without improving maximal exercise tolerance. These effects are beneficial in hypertension and angina pectoris [1].

1. Introduction

Beta blockers for many years have been established as first line therapy in management of hypertension [2,3]. Nebivolol is a third generation, highly selective β_1 adrenoceptor antagonist indicated for treatment of essential hypertension [1]. Essential hypertension, is a condition associated with endothelial dysfunction which is caused by production of oxygen free radicals that destroy nitric oxide and impair its beneficial and protective effects on vessel wall [4]. In addition to its beta blocking effects, nebivolol has an endothelium dependent vasodilator property which is mediatede via L-arginine/ NO pathway[5].Apart from vasodilatation, NO also serves important functions like inhibition of platelet and leucocyte adhesion to vascular endothelium, inhibits smooth muscle hyperplasia following vascular injury and scavenging superoxide anion. Endothelial dysfunction is a marker of cardiovascular disorders [6].

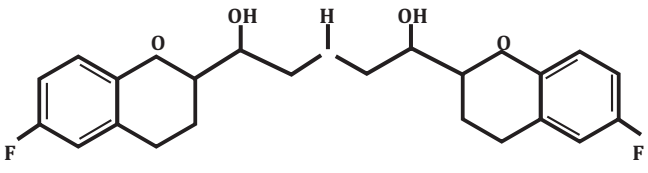
2.History of Nebivolol

Nebivolol was first introduced in U.K in 1999 for treatment of essential hypertension [1]. Later Mylan Laboratories licensed the U.S. and Canadian rights to nebivolol from Janssen Pharmaceutical N.V. in 2001. Nebivolol is registered and marketed in more than 50 other countries, including the In India, nebivolol is available as Nebilong 5 mg (Micro Labs) Nebicard-5 (Torrent), Nubeta (Nicholas Piramal) and Nodon (Cadila Pharmaceuticals).

3.Chemical characteristics

Nebivolol is a lipophilic β1 blocker, devoid of intrinsic sympathomimetic and membrane stabilizing activity. The chemical structure of nebivolol represented by figure 1[7]

Figure. 1 Chemical structure of Nebivolol [7].



3.1.Pharmacodynamics

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 [8,9]. The combination has greater antihypertensive activity than either enantiomer alone [10]

Nebivolol binds to the β_1 receptor on cell membrane leading to activation of adenyl cyclase resulting in accumulation secondary messenger cAMP. This cAMP dependent protein kinase

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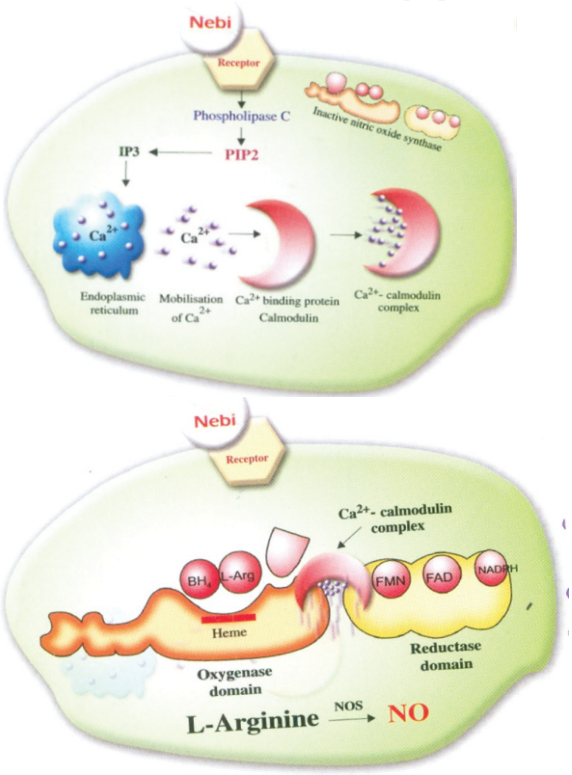
Figure. 2 Mechanism of action of Nebivolol [11]



Coupling of nitric oxide synthase (NOS)Increases NO production via L- arginine / NO pathway

phosphorylates specific proteins causing modification of actions[11]. Nebivolol has an endothelium dependent vasodilatory effect, which is mediated via the L- arginine \NO pathway [5] figure 2 shows Novel mechanism of action for NO synthesis : [12]

Nebivolol induces nitric oxide production via activation of β_3 adrenergic receptors[13]. This activates phospholipase C, which breaks down the membrane phospholipid PIP_2 (Phosphotidyl inositol bisphosphate) to IP_3 (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.

$$\text{L-arginine} + O_2 + \text{NADPH} \xrightarrow{\text{NOS}} \text{L-citrulline} + \text{NO} + \text{NADP}$$

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) →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 cells. This results in a subsequent rise in endothelial NO synthase – dependent NO production. This mechanism leads to effective control of blood pressure by vasodilatation of blood vessels.

Other actions produced by nebivolol are

- 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 out put and total peripheral resistance when given at the dose of 5mg once daily [14,15,16].
- Decreases resting heart rate [17,18] and reduces exercise induced tachycardia[19].
- Reduces total cholesterol and low density lipoprotein levels [18,20,21].
- Reduces plasma renin and aldosterone levels [20].

4.Pharmacokinetic

Absorption:

Nebivolol is available in 2.5mg, 5mg and 10mg oral tablet, rapidly absorbed after oral administration. The mean peak plasma drug concentration (Cmax) is 1.42µg/L. The time to reach T max for racemic mixture is 0.5-2hrs and is not affected by presence of food. For most individuals, steady state plasma concentration is achieved within 1 day for nebivolol and in a few days for active metabolites [22]. Oral bioavailability is 12% in extensive metabolisers and 96% in poor metabolisers, with plasma half life of 10.3hrs and 31.9hrs respectively [2,23].

Distribution:

The plasma protein binding is 98%, with limited distribution in adipose tissue due to its lipophilicity and hence no need for dosage adjustment in obese patients. The volume of distribution being 695-2755 litres [23,24]

Metabolism and Excretion:

It undergoes extensive first pass metabolism and produces active β- blocking hydroxylated metabolites. The metabolism of nebivolol shows genetic polymorphism in gene encoding the CYP2D6 isoenzyme where individuals may be phenotypically divided as “poor” or “extensive”metabolizers [10,22]. The poor metabolisers are unable to adequately hydroxylate aromatic moiety of the drug thus retaining t of high concentration of unchanged drug. In extensive metabolisers there is formation of the active hydroxyl metabolites,with low concentration of unchanged drug.. Stereoselective Radioimmunoassay measures active fractions of the isomers and hydroxylated metabolites [10,25].

Elimination half life of nebivolol is about 10hrs, increased by 5 times in poor metabolisers [7,10,26] and for its metabloites it is about 24hrs.. 38% of dose is excreted in urine and 48% in faeces. [7,10,22].

Dosage and administration:

The recommended dose in mild to moderate essential hypertension is 5mg once daily[7].

In the elderly and in patients with renal insuffiency, initial dose is l 2.5mg with subsequent upward dose titration if necessary. It can be used as monotherapy or in combination with other antihypertensive agents. Additive anti-hypertensive effects are observed with hydrochlorothiazide 12.5 to 25mg. The use of the drug in children and patients with hepatic insuffiency is not advised.

Adverse effects:

Nebivolol 5mg once daily is well tolerated. [2].The adverse events are transient and mild to moderate [27,28] and not dose related [29,30] .The adverse effects with a frequency of 1-10% incidence included headache, dizziness, paraesthesias, dyspnoea, constipation, nausea, diarrhea, tiredness and oedema. The less frequently reported are impaired vision, bradycardia, heart failure, hypotension, bronchospasm, pruritus and impotence.

Uses:

1. Essential hypertension[4]
2. Angina pectoris[1]

Table.1 Drug interactions: [22,23]

Drug class	Examples	Outcome
Calcium channel blockers	Verapamil Diltiazem	Risk of atrio-ventricular block and Bradycardia.
Anti-arrhythmic agents	Amiodarone Flecainide	Increased risk of myocardial depression. Risk of AV block and bradycardia.
Oral anti-diabetic agent	Chlorpropamide	May mask certain symptoms of Hypoglycemia.
Anti-depressants and Anti-psychotics	MAO-Is Phenothiazines	May enhance hypotensive effect.
Compounds metabolized by CYP2D6 isoenzyme	SSRIs Dextrometorphan	May alter plasma drug concentration because nebivolol gets metabolized by the same isoenzyme

Contraindications: [1]

Nebivolol is contraindicated in patients with:

- Cardiogenic shock
- Uncontrolled heart failure
- Sick sinus syndrome
- Second and third degree heart block
- History of bronchospasm and bronchial asthma.
- Untreated pheochromocytoma
- Metabolic acidosis.
- Hepatic insuffiency or impared liver function
- Bradycardia
- Hypotension
- Pregnancy and lactation
- Severe peripheral circulatory disturbances

Nebivolol is used with caution in patients with:

- Raynaud's disease.
- First degree heart block.
- Prinzmetal's angina.
- Diabetes.
- Chronic obstructive pulmonary disease.
- History of psoriasis.

Conclusion:

Nebivolol is a third generation, highly selective β_1 adrenoceptor antagonist indicated for treatment of essential hypertension. It achieves blood pressure control by dual mechanism i.e, by blocking β_1 receptors and by endothelium dependent vasodilator effect. It is well tolerated in both short and long term treatment. It is also used in treatment of angina and other atherosclerotic conditions because of its $\beta_1$blocking property, reduction in myocardial oxygen consumption and heart rate.

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