

A DESCRIPTIVE REVIEW ON THE PHARMACOLOGICAL PROPERTIES OF HIGHLY SELECTIVE BETA BLOCKER 'NEBIVOLOL'

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ABSTRACT

This review focuses on “Nebivolol” a novel drug that has beta adrenergic blocking effect, especially the blockage of beta 1 receptor selectively so classified as third generation beta blocker. In this article the pharmacological effects of nebivolol are discussed along with its mechanism of lowering blood pressure in hypertensive patients and its vasodilator action in patients of erectile dysfunction. Nebivolol is also beneficial in reducing the mortality rate in cardiac patients as it prevents the target organ damage by neutralizing oxygen free radical. Nebivolol is rapidly absorbed and distributed well after being administered oral. Precaution is needed while using Nebivolol as it can result in severe allergic reactions in some patients. This article also

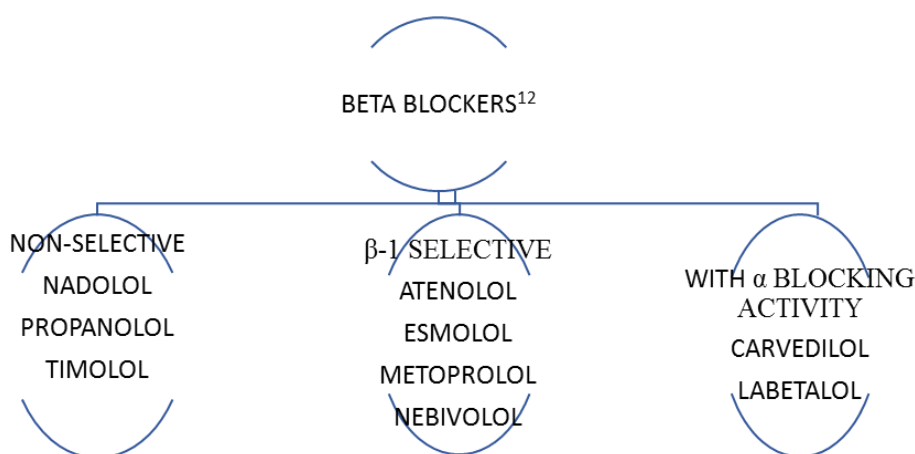
explains the uniqueness of Nebivolol with respect to other beta blockers. Nebivolol is unique in its mechanism of Producing vasodilatory effects by release of nitric oxide which is not associated with other beta blockers.

KEYWORDS: Nebivolol, hypertension, erectile dysfunction, pharmacological effects, nitric oxide.

INTRODUCTION

Nebivolol is a highly selective beta blocker that has beta-1 adrenergic receptor blocking effects selectively. It belongs to third generation beta blockers.^[1-2] Nebivolol is beneficial in many cardiovascular problems and helps to reduce the mortality rate in patients with cardiovascular problems.^[3-4] The mechanism of nebivolol is unique in its action as in addition to beta adrenergic blocking effects and its selectivity for beta 1 activity,^[5] it also releases

nitric oxide that causes vasodilation of blood vessels and thus reduces many cardiovascular problems that may develop as a result of vascular spasm. Nebivolol at higher doses also binds with beta-2 receptor.^[6] Nebivolol also decreases reactive oxygen species mediated target organ damage.^[7] Thus in this manner nebivolol is a drug of choice in patients with cardiovascular problems and helps these patients to improve their health status and quality of life by taking nebivolol.^[8] The aim of this review article is to study the pharmacological effects of nebivolol and to identify the mechanism by which it is playing its role in treating various cardiovascular disorders such as coronary artery disease, heart attack, and heart failure. For decades Beta blockers remained a drug of choice in angina, heart attack, hypertension and other cardiovascular disorders.^[9] It was thought that they prevent the recurrence of heart attacks and sudden heart failure. But some recent studies showed that the role of Beta blockers in treating hypertension is not recommended as a first line therapy.^[10] Moreover the new generation of Beta blocker such as Nebivolol are most effective in treating and preventing the cardiovascular diseases as compared to the older generations. As nebivolol is a beta-adrenergic blocking agent so in order to understand its mechanism it is necessary to elaborate the activity of the beta receptors and their effects.^[11]



Beta 2 adrenergic receptors are mainly located in the lungs, GI tract, muscles, liver and uterus.^[13]

Beta-1 Adenergetic Receptor

It is a G-protein coupled receptor. The actions of Beta-1 receptor includes the following:

- It stimulates the salivary glands to produce more saliva.
- It causes an increase in cardiac output
- It also increases the heart rate

- It increases the activity of AV node.
- It increases the release of Renin.
- It also increases Lipolysis.^[14] It also causes the relaxation of urinary bladder walls.^[15]

Hypertension specifically the essential hypertension and other associated conditions are now being treated with nebivolol.^[16] The side effects profile of nebivolol is listed below which includes

- Tiredness
- Headache
- Slow heartbeat
- Leg swelling
- Nausea
- Vomiting

Few serious side effects include

- Chest pain
- Extremely slow heart rate
- Shortness of breath
- Fainting
- Light-headedness.^[17]

Most common adverse effects effect of nebivolol includes bradycardia and hypotension. Adverse effects that are associated with high doses of nebivolol are dizziness, hypoglycaemia, fatigue and vomiting.^[18] Other adverse effects are bronchospasm and heart block.^[19]

Pharmacokinetic properties of nebivolol

ABSORPTION	Absorption is rapid and is not affected by food. ^[20]
DISTRIBUTION	Nebivolol is well distributed after oral absorption. ^[21]
METABOLISM	Hepatic metabolism, or by CYP2D6 mediated. ^[22]
ELIMINATION	Eliminated through kidney and faecal route. ^[23]

Contraindication of nebivolol includes decompensated heart failure, sick sinus syndrome, AV block, different heart problems and hepatic impairment.^[24] Interactions of nebivolol includes.

- **Sildenafil**

If nebivolol is taken along with sildenafil the amount of sildenafil decreases in the blood which results in decreased effects of sildenafil.^[25]

- **Alpha Blockers**

Taking these drugs with nebivolol can cause increased risk of low blood pressure when a person stands or changes posture (orthostatic hypotension).^[26]

- **Catechol-Amine Depleting Drugs**

Taking these drugs such as reserpine, guanethidine with nebivolol can markedly slow down the heart rate.^[27]

Nebivolol warnings

- Nebivolol may results in severe allergic reactions that's why always given with a warning for use. Major complications associated with allergic reaction includes

- Hives and rashes
- Tongue and throat inflammation
- Difficulty in swallowing and breathing

Nebivolol is strictly contraindicated in patients who previously had any sort of allergic reaction to it otherwise it may cause fatal consequences.^[29]

Alcohol interaction warning

Using alcohol with this drug can cause a sedative effect (slowed reflexes, poor judgment, sleepiness). This effect can worsen the drowsiness that's common with nebivolol.^[30]

Specific warnings to be considered with Nebivolol

Heart Disease: Nebivolol should not be use in following conditions related to heart:

- Cardiogenic Shock
- Unstable heart failure
- Second- or third-degree heart block
- Extremely shallow heart rate
- Sick Sinus Syndrome (unless have a pacemaker).^[31]

Nebivolol can worsen heart failure by slowing the heart rate down to an unsafe level.^[32]

Circulation problems: This drug can worsen peripheral vascular disease.^[33]

Breathing difficulties: It can make breathing more difficult.^[34]

Diabetic Patients: This drug may hide some of the signs related to decreased level of blood sugar, especially fast heart rate.^[35] Blood sugar level should be monitored regularly if the patients is taking insulin or any other antidiabetic drug.^[39]

Overactive thyroid gland: This drug may mask the signs and symptoms of an overactive thyroid gland (hyperthyroidism), such as a fast heart rate. If this drug is stopped suddenly, symptoms of hyperthyroidism may get much worse and an urgent medical attention may be needed.^[40]

An adrenal gland tumour: Tumor of adrenal gland i.e. pheochromocytoma may cause prompt fluctuations in blood pressure that may be difficult to control and needs careful usage of nebivolol.

Liver Disease: Nebivolol is processed by liver so it should be use cautiously in hepatic patients because improper functioning of liver may cause stay of drug in body longer and may increase the risk of side effects.^[41]

Kidney Disease: Nebivolol is removed from body by kidneys. If kidneys aren't working properly, the drug may accumulate in the body to cause serious side effects so it should be avoided in patients with kidney disease.

Warnings for special groups

For pregnant women: Research data in animals has shown adverse effects to the foetus if the mother is taking nebivolol. However, there haven't been enough studies done in humans to get ascertain about the mechanism that how the drug might affect a foetus. Still, the use of beta-blockers during the third trimester may raise the risk of certain problems in a new-born. These problems include low blood pressure, abnormal heart rhythm, and slowed breathing.

Nebivolol should only be used during pregnancy if the potential benefit justifies and surpass the potential risk to the pregnant lady.^[42]

For women who are breastfeeding: It isn't known by sufficient data whether nebivolol passes into breast milk. If it does, there's a possibility of serious side effects in children who breastfeed from mothers taking this drug. These side effects include a very slow heart rate.

For children: This drug hasn't been studied in children. It shouldn't be used in people younger than 18 years of age.

For people having surgery: Before any surgical procedure, patients must be investigated about the use of Nebivolol or other medications because heart rate should be precisely monitored if the patient is taking nebivolol.^[43]

DOSAGE: The dosage and strength of nebivolol is given in the following chart.^[37]

Dosage	Strength
Tablet form	2.5mg/1
Tablet form	20mg/1
Tablet form	10mg/1
Tablet form	5mg/1

Effectiveness of nebivolol is same in different age, race and sex. The blood pressure lowering effect of nebivolol comes within two weeks and may last up to twenty-four hour of interval.^[38]

In special population the nebivolol effects are somewhat questionable as it is teratogenic category C.^[39] Most of the studies conducted as labour and delivery, nursing mother or paediatric studies were done on rats only.^[40]

The brands name of nebivolol available in Pakistan are as follows.^[41]

Brand name	Generic name
Nebix	Nebivolol hydrochloride
Byscard	Nebivolol
Byvalson	Nebivolol
Nebil	nebivolol

In some articles the serious side effects of nebivolol found specifically hyperkalaemia and it is concluded from those articles that this drug causes serious increment in the blood serum level of potassium.^[42] While some other articles gave us a review on its prophylactic effects on indomethacin induced gastric ulcers.^[43]

MATERIALS AND METHODS

The inclusion criteria of this article contain all the relevant information including the method of searching which is based on randomised controlled trials focusing the information on nebivolol as an effective beta blocker and it includes all the pharmacological activities that are very important before prescribing this medication.^[36]

While the exclusion criteria of this review article is that it takes information only from the clinical studies and none of the preclinical studies are taken.

CONCLUSION AND DISCUSSION

With the advancement in knowledge of various diseases, newer therapeutic agents and advancements are being made to find out better ways of coping up with various diseases and suggesting novel methods of treatment.^[44] It also brings advanced and safer agents for therapeutic uses.^[45]

Nebivolol is a novel beta-adrenergic blocker that has unique pharmacological properties, compared with other available drugs in this class.^[46] Nebivolol appears to be more effective than other antihypertensive drugs in lowering blood pressure and possesses benefits for patients with heart failure and other cardiovascular problems.^[47] Nebivolol is unique from other beta blockers in the sense that they are nitric oxide releasers that cause vasodilatory effects and plays its more important in many diseases such as in heart problems, high blood pressure, erectile dysfunction.^[48] Erectile dysfunction is a serious problem that man are facing now a days and with the help of this novel drug it is possible to treat this problem as it can play role in erection of penis by its vasodilatory effect. Also, it has lower endothelial function at doses lower than 10 mg,^[49] nebivolol is special in a sense that it does not increase heart rate with exercise. Nebivolol is also a drug that can reduce the mortality rate in heart failure patients.

In short nebivolol is a drug of choice for the treatment of hypertensive patients, erectile dysfunction patients and the patients with various other heart problems.^[50]

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