

NEBIVOLOL A NOVEL SOMEWHAT DIFFERENT BETA ADRENERGIC RECEPTOR BLOCKER

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ABSTRACT

Nebivolol is a highly selective β_1 adrenoceptor blocker available clinically and is devoid of intrinsic sympathomimetic activity, inverse agonistic activity, and α_1 receptor blocking properties along with peripheral vasodilatation and nitric oxide (NO) induced benefits such as antioxidant activity and reversal of endothelial dysfunction. Nebivolol is the racemic mixture of 2 isomers with 4 asymmetric centres. The *d*-isomer is the active β -blocking component, while the *l*-isomer is responsible for the release of nitric oxide. Nebivolol has a hemodynamic profile different from classic β receptor antagonists that it acutely lowers arterial blood pressure without depressing left ventricular function, and reduces systemic vascular resistance. Nebivolol shown to inhibit platelet aggregation and thrombus formation, it has also has antiproliferative effects and reverses endothelial dysfunction in animal models of oxidative stress. Clinically, this compound has been proven to have antihypertensive and anti-ischemic effects as well as beneficial effects on hemodynamics. The tolerability of nebivolol has been shown to be superior to that of other beta blocker. Further studies are now necessary to compare the benefit of nebivolol with that of other drugs in the same class and to prove its claims of superiority and novelty of action, most importantly, its prognostic impact in patients with hypertension and its potential benefit in other comorbid conditions.

Keywords- Nebivolol, β_1 adrenoceptor blocker.

INTRODUCTION

Hypertension is currently the leading risk resulting in considerable death and disability worldwide and accounted for 9.4 million deaths and 7 per cent of disability adjusted life years (DALYs) in 2010¹. India, the world's largest democracy, is undergoing a rapid economic growth. This growth has been accompanied by demographic, lifestyle and cultural changes which have had a large impact on the health profile of India's citizens and placed a significant strain on the country's healthcare system²⁻⁴. In India, hypertension is the leading non communicable disease (NCD) risk and estimated to be attributable for nearly 10 per cent of all deaths⁵. Adult hypertension prevalence has risen dramatically over the past three decades from 5 per cent to between 20-40 per cent in urban areas and 12-17 per cent in rural areas⁶⁻⁷. The number of hypertensive individuals is anticipated to nearly double from 118 million in 2000 to 213 million by 2020.⁷ It is estimated that 16 per cent of ischaemic heart disease, 21 per cent of peripheral vascular disease, 24 per cent of acute myocardial infarctions and 29 per cent of strokes are attributable to hypertension underlining the huge impact effective hypertension prevention and control can have on reducing the rising burden of cardiovascular disease (CVD)⁸.

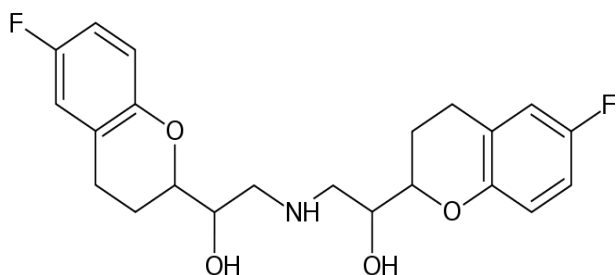
The management of hypertension involves lifestyle modifications, pharmacological treatment, or both. Weight reduction for overweight or obese patients, adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, moderate consumption of alcohol, and physical activity are all essential to decreasing blood pressure and enhancing the efficacy of pharmacotherapeutic regimens⁹.

Pharmacological treatment includes management with one or more agents belonging to the following drug classes: thiazide diuretics, beta blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). Although thiazide diuretics are recommended as the first-line therapy for most patients with hypertension, beta blockers have a compelling indication for use in patients with high-risk conditions such as heart failure, MI, coronary disease, and diabetes^{9,10}. Beta blockers exert antihypertensive effects by reducing myocardial contractility, heart rate, and cardiac output^{9,10}. Central inhibition of sympathetic nervous system outflow, inhibition of the renin-angiotensin system by reducing renin release from the juxtaglomerular apparatus, and resetting or altered sensitivity of baroreceptors may also contribute to the BP-lowering effects of this drug class¹¹⁻¹³. Beta blockers differ in many of their pharmacological properties, including β_1 and β_2 -adrenergic receptor selectivity and vasodilatory capabilities.

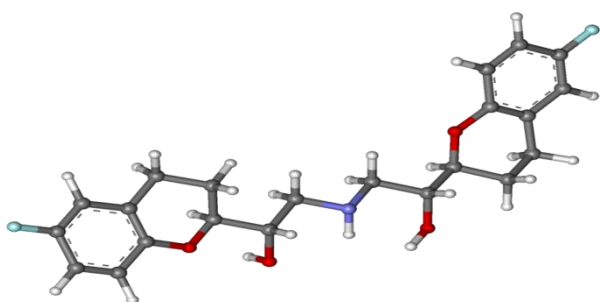
Nebivolol (α,α' -[iminodimethylene]bis[6-fluoro-2-chrommethanol) belongs to third generation selective β -Adrenergic Receptor Blocker is somewhat different from its class. It is novel in its class by possessing other favourable effect apart from anti hypertensive property. It appears to be the most selective β_1 receptor antagonist available clinically and is devoid of intrinsic sympathomimetic activity, inverse agonistic activity, and α_1 receptor blocking properties¹⁰. It does not alter exercise capacity in healthy individuals but does inhibit both ADP and collagen-induced platelet aggregation¹¹. Along with

peripheral vasodilatation and nitric oxide (NO)-induced benefits such as antioxidant activity and reversal of endothelial dysfunction neбиволol facilitates better protection from cardiovascular events^{14,15}.

In dec 18, 2007 neбиволol was approved by FDA for treatment of hypertension. In Europe it is also approved for heart failure. Neбиволol is the racemic mixture of 2 isomers with 4 asymmetric centres and is at present the only β -blocker whose structure differs fundamentally from that derived from propranolol. The *d*-isomer has the SRRR configuration, and the *l*-isomer is RSSS. The *d*-isomer is the active β -blocking component, while the *l*-isomer is responsible for the release of nitric oxide¹⁶⁻¹⁸.



Structure of Neбиволol



Ball-and-stick model of neбиволol molecule

Mechanism of action;

A number of mechanisms combine to determine the hemodynamic changes induced by neбиволol. These include a negative chronotropic effect, inhibition of sympathetic outflow from cerebral vasomotor centers, inhibition of peripheral α_1 -adrenoceptors¹⁹, suppression of renin activity, and most importantly, decreased peripheral vascular resistances. Interestingly, although neбиволol's *D*-isomer appears to possess relevant selective β_1 blocking and mild vasodilatory properties, the *L*-isomer determines the stimulation of eNOS and subsequent endothelium-dependent vasodilation²⁰, and only at suprapharmacologic dosages does it exert β -blocking effects²¹.

These differences between isomers might well have clinical implications, and separate administration of 1 of the 2 could be hypothesized for selected patients. In combination, the 2 stereoisomers of neбиволol cooperate in determining the hemodynamic impact of the drug^{21,22}. The very high selectivity for β_1 versus β_2 -adrenergic receptors of the *d*-isomer explains the limited effects on airway reactivity and insulin sensitivity^{23,24} as well as the lesser negative inotropic effect of neбиволol in patients with heart failure^{14,25}. This selectivity tends to be overcome at

dosages >10 mg and in poor metabolizers, causing the loss of this positive characteristic of neбиволol.

Pharmacokinetic Profile²⁶:

Neбиволol is well absorbed after oral administration. The metabolism of neбиволol is subject to genetic polymorphism; phenotypically, individuals may be characterised as 'poor' (slow) or 'extensive' (fast) metabolisers. After a single 5mg oral dose, peak plasma drug concentrations (C_{max}) for unchanged *d*, *l*-neбиволol were 1.48 $\mu\text{g/L}$ in fast metabolisers and for active fractions of *d*- and *l*-neбиволol plus their corresponding hydroxylated metabolites were 7.3 and 13.1 $\mu\text{g/L}$, respectively, in hypertensive patients. Repeated doses increased the C_{max} values for the individual *d*- and *l*-enantiomers and their respective metabolites. Time to C_{max} after oral administration of neбиволol is reported to be about 0.5 to 2.0 hours and is not significantly affected by the presence of food. Generally, steady-state plasma concentrations are achieved within 1 day for neбиволol and within a few days for the active metabolites. Obesity does not appear to affect the total distribution volumes and total body clearance rates (per kilogram body weight) of unchanged neбиволol (racemate or each enantiomer).

Extensive first-pass metabolism after oral administration of neбиволol produces active β -blocking hydroxy-metabolites. Elimination half-lives for the unchanged compound (racemate or each enantiomer) average about 10 hours, but are reported to increase by up to 5 times in poor metabolisers. Elimination half-lives for the hydroxy-metabolites of both enantiomers average about 24 hours in extensive metabolisers, but are almost doubled in poor metabolisers. The absolute oral bioavailability of neбиволol is 12% in extensive metabolizers and 96% in poor metabolizers. However, a safety trial in both extensive and poor metabolizers has shown no safety or efficacy differences between these patient groups. One week after administration, 38 and 48%, respectively, of the neбиволol dose is excreted in urine and faeces; unchanged neбиволol accounts for <0.05% of the amount recovered in the urine. Plasma concentrations of neбиволol (both enantiomers) and its hydroxy metabolites are elevated in patients with renal disease²⁶.

Pharmacodynamic properties:

Neбиволol has a hemodynamic profile different from classic β receptor antagonists such as atenolol, propranolol, and pindolol. It acutely lowers arterial blood pressure without depressing left ventricular function, and reduces systemic vascular resistance. This reduction in systemic vascular resistance is due to a direct vasorelaxant effect that is mediated at least in part by NO²⁷. Evidence of eNOS dependent vasodilator effects of neбиволol was also reproduced in humans in the arterial and venous circulation, where both direct endothelium-dependent vasodilation and increased responsiveness to other specific stimuli such as hyperemia were reported. Remarkably, the magnitude of this effect was similar across hypertensive patients and healthy volunteers, which shows that the presence of vascular disease does not limit the endothelium-dependent vasodilator capacity and hemodynamic benefit achievable pharmacologically^{28,29}.

Effects of intra-arterial infusion of nebivolol on forearm blood flow in healthy control subjects and patients with essential hypertension^{28,30}. In both groups, nebivolol but not atenolol caused vasodilation, an effect that was antagonized by endothelial nitric oxide synthase (eNOS) inhibition. Nebivolol alone markedly improved endothelial function in hypertensive patients³¹. Nebivolol, but not other β -blockers, inhibits phorbol ester (PDBu) induced superoxide production in neutrophils from hypercholesterolemic rabbits³². Like other β -blockers, nebivolol has important electrophysiologic properties because it increases the ventricular fibrillation threshold, therefore reducing ventricular arrhythmias in animal models of ischemia- or drug-induced cardiomyopathy³³, and it reduces QT dispersion, a marker of arrhythmic risk³⁴. Further, nebivolol reduces P-wave dispersion on the electrocardiogram, which would attenuate the risk of atrial fibrillation, one of the leading causes of death in heart failure and hypertension³⁵.

In another study, the effect of nebivolol on small artery distensibility in patients with hypertension was compared with that of atenolol. Both drugs were equivalent in reducing BP, but only nebivolol improved small artery distensibility, a measure of arterial compliance or "stiffness"³⁶. Arterial stiffness has been shown to be an independent predictor of mortality in patients with essential hypertension. Drugs that reduce stiffness may therefore confer a survival advantage³⁷. In an animal model comparison with atenolol, nebivolol infusion showed a statistically significant reduction in a measure of arterial distensibility, namely pulse wave velocity, with no change in mean arterial pressure³⁸. In contrast, atenolol had no effect on pulse wave velocity despite a small drop in mean arterial pressure. This difference suggests that the release of NO mediated by nebivolol, independent of a beta-adrenoceptor-dependent mechanism, an effect not seen with older beta-blockers such as atenolol, may be of particular benefit in patients with impaired arterial compliance, such as those with isolated systolic hypertension³⁸.

In vitro, nebivolol, propranolol, and carvedilol have all been shown to inhibit both adenosine diphosphate- and collagen-induced platelet aggregation; however, the effect of nebivolol appears to be significantly greater, and it is lost after inhibition of eNOS³⁹. Further, therapy with nebivolol causes a significant decrease in mean platelet volume and plasma sP-selectin levels and is associated with favorable modifications of hemostatic and fibrinolytic status, including reduced plasma levels of fibrinogen plasma activator inhibitor-1, homocysteine, and endothelin-1⁴⁰.

Recently it was demonstrated that nebivolol, but not other β -blockers, improves endothelial function, reduces vascular superoxide production via prevention of eNOS uncoupling, reduces vascular macrophage infiltration, and inhibits NAD(P)H oxidase-dependent superoxide production in neutrophils isolated from hyperlipidemic rabbits⁴¹. Similarly, in a model of angiotensin II-induced oxidative stress⁴², we observed that nebivolol, but not metoprolol, normalizes endothelial function, reduces superoxide formation, increases NO bioavailability, and

inhibits up-regulation of the activity and expression of the vascular NAD(P)H oxidase⁴², thus preventing eNOS uncoupling. Finally, nebivolol treatment has been demonstrated to inhibit the oxidized low-density lipoprotein-induced inactivation of NO⁴³ and to reduce the levels of the circulating eNOS inhibitor asymmetric dimethyl-arginine, which likely contributes to increase vascular NO bioavailability⁴⁴.

Nebivolol causes down-regulation of a number of genes involved in inflammatory processes, oxidative stress, and smooth muscle cell proliferation^{45,46}. Such antiproliferative and proapoptotic effects have obvious potential implications in the prevention and treatment of atherosclerosis. Of interest, this antiproliferative action (along with that of other NO donors), although being NO-mediated, appears to be independent of cyclic guanosine monophosphate⁴⁷. In agreement with these findings, nebivolol has been shown to inhibit the expression of inflammatory proteins and factors involved in vascular remodeling such as metalloproteinases and protease inhibitor⁴⁸⁻⁵⁰. In hyperlipidemic animals, augmentation of NO with nebivolol increased plaque stability⁵¹. Further, nebivolol inhibited neointima formation in a murine model of vascular injury⁴⁹, and it prevented cardiac and renal modifications in a rat model of insulin resistance⁵². Finally, nebivolol inhibited the development of atherosclerosis in cholesterol-fed rats⁵³.

The primary indications for which nebivolol has been developed and studied include systemic hypertension, heart failure, and although less data are available, coronary artery disease. However, the hemodynamic effect of nebivolol appears to be different from that of atenolol. In a double-blind, randomized, prospective study in patients with essential hypertension, atenolol reduced cardiac output, stroke volume, and heart rate. In contrast, nebivolol reduced peripheral resistance and increased stroke volume, preserving cardiac output. The effects of nebivolol demonstrated in this study suggest that the drug may be important in treating heart failure, where preservation of cardiac output is critical⁵⁴.

Nebivolol 5 mg/day was compared with metoprolol 100 mg BID in 80 newly diagnosed hypertensive patients. After 6 months of treatment, the researchers found that both drugs significantly reduced BP and heart rate, with a more profound bradycardic effect seen in the metoprolol group. In contrast, only nebivolol significantly reduced oxidative stress, insulin resistance index, and plasma levels of P-selectin, a cell-surface adhesion molecule believed to play a role in the initiation of atherosclerosis⁵⁵. A number of randomized, double-blind, placebo-controlled trials have investigated the efficacy and tolerability of 5 to 10 mg of nebivolol therapy in patients with mild-to-moderate essential hypertension. Nebivolol has a relatively modest impact on diastolic blood pressure⁵⁶, a characteristic that is believed to contribute to the safety profile of the drug.

Nebivolol 2.5–5 mg/day was compared with the calcium channel antagonist, amlodipine, 5–10 mg/day in elderly patients (≥ 65 years). In this double-blind, multicenter, randomized trial, efficacy was similar between the two groups. Both drugs were well tolerated, however, there

was a higher incidence of adverse events such as headache and ankle edema in the group treated with amlodipine⁵⁷.

In terms of effectiveness on systolic blood pressure, studies suggest that nebivolol compares at the same level with other β -blockers and Ca^{2+} -antagonists and is somewhat more potent than angiotensin-converting enzyme (ACE) inhibitors. The typical onset of maximal nebivolol antihypertensive effect occurs after 2 to 8 weeks of therapy, which is intermediate between ACE inhibitors (slower) and amlodipine (faster). In recent meta-analyses, the percentage of patients who achieved target blood pressure levels was somewhat greater compared with ACE inhibitors and comparable with angiotensin-II blockers or Ca^{2+} -channel antagonists^{58,59,60}.

The largest double-blind study in hypertension included 909 patients with mild-to-moderate hypertension. Nebivolol in doses of 1.25–40 mg/day were compared with placebo over 12 weeks. Placebo-subtracted reductions in trough sitting BP (SBP/DBP) ranged from 6.6/5.1–11.7/8.3 mm Hg and were dose dependent. Reported adverse events were: headache (7.1 vs 7.4% placebo, fatigue (3.6 vs 2.5% placebo, nasopharyngitis (2.9% vs 7.4% placebo), diarrhea (2.8% vs 2.5% placebo) and dizziness (2.8 vs 3.7% placebo). The incidence of typical beta-blocker adverse effects was very low and no different from placebo including erectile dysfunction (0.2% vs 0.0% placebo), decreased libido (0.1% vs 0.0% placebo), dyspnea (1.0% vs 0.0% placebo) and bradycardia (0.7% vs 0.0% placebo)⁶¹.

Results of previous pharmacokinetic studies suggest that nebivolol 5 mg may not conform completely to the definition of a classic beta-blocker demonstrating additional antihypertensive effect due to endothelial NO release-mediated vasodilation. This meta-analytic study on Efficacy and tolerability of nebivolol compared with other antihypertensive drugs showed that nebivolol 5 mg achieved similar or better rates of treatment response and BP normalization than other drug classes and other antihypertensive drugs combined, with similar tolerability to placebo and significantly better tolerability than losartan, CCAs, other beta-blockers, and all antihypertensive drugs combined. Although not definitive, this meta-analysis suggests that nebivolol 5 mg is likely to have advantages over existing antihypertensives and may have a role in the first-line treatment of hypertension⁶².

In elderly heart failure patients with a wide range of ejection fraction, mild and moderate impairment of renal function did not interact with the effect of nebivolol on clinical outcomes. Furthermore, nebivolol was well tolerated in participants of the elderly patient trial with moderate renal impairment. Thus, mild to moderate renal dysfunction, even in the elderly, should not present a limitation to the use of nebivolol in HF patients⁶³.

A post-marketing surveillance study on Efficacy, tolerability and safety of nebivolol in patients with hypertension and diabetes, Nebivolol treatment was associated with a significantly reduced BP, improved blood glucose and LDL cholesterol levels and was well tolerated in hypertensive patients with concomitant DM⁶⁴. A study on clinical and economic aspects of the use of

nebivolol in the treatment of elderly patients with heart failure shows that nebivolol is well tolerated and effective in reducing mortality and morbidity in older patients, and that the beneficial clinical effect is present also in patients with mildly reduced ejection fraction. Moreover, nebivolol appears to be significantly cost-effective when prescribed in these patients. However, further targeted studies are needed to better define the efficacy as well as safety profile in frail and older patients with comorbid diseases⁶⁵.

Side effect:

Several studies have suggested that nebivolol has reduced typical beta-blocker-related side effects, such as fatigue, clinical depression, bradycardia, or impotence⁶⁶⁻⁶⁸. Nebivolol appears to have a minor, if any, effect on libido and sexual performance, which likely ensues from a compensatory effect of the increased NO release⁶⁹. Common adverse effects reported with nebivolol in clinical trials included fatigue, headache, dyspnea, insomnia, dizziness, and paresthesia; however, the incidence of these symptoms was not different in placebo-treated subjects (0–5%)⁷⁰. Importantly, nebivolol does not appear to modify low-density lipoprotein cholesterol or total cholesterol levels, and it does not seem to precipitate diabetes. nebivolol's greater selectivity for β_1 -receptors results in improved tolerability: in patients with mild asthma, nebivolol induced a mild, clinically insignificant reduction in respiratory parameters^{71,72}. After a 4- and 12-week treatment on hypertensive patients, the use of nebivolol actually increased peak expiratory flow and quality-of-life parameters⁷³.

Interaction⁷⁴⁻⁷⁶:

Because it is metabolized by CYP450-2D6, nebivolol is potentiated by inhibitors of this enzyme, such as quinidine, propafenone, fluoxetine, paroxetine, and any coadministration should be avoided. Nebivolol should generally be avoided by patients taking other myocardial depressants or atrioventricular conduction inhibitors, specifically dihydropyridine calcium-channel blockers or anti-arrhythmic medications, because of the increased risk of bradycardia. No pharmacokinetic interactions were observed in healthy adults between nebivolol (10 mg daily for 10 days) and furosemide (40 mg single dose), hydrochlorothiazide (25 mg once daily for 10 days), or spironolactone (25 mg once daily for 10 days). In the case of concomitant nebivolol and clonidine (Catapres, Boehringer Ingelheim), nebivolol should be discontinued several days before the clonidine dose is tapered.

Contraindication⁷⁷:

According to FDA, Nebivolol is associated with a number of serious risks. It is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh > B) and in patients who are hypersensitive to any component of the product. Nebivolol therapy is also associated with warnings regarding abrupt cessation of therapy, cardiac failure, angina and acute myocardial infarction, bronchospastic diseases, anesthesia and major surgery, diabetes and hypoglycemia, thyrotoxicosis, peripheral

vascular disease, non-dihydropyridine calcium channel blockers use, as well as precautions regarding use with CYP2D6 inhibitors, impaired renal and hepatic function, and anaphylactic reactions.

In late August 2008, the FDA issued a Warning Letter to Forest Laboratories citing exaggerated and misleading claims in their launch journal ad, in particular over claims of superiority and novelty of action written that "FDA is not aware of any substantial evidence or substantial clinical experience that demonstrates that Bystolic represents a 'novel' or 'next generation' beta blocker for the treatment of hypertension. Indeed, we are not aware of any well-designed trials comparing Bystolic to other β -blockers. Furthermore, FDA is not aware of any data that would render Bystolic's mechanism of action 'unique.'"

CONCLUSION

Beta-blockers are important class of drug in the management of hypertension and heart failure and in

reducing cardiovascular risk. Nebivolol is highly cardioselective beta-blocker with antihypertensive efficacy similar to that of other beta-blockers, but with tolerability better than older agents in its class. It is novel in its class by possessing other favourable effect apart from anti hypertensive property. It appears to be the most selective β_1 receptor antagonist available clinically and is devoid of intrinsic sympathomimetic activity, inverse agonistic activity, and α_1 receptor blocking properties¹⁰. It does not alter exercise capacity in healthy individuals but does inhibit both ADP and collagen-induced platelet aggregation¹¹. Along with peripheral vasodilatation and nitric oxide (NO)-induced benefits such as antioxidant activity and reversal of endothelial dysfunction nebivolol facilitates better protection from cardiovascular events^{14,15}. Clinically, this compound has been proven to have antihypertensive, anti-ischemic effects, antioxidant as well as beneficial effects on metabolic profile.

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