

Nebivolol: a novel beta-blocker with nitric oxide-induced vasodilatation

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Abstract: Nebivolol is a novel beta₁-blocker with a greater degree of selectivity for beta₁-adrenergic receptors than other agents in this class and a nitric oxide (NO)-potentiating, vasodilatory effect that is unique among beta-blockers currently available to clinicians (neбиволol is approved in Europe and is currently under review in the US). A NO-potentiating agent such as neбиволol may have an important role in hypertensive populations with reduced endothelial function such as diabetics, African-Americans and those with vascular disease. Nebivolol is a racemic mixture with beta-blocker activity residing in the *d*-isomer; in contrast, *l*-neбиволol is far more potent in facilitating NO release. Nebivolol is unique among beta-blockers in that, at doses <10 mg, it does not inhibit the increase in heart rate normally seen with exercise. The efficacy of neбиволol has been tested successfully in clinical trials against other agents including other beta-blockers, angiotensin-converting enzyme-inhibitors and calcium channel antagonists in patients with hypertension, angina, and congestive heart failure. The tolerability of neбиволol has been shown to be superior to that of atenolol and metoprolol. In controlled clinical trials, neбиволol has a side effect profile that is similar to placebo, in particular as it relates to fatigue and sexual dysfunction. This article will review published clinical data regarding this cardioselective beta-blocker.

Keywords: neбиволol, hypertension, beta-blocker

Introduction

Goal blood pressure (BP), defined as <140/90 mm Hg in uncomplicated hypertension, is attained by only 34% of hypertensive patients in the US (Chobanian et al 2003), 24% of patients in France (Chamontin et al 1998), and 13% of patients in Canada (Joffres et al 2001). These low rates of achieving goal BP indicate that a more aggressive approach to BP management is required on a global scale. One of the most important classes of antihypertensive agents, beta-blockers play a critical role in reducing cardiovascular risk in hypertensive patients. A meta-analysis including almost 19 000 patients concluded that beta-blocker therapy was associated with a 42% reduction in heart failure, a 29% reduction in stroke risk, and a 7% reduction in coronary heart disease in hypertensive patients (Psaty et al 1997). The specific mechanism of action of beta-blockers that reduces BP is not completely understood, however, likely mechanisms include an effect on heart rate, inhibition of the sympathetic nervous system, and inhibition of the renin-angiotensin system. Nebivolol is a novel, highly selective beta-blocker with nonadrenergic vasodilating properties. It has been approved for the treatment of essential hypertension and congestive heart failure in Europe and is currently under review for the treatment of hypertension in the US.

Pharmacokinetics

Nebivolol is a racemic mixture of equal proportions of *d*- and *l*-isomers. The beta-blocker activity resides in the *d*-isomer while the facilitation of nitric oxide (NO)

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release is found in the *l*-enantiomer (Van Neuten and De Cree 1998; Mason et al 2005).

Nebivolol is well absorbed after oral administration. Peak plasma concentrations are reached in 0.5–2 hours and steady-state plasma levels are reached in 24 hours (McNeely and Goa 1999). Nebivolol has a superior trough-to-peak efficacy ratio compared with atenolol, allowing for “true” once daily dosing (Simon and Johnson 1993). Absorption of the drug following oral administration is not affected by food, age, gender or body weight (McNeely and Goa 1999; Cheymol et al 1997). Nebivolol is metabolized by the liver, and undergoes extensive first-pass metabolism to active moieties via the cytochrome (CYP)2D6 enzymatic pathway (Gu et al 2003; Weber 2005). The mean terminal half-life is approximately 10 hours (Cheymol et al 1997). Less than 0.1% of unchanged drug is excreted in urine (Shaw, Liu, Zachwieja, et al 2005). Metabolism of nebivolol is subject to a debrisoquine-type genetic polymorphism (Weber 2005). The small percentage of patients who are deficient in CYP2D6 enzyme activity (7% of Caucasians, 2% of African-Americans, 2% of Asians) are considered poor metabolizers of nebivolol (Relling et al 1991; Evans et al 1993; Mizutani 2003). The absolute oral bioavailability of nebivolol is 12% in extensive metabolizers and 96% in poor metabolizers (Van Peer 1991). However, a safety trial in both extensive and poor metabolizers has shown no safety or efficacy differences between these patient groups (Lacourcière et al 2000).

No significant difference in efficacy or safety have been found in patients with mild or moderate renal disease; patients with severe renal impairment may need a lower initial dose due to impaired clearance (Shaw, Liu, Zachwieja, et al 2005). Similarly, a lower starting dose may be needed in patients with mild or moderate hepatic impairment due to alteration in the drug’s pharmacokinetics in these patients (Shaw, Liu, Tu, et al 2005).

Clinical perspective

Nebivolol has a hemodynamic effect suggestive of direct vasodilatation (Gao et al 1991; Van Rooy et al 1991). Evidence in the literature indicates that the vasodilation associated with nebivolol is due to its effects on the L-arginine/NO pathway in the endothelium of various regional vascular beds (Bowman et al 1994; Cockcroft et al 1995; Dawes et al 1999; Ritter 2001; Tzemos et al 2001). Using the dorsal hand vein dilatation model, researchers found that nebivolol had a venodilator effect on the human hand whereas atenolol did not. Further, this effect was inhibited by L-NMMA (N^G-monomethyl L-arginine), an inhibitor of

NO synthase, indicating that the increased blood flow was due to activation of the L-arginine/NO pathway (Bowman et al 1994). This finding was confirmed in hypertensive patients who showed signs of vasodilatation in forearm arteries after nebivolol infusion. The fact that this vasodilatation was inhibited by L-NMMA supports that it is due to activation of the L-arginine/NO pathway (Cockcroft et al 1995; Dawes et al 1999). The endothelial-dependent vasoconstrictive response seen with L-NMMA infusion was inhibited by nebivolol and not by atenolol (Ritter 2001; Tzemos et al 2001).

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” (Arosio et al 2002). 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 advantage (Laurent et al 2001). 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 pressure (McEniery et al 2004). 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 hypertension (McEniery et al 2004).

Clinical trials also show that nebivolol has an anti-oxidative effect (de Groot et al 2004; Pasini et al 2005). In a study of 20 hypertensive patients compared with 20 matched healthy subjects, nebivolol reduced the oxidative inactivation of NO, a result not seen with atenolol (Pasini et al 2005). In addition, nebivolol inhibited vascular smooth muscle proliferation in a rat aortic smooth muscle cell model via an apparent NO-dependent mechanism (Ignarro et al 2002). Both of these findings suggest that nebivolol may offer anti-atherosclerotic activity, a particular benefit, if verified, in patients with arterial disease.

Nebivolol comparative efficacy

Clinical trials suggest that on a weight-for-weight basis, nebivolol is ten times more potent than atenolol. In one study, the effect of doses of nebivolol (2.5 mg/day, 5.0 mg/day, and

10.0 mg/day) on exercise-induced increases in heart rate and blood pressure in 25 male hypertensive volunteers was compared with that of atenolol 50 mg/day and 100 mg/day and of placebo using a double-blind, crossover design and a parallel, placebo group (n=7) (Simon and Johnson 1993). At 24 hours after dosing, sitting and standing diastolic and systolic blood pressures and heart rates (at rest and during submaximal exercise) were reduced to the same extent by nebivolol and atenolol.

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 (Kamp et al 2003). 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 critical.

Nebivolol 5 mg/day was compared with metoprolol 100 mg twice daily (BID) in 155 patients with mild-to-moderate essential hypertension (Uhlir et al 1991). Target blood pressure was attained in 79% of nebivolol-treated patients and 66% of those in the metoprolol group. There were fewer adverse events reported by patients in the nebivolol group. In a second study, nebivolol 5 mg/day was compared with metoprolol 100 mg BID in 80 newly diagnosed hypertensive patients (Celik et al 2006). 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 atherosclerosis (Celik et al 2006).

Nebivolol 5 mg/day was also compared with the angiotensin-converting enzyme (ACE) inhibitor lisinopril 20 mg/day in 68 patients with uncomplicated mild-to-moderate hypertension, treated for 12 weeks. The primary endpoints of the study were response rate, where patients were defined as "normalized" responders if their blood pressure values were <140/90 mm Hg at study end, or as "non-normalized" responders if the reduction in blood pressure was ≥ 10 mm Hg compared with baseline; and changes in sitting blood pressure at the end of the study. Patients were randomly assigned to one of the study arms, however, a significant difference in sitting diastolic blood pressure (DBP) was found between the 2 groups at baseline.

Analysis of covariance of the raw data including baseline values as covariate suggested that DBP and heart rate were significantly lower in the nebivolol-treated group at week 8. This difference disappeared, however, when an analysis of variance for repeated measures was performed, which indicated a significant reduction in systolic blood pressure (SBP), DBP, and heart rate in both groups. There was a statistically significant difference in favor of the nebivolol group in the distribution of responders and non-responders at week 8. Lisinopril and nebivolol were equally well tolerated (Rosei et al 2003).

Nebivolol 2.5–5 mg/day was compared with the calcium channel antagonist, amlodipine, 5–10 mg/day (Mazza et al 2002) 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 amlodipine. In a double-blind study, the efficacy of nebivolol 5 mg/day was compared with that of the sustained-release calcium channel antagonist, nifedipine, 20 mg/BID in 51 patients with mild-to-moderate hypertension over a 12 week-treatment period (Lacourcière et al 1992). The treatment response rate was 69% for nebivolol and 59% for nifedipine. Both treatment groups showed a significant reduction in BP, with no significant difference in BP reduction between the groups either in clinic BP or in 24-hour ambulatory BP. Nebivolol appeared to be superior to nifedipine in preventing the usual early morning increase in BP. Beta-blockers have usually been found to increase plasma cholesterol (Ames 1986; Lacourcière et al 1990). However, both agents were associated with a significant decrease in cholesterol after 12 weeks of treatment, 5% and 3%, for nebivolol and nifedipine, respectively.

The largest double-blind study in hypertension included 909 patients with mild-to-moderate hypertension (Weiss et al 2005). 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).

Nebivolol tolerability

In controlled clinical trials, nebivolol demonstrates a side effect profile similar to placebo, most notably in regards to side effects commonly associated with beta-blockers, such as fatigue and sexual dysfunction (Weber 2005). Quality of life was evaluated in a double-blind, randomized trial of 314 patients with hypertension who were treated with either nebivolol 5 mg/day or losartan 50 mg/day for 12 weeks (Van Bortel et al 2005). The two agents had an equivalent effect in reducing SBP but the decrease in DBP was slightly greater with nebivolol. Interestingly, the side effect profile of losartan, an angiotensin receptor antagonist known for few side effects, was no different than that of nebivolol. In a separate study, nebivolol (5 mg/day) was compared with atenolol (50 mg/day) and placebo in 364 patients in general practice (Van Nueten et al 1998). There was no significant difference in BP or in sitting heart rate between the treatment groups, and there was no significant difference in the incidence of side effects between the groups, except for significantly more complaints of sexual dysfunction in the atenolol group.

Beta-blockers have been associated in the past with a risk of sexual dysfunction, however recent meta-analysis suggests that the risk of this adverse event is not substantial (Ko et al 2002). A recent clinical trial studied 29 out of 44 hypertensive men who complained of erectile dysfunction while taking atenolol, metoprolol or bisoprolol. The researchers found that after switching to nebivolol therapy, 20 of the 29 noted significant improvement in erectile function without a significant change in BP (Doumas et al 2006). It is reasonable to speculate that this improvement in erectile function may be due to the involvement of NO in erectile dysfunction and its potentiation with nebivolol therapy (Doumas et al 2006).

Nebivolol in other cardiovascular diseases

Nebivolol (5 mg/day) versus placebo has been evaluated in the treatment of angina (Cherchi et al 1991). In a placebo-controlled trial of 16 patients, nebivolol therapy significantly prolonged treadmill time to 1 mm ST depression from 555 ± 37 sec to 667.5 ± 49 sec ($p < 0.05$). Anginal threshold was also significantly delayed from 697 ± 51 sec to 767 ± 64 sec ($p < 0.05$). Further testing of nebivolol in a dose ranging, single-blind trial (2.5 mg/day, 5 mg/day, and 10 mg/day) was performed in 10 patients with stable angina; 5 of the patients also had a history of myocardial infarction (Ulvenstam

1991). The doses were titrated in 2 week intervals in this trial. The time to 1 mm ST change increased at all 3 doses of nebivolol compared with placebo.

In a double-blind, placebo-controlled study of maximal and submaximal exercise testing conducted in patients with ischemic left ventricular dysfunction but no overt signs of heart failure, both atenolol and propranolol reduced resting heart rate and improved left ventricular ejection fraction compared with placebo. Only nebivolol produced a parallel, downward shift of the pressure-volume relationship during early diastolic filling and improved the early peak filling rate compared with placebo (Rousseau et al 1996). In addition, compared with baseline, nebivolol therapy increased maximal exercise duration by 44 sec, a statistically significant difference from baseline ($p = 0.007$ vs baseline), whereas the improvements seen with placebo and atenolol, 7 sec and 13 sec respectively, were not statistically significant changes from baseline.

In patients with ischemic left ventricular dysfunction without clinical congestive heart failure (Stoleru et al 1993), maximal exercise function increased more in those treated with nebivolol 5 mg/day than in those treated with atenolol 50 mg/day ($p < 0.0077$). This was associated with an improved pressure-volume relationship during early diastolic filling and improved early peak filling rate. An improvement in left ventricular ejection fraction and cardiac output was found with nebivolol, but not with atenolol.

The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) was a double-blind, randomized, multicenter placebo-controlled trial conducted in Europe. SENIORS was the first randomized, controlled clinical trial with the power to demonstrate efficacy specifically in elderly patients with heart failure. The aim of the study was to assess the effect of nebivolol on mortality and cardiovascular hospital admissions in elderly patients (≥ 70 years) with heart failure, regardless of ejection fraction (Flather et al 2005). The SENIORS researchers note that this age inclusion criterion makes the study population closely resemble the actual population of heart failure patients, where the average age is 76 years; in contrast, the average age of patients enrolled in previous, large heart failure studies was 63 years.

All 2128 patients enrolled in the SENIORS study had a history of chronic heart failure, as evidenced by hospital admission within the past 12 months with a diagnosis of congestive heart failure on discharge or a documented ejection fraction of 35% or less within the previous 6 months. Following randomization, 1067 patients received

nebivolol 1.25 mg/day titrated to 10 mg/day; 1061 patients received placebo. The primary outcome of the study was a composite of all-cause mortality or cardiac hospitalization (time to first event) during a 21 month follow up period. At baseline, the mean ejection fraction was 36%, with 35% of patients having an ejection fraction >35%. More than two thirds of patients (68%) had a history of coronary artery disease. The primary outcome occurred in 31.1% (n=332) of nebivolol-treated patients and 35.3% (n=375) of patients receiving placebo (hazard ratio [HR] 0.86; 95% confidence interval [CI]: 0.74–0.99; p=0.039). The all-cause mortality rate was 15.8% (n=169) in the nebivolol group and 18.1% (n=192) in the placebo group (HR 0.88, 95% CI 0.71–1.08; p=0.21) Subgroup analysis by age less than the median age in SENIORS (75.2 years) in patients with an ejection fraction less than 35% allowed comparison with the results of previous trials; the HR for primary outcome was 0.73 (95% CI, 0.56–0.96), the HR for all cause mortality alone was 0.62 (95% CI, 0.43–0.89). These results suggest that the efficacy of nebivolol in this patient subgroup is similar to that seen in previous studies conducted with bisoprolol, metoprolol, and carvedilol (Flather et al 2005).

Nebivolol efficacy in black hypertensive patients

The efficacy and tolerability of nebivolol in black hypertensive patients was assessed in a randomized, placebo-controlled, multicenter trial conducted in Europe and the US that included 509 patients with essential hypertension (Van Neuten et al 1997). Doses of 0.5 mg/day, 1.0 mg/day, 2.5 mg/day, 5 mg/day and 10 mg/day of nebivolol were compared with placebo. Doses of nebivolol at 2.5 mg/day, 5 mg/day, and 10 mg/day were shown to be more effective than placebo in a dose-dependent manner. There was no significant difference in efficacy seen between black (22% of the study population) and white patients, with response rates of 58% and 62%, respectively (response defined as reduction of DBP to <90 mm Hg or by ≥10 mm Hg from baseline). The drug was well tolerated.

The efficacy of nebivolol in black patients may in part be due to improved NO levels. The importance of NO in black patients has been shown in the treatment of congestive heart failure where a regimen of hydralazine and nitrates reduced mortality by 43% over a standard regimen including an ACE inhibitor and a beta-blocker (Taylor et al 2004). Nebivolol has been shown to restore NO bioavailability in blacks to the level observed in whites, independent of beta₁-

selective blockade, by augmenting NO release and reducing nitroxidative stress in the vascular endothelium (Mason et al 2005). These findings suggest that nebivolol may be a more effective antihypertensive in black patients than older beta-blockers.

Conclusions

Beta-blockers are important agents in cardiovascular medicine, proving critically important in the management of hypertension and heart failure and in reducing cardiovascular risk. Nebivolol is a novel highly cardioselective beta-blocker with antihypertensive efficacy similar to that of other beta-blockers, but with tolerability better than older agents in its class, which may permit nebivolol to be used more widely and effectively than other beta-blockers. Nebivolol's vasodilating effect, its anti-atherosclerotic effect, and its positive effects on arterial compliance suggest that it may provide more cardiovascular benefits than traditional beta-blockers, particularly in patients with isolated systolic hypertension, diabetics, black patients, and patients with known vascular disease.

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