Continuing evolution of the role of β-blockers in the treatment of hypertension

The β-blockers have evolved into one of the most prescribed classes of drugs for the treatment of cardiovascular disease in general, and hypertension in particular. However, the class is one of the more heterogenous groups in pharmacological agents. The evolution of the β-blockers has included increased selectivity for the β1 receptor (cardioselective) and, more recently, development of β-blockers with vasodilating properties. As a result of this evolution, the current vasodilating β-blockers, i.e., nebivolol and carvedilol, have a better hemodynamic profile and are devoid of many of the troublesome side effects, for example, fatigue, sexual dysfunction and increased insulin resistance and disturbances in glucose metabolism, found in the traditional β-blockers. Nebivolol produces vasodilation by a mechanism that includes increased bioavailability of nitric oxide that may bring other benefits. With these improvements in design, the future for the use of β-blockers appears bright.

KEYWORDS: β-blockers, carvedilol, hypertension, nebivolol, nitric oxide

Thomas D Giles
Tulane University School of Medicine, 109 Holly Drive, Metairie, New Orleans, LA 70005, USA
Tel:. +1 504 834 8668
Fax: +1 504 836 0822
tgiles4@cox.net

The classification of α- and β-adrenoceptors by Ahlquist and colleagues in 1948 provided the foundation for the development of drugs that could modulate the sympathetic nervous system (SNS) [1]. The first β-blocker, pronethalol, developed by Sir James Black, was limited clinically due to safety concerns. However, the subsequent development of its successor, propranolol, earned Black the Nobel Prize for Medicine in 1988, and revolutionized the process of the laboratory development of cardiovascular drugs [2]. The development of the β-blocking class of drugs provided clinicians with new tools to treat many cardiovascular disorders that now include: hypertension, heart failure, angina pectoris, certain arrhythmias, post-myocardial infarction ventricular dysfunction and high-risk patients, including those with diabetes mellitus [3–5].

The first widely used β-blocker, propranolol, had equal blocking properties at both the β1 and β2 adrenoceptor subtypes. Since blocking β2 receptors produced unwanted side effects (e.g., vasoconstriction and bronchoconstriction), new (second-generation) drugs were developed that were more selective for the β1 receptor, for example, metoprolol and atenolol. These drugs were called cardioselective. However, at higher doses, blockade occurred at both receptors [6].

The traditional β-blocking drugs are associated with many side effects, including fatigue, sexual dysfunction (erectile dysfunction), cold hands and weight gain [7], and have limited efficacy in obese patients [8]. Moreover, these traditional β-blockers have a propensity to increase insulin resistance and hasten the appearance of hyperglycemia (diabetes mellitus). Additionally, the use of β-blockers in African–American hypertensive patients may be limited owing to the fact that traditional β-blockers are less effective in lowering blood pressure (BP) in hypertensive African–American patients compared with hypertensive Caucasian patients [9,10].

The newer ('third-generation') β-blocking drugs are characterized by the ability to produce vasodilation, and include carvedilol, labetalol and nebivolol. Carvedilol and labetalol achieve vasodilation by interfering with the α1 adrenoceptor, whereas nebivolol utilizes a mechanism that is endothelial dependent and results in increased bioavailability of nitric oxide (NO) (*vide infra*).

Recent studies of traditional β-blockers

Despite their less-than-desirable side effect profile, the traditional β-blockers have been considered as 'first-line' therapy in the management of hypertension by every report of the US Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension (JNC), including the JNC 7 report [3]. However, a meta-analysis of 13 randomized clinical trials of β-blockers in the management of hypertension, published in 2005 [11], concluded that atenolol was not as effective as other antihypertensive drugs in the treatment of hypertension and that, in comparison with other antihypertensive drugs, the

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effects of β-blockers were associated with an increased incidence of stroke. It was suggested that atenolol should not be used in the treatment of primary hypertension, and should not be used as a comparator in future randomized controlled trials of antihypertensive drugs. This suggestion was taken in the preparation of the UK's National Institute for Health and Clinical Excellence (NICE) guidelines for the treatment of hypertension [12]. However, the suggestion was extended to all β-blockers, even though the data upon which it was based virtually all originated from studies of atenolol.

One randomized clinical trial that utilized atenolol as the comparator drug was the Losartan Intervention for Endpoint Reduction (LIFE) Study [13]. In this study of hypertensive patients with left ventricular hypertrophy, the atenolol arm was approximately 25% more likely than the angiotensin receptor blocker, losartan, arm to be associated with stroke events [13]. Nevertheless, atenolol was more effective in preventing ischemic events and more effective than losartan in African–American subjects. However, the atenolol-based therapy was at least equivalent to angiotensin-converting enzyme (ACE) inhibitor-based therapy in improving cardiovascular and metabolic outcomes in the UK Prospective Diabetes Study (UKPDS) when examining the importance of achieving tight blood pressure control in patients with Type 2 diabetes mellitus [14].

Atenolol, more than any other traditional β-blocker, appears to be associated with significantly higher rates of all-cause mortality, cardiovascular mortality and stroke [11]. It should be noted that in most clinical trials, atenolol was dosed once daily, often at a dose of 50 mg. It has been demonstrated in many subjects that atenolol is not a once-a-day drug, and thus the patient is subjected to intermittent periods of withdrawal – definitely an untoward event. In the International Verapamil–Trandolapril Study (INVEST), where atenolol was dosed twice daily, the β-blocker fared as well as the other treatment regimens tested [15].

Atenolol therapy was also evaluated in the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) [16]. In this study, conducted in a large cohort of relatively high-risk middle-aged hypertensive patients, a comparison of atenolol (usually paired with a thiazide) with the calcium channel blocker amlodipine (usually paired with perindopril) revealed that major cardiac and stroke outcomes clearly favored the calcium channel blocker/ACE inhibitor treatment arm [16]. The trial was terminated prematurely owing to excess mortality in the patients randomized to the β-blocker arm.

Explanations for this disappointing result are not entirely clear. However, a clue is available from a substudy of ASCOT, the Conduit Artery Function Evaluation (CAFÉ) trial. In this trial, a noninvasive technique was used to compare the effects of atenolol-based therapy and amlodipine-based therapy on central (aortic) and peripheral blood pressure [17]. Importantly, whereas the two treatment arms had similar blood-pressure-lowering effects when measured in the brachial artery, the β-blocker treatment was significantly less effective than the calcium channel blocker treatment in reducing central pressure. This difference in effectiveness of blood pressure lowering is particularly important, since both cardiac and stroke events are directly affected by the central blood pressure. These data may provide an explanation for the apparent failure of traditional β-blockers to reduce major clinical events to the same extent as other antihypertensive therapies, for example, the LIFE trial.

Third-generation β-blockers

The third-generation β-blockers are characterized by the ability to produce arterial dilation and reduce peripheral vascular resistance, in addition to blocking the β-receptor. Traditional β-blocking drugs targeted two primary adrenergic receptors of norepinephrine. β1 receptors predominate in healthy cardiac muscle, while β2 receptors predominate in the bronchi. Traditional β-blockers, such as propranolol, are nonselective and block both β1 and β2 receptors [6]. Second-generation β-blockers, such as acebutolol, atenolol, bisoprolol and metoprolol, offer more selective β1 or β2 blockade [6].

Third-generation, vasodilating β-blockers, i.e., bucindolol, labetolol, carvedilol and nebivolol, vary in their selectivity [18]. Carvedilol is nonselective with inhibition of the α1 receptor. Labetolol is nonselective with a higher affinity for the α1 receptor than for β1 and β2 receptors.

Carvedilol is a nonselective β-blocker and provides α1-receptor blockade. The α1 receptors mediate endothelial function and vasoconstriction in peripheral vessels, regulate blood flow to the kidneys, and have been linked to conditions such as myocardial hypertrophy and benign hyperplasia of the periurethral prostate.

Nebivolol, recently approved for use in the treatment of hypertension in the USA, has been shown to have higher β1 selectivity than other β-blockers, and endothelium-dependent

vasodilation associated with increased bioavailability of NO [19]. Nebivolol is a racemic mixture of D-nebivolol (+SRRR) and L-nebivolol (-RSSS), and both enantiomers appear to vasodilate equally [20]. The L-enantiomer is responsible for the increased bioavailability of NO, while the D-enantiomer is primarily responsible for blockade of the β-receptor [18]. The exact mechanism for the increased bioavailability is not completely known, but may involve the β3 receptor subtype and modulation of asymmetric dimethylarginine (ADMA).

Adverse side effects

The third-generation β-blockers as a group are associated with fewer adverse drug reactions and are associated with potentially beneficial effects on arterial vasculature. In particular, third-generation β-blockers differ from traditional β-blockers with regard to benefit–risk, concerning the adverse effect on diabetes and insulin sensitivity. For example, traditional, older β-blockers (propranolol, atenolol and metoprolol) decrease insulin sensitivity. However, as discussed below, recent metabolic studies report that third-generation vasodilating β-blockers have beneficial effects on insulin sensitivity as well as on atherogenic risk factors and endothelial function.

Carvedilol

The Glycemic Effects in Diabetes Mellitus/Carvedilol–Metoprolol Comparison in Hypertensives (GEMINI) trial, a double-blind randomized trial involving 1235 participants at 205 sites, studied the metabolic effects of carvedilol versus metoprolol in patients with Type 2 diabetes and hypertension [21]. Patients were randomized to receive metoprolol (50 mg twice daily [b.i.d.], titrated up to 200 mg b.i.d.) or carvedilol (6.25 mg b.i.d., titrated up to 25 mg b.i.d.) for 35 weeks. Similar blood pressure levels were achieved in the two groups. Mean hemoglobin A1C (HbA1c) increased significantly in the metoprolol group (0.15%, $p < 0.001$), but not in the carvedilol group (0.02%, $p = 0.65$), and insulin sensitivity improved significantly with carvedilol (-9.1%, $p = 0.004$), but not metoprolol (-2.0%, $p = 0.48$). Progression to microalbuminuria was less frequent with carvedilol than with metoprolol (6.4 vs 10.3%, $p = 0.04$). GEMINI is the first large-scale randomized trial to evaluate the addition of β-blockers to ACE inhibitors or angiotensin receptor blockers to achieve the recommended blood pressure target of less than 130/80 mmHg for patients with Type 2 diabetes; in these high cardiovascular risk patients, carvedilol successfully achieved the blood pressure goal while maintaining glycemic control.

Nebivolol

Nebivolol is a novel third-generation, cardioselective (β1-adrenoceptor) lipophillic, vasodilatory β-blocker [22], and produces endothelium-dependent vasodilation [21–23] mediated through the L-arginine/NO pathway. Nebivolol is the most cardioselective β-blocker when assessed in human myocardium [24]. In Europe, nebivolol is currently approved and well tolerated in the treatment of hypertension, coronary artery disease, myocardial infarction, heart failure and left ventricular dysfunction.

The hemodynamic effects of nebivolol differ from those of older traditional β-blockers. In hypertensive patients, nebivolol administration was associated with a decrease in peripheral vascular resistance, and preserved cardiac output, stroke volume and left ventricular function [25]. Nebivolol, unlike atenolol, has demonstrated efficacy in reducing central aortic pressure [25].

Study of nebivolol in an African–American hypertensive population

Hypertension and its associated cardiovascular and renal complications occur disproportionately more often among African–Americans compared with Causcasians.

In a study of 300 African–Americans with Stage I or II hypertension (sitting diastolic blood pressure [SiDBP] ≥95 mmHg and ≤109 mmHg) treated with placebo or once-daily nebivolol (2.5, 5, 10, 20 and 40 mg), all doses of nebivolol decreased BP, and a clear dose response was observed, with numerically greater reductions in both SiDBP and sitting systolic blood pressure (SiSBP) with increasing nebivolol doses up to 20 mg [26]. Response rates in African–American patients at the end of the treatment period were significantly higher for nebivolol at doses of 5, 10, 20 and 40 mg compared with placebo (58.0, 58.8, 64.0 and 56.9 versus 26.5%, respectively; $p \leq 0.002$). It is possible that these effects in black patients are related to the NO mechanism of vasodilation of nebivolol. Nebivolol has been found to decrease oxidative stress and restore NO bioavailability in black subjects [27,28].

Adverse & metabolic effects of nebivolol

The side-effect profile of nebivolol is similar to placebo [29]. In particular, there appears to be no

adverse effect on sexual function in general, and erectile function in particular [30]. Nebivolol, in comparison with metoprolol, increased insulin sensitivity in patients with hypertension [31,32].

Although there has yet to be any clinical trials investigating the antihypertensive effects of nebivolol in elderly patients, data from the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization Seniors with Heart Failure (SENIORS) trial have shown that nebivolol is well tolerated in elderly patients with chronic heart failure, and nebivolol reduced the risk of mortality and morbidity, as well as hospitalization rates [33].

Hypertension treatment guidelines & the third-generation β-blockers

The latest edition of the guidelines of the European Society of the Cardiology/European Society of Hypertension, after considerable evaluation of all available data, continue to included the β-blockers among the other major drug classes as first-line considerations [34]. However, of note is the fact that these guidelines emphasize the positive attributes of the newer vasodilatory β-blockers, nebivolol and carvedilol, and recommend that they be the agents of choice. Likewise, the American Association of Clinical Endocrinologists, while recommending that β-blockers be strongly considered as additive therapy in diabetic patients already receiving an ACE inhibitor or an angiotensin receptor blocker, emphasize a preference for the vasodilatory agents [35].

Future perspective

At present, the β-blockers are among the most prescribed drugs for the treatment of cardiovascular disease. The traditional β-blockers, particularly atenolol, have been criticized recently and may have accounted for a reduction in use. However, the third-generation β-blockers have reawakened interest in the use of β-blockers in the treatment of hypertension and other cardiovascular diseases.

It is now possible for patients to enjoy the benefits of β-blockade in reducing cardiovascular mortality, in particular sudden death and morbidity, while avoiding the unwanted side effects on glucose metabolism, sexual function and fatigue and cold extremities. The hemodynamic profiles, and placebo-like adverse effect profile, will almost assure the continued use of this drug class for the foreseeable future. Of course, many of the traditional β-blockers have reached generic status and often cost much less. However, given the need for combination therapy and quality-of-life issues, a new generation of β-blockers is likely to prevail.

Nebivolol is of particular interest since the mechanism of vasodilation involves the increased bioavailability of NO. Regardless of the mechanism, the increase of endothelial-derived NO by nebivolol may provide additional benefits to those derived from modulating the SNS. NO modulates endothelial adhesion molecules, growth of smooth muscle cells and the inflammatory response. Moreover, the production of NO by the endothelium does not produce tachyphylaxis, as has been seen with NO donors, for example, the organic nitrates.

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Executive summary

- Despite providing great clinical benefits, older generation β-blockers are associated with many adverse side effects, for example, fatigue, sexual dysfunction and cold hands, and may have a deleterious effect on metabolic parameters such as serum glucose and lipids, thereby making them potentially unsuitable in certain patient groups (e.g., those with diabetes or metabolic syndrome). Moreover, β-blockers have been shown to have reduced efficacy in black and older populations.
- Newer (third-generation) vasodilating β-blockers, such as nebivolol and carvedilol, have placebo-like side effects and appear to be free of adverse effects on metabolic parameters. As such, these third-generation β-blockers may be a potential treatment option for hypertension treatment in patients, particularly those with diabetes or metabolic syndrome.
- Whereas traditional β-blockers are not deemed suitable in certain patient populations, such as African–American patients, owing to the fact treatment response rates are generally low, nebivolol is effective, an effect that may be due to its ability to increase nitric oxide availability. Hypertensive patients often show endothelial dysfunction and a reduction in nitric oxide bioavailability, and this can be more pronounced in African–American patients. Additionally, nebivolol, unlike traditional non-vasodilating β-blockers, has been shown to lower central aortic pressure.

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