Carvedilol, a novel vasodilating beta-blocker with the potential for cardiovascular organ protection

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Carvedilol is a vasodilating β-blocker currently marketed for the treatment of mild to moderate hypertension and application is being filed to the FDA for treatment of congestive heart failure. Carvedilol reduces peripheral vascular resistance by blocking arterial α-receptors, thereby producing vasodilation, while preventing reflex tachycardia by blocking cardiac β1- and β2-adrenoceptors. In addition to the safety and efficacy of carvedilol as an antihypertensive agent, experimental studies indicate that carvedilol also provides significant cardioprotection in animal models of acute myocardial infarction as well as protection against the vascular remodelling that occurs following injury of the vasculature. Recent pharmacological studies have uncovered several novel properties of carvedilol which may function to protect the heart and vasculature from chronic pathological processes, such as ischaemia, atherosclerosis and the remodelling that occurs in the heart and blood vessels as a consequence of pressure overload, injury or shear stress. Specifically, carvedilol, likely as a result of the carbazol moiety, is a potent anti-oxidant. In physicochemical, biochemical and cellular assays, carvedilol and several of its metabolites inhibit lipid peroxidation, scavenge oxygen free radicals, inhibit the formation of reactive oxygen radicals and prevent the depletion of endogenous antioxidants, such as vitamin E and glutathione. Moreover, carvedilol blocks the oxidation of low-density lipoproteins (LDL), and thereby prevents the formation of oxidized-LDL which is believed to stimulate foam cell formation and augment the development of atherosclerotic plaque. The ability of carvedilol to prevent the formation of oxidized LDL, in addition to the general anti-oxidant properties of the compound, results in the protection of the endothelium from oxygen free radical injury, and thereby prevents the subsequent events triggered by endothelial damage.

Recently, carvedilol has also been shown to inhibit vascular smooth muscle cell proliferation and migration. Because carvedilol can inhibit vascular smooth muscle cell proliferation induced by a wide variety of mitogens (e.g. growth factors, angiotensin II, endothelin, thrombin), it is likely that the site of inhibition occurs at some point beyond the specific mitogen receptors, possibly at a distal common pathway that affects the smooth muscle cell cycle. These unique activities of carvedilol have also been confirmed in vivo in a rat model of neointimal formation following vascular injury by balloon angioplasty, where vascular smooth muscle cell migration and proliferation are the key processes involved in the formation of neointima leading to vascular stenosis. In this model, carvedilol suppressed neointimal growth to a remarkable extent (>5% inhibition of neointimal formation) at a dose that is similar to the antihypertensive dose used clinically in hypertensive patients.

Taken together, these unique multiple actions of carvedilol provide not only for adequate control of elevated blood pressure, but may also provide for protection of the heart and vasculature from secondary damage due to hypertension itself, as well as from other causes, such as ischaemia, pressure overload, shear stress, vascular injury and atherosclerosis.

(Eur Heart J (1996); 17 (Suppl B): 24-29)

Key Words: Carvedilol, hypertension, atherosclerosis, anti-oxidant, cardioprotection, vascular protection, smooth muscle cells.

Introduction

Carvedilol (Fig. 1) is a novel, multiple action antihypertensive drug currently marketed for the treatment of mild to moderate hypertension. The antihypertensive effect of carvedilol results from a reduction in peripheral vascular resistance consequent to vascular α1-adrenoceptor blockade. The lack of reflex tachycardia observed with carvedilol is due to blockade of myocardial β1- and β2-adrenoceptors. These combined actions of carvedilol eliminate several of the unwanted side effects associated with arterial vasodilators, such as hydralazine and the calcium channel blockers. Clinical studies have clearly demonstrated that carvedilol is an...
Carvedilol and cardiovascular organ protection potential

Carvedilol = 1-(9H-Carbazol-4-yloxy)-3-[[2-<2-methoxyphenoxy)ethyl]amino]-2-propanol

Figure 1 The chemical structure of carvedilol. The asterisk denotes the point of asymmetry, and the portions of the molecule responsible for \(\alpha\)-blockade, \(\beta\)-blockade and anti-oxidant activity are indicated.

effective antihypertensive agent when used either as monotherapy or in combination with other antihypertensive drugs. In addition to lowering systemic arterial blood pressure, carvedilol increases exercise capacity, reduces myocardial oxygen consumption, increases total exercise time and increases the time to 1 mm ST-segment depression in patients with chronic stable angina. Furthermore, clinical trials in patients with ischaemic cardiomyopathy have suggested that carvedilol significantly improves exercise time, increases stroke volume index, decreases pulmonary capillary wedge pressure and increases ejection fraction. Based on these observations, large, multicentre, randomized and placebo-controlled clinical trials of carvedilol in patients with congestive heart failure are now in progress.

Recently, new findings have emerged which demonstrate that carvedilol has additional chemical and biological effects that may bear significantly on cardiovascular organ protection, specifically in the heart and vasculature. This review will highlight these new findings and discuss the mechanisms of carvedilol that are associated with the cardiac and vascular protective actions observed in experimental animal models.

Cardioprotection

Because carvedilol has several actions in addition to \(\beta\)-adrenoceptor blockade which could also provide cardioprotection, (e.g. \(\alpha\)-adrenoceptor blockade, calcium channel blockade and antioxidant activity), we have explored whether these additional pharmacological activities could add to the myocardial protection that is likely to result from the \(\beta\)-adrenoceptor blocking action of carvedilol. To this end, the effects of carvedilol on infarct size, arrhythmias and survival of animals subjected to acute myocardial infarction were investigated in detail and compared to a drug that possesses only \(\beta\)-blocking activity, propranolol. Table 1 and Figure 2 summarize the extensive studies that have been performed, and which have been discussed in detail in previous reviews. In brief, carvedilol reduces infarct size in five different species, namely the rat, rabbit, dog, cat and pig. The efficacy of carvedilol has been observed in both permanent ischaemia models as well as in transient ischaemia/reperfusion models (i.e. coronary artery occlusion followed by reperfusion). Carvedilol dramatically reduced histological damage and life-threatening ventricular arrhythmias, and at the same time improved survival rate. In all studies, the efficacy of carvedilol was greater than that observed with propranolol at equivalent \(\beta\)-block doses, suggesting that the other actions of carvedilol provide additional cardioprotection beyond that afforded by the \(\beta\)-blocking effect of the drug. Furthermore, another vasodilating, \(\beta\)-blocker, celiprolol, which blocks myocardial \(\beta_1\)-adrenoceptors and stimulates both myocardial and vascular \(\beta_2\)-adrenoceptors, was devoid of myocardial protection, suggesting that cardioprotection is not a universal feature of vasodilating, \(\beta\)-blockers per se. These studies, while confirming the myocardial protection that is provided by the \(\beta\)-blocking activity of carvedilol, are noteworthy because of the unprecedented high degree of cardioprotection provided by carvedilol (compared to \(\beta\)-blockers or other vasodilating \(\beta\)-blockers), especially in the pig model of myocardial ischaemia and reperfusion where nearly complete (>90%) protection against myocardial necrosis was observed. This high level of salvage of ischaemic myocardial tissue in a model known to involve oxygen radical-mediated reperfusion injury led to the proposal that carvedilol may possess oxygen free radical scavenging activity.
Anti-oxidant effects of Carvedilol

The anti-oxidant activity of carvedilol was examined in a variety of in vitro assay systems, including physicochemical, biochemical and cellular models, as well as in vivo models. The data, included in Table 2, indicate that carvedilol directly interacts with oxygen free radicals, a conclusion that is based on electron paramagnetic resonance studies showing that carvedilol prevents electron adduct formation in both aqueous (DMPO) or lipid (MNP) environments containing either superoxide- or hydroxyl-radical generating systems (i.e. vitamin C/Fe²⁺ and DHF/Fe³⁺-ADP, respectively)[16]. Furthermore, carvedilol prevents lipid peroxidation in brain and heart membranes both in vitro and in vivo[17]. As a result of the anti-oxidant activity, carvedilol prevents the depletion of the endogenous anti-oxidants, a-tocopherol (vitamin E) and glutathione, from tissues subjected to oxidative stress. Finally, carvedilol protects a variety of cultured cells (neurons, vascular smooth muscle cells and endothelial cells) from oxygen radical induced damage when subjected to either artificial oxygen-radical generating systems, such as Fe²⁺/vitamin C, or endogenous oxygen radical generating systems, such as xanthine-xanthine-oxidase generation of superoxide ions or activated neutrophil-mediated cell damage which involves the release of superoxide ions. This effect of carvedilol to inhibit neutrophil-mediated cell damage may result from the ability of carvedilol both to scavenge superoxide ions and to inhibit the production of superoxide radicals, the latter being inferred from the observation that carvedilol inhibits superoxide release from phorbol ester-activated neutrophils[18].

The anti-oxidant effect of carvedilol is unique in that this activity is not shared by a large number of other, structurally dissimilar beta-blockers, such as propranolol, labetalol, atenolol, pindolol, celiprolol and carazolol. In addition, the 21-aminosteroids, also referred to as the ‘lazaroids’, typified by U76004 or U74500, while being effective inhibitors of lipid peroxidation in some biochemical assays, do not inhibit DMPO adduct formation in chemical assays, indicating that these compounds, in contrast to carvedilol, do not directly scavenge oxygen free radicals.

Several important observations must be noted with respect to the anti-oxidant activity of carvedilol. The protection afforded by carvedilol against oxidative stress to cell systems is time-dependent. Thus, prolonged exposure of carvedilol (5–7 days) to cells in culture increases the anti-oxidant potency of carvedilol by more than 10-fold compared to acute (20–30 min) exposure of the drug. As such, in many in vitro assay systems involving acute exposure of carvedilol, the EC₅₀ for the antioxidant activity of the drug is approximately 1–10 μM (Table 2), which is somewhat higher than the plasma levels of carvedilol observed clinically. In contrast, in the more chronic studies, where exposure to carvedilol lasts for up to 1 week, the antioxidant potency of the drug is well within clinically relevant concentrations (i.e. EC₅₀ values for anti-oxidant activity of 100–300 nM). The dramatic increase in antioxidant potency of carvedilol that occurs with prolonged exposure to the drug has been attributed to the high lipophilicity of the compound and its likely accumulation in the plasma membrane of cells. In addition, several metabolites of carvedilol have been found in human plasma and urine that exhibit even greater anti-oxidant potency than carvedilol. Thus, SB 209995 (BM 910183) and SB 211475 (BM 910228) are approximately 40–50-fold more potent than carvedilol in inhibiting the oxidation LDL by macrophages[19], indicating that they may also provide anti-oxidant activity in vivo at low nanomolar concentrations. To this point, the anti-oxidant activity of carvedilol is not simply an in

Table 2  Anti-oxidant effects of carvedilol

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter</th>
<th>IC₅₀(μM)</th>
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<tbody>
<tr>
<td>Swine cardiac membranes</td>
<td>TBARS</td>
<td>5.1</td>
</tr>
<tr>
<td>Rat cardiac microsone</td>
<td>TBARS</td>
<td>3.9</td>
</tr>
<tr>
<td>Rat brain homogenate</td>
<td>TBARS</td>
<td>8.1</td>
</tr>
<tr>
<td>Rat brain homogenate</td>
<td>a-tocopherol depletion</td>
<td>17.6</td>
</tr>
<tr>
<td>Human LDL</td>
<td>TBARS</td>
<td>3.8</td>
</tr>
<tr>
<td>(macrophages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine endothelial cells</td>
<td>TBARS</td>
<td>2.6</td>
</tr>
<tr>
<td>DHF/Fe³⁺-ADP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine endothelial cells</td>
<td>glutathione depletion</td>
<td>1.8</td>
</tr>
<tr>
<td>DHF/Fe³⁺-ADP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>xanthine-xanthine oxidase</td>
<td>TBARS</td>
<td>3.8</td>
</tr>
</tbody>
</table>

TBARS, thiobarbituric acid reactive substance; DHF, dihydroxyfumarate.

Carvedilol and cardiovascular organ protection potential

Vascular protection by carvedilol

Because hypertension and left ventricular hypertrophy are major risk factors for myocardial infarction, studies to assess the ability of carvedilol to reduce left ventricular hypertrophy were performed. Spontaneously hypertensive rats, fed chronically with carvedilol (1200 ppm in the diet), were examined for left ventricular hypertrophy as well as vascular smooth muscle hypertrophy following 10 weeks of treatment. The results clearly demonstrated that carvedilol significantly reduced left ventricular wall thickness and the medial diameter of resistance vessels. Interestingly, the marked reductions in cardiac and vascular hypertrophy produced by carvedilol were associated with only modest reductions in systemic arterial blood pressure. This observation prompted the exploration of possible growth-inhibiting properties of carvedilol in vascular smooth muscle cells that may be unrelated to the antihypertensive actions of the drug. Indeed, when carvedilol was added to cultured human or rat vascular smooth muscle cells stimulated to proliferate with various growth factors and mitogens, such as thrombin, angiotensin II, endothelin-1, FGF, PDGF or serum, a concentration-dependent inhibition of cell proliferation, as assessed by either $^3$H-thymidine incorporation into DNA or direct cell counts, was observed. This unique antiproliferative action of carvedilol is not shared by other antihypertensives, including angiotensin converting-enzyme inhibitors, calcium channel antagonists or $\beta$-blockers.

Further exploration of the effects of carvedilol on vascular smooth muscle biology revealed yet another important activity that is also related to vascular protection, namely the ability of carvedilol to inhibit vascular smooth muscle cell migration. Vascular smooth muscle cell migration, in addition to proliferation, is believed to be of fundamental importance in neointima formation following both acute vascular injury, as

Figure 3  Survival rate percentages for sham splanchnic artery occlusion (SAO) and SAO rats given vehicle, propranolol, carvedilol and superoxide dismutase (SOD). Bar heights represent actual percentage values; the fractions represent number of rats to survive at 120 min over the total number of rats in each group.
may occur in percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) procedures, and chronic vascular pathological processes, such as atherosclerotic plaque formation. The ability of carvedilol to inhibit vascular smooth muscle cell migration has been demonstrated in both rat and human vascular smooth muscle cells stimulated to migrate by various chemoattractants (e.g. PDGF, osteopontin)\(^{(22)}\).

Inasmuch as carvedilol inhibits both vascular smooth muscle cell migration and proliferation in vitro, and since both of these processes are involved in vascular remodelling in response to injury, the ability of carvedilol to provide vascular protection was determined in vivo in a model of vascular injury where strong stimuli exist for both vascular smooth muscle cell proliferation and migration. The model studied is the well-characterized rat model of neointimal formation following balloon angioplasty of the carotid artery. This model is analogous to PTCA in humans in which mechanical injury to the blood vessel wall initiates a series of events leading to vascular smooth muscle cell migration into the intimal layer, as well as smooth muscle proliferation, to result in a profound vascular stenosis due to neointima formation\(^{(23,24)}\). The administration of carvedilol (1 mg. kg\(^{-1}\), given twice daily starting 3 days before angioplasty and maintained throughout 14 days thereafter), dramatically inhibited, by more than 85%, neointimal growth\(^{(25)}\). In contrast, \(\beta\)-blockers as well as \(\alpha_1\)-adrenoreceptor antagonists are devoid of activity in this model, indicating that these actions of carvedilol are not responsible for the effects observed, and that some other activity of the drug, such as the ability to inhibit vascular smooth muscle cell proliferation and migration, must be involved. These in vitro and in vivo studies collectively demonstrate that carvedilol has the unique capacity to preserve vascular integrity even under conditions of profound vascular injury. It is important to note that the efficacy of carvedilol in the rat carotid balloon angioplasty model occurred at a dosing regimen that is similar to the dosing regimen used clinically in humans for the management of hypertension.

Thus, carvedilol inhibits vascular smooth muscle cell migration and proliferation both in vitro and in vivo. These properties may allow carvedilol to protect blood vessels not only from injury induced by shear stress or mechanical intervention (e.g. PTCA, CABG), but also from chronic pathological processes, such as atherosclerosis and diabetic vasculopathy. It is noteworthy that carvedilol also inhibits the deposition of atherosclerotic plaque in a rabbit model of atherosclerosis, and decreases the number of foam cells in the atherosclerotic lesions. The ability of carvedilol to decrease the number of foam cells in aortic lesions may result from the ability of the drug to inhibit LDL oxidation (and thereby block foam cell formation) and/or the ability of carvedilol to block the adhesion of leukocytes to vascular smooth muscle cells (unpublished observations).

### Summary

Carvedilol is a new vasodilating, \(\beta\)-blocker with established efficacy in the treatment of mild to moderate hypertension. Furthermore, recent experimental studies indicate that carvedilol possesses additional actions. The anti-oxidant activity of carvedilol resides in the carboxyl moiety of the molecule, and this action is not shared by other \(\beta\)-blockers. Carvedilol and several of its metabolites are as effective in inhibiting lipid peroxidation as the 21-aminosteroids (lazaroids) and probucol, the latter being anti-oxidant that is claimed to be efficacious in the prevention of atherogenesis. The anti-oxidant activity of carvedilol has been established in physicochemical, biochemical and cellular assay systems using diverse methodologies, and can be demonstrated in vivo at low doses. The ability of carvedilol to preserve the endogenous anti-oxidants, vitamin E and glutathione, are of special importance in view of recent reports associating low levels of the anti-oxidant vitamins with increased risk of cardiovascular morbidity and mortality. Although the anti-oxidant activity of carvedilol can be clearly assigned to the carboxyl moiety, no pharmacophore in carvedilol can yet be assigned to the inhibitory actions on vascular smooth muscle cell proliferation and migration. The ability of carvedilol to inhibit vascular smooth muscle cell proliferation and migration most probably involves 'down stream' signal transduction events associated with the smooth muscle cell cycle, such as the \(G_0\rightarrow G_1\) and \(G_1\rightarrow S\) phases. Support for this hypothesis can be inferred from the inhibitory effect of carvedilol on the mitogenic activity of a variety of growth factors which act on different receptors and which utilize different signal transduction mechanisms (e.g. G-proteins, tyrosine kinases, etc.). Although the precise mechanisms responsible for the action of carvedilol to inhibit vascular smooth muscle cell migration and proliferation are not known with certainty, the potential medical utility of these novel pharmacological effects can easily be recognized. Thus, not only does carvedilol normalize blood pressure, but the drug also has the potential to inhibit the cardiovascular risk factors of left ventricular hypertrophy and vascular hypertrophy, as well as to inhibit several of the processes involved in atherosclerosis. In addition, it is likely, although not yet established, that carvedilol may find utility in yet another important medical problem, namely the profound vascular remodelling that occurs following PTCA and which leads to vascular stenosis. Based on these additional activities of carvedilol that are associated with cardioprotection and vascular protection in animals, clinical studies are in progress to assess the ability of carvedilol to reduce infarct size following acute myocardial infarction and to prevent restenosis following PTCA.

Finally, carvedilol may mark a new era of multiple action cardiovascular drugs aimed to treat multiple risk factors involved in cardiovascular disease rather than simply correcting one isolated aberrant variable, such as elevated blood pressure. Further research along
these lines may lead to molecules with yet more complex actions having broader prospects for the prevention and treatment of cardiovascular disorders.

References


