International Journal of Pharma and Bio Sciences V1(2)2010

CARVEDILOL – A NOVEL "LOOK" AT β-BLOCKERS IN MANAGEMENT OF CARDIOVASCULAR DISEASE

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ABSTARCT

Physiologically, cardiovascular functions are regulated by a variety of central and peripheral mechanisms that control vascular tone, blood pressure and cardiac functions. Under certain pathological conditions, physiological control is disturbed leading to serious cardiovascular disorders such as hypertension, cardiac arrhythmias and heart failure. These detrimental effects possibly occur due to chronic over-activation of the sympathetic systems and cardiovascular α and β adrenergic receptors. Sustained adrenergic activation and norepinephrine release raise cardiac output and heart rate, which then increase myocardial oxygen demand, ischemia, and oxidative stress. At the same time, peripheral vasoconstriction elevates blood pressure and increases both cardiac preload and afterload, causing additional stress on the ventricles and may end up by heart failure. There are now three available generations of β-adrenergic antagonists. Although very effective in management of cardiovascular disorders, the first generation drugs were suffering from some considerable side effects especially in asthmatic and diabetic patients. These adverse effects were significantly reduced upon the introduction of the second generation of β-blockers but such agents still have some adverse interactions. Fortunately during the last decade a third generation drugs have been developed and proved very particular efficiency in treatment of cardiovascular disorders associated with other serious co-morbidities. This short review will focus on **"carvedilol"** as a novel 3rd generation β-blocker that revolutionized therapy with β-adrenergic antagonists in hypertension and heart failure. Carvedilol's mechanism of action, pharmacokinetics, dosage and administration as well as its side effects and tolerability are also discussed.

CARVEDILOL – A NOVEL "LOOK" AT β-BLOCKERS IN MANAGEMENT OF CARDIOVASCULAR DISEASE

INTRODUCTION

The plasma half-live of the various β-blockers ranges from just 9 minutes for esmolol to 24 hours for nadolol and penbutolol (median half-live of the class is about 6 hours), but the effective half-life is longer mainly because of the active metabolites.

Carvedilol is rapidly absorbed after an oral dose, reaching peak plasma drug concentrations within 1 to 2 hours. Absorption is delayed an additional 1 to 2 hours when the drug is administered with food **(Morgan, 1994).** The plasma half-life of carvedilol ranges from 7 to 10 hours in most subjects; thus, the drug requires twice-daily dosing. In plasma, 98% of the drug is bound to plasma proteins, predominantly to albumin **(Morgan, 1994).** Due to the high plasma protein binding capacity of carvedilol, it is not cleared significantly by hemodialysis **(Chen and Chow, 1997).**

Carvedilol is almost exclusively metabolized by the liver and undergoes extensive first-pass metabolism. Three active metabolites of carvedilol have been identified, but none of these compounds appears to contribute to carvedilol's β-blocking activity. Less than 2 percent of a given dose is excreted unchanged in the urine. Carvedilol's metabolism is affected by genetic polymorphism of cytochrome P-450 2D6 activity. Drugs that inhibit cytochrome P-450 2D6 activity, such as quinidine, paroxetine, fluoxetine, and propafenone, may also increase plasma carvedilol concentrations. Thus, patients taking these drugs may be at particularly high risk of hypotension due to excessive α-adrenoreceptor blockade **(Stafylas and Sarafidis, 2008).**

Clearance of carvedilol is delayed in patients over 65 years of age. On average, their plasma carvedilol concentrations are 50% higher than in younger patients **(Frishman, 1998).** The pharmacokinetics of carvedilol are significantly altered in patients with liver disease and to a lesser extent in the presence of renal failure **(Neugebauer *et al.*, 1992; Frishman, 1998).** Less than 2% of the parent drug recovers in the urine **(Frishman, 1998).** Some of the metabolites of carvedilol have β-adrenoreceptor antagonist activity, and one 4-hydroxyphenyl metabolite is approximately 13 times as potent as carvedilol in this regard. Approximately 60% of these metabolites are secreted with bile and excreted with the faeces **(Frishman, 1998).**

MECHANISMS OF CARDIOVASCULAR ACTIONS OF CARVEDILOL COMPARED TO OTHER β-BLOCKERS

First generation β-blockers, such as propranolol, block both β_1- and β_2-receptors. Through β_1-receptor blocking, these compounds induce the well known inhibitory effects on the function of the sinus and atrioventricular nodes and on myocardial contraction (negative chronotropic, dromotropic, and inotropic effect). By blocking the β_2-receptors, they cause contraction of smooth muscle with a risk of bronchospasm in predisposed individuals **(Kaplan, 2005; Opie and Yusuf 2005).**

Second-generation agents, such as atenolol and metoprolol have more selectivity for cardiac β_1-receptors, but show relative low selectivity, when given in low doses, for the β_2-receptors. They are preferable in patients with chronic lung disease or in chronic smokers **(Stafylas and Sarafidis, 2008).**

Although β_1-selective blockers are cardioselective, selectivity is dose dependent, and at high doses β_1-selective agents may also antagonize β_2-adrenergic receptors **(Egan *et al.*, 2005).** Classic beta-blockers

CARVEDILOL – A NOVEL "LOOK" AT β-BLOCKERS IN MANAGEMENT OF CARDIOVASCULAR DISEASE

reduce blood pressure primarily by decreasing cardiac output, but systemic vascular resistance (SVR) is not usually significantly changed **(Messerli and Grossman, 2004).** Inhibition of norepinephrine binding to β-adrenergic receptors results in decreased heart rate and myocyte contractility **(Packer, 1998).** Even in small doses, β-blockers begin to lower BP within a few hours **(Kaplan, 2005).**

Unlike traditional β-blockers, **carvedilol** blocks norepinephrine binding to α_1-adrenegric receptors as well as β_1- and β_2-adrenegeric receptors **(Pedersen and Cockcroft, 2007)**. The β-blocking actions of carvedilol are generally evident in humans within one hour of administration. As α_1-adrenergic receptors mediate vasoconstriction, then α_1-blockade results in vasodilation of the peripheral arteries, decreasing systemic SVR and lowering blood pressure **(Fonarow, 2004; Sica 2007).** These effects are evident within about 30 minutes of administration. In addition, preclinical evidence suggests that carvedilol can also produce nitric oxide-mediated vasodilation **(Kozlovski *et al.,* 2006).** At high dosages carvedilol also has calcium antagonist properties **(Opie and Yusuf 2005).** Another advantage of carvedilol is that it does not possess intrinsic sympathomimetic activity **(Toda, 2003).**

ROLE OF β-BLOCKERS IN HEART FAILURE THERAPY

Although acute treatment with β-blockers decreases blood pressure and cardiac contractility, long-term administration of β-blockers is associated with significant increases in ejection fraction **(Anthonio *et al*., 1999; Lechat *et al*., 2001)** and cardiac function and a decrease in left ventricular (LV) end diastolic pressure **(Dibona and Sawin, 1999; Hjalmarson *et al*, 2000).** β-blockers reverse the deleterious changes associated with LV remodeling and decrease myocardial mass and LV volume, leading to improved hemodynamics. β-blockers may also mediate benefit via regulating heart rate and decreasing cardiac arrhythmias **(Lechat *et al*., 2001).** These direct cardiac effects led to the hypothesis that β-blockers would provide substantial clinical benefits in patients with heart failure. The use of β-blockers is associated with a consistent 30% reduction in mortality and a 40% reduction in hospitalizations in patients with heart failure **(Doughty *et al.,* 1997; Avezum *et* al., 1998).** For example, treatment with the β-blocker metoprolol proved association with a 34% decrease in all-cause mortality, a 38% decrease in cardiovascular mortality, a 41% decrease in sudden death, a 49% decrease in death caused by progressive heart failure, and a 35% reduction in hospitalizations caused by heart failure **(Packer *et al*., 1996; Cohn *et al*., 1997; Goldstein and Hjalmarson, 1999).**

Carvedilol, a third-generation β-blocker with β_1, β_2 and α_1 blocking properties as well as antioxidant activity, was extensively tested in the US Carvedilol Heart Failure Program **(Bristow *et al*., 1996; Colucci *et al*., 1996)** on patients with mild, moderate, or severe heart failure. Carvedilol therapy was associated with a significant reduction in overall mortality rate by 65%.

DOSING AND ADMINISTRATION OF CARVEDILOL IN HF PATIENTS

Carvedilol is supplied in tablet form and is available in four dosage strengths: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg. It is indicated for the treatment of clinically stable heart failure. Patients taking diuretics, digitalis or ACE inhibitors should be taking stable dosages of these medications before carvedilol therapy is initiated. Carvedilol may also be used in

CARVEDILOL – A NOVEL "LOOK" AT β-BLOCKERS IN MANAGEMENT OF CARDIOVASCULAR DISEASE

patients unable to tolerate an ACE inhibitor and in those not taking digoxin, hydralazine (apresoline) or nitrate therapy. In most cases, however, ACE inhibitor therapy should be initiated and stabilized before the introduction of carvedilol therapy.

CARVEDILOL – SIDE EFFECTS AND TOLERABILITY

Side effects of β-blockers, in general, include bradycardia, hypotension, temporary worsening of heart failure and fatigue. Despite this, most symptoms usually do not lead to withdrawal of the medication. For example, in the US carvedilol heart failure study dizziness was seen in 33% of those taking carvedilol and 20% in those taking placebo but was not associated with withdrawal of study medication **(Bristow *et al.*, 1996).** Interestingly, not all studies have confirmed that β-blockers are a major cause of fatigue **(Ko *et al.*, 2002).**

Carvedilol is generally well-tolerated. The most frequently reported adverse effects include dizziness, hypotension and fatigue **(Packer *et al.*, 1996; Chen and Chow, 1997).** Less common adverse effects included diarrhea, bradycardia, insomnia, dyspnea, and pharyngitis. Rare reports of liver function abnormalities have been noted. However, no deaths have been reported, and the mild hepatic injury appears to have been reversed once the drug was discontinued. Rare cases of thrombocytopenia have also been reported (**Packer *et al.*, 1996).** Older patients (>70 years) tolerate carvedilol as frequently and to the same doses as patients under 70 years. Carvedilol seems not to have adverse effects on cognitive function or functional capacity in elderly patients.

SUMMARY AND CONCLUSION

Developed nearly half a century ago by Sir James Black, β-blockers have become the most extensively scrutinized treatment for a wide range of cardiovascular ailments e.g. hypertension, ischemic heart disease and heart failure. In particular, basic science mechanistic studies, and large, randomized controlled clinical trials support the value of β-blockers for patients with heart failure caused by systolic dysfunction.

Carvedilol is a 3rd generation β-antagonist that blocks β_1, β_2 and α_1 adrenergic receptors. The varied mechanisms of action of carvedilol allow it to be an effective treatment of hypertension, heart failure, and post myocardial infarction left ventricular dysfunction (MI LVD), with less of the metabolic and tolerability concerns associated with traditional beta-blockers.

The key difference of carvedilol from the majority of beta-blockers appears to be vasodilation mediated by α_1-adrenergic receptor blockade, which decreases total peripheral resistance. Furthermore, carvedilol's antioxidant and anti-inflammatory effects may provide additional cardio-protective effects beyond that of traditional beta-blockers.

Carvedilol has a long history and a proven track record in the treatment of hypertension and cardiac dysfunction. In addition, the once-daily formulation of carvedilol provides a more convenient option and may confer an adherence benefit over the twice-daily formulation in conditions traditionally prone to noncompliance such as hypertension and post myocardial infarction left ventricular dysfunction. So, the introduction of carvedilol in treatment of cardiovascular disease surely has transferred β-blockers to a new era of effectiveness and improved greatly understanding of management of serious

CARVEDILOL – A NOVEL "LOOK" AT β-BLOCKERS IN MANAGEMENT OF CARDIOVASCULAR DISEASE

cardiovascular disorders especially in presence of other co-morbidities.

REFERENCES

1. Anthonio RL, Brouwer J, Lechat P, et al. 1999. Different effects of bisoprolol on heart rate in patients with ischemic or idiopathic dilated cardiomyopathy (a 24-hour Holter substudy of the Cardiac Insufficiency Bisoprolol Study [CIBIS]). *Am J Cardiol*. 83: 1286-1289, A10.
2. Avezum A, Tsuyuki RT, Pogue J, Yusuf S. 1998 Beta blocker therapy for congestive heart failure. *Can J Cardiol*. 14:1045-1053.
3. Bristow MR, Gilbert EM, Abraham WT, et al. 1996. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation*, 94: 2807-2816.
4. Chen BP and Chow MS. 1997. Focus on carvedilol: a novel beta-adrenergic blocking agent for the treatment of congestive heart failure. Formulary 32(8): 795-805.
5. Cohn JN, Fowler MB, Bristow MR, et al. 1997. Safety and efficacy of carvedilol in severe heart failure: the US Carvedilol Heart Failure Study Group. *J Card Fail*. 3: 173-179.
6. Colucci WS, Packer M, Bristow MR, et al. 1996. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. *Circulation*, 94: 2800-2806.
7. Dibona GF, Sawin LL. 1999. Effect of metoprolol administration on renal sodium handling in experimental congestive heart failure. *Circulation*. 100: 82-86.
8. Doughty R, Rodgers A, Sharpe N, MacMahon S. 1997. Effects of beta-blocker therapy on mortality in patients with heart failure. *Eur Heart J*. 18: 560-565.
9. Egan BM, Basile J, Chilton RJ, et al. 2005 . Cardioprotection: the role of beta-blocker therapy. *J Clin Hypertens (Greenwich)*, 7:409–16.
10. Fonarow GC. 2004. Managing the patient with diabetes mellitus and heart failure: issues and considerations. *Am J Med*, 116 : 76S-88S.
11. Frishman WH. 1998. Carvedilol. *N Engl J Med*, 339:1759-1765.
12. Goldstein S, Hjalmarson A. 1999. The mortality effect of metoprolol CR/XL in patients with heart failure: results of the MERIT-HF Trial. *Clin Cardiol*. 22: V30-V35.
13. Hjalmarson A, Goldstein S, Fagerberg B, et al. 2000. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF): MERIT-HF Study Group. *JAMA*. 283: 1295-1302.
14. Kaplan N. 2005. Systemic hypertension: mechanisms and diagnosis. In Zipes D, Libby P, Bonow R, et al. eds. Braunwald's Heart Disease. A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, Pensylvania: Elsevier Saunders. p 959-987.
15. Ko DT, Hebert PR, Coffey CS, et al. 2002. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA*, 288: 351-357.
16. Kozlovski VI, Lomnicka M, Chlopicki S. 2006. Nebivovol and carvedilol induce NO-dependent coronary vasodilatation that is unlikely to be

CARVEDILOL – A NOVEL "LOOK" AT β-BLOCKERS IN MANAGEMENT OF CARDIOVASCULAR DISEASE

mediated by extracellular ATP in the isolated guinea pig heart. *Pharmacol Rep*, 58: 103-110.

17. Lechat P, Hulot J-S, Escolano S, et al. 2001. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. *Circulation*. 103: 1428-1433.

18. Messerli FH, Grossman E. 2004. beta-Blockers in hypertension: is carvedilol different? *Am J Cardiol*, 93: 7B-12B.

19. Morgan T. 1994. Clinical pharmacokinetics and pharmacodynamics of carvedilol. *Clin Pharmacokinet*, 26:335–46.

20. Neugebauer G, Gabor M, Reiff K. 1992. Disposition of carvedilol enantiomers in patients with liver cirrhosis: evidence for disappearance of stereoselective fi rst-pass extraction. *J Cardiovasc Pharmacol*, 19 Suppl 1:S142–S6.

21. Opie L, Yusuf S. 2005. Beta-blocking agents. In Opie LH, Gersh B eds. Drugs for the Heart. 6th ed. Philadelphia, Pensylvania: W.B. Saunders Company. p 1–32.

22. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. 1996. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 334: 1349-1355.

23. Packer M. 1998. Beta-adrenergic blockade in chronic heart failure: principles, progress, and practice. *Prog Cardiovasc Dis*, 41:39–52.

24. Pedersen ME, Cockcroft JR. 2007. The vasodilatory beta-blockers. *Curr Hypertens Rep*, 9:269–77.

25. Sica DA. 2007. beta-Blockers in Hypertension: A Reassessment of the Benefit of Combined alpha-/beta-Blockade. *J Clin Hypertens (Greenwich)*, 9:4–9.

26. Stafylas PC and Sarafidis PA. 2008. Carvedilol in hypertension treatment. Vascular Health and Risk Management 4(1) 23-30.

27. Toda N. 2003. Vasodilating beta-adrenoceptor blockers as cardiovascular therapeutics. *Pharmacol Ther*, 100: 215-234.