ОБЗОРИ

REVIEWS

CARVEDILOL – A THIRD GENERATION BETA-BLOCKER IN TREATING HYPERTENSION

JAYACHANDRA SRINIVASA

Santhiram Medical College, Nandyal, AP, India

КАРВЕДИЛОЛ – ТРЕТО ПОКОЛЕНИЕ БЕТА-БЛОКЕР ПРИ ЛЕЧЕНИЕ НА ХИПЕРТОНИЯ

JAYACHANDRA SRINIVASA

Santhiram Medical College, Nandyal, AP, India

Summary. *Hypertension is a chronic medical condition in which the systemic arterial blood pressure is elevated. Persistent hypertension is one of the risk factors for stroke, myocardial infarction, heart failure and arterial aneurysm, and is a leading cause of chronic kidney failure. The β-blockers have been used for hypertension treatment for over 40 years, but their effect on cardiovascular morbidity and mortality in hypertensive patients remains divisive and its use in uncomplicated hypertension is presently under discussion. Carvedilol, a vasodilating non-cardioselective β-blocker, is a compound that seems to give the prospect to the physician to use a cardioprotective agent without the concerning hemodynamic and metabolic actions of traditional β-blocker therapy. This article attempts to examine the potential use of this agent for hypertension treatment. Carvedilol maintains cardiac output, has a less extended effect on heart rate and reduces BP by decreasing vascular resistance. Furthermore, a number of studies have shown that carvedilol has a beneficial or at least neutral effect on metabolic parameters, such as glycemic control, insulin sensitivity, and lipid metabolism, indicating that it could be used in patients with the metabolic syndrome or diabetes without negative consequences. However, future prospective clinical trials are needed to draw a definite conclusion.*

Key words: carvedilol, beta-blockers, hypertension

Резюме. *Хипертонията е хроничен медицински проблем, при който системното артериално кръвно налягане е повишено. Трайната хипертония е един от рисковите фактори за инсулт, миокарден инфаркт, сърдечна недостатъчност и артериална аневризма и е водеща причина за хронична бъбречна недостатъчност. Бета-блокерите се използват за лечение на хипертонията над 40 години, но ефектът им за кардиоваскуларната заболяемост и смъртност при хипертоници е противоречив и използването им при неусложнена хипертония днес е дискусионно. Карведилол, съдоразширяващ некардиоселективен β-блокер, е съединение, което може да предостави на лекарите възможност за използване на кардиопротективно средство без опасения от хемодинамичните и метаболитни ефекти на лечението с традиционните β-блокери. Публикацията прави опит да изследва потенциалната употреба на това средство за лечението на хипертония. Карведилолът поддържа минутния сърдечен обем, има по-слаб ефект върху сърдечната честота и понижава кръвното налягане чрез намаляване на съдовата резистентност. Освен това редица изследвания показват, че карведилол има благоприятен или най-малкото неутрален ефект върху метаболитните параметри като гликемичния контрол, инсулиновата чувствителност и липидния метаболизъм, което показва, че той може да се използва без отрицателни последствия при пациенти с метаболитен синдром или диабет. Необходими са обаче бъдещи проспективни клинични проучвания, за да се направят окончателни изводи.*

Ключови думи: *карведилол, бета-блокери, хипертония*

INTRODUCTION

Hypertension represents the most common cardiovascular risk factor. Its prevalence is continuously rising, affecting more than 25% of the adult population in developed societies [1, 2, 3]. Previous studies have clearly shown longitudinal associations between hypertension and coronary artery disease, myocardial infarction, stroke, congestive heart failure, and peripheral vascular disease [4, 5]. The USA Joint National Committee Guidelines (JNC 7) on hypertension published in 2003 simplifies the classification of BP for adults. According to this classification, the normal BP level is less than 120/80mm of Hg . Systolic BP levels between 120 and 139 mm Hg and diastolic between 80 and 89 mm Hg are now designated as prehypertension (previously designated normal and high normal). Hypertension is still defined as a systolic BP level of 140 mm Hg or higher or diastolic BP level of 90 mm Hg or higher, but it is now stratified into 2 stages) [6]. Even the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) published their own guidelines on hypertension treatment in 2003 [7]. In the pharmacological management of hypertension, beta-blockers are no longer recommended as first-line therapy, as they may be less effective in reducing major cardiovascular events, particularly stroke, than other drug combinations [8]. They act as though patients were made hemodynamically “older” by decreasing cardiac output and increasing systemic vascular resistance [9] and do not reduce pulse pressure or arterial compliance [10]. These properties make them less effective in treating systolic hypertension and relatively ineffective and poorly tolerated in the elderly patient [9]. But on the other hand carvedilol, as a vasodilating beta-blocker, contrasts with the hemodynamic profile of traditional beta-blockers in hypertensive patients; it maintains cardiac output, decreases blood pressure by decreasing systemic vascular resistance and increases renal blood flow [11, 12] and appears to exert a regressive effect on LV hypertrophy [13]. The present article reviews the existing data on the effects of carvedilol on blood pressure whether this agent could be useful in the treatment of hypertension when compared to the other beta-blockers.

PHARMACOKINETICS AND PHARMACODYNAMICS OF CARVEDILOL

Carvedilol is a third-generation, vasodilating noncardioselective β-blocker which doesn’t have intrinsic sympathomimetic activity. Additionally, it has blocking effects at vascular α1-receptors [14]. Experimental models exhibit that carvedilol blocks α1-, β1-, and β2- adrenergic receptors [15] without showing high levels of inverse agonist activity. As it has no inverse agonist activity and intrinsic sympathomimetic activity, so it reduces the side-effects and makes the compound better tolerated than the other β-blockers [16].

Carvedilol is rapidly absorbed after an oral dose, reaching peak plasma drug concentrations within 1 to 2 hours. Food will interfere with the absorption of the drug. The plasma half-life of carvedilol varies from 7 to 10 hours in most subjects; so the drug needs twice-daily dosing. In blood, 98% of the drug are bound to plasma proteins, mainly to albumin [17]. The pharmacokinetic profile is not altered in the elderly or in patients with renal disease. However, bioavailability of the oral medication is greatly increased in patients with liver disease [17]. Carvedilol is almost exclusively metabolized by the liver and its metabolism is influenced by genetic polymorphism of cytochrome P-450 2D6 activity. Less than 2% of the parent drug are excreted in the urine. One of its metabolite, 4-hydroxyphenyl metabolite, is having β-adrenoreceptor-antagonist activity, which is approximately 13 times as potent as carvedilol. Nearly 60% of these metabolites are secreted with bile and excreted with the faeces [18, 19].

Dosage and administration: Most patients with mild-to-moderate hypertension react to an oral carvedilol dose of 25 mg administered once daily but if necessary this can be increased to 50 mg/day. All patients must initially get 12.5 mg daily for the first 2 days of therapy, and the maximum total daily dosage should not exceed 50 mg. The recommended dosage for elderly hypertensive patients is 12.5 mg once daily; this can be titrated (at intervals of 2 weeks) up to a maximum of 50 mg/day. In

clinical studies, most patients with stable angina pectoris or congestive heart failure received 12.5 to 50 mg twice daily [15].

EFFECTS OF CARVEDILOL IN HYPERTENSION

Majority of antihypertensive agents cause a decrease in vascular resistance while sparing cardiac output, but traditional β-blockers follow a different rule. The non-vasodilating β-blockers reduce BP by decreasing in cardiac output, sympathetic outflow, and, probably, renin release while systemic vascular resistance remains unchanged or even enhanced [20, 21]. R. Eggertsen et al. showed that carvedilol given orally (25 mg b.i.d. or 50 mg b.i.d) has a useful antihypertensive effect both acutely and during prolonged treatment of hypertension. It is well tolerated and its hemodynamic profile is attractive [22]. In a clinical trial, M. E. Heber et al. suggested that carvedilol will be a useful first-line drug for treatment of essential hypertension, and its vasodilating action may have a more favorable effect on left ventricular function than conventional beta-blocking drugs [23]. A randomized controlled trail in 81 elderly patients (greater than or equal to 60 years) with essential hypertension showed that carvedilol (25 mg/once daily) is an alternative substance for lowering high blood pressure in elderly hypertensive patients [24].

Carvedilol appears to lower BP by decreasing peripheral vascular resistance, without affecting cardiac output; due to the α1-adrenergic blocking effect, which accounts for its vasodilatory effects. This hemodynamic effect of carvedilol is similar to those of ACE inhibitors and calicum channel blockers [18] and it can be estimated to have a more steady BP lowering effect than the traditional β-blockers, such as atenolol or metoprolol [20].

Hypertension is associated with the development of left ventricular hypertrophy (LVH). Most of antihypertensive agents have been shown to cause regression of LVH, however β-blockers seem to be less effective to this end [22, 23]. Atenolol failed to reduce LVH in the elderly when compared with verapamil as shown by Schulman et al. (1990) [25]. Galzerano et al. (2005) [26] reported a superior left ventricular mass regression with telmisartan versus carvedilol, the latter may have a more beneficial effect on LVH compared with the conventional β-blockers, due to its vasodilating properties [20, 27].

Hypertension is a significant risk factor and is present in 75% of patients with heart failure, so that effective reduction of blood pressure reduces the risk of heart failure by 30-50%. R. Cristodorescu et al. (2004) have studied the effectiveness and tolerance of beta-blockers (meteoprolol, bisoprolol or carvedilol) given on the top of the conventional therapy in heart failure due to left ventricle systolic dysfunction in patients > or = 70 years (n = 57, group 1) and < 70 years (n = 101, group 2) and they have concluded that beta-blockers should be tried in all heart failure patients without contraindication irrespective of age [28]. Further more, a meta-analysis of randomized trials (n = 4217) of two multi-national, double-blinded, placebo-controlled randomized trials, CAPRICORN (Carvedilol Post-infarct Survival Control in Left Ventricular Dysfunction Study) and COPERNICUS (Carvedilol Prospective Randomized, Cumulative Survival study) suggested that the benefits of carvedilol therapy in patients with systolic left ventricular dysfunction with or without symptoms of heart failure are consistent even in the presence of mild to moderate chronic kidney disease [29]. In a recent study (Coreg and Lisinopril Combination Therapy in Hypertensive Subjects – COSMOS study) of combining extended-release carvedilol (carvedilol CR) with the ACEI lisinopril showed that post hoc assessment combining all high-dose groups did produce significant 24-hour mean BP reduction when compared with the high-dose monotherapy groups [30].

EFFECTS OF CARVEDILOL ON INSULIN SENSIVITY (IS) AND LIPID METABOLISM

Jacob et al. (1996) compared the effects of carvedilol and metoprolol in 72 hypertensive patients and observed a 14% increase in IS estimated with the clamp with carvedilol afterwards, whereas metoprolol was associated with a reduction in this parameter [31]. In another study, Giuglano et al. investigated the effects of carvedilol and atenolol in 45 patients with both hypertension and type 2 diabetes.

After 24 weeks of treatment, fasting plasma glucose and HbA1c were decreased and IS measured with the clamp was increased with carvedilol, whereas atenolol had the opposite results [32]. In the Carvedilol or Metoprolol European Trial (COMET) study [33], the risk for new-onset diabetes was 22% lower in patients receiving carvedilol than those receiving metoprolol. In addition, the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) multi-center trial, that compared carvedilol with metoprolol treatment in 1235 subjects with hypertension and type 2 diabetes showed a significant decrease in the HOMA-IR index of about 9% with carvedilol. These findings clearly support a less detrimental effect of vasodilating compared with older β-blockers on glycemic control and insulin sensitivity and suggest that among the class of β-blockers, the former agents should be preferred in subjects with components of metabolic syndrome, impaired glucose tolerance or type 2 diabetes [34].

In contrast to older β-blockers, carvedilol seems to have a neutral or beneficial effect on lipoprotein lipase activity and levels of triglycerides and HDL [34]. In 45 patients with non-insulin-dependent diabetes and hypertension who were treated for 24 weeks, patients receiving carvedilol had a more favorable effect compared with atenolol in lowering triglyceride levels, increasing HDL levels, and decreasing lipid peroxidation [32].

Carvedilol appears to offer particular advantages in the treatment of hypertension with comorbid conditions, including coronary artery disease, stroke, hypertension, renal failure, diabetes, and atrial fibrillation, that can independently contribute to the progression of heart failure [35].

These exclusive features are thought to be that carvedilol will exert a more beneficial effect on cardiovascular morbidity and mortality than the traditional beta-blockers as suggested by the Carvedilol or Metoprolol European Trial (COMET), although these findings are not universally accepted [36]. Whether newer BBs, such as carvedilol, which show vasodilatory properties and a more favorable hemodynamic and metabolic profile, will be more efficacious in reducing morbidity and mortality remains to be determined [37].

CONCLUSION

Carvedilol, a vasodilating noncardioselective β-blocker, represents an opportunity to use a cardioprotective agent without the concerning hemodynamic and metabolic responses associated with traditional β-blocker therapy. With the available evidence, it is possible to conclude that carvedilol could be a valuable tool in the clinicians' hand in the management of hypertension. However, future prospective clinical trials are warranted to draw a definite conclusion.

References

1. Wolf-Maier, K. et al. Hypertension treatment and control in five European countries, Canada, and the United States. – Hypertension, **43**, 2004, 10-17.
2. Sarafidis, P. A. et al. Prevalence, awareness, treatment and control of hypertension in employees of factories of Northern Greece: the Naoussa study. – J. Hum. Hypertens., **18**, 2004, 623-629.
3. Sarafidis, P. A. et G. L. Bakris. State of hypertension management in the United States: confluence of risk factors and the prevalence of resistant hypertension. – J. Clin. Hypertens. (Greenwich), **10**, 2008, № 2, 130-139.
4. MacMahon, S. et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. – Lancet, **335**, 1990, 765-774.
5. Stamler, J., R. Stamler et J. D. Neaton. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. – Arch. Intern. Med.,**153**, 1993, 598-615.
6. Chobanian, A. V. et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. – JAMA, **289**, 2003, 2560-2567.
7. ESH-ESC Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. – J. Hypertens., **21**, 2003, 1011-1053.
8. Hypertension: management of hypertension in adults in primary care, NICE Clinical guideline (June 2006).
9. Messerli, F. H., E, Grossman et U. Goldbourt. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. – JAMA, **279**, 1998, 1903-1907.
10. O'Rourke, M. Arterial stiffening and vascular/ventricular interaction. – J. Hum. Hypertens, **8**, 1994; Suppl 1:S9-15.
11. Dupont, A. G. et al. Effect of carvedilol on ambulatory blood pressure, renal hemodynamics, and cardiac function in essential hypertension. – J. Cardiovasc. Pharmacol., **10**, 1987, Suppl 11, S130-S136.

12. W e b e r , K. et al. Comparison of the hemodynamic effects of metoprolol and carvedilol in hypertensive patients. – Cardiovasc. Drugs Ther., **10**, 1996, 113-117.
13. E l i o t , H. et al. Carvedilol, a novel cardiovascular agent, inhibits development of vascular and ventricular hypertrophy in spontaneously hypertensive rats. – Clin. Experimental Hypertension, **16**, 1994, № 2, 163-177.
14. O p i e , L. et S. Yusuf. Beta-blocking agents. – In: Opie L. H., Gersh B., editors. Drugs for the Heart, 6. Philadelphia, Pensylvania: W. B. Saunders Company, 2005, pp. 1-32.
15. M c T a v i s h , D. et al. Carvedilol. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. – Drugs, **45**, 1993, 232-258.
16. Y o s h i k a w a , T. et al. Cardiac adrenergic receptor effects of carvedilol. – Eur. Heart J., **17**, 1996, (Suppl B), 8-16.
17. M o r g a n , T. Clinical pharmacokinetics and pharmacodynamics of carvedilol. – Clin. Pharmacokinet., **26**, 1994, 335-346.
18. F r i s h m a n , W. H. Carvedilol. – N. Engl. J. Med., **339**, 1998, 1759-17565.
19. P a n a g i o t i s , C. Stafylas, Pantelis A Sarafidis. Carvedilol in hypertension treatment. – Vasc. Health Risk Manag., **4**, 2008, № 1, 23-30.
20. M e s s e r l i , F. H. et E. Grossman. Beta-blockers in hypertension: is carvedilol different? – Am. J. Cardiol., **93**, 2004, 7B-12B.
21. B l a c k , H. R. et D. A. Sica. A modern perspective on beta-blocker use in hypertension: clinical trials and their influence on clinical practice. – J. Clin. Hypertens. (Greenwich), **9**, 2007, 10-18.
22. E g g e r t s e n , R. et al. Haemodynamic effects of carvedilol, a new beta-adrenoceptor blocker and precapillary vasodilator in essential hypertension. – J. Hypertens., **2**, 1984, № 5, 529-534.
23. H e b e r , M. E. et al. Carvedilol for systemic hypertension. – Am. J. Cardiol., **59**, 1987, № 5, 400-405.
24. K r ö n i g , B. et al. Blood-pressure-lowering effect of carvedilol vs nitrendipine in geriatric hypertensives. – Eur. J. Clin. Pharmacol., **38**, 1990, Suppl 2, S167-70.
25. S c h u l m a n , S. P. et al. The effects of antihypertensive therapy on left ventricular mass in elderly patients. – N. Engl. J. Med., **322**, 1990, 1350-1356.
26. G a l z e r a n o , D. et al. Three-dimensional echocardiographic and magnetic resonance assessment of the effect of telmisartan compared with carvedilol on left ventricular mass a multicenter, randomized, longitudinal study. – Am. J. Hypertens., **18**, 2005, 1563-1569.
27. W h y , H. J. et P. J. Richardson. Effect of carvedilol on left ventricular function and mass in hypertension. – J. Cardiovasc. Pharmacol., **19**, 1992, Suppl 1, S50-4.
28. C r i s t o d o r e s c u , R. et al. The effectiveness and tolerance of betablockers in elderly patients (> or = 70 years) with heart failure. – Rom. J. Intern. Med., **42**, 2004, 103-110.
29. W a l i , R. K. et al. Efficacy and safety of carvedilol in treatment of heart failure in chronic kidney disease: a meta-analysis of randomized trials. – Circ. Heart Fail., 2010; Oct 29. [Epub ahead of print]
30. B a k r i s , G. L. et al. Effect of combining extended-release carvedilol and lisinopril in hypertension: results of the COSMOS study. – J. Clin. Hypertens. (Greenwich), **12**, 2010, № 9, 678-678.
31. J a c o b , S. et al. Differential effect of chronic treatment with two beta-blocking agents on insulin sensitivity: the carvedilol-metoprolol study. – J. Hypertens., **14**, 1996, 489-494.
32. G i u g l i a n o , D. et al. Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension. A randomized, controlled trial. – Ann. Intern. Med., **126**, 1997, 955-959.
33. P o o l e -W i l s o n , P. A. et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. – Lancet, **362**, 2003, 7-1.
34. B a k r i s , G. L. et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. – JAMA, **292**, 2004, 2227-2236
35. S t r o e , A. F. et M. Gheorghiade. Carvedilol: beta-blockade and beyond. – Rev. Cardiovasc. Med., **5**, 2004, Suppl 1, S18-27.
36. R e i t e r , M. J. Cardiovascular drug class specificity: beta-blockers. – Prog. Cardiovasc. Dis., **47**, 2004, 11-33.
37. D e C a t e r i n a , A. R. et A. M. Leone. The role of beta-blockers as first-line therapy in hypertension. – Curr. Atheroscler. Rep., **5**, 2011. [Epub ahead of print].

Постъпила – 18.11.2010 г.

✉ *Address for correspondence:*

Assist. Prof. Jayachandra Srinivasa, MBBS, MD, PhD
Santhiram Medical College and Hospital
Nandyal, AP
India
e-mail: jayachandra.srinivasa@gmail.com