ORIGINAL ARTICLE

Antihypertensive Efficacy of Carvedilol and Amlodipine in Patients of Mild to Moderate Hypertension – A Comparative Study

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Abstract

In this prospective randomized parallel study, the antihypertensive effect of oral carvedilol and amlodipine was evaluated on systolic blood pressure (SBP) and diastolic blood pressure(DBP) in patients of mild to moderate hypertension over a period of 12 weeks. Eighty two patients who fulfilled the inclusion criteria were randomized to receive amlodipine (n=42) 5-10mg/day and carvedilol (n=40) 25-50mg/day. Blood pressure was recorded in the sitting and standing position during follow up visits at 2,4,8 and 12 weeks using mercury sphygmomanometer. Dosage adjustments if needed were made at 4 and 8 weeks of study. Both carvedilol and amlodipine produced a statistically significant ($P<0.001$) and dose related fall in SBP and DBP , which became evident at two weeks of initiation of therapy and continued till 12 weeks. On comparative analysis of the effect of carvedilol and amlodipine on BP, amlodipine produced a greater fall in sitting and standing SBP at all study intervals as compared to carvedilol, with statistically significant fall at 8 and 12 weeks ($P<0.01$). However, the fall in sitting and standing DBP was statistically comparable with both the drugs. The findings of the present study indicate that carvedilol has become an alternative treatment for mild to moderate hypertension.

Key Words

Hypertension, Amlodipine, Carvedilol

Introduction

Hypertension is a common cardiovascular condition affecting a quarter of all adults in United States and approximately one billion individuals world wide (1). Even in our country the prevalence is quite high in both the sexes in urban as well as rural population (2). Untreated hypertension is associated with various cardiovascular, cerebrovascular and renal complications. However, the treatment of such patients with the antihypertensive agents is able to reduce these complications significantly (1). The large number of antihypertensive drugs presently available are effective in lowering blood pressure (BP) in 50-60% of hypertensive patients when used as monotherapy (3). Non-selective ß-blockers like propranolol lower BP through $ß_1$ mediated antagonism negative ionotropism and cause vasoconstriction by $ß_2$ (4). Conversely ∝-blockers and calcium channel blockers are vasodilators and lower the BP by decreasing peripheral vascular resistance (5). Vasoconstrictors as well as vasodilators may be associated with adverse effects such as cold extremities in the first case (4) and edema, tachycardia and headache in the second case (5). By combining these two types of drugs one may reduce number of adverse effects. However, this can complicate the treatment regimens and patient compliance may be reduced. Carvedilol is a novel 3rd generation non-selective ß-blocking agent with $∝_1$-blocking property without intrinsic sympathomimetic activity. Amlodipine, which belongs to the 1,4

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dihydropyridine class of calcium channel antagonist, is an effective antihypertensive when used as monotherapy or in combination (5,7). The present study was conducted to evaluate antihypertensive efficacy of carvedilol and to compare it with a conventional drug amlodipine in patients of mild to moderate hypertension in our set up..

Material and Methods

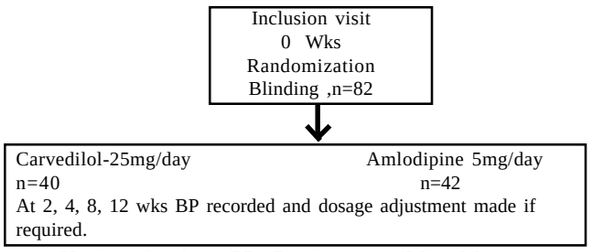
The study was conducted according to ICMR guidelines in the Postgraduate Department of Pharmacology and Therapeutics in collaboration with the Postgraduate Department of Medicine, of Government Medical College Jammu, over a period of three months where a prospective, randomized, single blind, parallel design after obtaining permission from institutional ethics committee and written informed consent from the patients.

All newly diagnosed cases of both sexes, in age group of 30-65 years having mild to moderate uncomplicated hypertension (1,8), attending medical OPD and cardiology clinic who showed a systolic blood pressure (SBP) of 140-179 mmHg and a diastolic blood pressure (DBP) of 90-109 mmHg on two separate weekly visits were enrolled for the study (Table-1). Blood pressure (BP) was measured on same arm by same investigator using an appropriate cuff with a standard mercury sphygmomanometer after at least 10 minutes of rest with the patient in the sitting position and after two minutes in standing position as per JNC VII guidelines (1). In each position, a mean of three recordings(each one minute apart) was taken. Phase I and V korotkoff's sounds were used to determine SBP and DBP respectively. Patients were required to attend the clinic for a total of 7 visits including 2 preinclusion visits (-2 and -1 wks i.e. 2 and 1week before randomization), inclusion visit 0 wks (at randomization) and 4 follow up visits. In the first preinclusion visit (-2 wks) a detailed medical history was taken, physical examination was done and BP was recorded to ascertain the degree of hypertension. In the second preinclusion visit (-1wk) BP was recorded again to confirm the degree of hypertension and in addition they were subjected to investigations like Hb% TLC, DLC, ESR, BT, CT, biochemical tests- LFT, RFT, blood sugar fasting, urine for routine examination, ECG and X-ray chest. Patients were screened for the exclusion criteria like hypertension with target organ damage, associated ischemic heart disease,heart blocks , cerobrovascular disease, renal and hepatic disease, endocrine abnormalities, pregnancy and lactation, concurrent drug therapy, chronic smokers and alcoholics. All participants were prohibited from participating in other clinical studies for the duration of this study.

A total of 82 patients fulfilling the inclusion criteria were randomized to receive carvedilol and amlodipine for a period of 12 weeks. For the purpose randomization, 82 opaque envelopes containing randomization numbers (study drug codes) generated with the help of table of random numbers were prepared in advance by an independent investigator not related to our study. After a study participant was found to be eligible for the study, an envelop was opened by another person in the department and the patient was put on the treatment as found in the envelop in the coded form. Finally 40 and 42 patients were randomized to receive tablet carvedilol and tablet amlodipine respectively for a period of 12 weeks (Table-1). All patients were advised to take salt restricted diet. Carvedilol was given in dose of 12.5 mg once daily for first two days followed by 25mg/day once daily. Amlodipine was used 5mg/day. The drugs were given to the patients in identical air tight containers. They were advised to take the drug daily at the fixed time in the evening as mentioned in their respective prescriptions. The drugs used for the study were provided by Intas Pharmaceuticals Ltd. Carvedilol (25mg) and Amlodipine (5mg). During each follow up visits at 2, 4, 8 and 12 weeks of study detailed history was taken to detect any adverse effect, BP was recorded in the morning following the evening dose and dosage adjustments if needed were made at 4 and 8 weeks of study in those patients who still had a BP of more than desired level of 140/90 mmHg (1) . Compliance was assessed by interview and pill count. Adverse effects if any were noted. Effect of the individual drugs on BP in relation to baseline was statistically analysed using paired students 't' test. Inter group comparison of the effect of study drugs on BP was done using unpaired students 't' test.

'P' value less than 0.05 was considered statistically significant. Each parameter was expressed in mean ± SEM (Standard error of mean).

Fig.1: Flow chart showing study design.



n= Number of patients. BP= Blood pressure. Wks =Weeks

Results

Carvedilol was used in dose of 25mg/day in 40 cases. BP of 15 patients was controlled (to the desired level of < 140/90mmHg) with this dosage. However, in 25 cases whose BP could not reach the desired level at 4 weeks of the study, dose of carvedilol was increased to 37.5mg/day. Out of these 25 cases, BP of 5 patients was controlled with this dose. In remaining 20 patients the dose was further increased to 50mg/day. However, average dose of carvedilol used was 41.56mg/day.In the amlodipine group, out of 42 patients 20 patients responded to amlodipine in the dose of 5mg. Whereas in 22 patients who still had a BP of >140/90mmHg at 4weeks of the study, dose was increased to 10mg. Average dose of amlodipine used was 7.61mg/day. No further increments were given after 4weeks of therapy (Fig.1).

Both carvedilol and amlodipine produced a statistically significant (P<0.001) and dose related fall in mean sitting and standing SBP and DBP (Table-2,3). The effect became evident at 2 weeks of initiation of therapy and continued till 12 weeks. Both drugs were found to reduce BP to desired level of <140/90mmHg in 70% of cases. On comparing the effect of individual drugs on sitting as well as standing SBP and DBP the difference was statistically insignificant . On comparative analysis of the effect of carvedilol and amlodipine on BP, amlodipine produced a statistically greater (P<0.01) fall in sitting and standing SBP at 8 and 12 weeks as compared to carvedilol. However, the fall in sitting and standing DBP was statistically comparable with both the drugs at 8 and 12 week of study .

Table 1. Patients characterstics

Characterstics	Carvedilol (n=40)	Amlodipine (n=42)
Age(Years) (Mean±SEM)	50.30±1.55	51.69±1.47
Sex(male:female)	22:18	22:20
SittngBP(Mean±SEM)		
SBP	158±2.09	162.19±1.85
DBP	100.15±0.77	97.09±1.14
Standing BP(Mean±SEM)		
SBP	155.35±2.10	160.80±1.80
DBP	98.50±0.63	95.61±1.09

Table 2. Effects of carvedilol on blood pressure (n=40) (sitting & standing)

visit	Sitting Blood Pressure SBP (Mean±SEM)	DBP (Mean±SEM)	Standing Blood Pressure SBP (Mean±SEM)	DBP (Mean±SEM)
0wks	158.00±1.86	100.30±0.72	155.35±2.02	98.50±0.63
2Wks	149.95±1.94*	94.40±0.76*	147.80±1.99*	93.15±0.74*
4Wks	143.40±1.54*	90.10±0.54*	141.80±1.51*	88.90±0.55*
8Wks	140.35±1.33*	87.55±0.58*	139.15±1.36*	86.40±0.62*
12wks	138.24±1.19*	86.30±0.58*	136.10±1.16*	85.15±0.64*

[*Statistically significant from baseline (P<0.001)]

Table 3. Effects of amlodipine on blood pressure (n=42) (sitting & standing)

visit	Sitting Blood Pressure SBP (Mean±SEM)	DBP (Mean±SEM)	Standing Blood Pressure SBP (Mean±SEM)	DBP (Mean±SEM)
0 wks	162.19±1.68	97.09±1.14	160.80±1.70	95.61±1.09
2 wks	148.66±1.71*	90.28±1.03*	147.33±1.72*	89.33±1.02*
4 wks	141.00±1.51*	86.76±1.05*	140.57±1.48*	86.19±1.04*
8 wks	134.85±1.40*†	86.04±0.96*	134.23±1.41*†	85.33±0.98*
12wks	1.32.95±1.40*†	85.71±0.82*	131.66±1.41*†	84.57±0.82*

[*Statistically significant from baseline (P<0.001)]
n=Number of patients BP=Blood pressure SBP =Systolic blood pressure .DBP=Diastolic blood pressure.SEM= Standard error of mean.0Wks=Baseline values. 2Wks,4Wks,8Wks,12Wks=Values after 2,4,8 and 12 weeks of therapy respectively.
[† Statistically significant as compared to corresponding value of carvedilol (P<0.01)]

Discussion

Carvedilol has a dual mechanism of action viz.ß adrenoceptor blockade and vasodilation because of which it produces a reduction in blood pressure with no reflex tachycardia. It has an important role in the management of angina, heart failure as well as hypertension (6,9). In the present study, carvedilol produced a mean reduction of 20 and 14 mm of Hg in SBP and DBP respectively which was statistically significant (P<0.001). These findings are in agreement with published reports in which carvedilol has been found to be efficacious in management of mild to moderate hypertension (6,9). Amlodipine also caused a significant (P<0.001) fall in SBP and DBP of 29 and 12 mmHg respectively similar to other studies (7). On comparative analysis, amlodipine produced a greater fall (P<0.01) in SBP (29mmHg) than carvedilol (20 mmHg).

In our study carvedilol did not produce any significant postural changes in BP similar to the study by Ogihara *et al.* (10). This was possibly because of smaller initial dose of carvedilol. However, postural hypotension should be anticipated if the patients are administered initial higher dose of 50mg or 100mg (9). No evidence of any postural hypotension was seen in amlodipine group as well which is in conformity with previous studies (7,11).Both the drugs were well tolerated. There was no evidence of edema or fluid retention confirming results of Franchi and DiPerri (13). None of the patients discontinued treatment because of adverse effects.

Amlodipine is already one of the commonly used first line antihypertensive drug. The findings of present study coupled with earlier reports about carvedilol indicate that this drug is available as an alternative treatment for hypertension. The short duration of the study limits its usefulness. Even then, the study will lead to better understanding of dosage schedule and efficacy of these drugs. Thus it can prove to be of help when faced with the dilemma of choosing one drug over another.

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