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Comparison of efficacy and tolerability of different brands of amlodipine in patients with mild to moderate hypertension

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ABSTRACT

Background: The efficacy of amlodipine, a calcium channel blocker, in treating systemic hypertension is well established but the most efficacious brand of this drug is still uncertain. The cost of different brands of amlodipine is tremendously different which may affect decision-making in hypertension treatment. The purpose of this study was to compare the efficacy and safety of different brands of amlodipine (Amlodipine, Amlopress, and Norvasc) in the treatment of hypertension in adult patients.

Methods: This was a double-blind, randomized, three-sequence crossover study. Ambulatory patients with hypertension who had the inclusion criteria were enrolled. Patients were randomized and entered into three groups to receive either brand of amlodipine in a crossover method. After every four weeks of treatment completed, the other brand of drug was prescribed. The total period of the study was 12 weeks for all three drugs including four weeks for each brand.

Results: A total of 20 patients entered to the study, 15 completed the 12-week treatment schedule. The absolute reductions in seated and supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) were similar with all three brands during the 4 weeks of treatment. Headache, malaise and weakness were the most common reported adverse effects (AE) with all three drugs. Generic amlodipine had the most AE as compared with other brands. These AE were mild and did not require withdrawal of the drug.

Conclusion: There is no statistical difference in lowering blood pressure by three different brands of amlodipine thus everyone which has the lowest price can be the first choice.

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Introduction

Hypertension is a well-recognized risk factor for cardiovascular and cerebrovascular morbidity and mortality, which cause at least half of deaths in the elderly population (1). Calcium Channel Blockers (CCBs) are widely used in the treatment of hypertension. CCBs are useful in various diseases, such as angina pectoris, hypertension, hypertensive crisis, arrhythmia, left ventricular diastolic dysfunction, myocardial infarction, Raynaud's phenomenon, progressive systemic sclerosis, peripheral vascular diseases, chronic renal failure, Conn

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syndrome, pulmonary hypertension, migraine, and esophageal spasm (2-5).The perceived advantages of CCBs include efficacy, titratability and tolerability. In patients with chronic diseases like asthma, peripheral vascular disease, renal impairment and/or gout, there is no contraindication to treatment with these drugs. Furthermore, CCBs do not worsen lipid profiles and are effective in reducing left ventricular hypertrophy (6). CCBs can be prescribed in the presence of a wide range of cardiovascular risk factors and often improve quality of life (7, 8).

Amlodipine is a dihydropyridine CCB with high affinity for L-type calcium channels seeming a vasoselective CCB (4).

The antihypertensive activity of amlodipine relies on the blockade of calcium ion influx into vascular smooth muscle cells. Arterial blood pressure is lowered systemically by means of peripheral vasodilation, which also accounts for the adverse reactions typical of CCBs (e.g., peripheral edema and flushing) (5).

Amlodipine is a long-acting CCB which permits once-daily dosing (7). Thus, an occasional missed dose is unlikely to cause problems such as "myocardial stunning" which may be seen with missed doses of shorter-acting hypotensive agents. Controlled double-blind studies have shown that amlodipine significantly reduces both standing and supine Blood Pressure (BP), with these reductions maintained throughout the 24-hour dosing interval (9). A study assessed the efficacy of amlodipine by measurement of BP and heart rate in the supine, seated and standing positions and after exercise periodically during the study. BP was significantly reduced throughout the study with no change in heart rate (10). The comparative effects of the single dose per day of amlodipine and long-acting diltiazem were assessed in a parallel design showing that amlodipine is more effective than diltiazem in reducing systolic and diastolic BPs (11). Also, to evaluate the efficacy, tolerance and acceptance of once-daily amlodipine in the control of 24-hour BP, an open-label study was accomplished. It was well tolerated and well accepted by patients and there was a significant reduction in systolic and diastolic BPs indicating that amlodipine controls BP over a 24-hour period (12). An open, non-comparative study was conducted to assess the safety of amlodipine in patients with mild to moderate hypertension (Systolic Blood Pressure: 120-139, Diastolic Blood Pressure: 80-89, according to Joint National Committee (JNC) 7 guideline). The most common reported side effect was edema. The frequency of headache was almost identical in older and younger patients and edema, flashing and dizziness were seen only slightly more often in elderly patients (13). Patients with hypertension require highly effective medications with excellent tolerability profiles to maintain the motivation to continue treatment. The tolerability profile of an antihypertensive drug has a direct effect on patient compliance because hypertension is often asymptomatic and patients are reluctant to accept the adverse effects associated with treatment. The cost of treatment could influence the initial choice of an antihypertensive agent, although cost considerations should not predominate over efficacy and tolerability in any individual patient (14). Cost is an important factor in defining compliance because hypertension treatment is a chronic process and it has a long term expenses for the patients. One the aims of developing new antihypertensive medications are improvement in both efficacy and compliance.

The purpose of present study was to compare the effectiveness and safety of three amlodipine brands present in Iranian drug market in order to choose the drug with the highest quality and lowest cost.

Patients and Methods

The study was a 12-week, double-blind, randomized, three-sequence crossover with a four week interval for three brands of amlodipine. This study was conducted from October 2004 through August 2005. Men and women of at least 18 years of age with known essential hypertension responding to amlodipine entered to the study. Exclusion criteria were severe hepatic, renal diseases and/or recent myocardial infarction. Patients taking concomitant drugs that could affect BP were also excluded. The study was conducted in accordance with the institutional review board for human study at Tehran University of Medical Sciences. Written informed consent was obtained from all subjects.

Before admission, patients underwent a complete physical examination and their medical history was taken. Patients were randomized (random number generated by computer) into three groups and received one of the following three brands of amlodipine: Generic amlodipine formulated and manufactured by Modava, Iran; Amlopress® manufactured by Cipla, India; and Norvasc® manufactured by Pfizer, USA for four weeks. After first 4-weeks of treatment patients were crossed over to another brand and at the end of 8th week patients were crossed over to the last remaining brand. Patients were visited by their physician at the end of each 4-week treatment.

At each visit, the systolic and diastolic BP and heart rate were measured in both seated and supine position, and adverse events were recorded. Blood pressure was recorded manually to the nearest 2 mmHg by the same physician using a mercury sphygmomanometer and a cuff of an appropriate size; measurements were made using the same arm each time. Patients were seated and asked to rest with the cuff deflated around their arm for at least 5 minutes before BP readings were taken and for at least 1 minute between readings. Supine BP was measured after the patient had been sleeping for 2 minutes. BP

Table 1. Baseline characteristics of the patients.

Age*	62.9±10.3
Men/Women	3/12
Patients with hyperlipidemia	13
Patients with diabetes	3
Patients with family history of BP	5
Primary mean SBP (mmHg)*	139.7±16
Primary mean DBP (mmHg)*	76.7±6
Primary mean MAP (mmHg)*	97.7±8.2
Primary mean HR (bpm) *	69.4±8.4
Cigarette smoking patients	1

SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure
MAP: Mean Arterial Pressure
HR: Heart Rate
*= (Mean±SD)

was measured twice and the mean of the two readings was calculated. Heart rate was measured by counting the radial pulse for 30 seconds, repeating the count, and then taking the mean of the two readings. Heart rate was determined immediately before BP was measured in the sitting position.

Statistical analysis was performed using SPSS 11.5. Data were defined as means ± standard deviation (SD). Repeated measure Analysis of Variance (ANOVA) was used for analysis. *P* values <0.05 were considered to be statistically significant.

Results

Of the 20 patients entered into the study, 15 completed the 12-weeks treatment schedule. Reasons for having 15 patients at the end of study were: lost to follow-up, patient withdrawal, drug allergy and noncompliance. Remaining patients randomly assigned to one of the three sequences. The baseline characteristics of the patients are shown in table 1.

All three drugs were effective in lowering systolic and diastolic BP in seated and supine positions. There was no statistical difference in lowering BP between three drugs (*P*>0.05). Mean seated and supine BPs are shown in table 2.

Mean heart rate (HR) was 68.7±8.1 beats per minute (bpm) with amlodipine, 71.2±7.5 bpm with Amlopres® and 69.2±6.3 (bpm) with Norvasc® which showed no significant differences.

All adverse effects include pruritis, flashing, headache, vertigo, edema, cough, rash, dyspnea, GI disorder, nausea, diarrhea, tachycardia and malaise. Headache, malaise, and weakness were the most commonly reported adverse events. Most of the adverse events resulted from known side effects of CCBs; they were mild and did not require withdrawal of the drug. Generic amlodipine had the most adverse events compare with brands amlodipine (Figure 1); however, no serious adverse events occurred with this drug, and none of the patients who experienced an adverse event required additional drug therapy or hospitalization.

Discussion

The goal of antihypertensive therapy is the prevention of cardiovascular complications of high BP. Reduction of BP is essential, but it is not the only criterion for judging the success of treatment. The therapeutic regimen should be simple to follow and free of side effects that may necessitate cessation of treatment or increase other cardiovascular risk factors. Effective treatment may lead to cost saving in the long term. Tight control of BP substantially reduces the cost of complications, and is cost-effective compared with other health care programs. Patients with mild to moderate hypertension require highly effective medications with excellent tolerability profiles to maintain the motivation to continue treatment. If monotherapy achieves control of BP, it has most benefits especially in chronic disease because of cost saving, low adverse effects, most compliance, and low drug interactions. Medication compliance is inversely to the number of tablets taken by patients (15). The efficacy of amlodipine in controlling systemic hypertension has been reported repeatedly (16, 17). The ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial/Blood Pressure Lowering Arm) has recently shown that an amlodipine-based regimen has greater benefits than an atenolol-based regimen (18).

This is the first study comparing the antihypertensive properties of three different brands of amlodipine available in Iranian drug market. Our primary goal was to study the efficacy and tolerability of three brands of amlodipine present in Iranian drug market. In controlling BP in patients with mild to moderate hypertension,

Table 2. Differences in systolic and diastolic BP in seated and supine position

Position	Amlodipine		Amlopress		Norvasc	
	DBP	SBP	DBP	SBP	DBP	SBP
Seated	74±8.7	130.1±12.6	72.2±7.0	127.1±7.5	75.5±6.9	134.5±10.1
Supine	71.3±8.6	131.2±12.3	69±7.3	127.1±7.8	71.9±7.8	132.7±12.3

Data are shown as mean ± SD. SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

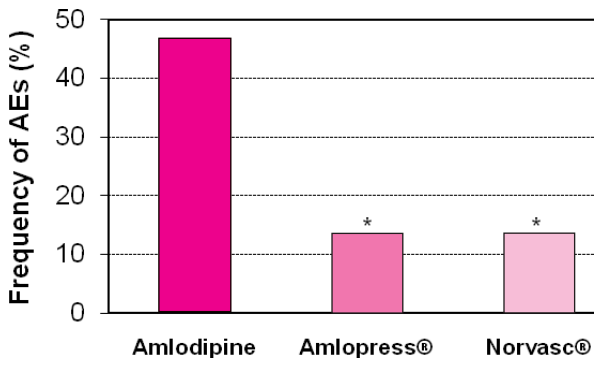

Figure 1. Frequency of adverse events observed in patients under regimen of different brands of amlodipine.
* The difference between generic amlodipine and brands (Amlopress® and Norvasc®) is significant at $P<0.05$.

generic amlodipine and two other brands were all highly effective. The reductions in both systolic and diastolic BP were similar with all three brands. There was no statistical difference in lowering blood pressure between three drugs in seated and supine positions. The incidence of adverse events in a research study is often higher than in clinical practice because patients are both questioned directly and given the opportunity to report adverse events spontaneously (7,19). Also all adverse events are recorded without filtering. The incidence of side effects in the present study was low, but none of them were considered to be serious. This result was similar to Mroczek et al., (20) study that patients received amlodipine for hypertension control and none of them showed serious adverse effect. Headache, malaise and weakness occurred most frequently in patients in our study. These results show that Iranian populations maybe more sensitive in these adverse effects than the other ones. According to our findings, there was no significant difference in efficacy and tolerability of these three products. However, there was a significant difference in cost of therapy. Since cost is a predominant factor in patient's compliance. In conclusion, we can start treatment with a product such as Iranian generic drug to enhance compliance and efficacy of treatment and if the patient showed adverse effects that couldn't tolerate it, physician can switch to other brand with higher cost.

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