AVFT v.19 n.2 Caracas jul. 2000

Influence of age and Arterial Blood Pressure on the Anti-hypertensive action of Dihydro-pyridine compounds in Hypertensive Patients

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ABSTRACT

To study the antihypertensive effect of dihydropyridines and correlate with the patient's age, the degree of hypertension and mean arterial pressure, in three groups of eight hypertensive patients with mild, moderate and severe hypertension selected from the Clinical Pharmacology Unit of Vargas Hospital in Caracas. Mean age, weight and height of the selected patients were 55.66 ± 3.4, years, 67 ± 3.05 Kg and 1.63 ± 0.01 m, respectively. Three acute experimental designs compared with placebo were followed and each group of patients received amlodipine, nitrendipine or isradipine at different times, in single doses of 10, 20 and 5 mg, respectively. The cardiovascular parameters evaluated were: mean arterial pressure, systolic blood pressure, diastolic blood pressure and cardiac frequency at regular intervals during 48, 6 and 24 hours for amlodipine, nitrendipine and isradipine, respectively.

Acute administration of amlodipine (10 mg) to hypertensive patients, significantly reduced blood pressure form 185 ± 11.21/100 ± 7.07 to 150.5 ± 10.6/88.6 ± 7.8 mmHg at 8 hours and to 162 ± 10.9/91 ± 5.6 mmHg at 48 hours. Cardiac frequency also increased significantly at 8 and 48 hours in 10 and 9 beats/min, respectively. There was a positive correlation between patient's age and mean arterial pressure decrease and also between pretreatment and decreased arterial pressure. Two hours after acute administration of isradipine (5 mg) to hypertensive patients, blood pressure decreased significantly from 179.50 ± 7.6/100.26 ± 3.28 mmHg to 143.75 ± 4.7/82 ± 5.18 mmHg. Cardiac frequency increased in 5 beats/min at the same time of measure. There was a positive correlation between patient's age and arterial pressure decrease and a slight but not significant correlation between pretreatment and mean arterial blood pressure decrease. Acute dose of nitrendipine (20 mg) to hypertensive patients induced a significant fall of arterial blood pressure from 172.25 ± 7.8/107.13 ± 3.58 to 134.5 ± 5.08/81 ± 5.84 mmHg two hours after the administration of the drug, and the cardiac frequency increased significantly in 11 beats/min during this time. There was no significant correlation between patient's age and the mean arterial pressure fall, neither between pretreatment and the decrease of arterial blood pressure.

Key Words: Arterial blood pressure, Age, Hypertension, Amlodipine, Nitrendipine, Isradipine.

INTRODUCTION

Dihydropyridine calcium antagonists have been used for many years in the treatment of angina pectoris and hypertension. According to the common view, their mechanism of action is based on an inhibition of the smooth muscle L-type calcium flow, thus decreasing intracellular calcium concentration and inducing smooth muscular relaxation[1]. This group of drugs have become a promising class of therapeutic agents in the management of various cardiovascular diseases such as hypertension and coronary artery disease[2]. Among the calcium channel blockers, nitrendipine, a dihydropyridine derivative, also reduced mortality and cardiac events in elderly patients with diabetes and systolic hypertension, more than comparable patients without diabetes[3]. Research with this drug have been focused in many areas such as hemodynamic response[2], one or twice daily dose[4], tolerance[5], sympathetic nervous system overactivity[6] and more recently on the prevention of dementia in aged patients with hypertension[7]. Newly developed dihydropyridine derivatives, amlodipine and isradipine, which also share the same mechanism of action that all dihydropyridines, have also been of great interest in many areas of research such as attenuation of morning blood pressure[8], effects in prediabetic hypertensive patients[9], long-term morbidity and mortality[10], interaction with open state of the L-type calcium channel[11], decrease of human arterial low density lipoprotein[12] and in the influence of race and dietary salt consumption on the antihypertensive efficacy[13]. However, no data are available in the literature regarding the effect of this class of antihypertensive drugs that correlate the patient's age, the degree of hypertension, mean arterial pressure and the antihypertensive effect, so we decided to address this question.

MATERIALS AND METHODS

Patients

Three groups of 8 patients with mild, moderate or severe hypertension were selected form the Clinical Pharmacological Unit of the Vargas Hospital in Caracas. The clinical characteristic of each group of patients are presented in tables 1, 2 and 3. All patients were clinically and biochemically evaluated and none of them showed alterations at any level of target organ such as brain, heart and kidney. Criteria of exclusion included recent myocardial infarct, diabetes mellitus or cerebro vascular accident. All patients were informed about the nature of this study according to the norm and criteria of the Helsinki declaration and they signed their consent to participate in the study.

Experimental design

An acute experimental design controlled with placebo was followed and amlodipine (10 mg), nitrendipine (20 mg) or isradipine (5 mg) were administered in single doses and the following cardiovascular parameters were evaluated: systolic blood pressure, diastolic blood pressure, mean arterial pressure and cardiac frequency. Cardiovascular parameters were evaluated prior and after drug administration at regular intervals during 6, 24 and 48 hours period for nitrendipine, isradipine and amlodipine, respectively. Patients received placebo during one week previously to the administration of the calcium channel blocker.

Methods

Arterial blood pressure was measured in triplicate using a sphygmomanometer. All patients were in the supine position and the measure was made at the same hour of the day (8:00 am). Calculation of the mean arterial pressure was made using the routine procedure of Korokoff. Cardiac frequency was evaluated through the electrocardiogram.

Statistic analysis

Results were expressed as the mean ± standard error of the mean of the systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial pressure (MAP) and heart rate (HR). Statistical differences between two data sets were determined by student's *t* test for small paired samples at 5% level of significance. Linear regression analysis was used to establish the correlation existing between the antihypertensive effect of the drugs and the determining factors.

A level of significance was set at 5% and the correlation coefficient set at r ž 0.70

RESULTS

A. Antihypertensive effect of amlodipine

Amlodipine produced a slight but not significant ($p > 0.05$) decrease of systolic, diastolic and mean BP and pulse one hour after administration. Two hours after the administration of the drug, all pressure parameters (SP, DP and MAP) decreased significantly ($p < 0.05$) when compared to baseline (time 0 hours), and pulse (Table 4). Arterial blood pressure reached maximal reduction between 4 and 24 hours after amlodipine administration and remained significant ($p <0.01$) during the following 48h. During this period of time there was also a significant increase of pulse. The greatest decrease in systolic BP occurred at 8 hours with a significant reduction ($p < 0.001$) of 35 mmHg (18.64%), while diastolic BP was reduced by 11.4 mm Hg (11.4%) at the same time of measure. The maximal pulse increase was of 13 beat/min at 24 hours, which represents a rise of 20.63%. (Table 4). There was positive correlation between mean pretreatment BP and the maximum decrease of MAP. It was seen that younger patients showed less decrease in MAP, while aged patients showed greater decrease. Decrease of mean arterial pressure in relation to age was between 13 mmHg in young patients and 36 mm Hg in aged patients. Statistical analysis showed a significant $r = 0.768$ value, with a $p = 0.04$.

We found no significant correlation between maximum decrease of MAP and pulse increase after amlodipine administration. Nevertheless, there was a slight correlation between mean pretreatment of arterial pressure and pulse increase after amlodipine administration with an $r = 0.630$ value. When questioned if this correlation was present before amlodipine administration, it was observed that the correlation index was non significant ($r = 0.553$).

B. Antihypertensive effect of nitrendipine

Nitrendipine at single 20 mg dosage produced a significant ($p < 0.05$) decrease of mean, systolic and diastolic pressure half an hour after its administration. This effect reached their maximum reduction between 2-4 hours after the administration of the drug and remained significant up to six hours (Table 5). Cardiac frequency increased significantly

between 30 min ($p < 0.05$) and two hours ($p < 0.01$) after the administration of the drug and this effect remained significant until six hours later ($p < 0.05$) [Table 5]. Systolic pressure was reduced in 40.5 mm Hg (23.50%) at 4 hours after nitrendipine administration. On the other hand, the maximal diastolic arterial pressure reduction was of 26 mmHg (24.4%) and occurred two hours after the administration of the drug (Table 5). Patients did not show significant correlation between mean arterial pressure and cardiac frequency before nitrendipine administration. On the other hand, a significant correlation was not shown between pretreatment mean arterial pressure and increase of cardiac frequency after nitrendipine administration, nor between maximum decrease of mean arterial pressure and increase of cardiac frequency. No correlation was seen between maximum decrease of mean arterial pressure and the degree of hypertension in the patients. There was a slight but not significant ($p > 0.05$) correlation between the age of patients and the hypotensive effect of nitrendipine (correlation coefficient was $r = 0.670$).

C. Antihypertensive effect of isradipine

lsradipine administration at single 5 mg/day doses to hypertensive patients produced a significant ($p < 0.05$) decrease of systolic, diastolic and mean arterial pressure with an increase in cardiac frequency, 30 min after the administration of the drug. The peak hypotensive effect of this drug was reached between 60 minutes and 2 hours after the administration and the effect continued significant ($p < 0.05$) until five hours later. The maximum decrease in systolic and diastolic arterial pressure was of 36.2 (20.1%)/18.83 (18.8%) mmHg, respectively (Table 6). Patients did not show correlation between mean arterial pressure and cardiac frequency before isradipine administration, nor between the decrease of mean arterial pressure and increase of cardiac frequency after isradipine administration. There was a slight but significant correlation between the degree of hypertension and the maximum decrease of mean arterial pressure. The correlation coefficient was $r = 0.697$, with a p value of 0.05. Regarding the antihypertensive effect of isradipine and patient's age, there was a positive correlation between aged patients and maximum decrease of arterial pressure. Statistical analysis revealed a correlation coefficient of 0.849, with a p value of 0.001.

Table 1: Clinical Characteristics of Hypertensive Patients Prior to the Study (Amlodipine Group)

SEX	AGE (Years)	WEIGHT (Kg)	HEIGHT (m.)	SP (mmHg)	DP (mmHg)	MAP (mmHg)	HR (Beats/min)	PRA (ng/ml/h)	ALD (pg/ml)
3F; 5M	56±3.81	71 ± 2.78	1.65 ± 0.04	185 ±11.21	100 ± 7.07	128.9 ± 6.68	64 ± 2.91	0.91 ± 0.09	152.8 ± 29.9

All parameters are expressed as mean ± standard error of the mean of n = 8 patients

***SP** Systolic blood pressure; **DP** Diastolic blood pressure; **MAP** Mean arterial pressure; **HR** Heart rate; **PRA** Plasma renin activity; **ALD** Serum aldosterone*

Table 2: Clinical Characteristics of Hypertensive Patients Prior to the Study (Nitrendipine Group)

SEX	AGE (Years)	WEIGHT (Kg)	HEIGHT (m.)	SP (mmHg)	DP (mmHg)	MAP (mmHg)	HR (Beats/min)	PRA (ng/ml/h)	ALD (pg/ml)

4F; 4M	53±88	69 ± 2.70	1.64 ± 0.03	172.25 ±7.80	107.13 ± 3.53	128.82 ± 4.86	67.63 ± 3.47	1.27 ± 0.09	69 ± 22.8

All parameters are expressed as mean ± standard error of the mean of n = 8 patients

***SP** Systolic blood pressure; **DP** Diastolic blood pressure; **MAP** Mean arterial pressure; **HR** Heart rate; **PRA** Plasma renin activity; **ALD** Serum aldosterone*

Table 3: Clinical Characteristics of Hypertensive Patients Prior to the Study (Isradipine Group)

SEX	AGE (Years)	WEIGHT (Kg)	HEIGHT (m.)	SP (mmHg)	DP (mmHg)	MAP (mmHg)	HR (Beats/min)	PRA (ng/ml/h)	ALD (pg/ml)
3F; 5M	57±3.03	61 ± 4.38	1.62 ± 0.03	179.51 ±6.65	100.26 ± 3.28	126.59 ± 2.73	66 ± 2.79	0.87 ± 0.17	87 ± 17.04

All parameters are expressed as mean ± standard error of the mean of n = 8 patients

***SP** Systolic blood pressure; **DP** Diastolic blood pressure; **MAP** Mean arterial pressure; **HR** Heart rate; **PRA** Plasma renin activity; **ALD** Serum aldosterone*

Table 4: Effect of Amlodipine on Systolic, Diastolic and Mean Blood Pressure and Heart Rate

in Hypertensive Patients

Parameters	**0h**	**1h**	**2h**	**3h**	**4h**	**5h**	**6h**	**7h**	**8h**	**24h**	**48h**
SP (mmHg)	185 ± 11.2	175 ± 8.8	170.7 ± 9*	162 ± 8*	163 ± 7.8*	162 ± 8.3**	156 ± 8.9**	153.2 ± 9.47***	150.5 ± 10.6***	153 ± 9.3***	162 ± 10.9**
DP (mmHg)	100 ± 7	96 ± 5.7	95.7 ± 5.8*	92.7 ± 6.1*	89.2 ± 5.4*	88.8 ± 6**	88.7 ± 6.6**	88.7 ± 6.9**	88.6 ± 7.8**	85.7 ± 5.2 *	91 ± 5.6*
MAP (mmHg)	128.3 ± 6.6	122.3 ± 5.7	120.6 ± 5.7*	116.9 ± 5.9**	113.3 ± 5.4***	112.8 ± 6.4***	110.7 ± 6.5***	110.2 ± 6.7***	110.3 ± 7.7**	108.3 ± 5***	113.3 ± 6.1**
HR (beats/min)	63 ± 2.9	60 ± 3	64 ± 3.2	65 ± 3.1	68 ± 3.6	73.5 ± 2.4***	72.7 ± 3.1***	70.7 ± 3.5***	73 ± 3***	76 ± 2.6***	71.7 ± 3*

All parameters are expressed as the mean ± standard error of mean of n = 8 patients

SP Systolic blood pressure; DP Diastolic blood pressure; MAP Mean arterial pressure; HR Heart rate;

**p < 0.05; **p < 0.01 ***p < 0.001*

Table 5: Effect of Nitrendipine on Systolic, Diastolic and Mean Blood Pressure and Heart Rate

in Hypertensive Patients

Parameters	**0h**	**0.5h**	**1h**	**2h**	**4h**	**5h**	**6h**

SP (mmHg)	172.25 ± 7.8	151.13± 8.18*	137.50 ± 4.8***	134.5 ± 5.08***	131.75 ± 5.85**	131.75 ± 8.64**	139.75 ± 8.64**
DP (mmHg)	107.13 ± 73.58	93.25 ± 4.96*	86.88 ± 4.27**	81 ± 5.84***	82.13 ± 4.92***	83.75 ± 7.54**	89.50 ± 5.91**
MAP (mmHg)	128.78 ± 4.87	112.51 ± 5.75*	103.73 ± 3.92***	98.79 ± 5.29***	99.30 ± 4.81***	99.71 ± 7.31**	106.23 ± 6.59**
HR (beats/min)	67.63 ± 3.47	74.50 ± 4.12*	78.75 ± 3.91**	78 ± 3.57**	74 ± 2.73*	72.75 ± 2.45*	75 ± 3.78*

All parameters are expressed as the mean ± standard error of mean of n = 8 patients

SP Systolic blood pressure; DP Diastolic blood pressure; MAP Mean arterial pressure; HR Heart rate;

**p < 0.05; **p < 0.01 ***p < 0.001*

Table 6: Effect of Isradipine on Systolic, Diastolic and Mean Blood Pressure and Heart Rate

in Hypertensive Patients

Parameters	**0 h**	**0.5 h**	**1 h**	**1.5 h**	**2 h**	**3 h**	**4 h**	**5 h**	**6 h**	**24 h**
SP (mmHg)	179.50 ± 7.6	155.42 ± 5.07*	146.80 ± 3.67*	143.43 ± 6.17*	143.75 ± 4.70***	150 ± 7.10*	154.50 ± 6.58	155 ± 6.24 *	159.66 ± 10.37	171 ± 10.31
DP (mmHg)	100.26 ± 3.28	90.85 ± 5.7*	83.14 ± 5.31**	81.43 ± 6.01*	82 ± 5.18*	81.50 ± 4.55*	86.25 ± 4.13**	87.25 ± 4.21*	87 ± 1.98*	94.83 ± 3.54*
MAP (mmHg)	126.59 ± 2.73	112.34 ± 4.34*	104.36 ± 4.59*	102.67 ± 5.07*	102.55 ± 3.97**	104.36 ± 405*	108.65 ± 3.08*	109.90 ± 3.93*	112.20 ± 3.16	120.18 ± 7.12
	65.88 ± 2.79	71.71 ± 1.97	72.71 ± 2.34	73.71 ± 3.58	71 ± 3.18	68.25 ± 3.13	69.50 ± 2.92	69.75 ± 4.12	67 ± 3.06	73.60 ± 4.80

All parameters are expressed as the mean ± standard error of mean of n = 8 patients

SP Systolic blood pressure; DP Diastolic blood pressure; MAP Mean arterial pressure; HR Heart rate;

**p < 0.05; **p < 0.01 ***p < 0.001*

Discussion

Drugs classified as calcium antagonists or calcium-channel blockers were introduced into clinical medicine in the 1960s and are now among the most frequently prescribed drugs for the treatment of cardiovascular diseases[14]. Although the currently available calcium antagonists are chemically diverse, they share the common property of blocking the transmembrane flow of calcium ion through voltage-gated L-type (slowly inactivating) channels[15]. These drugs have proved effectiveness in patients with hypertension, angina pectoris, and cardiac arrhythmias and may be beneficial in patients with left ventricular diastolic dysfunction, Raynaud's phenomenon, migraine, preterm labor, esophageal spasm, and bipolar disorders[16].

In the United States, amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil are currently approved for the treatment of patients with hypertension[17]. Each of these drugs lowers diastolic blood pressure during long-term oral administration at the recommended doses. Most are available in long-acting formulations that permit once-daily administration. In the United States, calcium antagonists are currently recommended as first-line therapy for hypertension only if there is a compelling reason not to administer a thiazide diuretic or a beta-blocker[17].

In the present study we report and compare the antihypertensive effects of three calcium channel blockers that belong to the dihydropyridine class. We found that amlodipine, nitrendipine and isradipine when administered at single acute doses of 10, 20 and 5 mg, respectively, have important differences in their cardiovascular effects such as the onset and the duration of the antihypertensive effect. Amlodipine for example, initiates its antihypertensive effect two hours after the dose was administrated and reached the maximum 24 hours later (Table 4.), which is in agreement with a previous report[18]. On the other hand, nitrendipine and isradipine do not differ in the initiation of the effect and in the time at which both drugs reached their maximum antihypertensive effect. Both drugs beginning to act both only 30 min after the administration and their maximum effect was reached 2 hours later (Tables 5, 6), but differ in their duration of action. In this regard, isradipine slightly maintains its effect during 24 hours, instead of nitrendipine, which effect lasts only 6 hours, which is in agreement with other reports concerning the antihypertensive effect of this calcium channel blocker[8,19].

In those aged 65-85 years, the major causes of death and disability are cardiovascular diseases (myocardial infarction, sudden death and stroke). Clinical trials in elderly patients have demonstrated unequivocally that effective blood pressure reduction in hypertensive patients up to age of 85 years significantly reduces this mortality and morbidity[19]. There are several reports in the literature regarding the use of calcium channel blockers in elderly patients[7,16,19]. This class of drugs are effective for the treatment of hypertension in older patients[20].

The fact that our results showed no correlation between cardiac frequency and maximum decrease of mean arterial pressure, nor with pretreatment arterial pressure in the nitrendipine group, suggests that instead of the antihypertensive effect of this drug and the sympathetic nervous system overactivity after the initiation of the treatment, nitrendipine probably may be in some way regulating the baroreceptor sensitivity, an effect seems with the angiotensin converting enzyme inhibitor enalapril[6].

On the other hand, the group of patients treated with amlodipine or isradipine showed a positive correlation between mean pretreatment arterial pressure and the maximum decrease of mean arterial pressure after treatment with this calcium channel blocker, although the initial mean arterial pressure was not statistically different from each other in all three groups of patients, which suggests that the difference observed between the groups of patients treated with amlodipine or isradipine and the group of patients treated with nitrendipine could be related to the pharmacokinetic differences between each calcium channel blocker[8].

In relation to the patient's age and the antihypertensive effect of all three calcium channel blockers used in this study, and although we only found a statistically positive

correlation between the decrease of mean arterial pressure and the age of the patients in the isradipine group, there is a tendency to correlation between this two parameters in the amlodipine and nitrendipine groups. It is worthy to mention that the decrease of mean arterial pressure was also greater in older than in younger patients, which probably suggest that the clearance of this drugs is decreased in older patients, as compared with younger patients; this difference results in higher serum drug concentrations in older patients, which agrees with that reported by Kelly and O'Malley[21]. This difference may be a factor in the perception that older patients have greater antihypertensive responses to calcium antagonists[22]. Intravenous administration of verapamil, diltiazem, or amlodipine results in a greater hypotensive effect in older than in younger patients with hypertension at a given drug concentration[23, 24, 25].

According with the discussion above we conclude that the antihypertensive response obtained with the use of dihydropyridine-type calcium channel blockers is influenced by the age of the patients, giving a much better response in older than in younger patients.

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