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EVALUATION OF THE EFFICACY AND TOLERABILITY OF EXTENDED-RELEASE FELODIPINE IN MILD HYPERTENSION: A RANDOMIZED, DOUBLE-BLIND, CROSS-OVER STUDY

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ABSTRACT

Felodipine is a new dihydropyridine calcium channel blocker which is effective in reducing blood pressure by decreasing peripheral resistance due to its selectivity of the smooth muscle in the resistance arteriolar vessels. This was done to assess antihypertensive activity and tolerability of an extended-release (ER) formulation of felodipine 10 mg WHO stages I and II single dose with placebo in mildly hypertensive patients. It involved a total of 50 patients who were randomly selected into either felodipine or placebo in a 4-week cross-over study shedding light to the last 4 weeks of single-blinded placebo treatment. The measurement of the blood pressure and heart rate was conducted after dosing 22-24 hours. The findings demonstrated that felodipine lowered systolic and diastolic blood pressure (9 and 8 mmHg, respectively) substantially as opposed to placebo without having an impact on the heart rate. There were minimal side effects when using the 10 mg dose of felodipine and these effects were comparable to the ones that conventional formulations have. The experiment proves that the delayed release Intervention in felodipine can effectively achieve 24 hours flux control in blood pressure and implies that its effect was not dissimilar to regular patients adherence and that it has added great value to the antihypertensive treatment.

KEY WORDS: Felodipine, extended-release formulation, antihypertensive efficacy, blood pressure control, patient compliance.

INTRODUCTION

Felodipine is a new dihydropyridine calcium block that is highly selective to smooth muscles in the arteriolar channel vessels [1]. The experimental studies have reported that it possesses more vascular selectivity than the other calcium channel blockers and no notable effects on cardiac conduction system [2], slight diuretic/natriuretic effect [3], high effectiveness in the treatment of hypertension and good tolerability [4]. There is no adverse effect on the myocardial vaction in patients suffering with coronary artery disease [5]. Felodipine has been shown to have a high tolerability and efficacy in single therapy of hypertension [6], and with beta-adrenoceptor antagonists [7-10] and with diuretics [11], or combinations of these Experiments on hypertension have shown that the prototype felodipine formula is effective between 10 and 40 mg fitted twice every day. The commonest adverse effects are related to the pharmacological effect of calcium channel blockers

(flushing, headache, and edema of the ankles). A 0-blocking agent may be used with the drug in order to become more effective and less liable to cause side effects [7-10]. A controlled-release formulation may also enhance the toleration and patient compliance. This would reduce the peak plasma concentration which is one of the side effects and keep the plasma concentration of felodipine constant over a 24 hours time period. This was done in order to compare the extend release (ER) formulation of 10 mg felodipine ER daily with placebo in patients with mild hypertension (WHO stages I and II).

The number of patients in which the study was carried out consisted of 50 patients with the population of 14 men within Group 1 and similar in Group 2. The average value of age of the patients was 48 and the average body weight was 75 kg. The patients were classified according to the success of treatment by completing an agreement between Group 1 which is compulsorily utilized in

felodipine and Group 2 in placebo. Table 2 revealed the measurement of the heartbeat rate and blood pressure conducted 22-24 hours after the final dose on 39 patients that were treated during 4 weeks by either felodipine or placebo. The average blood pressure in the time of systole (SBP) was lower in the group using the felodipine, 137.5 (11.8) mm Hg, unlike the control group 146.2(15.3) mm Hg, meaning a difference of -8.7 (2.93) mm Hg ($p = 0.0123$), thus showing that felodipine does help in reduction of systolic blood pressure. Of this result the CIs range was -13.65 to -3.74 mm Hg and this too proved the fact that the only significant drug to improve systolic blood pressure is felodipine. It was the same case with the diastolic blood pressure (DBP) where the felodipine group (86.2 +/- 5.9 mm Hg) experienced a high significant decrease in relation to the baseline of

94.5 +/- 6.7 mm Hg of the placebo group at a difference of -8.3 mm Hg ($p = 0.0003$). The result range in the DBP was -9.80 to -6.03 mm Hg which indicated that the effect of felodipine was greatly significant towards the drop in the DBP. The difference in the mean heart rate was small since the mean heart rate of felodipine group was 70.1 +/- 6.2beats per minute and the placebo group average 69.5 +/- 6.1beats per minute. Without achieving statistical significance (NS), the change in the heart rate was at +0.6 beats per minute, this value is contained in the confidence intervals of -2.45 to +3.69 beats per minute. Such results will probably mean that felodipine is an effective drug in becoming a reducing agent of both systolic and diastolic blood pressure yet have no influence on the rate of the heart when compared to placebo.

Table 1: Patients' characteristics at inclusion (n = 50)

Group 1	Group 2
Age (years)	48 ± 12
Sex (male)	14
Weight (kg)	75 ± 10

Table 2: Blood pressure and heart rate 22-24 h after the dose in 39 patients treated for 4 weeks with felodipine and placebo (mean values ± s.d.)

Parameter	Felodipine	Placebo	Difference (A)	F-P level	Confidence Intervals
SBP (mm Hg)	Mean: 137.5 s.d. ±11.8	146.2 ±15.3	-8.7	0.0123	-13.65, -3.74
DBP (mm Hg)	Mean: 86.2 s.d. ±5.9	94.5 ±6.7	-8.3	0.0003	-9.80, -6.03
HR (beats/min)	Mean: 70.1	69.5	+0.6	NS	-2.45, +3.69

Figure 1: Patient Characteristics at Study Inclusion, Study Population: n = 50

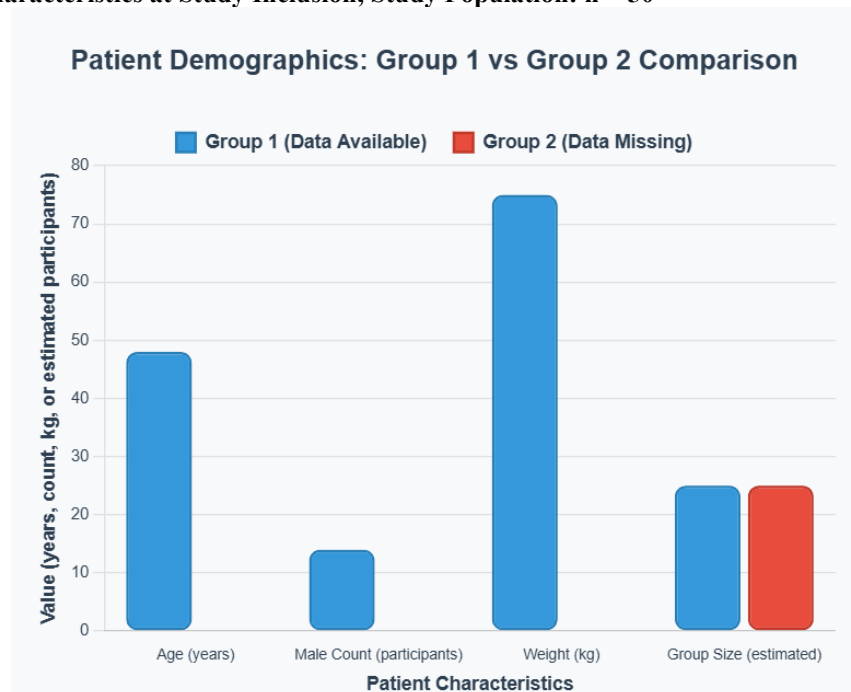
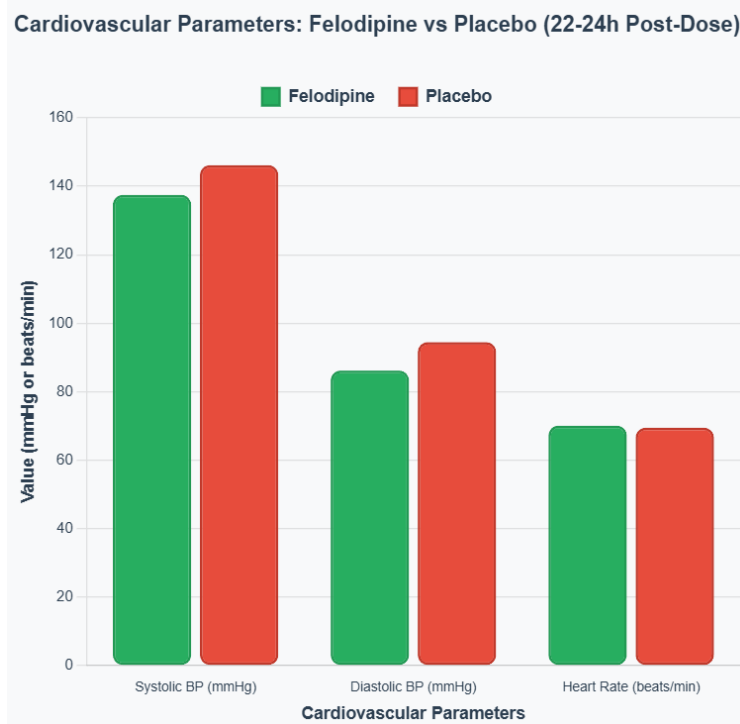


Figure 2: Felodipine vs Placebo Clinical Trial, Blood Pressure & Heart Rate Analysis (n = 39, 4-week treatment)

DISCUSSION

An Felodipine is a new derivative of dihydropyridines which is a blood pressure lowering acting on the peripheral resistance by the means of selectively on resistance smooth muscle of arteriolar [1]. This is one particular activity that is protective in terms of adverse effect on cardiac contractility and on conduction. [12] demonstrated that in case of the felodipine ER administration through once daily oral single dose in the morning, the drug discharge is prolonged. The 24 h peak/trough felodipine plasma level of the long-acting drug formulation is still comparable to the one that is attributed to the standard felodipine tablets drugs. Whereas the ordinary felodipine tablets reduce blood pressure levels of the patient after 12 hours and not 24 hours, the extended-release tablet formula reduces blood pressure levels all through the period of 24 hours by administering a single dose a day. In the treatment of hypertensive patients with the drug given as the sole drug or as monotherapy, [13] has not demonstrated any considerable advantage of once-a-day extended-release of felodipine over the two times a day conventional felodipine tablets. Our study which was aimed at testing the antihypertensive benefit of the new extended-release (ER) formulation of felodipine in essential hypertensive patients confirmed 24-hour blood pressure response to dosing once daily by felodipine ER 10 mg. Patients were arbitrarily assigned to either take felodipine or placebo as the initial treatment and after 4 weeks of treatment, which was conducted arbitrarily, the patients were allowed to

alter and use the other drug. Supine blood pressure was significantly reduced in our subjects by 4 weeks of felodipine treatment compared to the placebo; the heart rate was not changed. When the therapeutic intervention involved four weeks of felodipine, there was reduction in blood pressure by 9 mmHg of systolic and 8 mmHg of diastolic in comparison to placebo. The worsened blood pressure is minimal as we actually recalled the patients we put under investigation to be relatively mild in blood pressure levels towards the end of the run-in period (155 +/- 14/99 +/- 3 mm Hg). We decided to use a dose of 10 mg of felodipine that was lesser when compared to the one that was used [12] since the dose-response-relationship of the antihypertensive effect of felodipine indicated that a 5-mg-b.i.d. regimen of felodipine lowered the blood pressure in patients who had moderate hypertension [14]. In addition, the dose chosen was that, which would give the maximum safety and the least scale of the side effects i.e. the side effects of dihydropyridine are dosage dependent. We did not measure the blood pressure at the moment when we gave the drug and during the day and it is also the reason why we cannot compare the early, intermediate and the late effect but the probable thing that happens is that the non-hypertensive effect is maintained throughout the dosing period. The clinical data correspond to the ones described [12] in the sense that the new form of felodipine has a sustained concentration of the drug in the plasma. By means of standardized questionnaire, we assessed tolerability of the felodipine ER. The worst of side effects was

associated with the pharmacodynamic actions of vasodilator medications like headache, flush, palpitation and swelling of the ankles. Uncomfortable or severe side effects occurred in 5 of the patients who carried felodipine and 1 who carried placebo, requiring them to drop out the trial. The other side effects were mild or healed in the course of treatment. The new felodipine preparation had fewer side effects than the former felodipine preparation owing partly to decreased release of felodipine [4] and partly to comparative antianginal or cardiac protection [15, 16] as well as compared to many other antihypertensive agents [17].

CONCLUSION

On the whole, one can state that considering the fact that the formulation containing the drug known as an extended-release felodipine played which was used succedaily in daily regimen in 10 mg dosage allowed getting effective blood pressures and controlled the blood pressure of individuals with mild hypertension even after 24 hours after taking drugs, the formulation1* extended-release felodipine was tolerated thanks to which it is possible to state that the extended-release form of felodipine is a significant advancement within the realm of pharmaceutical market. This music has a capacity to increase patient adherence to antihypertensive medication.

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