Effect and Tolerability of Felodipine ER (Feloten^{R}) in the Treatment of Hypertension Assessed by Office Blood Pressure and Home Blood Pressure

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Objectives: *To assess the efficacy of once daily dose generic Felodipine ER, Feloten^{R} in terms of BP lowering as assessed by office BP measurement (OBPM) and Home BP monitoring (HBPM)*

Material and Method: *Mild and moderate hypertensive patients (n = 60) were enrolled by primary care physicians. After a 2 week run-in phase in which all patients received placebo, subjects received generic felodipine ER 5 mg for 3 weeks. After 3 weeks of treatment, patients whose blood pressure target was not achieved were given 10 mg of felodipine ER for 3 weeks. OBPM and HBPM were performed in the morning, noon, evening, and nighttime for 1 day at baseline, 3 weeks, and 6 weeks.*

Results: *After 6 weeks, Generic felodipine ER reduced the average systolic BP (SBP) and diastolic BP (DBP) measured by OBPM and HBPM. The effect on SBP showed every time on HBPM and was more pronounced in the morning (trough drug level). However, the effects on DBP were not significant in the morning and noon. No serious adverse drug side effect was detected.*

Conclusion: *Generic felodipine ER is effective in SBP reduction, in both OBPM and HBPM. It can be used once daily to control the blood pressure for 24 hours.*

Keywords: *Generic felodipine ER, Home blood pressure monitoring, Self blood pressure measurement, Calcium antagonist*

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The numbers of hypertensive patients is increasing in Thailand leading to more burden of cardiovascular diseases. This has effects on national health and cost. Treatment of hypertension can decrease cardiovascular burden including stroke and ischemic heart disease[1]. Calcium antagonists have become an established class for the treatment of hypertension. Their wide spread use is related to their recognized antihypertensive efficacy and low side effect[2]. They are suitable as monotherapy in cases of mild to moderate hypertension. The office blood pressure (OBP) control and 24-hour BP control reduce the cardiovascular event. Once daily dose felodipine extended release formulation (Felodipine ER) has been proven to effectively lower blood pressure all over 24 hours in hypertensive patients[3-5] and to improve compliance from a simple treatment schedule[6]. Home blood pressure monitoring (HBPM) was suggested as an alternative choice of BP monitoring by recent recommendations[7-9]. The benefits of HBPM are providing response to antihypertensive medication, improving patient adherence to therapy, and evaluating white-coat hypertension. A prospective study even suggests that HBPM has a better prognostic accuracy than office BP measurement in treated elderly hypertensive patients[10].

Each year, drug and health expenditure has increased since 1998 especially the growth of drug expenditure, which has increased dramatically, 147% in 1998 to 204% in 2002[11]. More than 6.12 million baht was spent in 2002. A huge number of hypertensive and cardiovascular patients made them one of the main health expenditure consumers. A generic drug is cheaper than an original drug. Since drug efficacy and safety are the priority concerning antihypertensive

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therapy, generic antihypertensive drug, Felodipine ER was studied.

Material and Method

Study Objective

The objective of the present study was to assess the efficacy of once daily dose (recommended) generic Felodipine ER in terms of BP lowering assessed by OBPM and HBPM after 6 weeks of treatment.

Patient Population

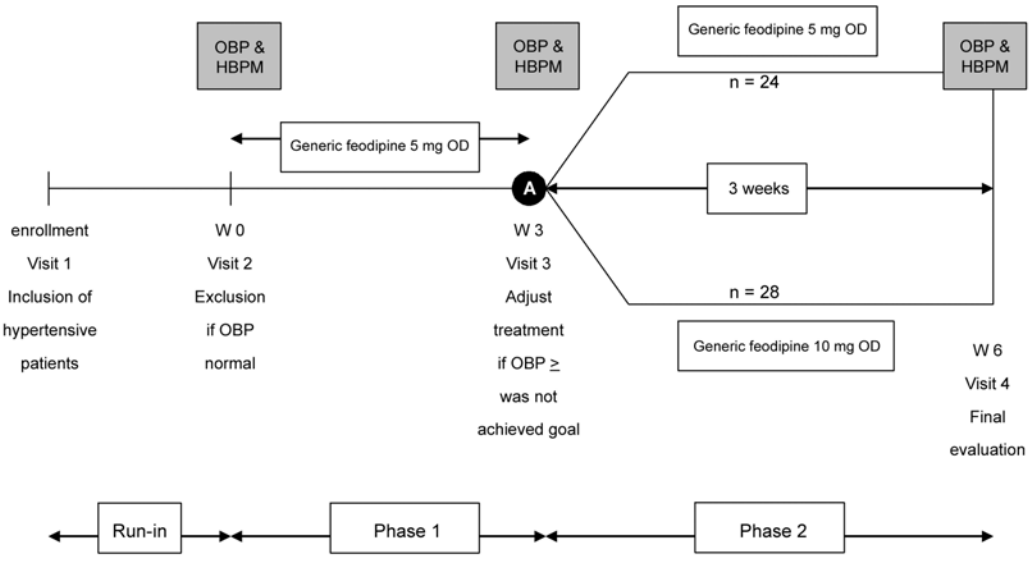
Patients > 18 years and < 80 years of age with stage 1 and 2 essential hypertension were enrolled in the present study. The authors excluded those with severely elevated BP (diastolic BP (DBP) > 120 mmHg or systolic BP (SBP) > 190 mmHg), those who were pregnant, or breast-feeding and those who could use HBPM by themselves. Those with a history of stroke, allergy or contraindication to calcium antagonist, renal insufficiency (serum creatinine > 2 mg/dl), chronic heart failure, alcoholic use and drug addict were also excluded. The protocol and informed consent were approved by Buddhachinaraj Hospital ethic committee. All patients gave their written informed consent before entering the present study.

Study design

The present study was a single blinded study. It was carried out in the hypertension clinic of primary care unit under the cover of Buddhachinaraj Hospital, Phitsanuloke and consisted of two phases (Fig. 1). After enrollment, the patients were asked to discontinue prior antihypertensive drugs and receive a placebo instead for 2 weeks (run-in period). A baseline OBP and HBP were taken in every patient. Then all patients received felodipine ER 5 mg (Feloten^{R}, Biopharm Chemical Ltd.) once daily for 3 weeks (Phase 1). At the end of the third week, the second OBP and HBP were measured. Patients whose BP remained uncontrolled (OSBP $\geq$ 140 mmHg or ODBP $\geq$ 90 mmHg in non-diabetic patients and OSBP $\geq$ 130 mmHg or ODBP $\geq$ 85 mmHg in diabetic patients)[12] entered the second phase with Feloten^{R} 10 mg for 3 weeks while those with normalized BP continued Feloten^{R} 5 mg for another 3 weeks. A third OBP and HBP were measured at the final visit (the end of week 6).

Office BP measurements and HBPM

At the end of the run-in period, phase 1 and phase 2, patients performed HBPM four times a day (before taking the placebo or Feloten^{R} in the morning, at noon, in the evening and at night time) for 1 day using an electronic BP measurement[13] (Omron SEM-2, Automatic Blood Pressure Monitor, Omron Healthcare Co., Ltd). After 5 minutes rest, a set of three seated BP measurements one minute apart were carried out, in the morning (between 6 and 10 AM), just before taking the study drug, at noon (between 11 AM and 1 PM), in the evening (between 5 and 7 PM) and at night time



HBPM = home blood pressure monitoring; OD = once daily; BP = blood pressure; W = week

Fig. 1 Study design

(between 9 and 12 PM). Data were recorded in the study form. Quality criteria used for an acceptable HBPM were at least 12 valid measurements. Incompatible values defined as follows: SBP < 60 or > 250 mmHg, DBP < 40 or > 150 mmHg and SBP-DBP < 10 mmHg.

Statistical analyses

Continuous variables such as age, blood pressure were shown as mean ± SD. The efficacy end-point was the difference from baseline in average SBP and DBP of office BP and HBP (arithmetic mean of all morning, noon, and evening and bedtime values) after 6 weeks of treatment. Treatment effects were analyzed using paired t-test, p-value < 0.05 reflected statistical significance. The authors reported the percentage of patients with normalized BP after 6 weeks of treatment based on both OBP (defined as SBP < 140 and DBP < 90 mmHg) and HBP (defined as SBP < 135 and DBP < 85 mmHg).

Safety evaluation

All adverse events and severity were recorded. Laboratory investigations were taken for CBC, serum BUN, creatinine, liver function test, uric acid, and electrolyte at baseline, after treatment for 3 weeks and 6 weeks.

Results

Patient participation

Of 60 patients enrolled at run-in phase, 57 patients successfully completed phase 1. Feloten^{R} 10 mg was administered in 28 of 57 patients. In phase 2, five patients dropped out due to adverse drug reactions (Fig. 2).

Baseline characteristics

The mean age of the volunteers was 54.4 ± 8.8 years with a mean body mass index (BMI) of 25.4 kg/m^2 (range 18-42). There were slightly more female subjects (55%). Average period of hypertension was 4.9 years. There were 25 diabetic patients (42%) and 21 obese patients (35%). As expected, SBP and DBP in HBP were 7.2 and 3.4 mmHg lower than OBP, SBP: 150.3 ± 8.9 vs. 143.1 ± 10.0 and DBP: 87.9 ± 8.3 vs. 83.5 ± 6.9) (Table 1). Serum BUN, creatinine and liver function tests were normal.

Efficacy of office BP measurements

Blood pressure values at 3 weeks and 6 weeks after treatment and changes from baseline are shown in Table 2. Feloten^{R} produced a significant reduction in office SBP and DBP at 3 weeks and 6 weeks after treatment compared with baseline except DBP at 3 weeks (at 3 weeks: SBP = -8.9 mmHg ($p < 0.001$) and ΔDBP = -0.9 mmHg ($p = 0.596$), at 6 weeks: ΔSBP = -16.3 mmHg ($p < 0.001$) and ΔDBP = -5.1 mmHg ($p = 0.004$). The percentage of patients with normalized BP at 6 weeks was 31 in 52 cases (59.6%). At the 6th week, 24 out of 52 patients (46%) received Feloten^{R} 5 mg while the others received Feloten^{R} 10 mg (53.8%) through phase 2.

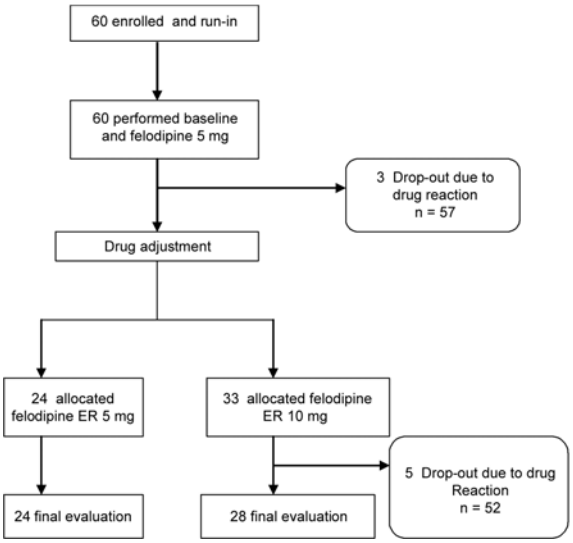


Fig. 2 Trial profile

Efficacy of HBPM

Mean blood pressure values at 3 weeks and 6 weeks after treatment and changes from baseline are shown in Table 2. Feloten^{R} produced a significant SBP

Table 1. Baseline characteristics of study patients (n = 60)

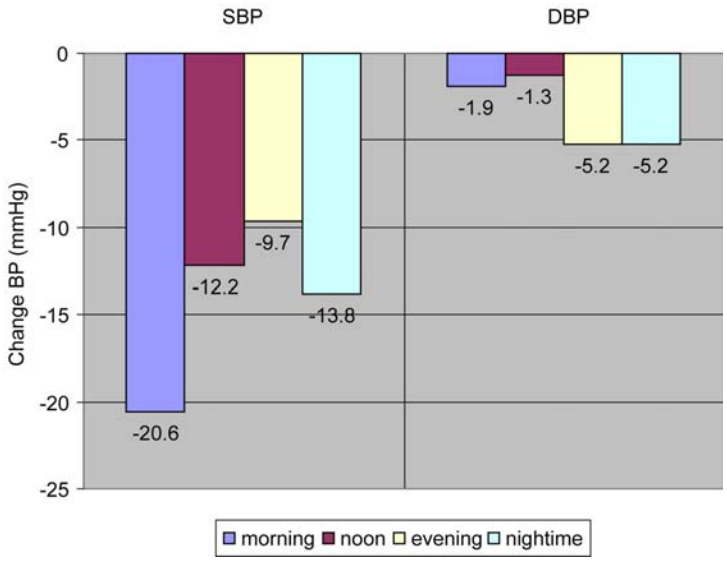
Characteristics	Mean ± SD
Age (years)	54.4 ± 8.8
Sex : female (number, (%))	33 (55)
Body mass index (kg/m^2)	25.4 ± 4.6
Diabetes (number, (%))	25 (42)
BMI > 28 kg/m^2 (number, (%))	21 (35)
Office BP values	
SBP (mmHg)	150.3 ± 8.9
DBP (mmHg)	87.9 ± 8.3
HBPM values	
SBP (mmHg)	143.1 ± 10.0
DBP (mmHg)	83.5 ± 6.9
Heart rate (beat/min)	79.8 ± 9.4

Table 2. Blood pressure values at 6 weeks and changes from baseline

	Blood pressure, mean (SD)	Δ from baseline, mean (SD)	p-value
Office BP			
At 3 weeks (n = 57)			
SBP (mmHg)	140.9 ± 10.9	-8.9 ± 12.9	<0.001
DBP (mmHg)	86.4 ± 8.3	-0.9 ± 12.7	0.596
At 6 weeks (n = 52)			
SBP (mmHg)	132.8 ± 8.2	-16.3 ± 11.9	<0.001
DBP (mmHg)	81.7 ± 8.2	-5.1 ± 12.4	0.004
HBPM BP			
At 3 weeks (n = 57)			
SBP (mmHg)	131.0 ± 8.1	-10.9	<0.001
DBP (mmHg)	81.7 ± 5.9	-1.7	0.065
At 6 weeks (n = 52)			
SBP (mmHg)	128.6 ± 7.3	-13.8	<0.001
DBP (mmHg)	80.5 ± 6.4	3.3	<0.001

reduction at 3 and 6 weeks after treatment, including DBP at 6 weeks (at 3 weeks: ΔSBP = -10.9 mmHg, at 6 weeks: ΔSBP = -13.8 mmHg and ΔDBP = -3.3 mmHg). DBP at 3 weeks was slightly decreased without statistical significance (ΔDBP = -1.7 mmHg, p-value = 0.065). After 6 weeks of treatment, SBP differences from baseline SBP were more pronounced in the morning than at other times (Fig. 3). In the morning, blood pressure was decreased from 149.4 to 128.8 mmHg in SBP, $p < 0.001$ and 84.3 to 82.3 mmHg in DBP, $p = 0.223$. At noon, blood pressure was decreased from 140.3 to 128.0 mmHg in SBP, $p < 0.001$ and 82.4 to 80.9 mmHg in DBP, $p = 0.390$. In the evening, blood pressure was decreased from 138.2 to 128.6 mmHg in SBP, $p = 0.003$ and 86.6 to 81.3 mmHg in DBP, $p = 0.003$. At nighttime, blood pressure was decreased from 141.9 to 128.9 mmHg in SBP, $p < 0.001$ and 81.88 to 75.35 mmHg in DBP, $p = 0.006$.

All SBP and DBP differences from baseline were statistically significant, except in DBP in the morning and noon. The percentage of patients with normalized BP measured by HBPM at 6 weeks was 37 cases (71.2%).



$p < 0.001$ for all values except DBP in the morning and at noon

Fig. 3 Mean morning, noon, evening and nighttime BP reduction, measured by HBPM after 6 weeks of treatment

Adverse events

The most common adverse event that caused dropout was somnolence (4 from 8 cases) as shown in Table 3. The others were headache (2 cases), palpitation (1 case), and arthralgia (1 case). BMI and HR were not significantly changed after treatment. Laboratory results including CBC, serum BUN, creatinine, liver function test, uric acid, and electrolyte were not significantly changed (Table 4).

Discussion

Calcium antagonists are widely used now in the treatment of hypertension. It is indicated for treating hypertensive patients in many guidelines. Felodipine ER is a dihydropyridine calcium antagonist with a half-life of 6-8 hours and a trough to peak ratio of 3-7 hours [14,15] that can be administered once daily. The efficacy of original felodipine ER daily dose was clearly demonstrated in many studies[1,16-18]. In the present study, the authors demonstrated that generic felodipine ER (Feloten^{R}) could reduce blood pressure effectively. BP normalization was found in 72.1% compared to 64% when original felodipine ER was used[16]. After 6 weeks of treatment, generic felodipine ER can reduce both SBP and DBP significantly, particularly on systolic blood pressure. The diastolic blood pressure after 3 weeks was not significantly reduced. In a previous study, original felodipine ER can reduce diastolic blood pressure significantly after 3 weeks of treatment (the baseline DBP was 102.8 $\pm$ 7.8 mmHg) since diastolic hypertension was a criteria of enrollment. Normal baseline diastolic blood pressure (83.5 $\pm$ 6.9 mmHg) in the present study may explain this difference between the present results and previous ones. On the other hand, delayed onset of action may be considered and it needs further study. Felodipine ER slightly reduced

Table 3. Rate of clinical adverse drug reactions

Clinical manifestation	Week 0, n (%)	Week 3, n (%)	Week 6, n (%)
Edema	3 (5)	1 (1.7)	0
Palpitation & flushing	0	1 (1.7)	0
Headache	0	2 (3.3)	0
Skin rash	0	0	0
Nocturia	1 (1.7)	0	0
Arthralgia	4 (6.7)	7 (11.7)	2 (3.3)
Vertigo	15 (25)	3 (5)	2 (3.3)
Somnolence	0	4 (7.0)	0

Table 4. Laboratory parameters

Laboratory parameters	Baseline (mean)	End of study (mean)	p-value*
Hemoglobin (g/dl)	13.1	13.0	0.161
White blood cell count (/mm3)	8.5	7.6	0.082
Platelet count (1000/mm3)	317.9	317.4	0.955
Serum BUN (mg/dl)	13.9	15.2	0.055
Creatinine (mg/dl)	0.9	0.9	0.767
SGOT (mg/dl)	22.5	20.6	0.461
SGPT (mg/dl)	21.8	19.2	0.655
Alkaline phosphatase (mg/dl)	55.3	56.9	0.989
Serum uric acid (mg/dl)	5.4	5.4	0.951
Serum sodium (mEq/L)	141.0	142.5	0.175
Serum potassium (mEq/L)	4.2	5.0	0.334
Serum chloride (mEq/L)	107.1	106.2	0.733
Serum bicarbonate (mEq/L)	23.7	23.8	0.773

* paired samples t-test

normal diastolic blood pressure. This may be a good property of antihypertensive drug especially for systolic hypertensive patients. That is why dihydropyridine calcium antagonist was recommended to treat those isolated systolic hypertension patients.

HBPM has become an established method to measure BP in the daily management of hypertensive patients as well as in certain clinical trials[19-21]. The present study measured BP four times per day to evaluate action of generic felodipine (extended release form) over 24 hours. The present result indicated that generic felodipine ER can lower systolic blood pressure at noon, in the evening, nighttime, and next morning. Thus, generic felodipine ER could be used once daily to control hypertension after 6 weeks of treatment. In the present study, it was found that HBPM is reliable as casual office measurement to monitor BP reduction in both systolic and diastolic blood pressure as in the HOT study: Home blood pressure monitoring substudy[17].

There was no serious side effect found in the present study (Table 3). The causes of dropping-out were somnolence, headache, palpitation, and arthralgia. These side effects were common in patients who received calcium antagonist[22]. The incidence of headache was comparable with the original drug[1,23]. Surprisingly, somnolence was the major causes of withdrawal from the present study whereas there was no previous report about this side effect. Because the hypnotic drugs were not controlled and recorded in the present study, this symptom should be observed in a further study. Although felodipine can cause transient tachycardia, the heart rate was not significantly changed in the present study. No serious metabolic effect occurred after treatment. There was significant change in value of serum sodium, SGOT and SGPT without clinical significance in the previous study[16]. Nevertheless, it was not found in the present study.

Conclusion

Feloten^{R}, a generic felodipine ER 5 to 10 mg once daily is effective in lowering blood pressure after 6 weeks of treatment and can be used in patients with mild to moderate hypertension.

Acknowledgment

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ประสิทธิภาพและความทนต่อยาเลียนแบบฟีโลดิปีนในการรักษาโรคความดันโลหิตสูง ประเมินโดยการวัดแรงดันโลหิตที่คลินิกและที่บ้าน

โตมร ทองศรี

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพของยาเลียนแบบฟีโลดีปีนอีอาร์ (Feloten®) ในการลดแรงดันโลหิตตลอด 24 ชั่วโมง โดยประเมินจากการวัดความดันโลหิตที่คลินิกและที่บ้าน*

วัสดุและวิธีการ: *ศึกษาในผู้ป่วยความดันโลหิตสูง ระดับที่ 1 และ 2 ที่ได้รับการรักษาโดยแพทย์หน่วยปฐมภูมิจำนวน 60 คน โดยหลังจากผู้ป่วยหยุดยาเดิมและได้รับยาหลอกเป็นเวลา 2 สัปดาห์ แล้วจึงเริ่มรับยาฟีโลดี-ปีนอีอาร์ (Feloten®) 5 มิลลิกรัม วันละครั้งหลังอาหารเช้า เป็นเวลา 3 สัปดาห์ หลังจากนั้นถ้าแรงดันโลหิตไม่ลดลงตามเกณฑ์ ผู้ป่วยจะได้รับการปรับยาเป็น 10 มิลลิกรัม นาน 3 สัปดาห์ ผู้ป่วยทุกรายจะได้รับการวัดแรงดันโลหิตทั้งที่คลินิกและที่บ้าน 3 ครั้งคือ ก่อนได้รับยา เมื่อได้รับยา 3 สัปดาห์ และเมื่อได้รับยา 6 สัปดาห์โดยการวัดแรงดันโลหิตที่บ้าน ผู้ป่วยวัดเองเวลาเช้าก่อนกินยา กลางวัน เย็น และก่อนนอน*

ผลการศึกษา: *หลังได้รับยา 6 สัปดาห์ ยาฟีโลดี-ปีนอีอาร์ (Feloten®) สามารถลดค่าเฉลี่ยแรงดันโลหิตทั้งขณะหัวใจบีบตัวและคลายตัวลดลงอย่างมีนัยสำคัญทั้งที่คลินิกและที่บ้าน และพบว่าแรงดันโลหิตขณะที่หัวใจบีบตัวลดลงตลอด 24 ชม. และเห็นได้ชัดเจนในตอนเช้า แต่แรงดันโลหิตขณะหัวใจคลายตัวลดลงอย่างไม่มีนัยสำคัญในตอนเช้า และตอนกลางวัน จากการศึกษาไม่พบผลข้างเคียงร้ายแรง*

สรุป: *ยาเลียนแบบฟีโลดีปีนอีอาร์ (Feloten®) สามารถลดแรงดันโลหิตได้ตลอด 24 ชม. ทั้งที่คลินิกและที่บ้านอย่างมีประสิทธิภาพ*