The Journal of International Medical Research
2002; 30: 330 – 336

Efficacy and Safety of Barnidipine Compared with Felodipine in the Treatment of Hypertension in Chinese Patients

CS LIAU, KL CHIEN, CL CHAO AND TM LEE

Department of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan, Republic of China

The efficacy and safety profiles of barnidipine in the treatment of hypertension were evaluated in an open parallel-group study. Fifty-nine Chinese patients with mild-to-moderate essential hypertension were randomized to receive either barnidipine or felodipine (5 mg once daily, titrated to 10 mg or 15 mg once daily, as indicated) for 12 weeks. Both drugs reduced blood pressures significantly with ≥ 68% of cases obtaining marked or moderate blood pressure reduction. Mean reductions in systolic and diastolic blood pressure for barnidipine treatment were 23.7 ± 13.5 mmHg and 12.7 ± 7.9 mmHg, and for felodipine, 24.3 ± 18.4 mmHg and 14.5 ± 10.0 mmHg, respectively. There was no significant difference between these two drugs in anti-hypertensive effect, heart rate, laboratory measurements or incidence of adverse events. The only difference was that more patients taking felodipine experienced palpitations. We conclude that barnidipine has similar efficacy and a similar safety profile to felodipine in the treatment of mild-to-moderate essential hypertension in Chinese patients.

KEY WORDS: BARNIDIPINE; FELODIPINE; CALCIUM CHANNEL BLOCKER; HYPERTENSION; CHINESE

Introduction

Hypertension is common in Taiwan. In a community study of individuals aged ≥ 35 years, the prevalence of hypertension was 28.5%.[1] In another study in Chinese patients aged ≥ 65 years living in Taiwan, the prevalence was 37%.[2] The control of hypertension is not satisfactory in most populations.[3,4] Compliance is one factor affecting blood pressure control, and medications with fewer adverse effects that allow once-daily administration are more acceptable to the patients.[5] Barnidipine is a long-acting calcium channel blocker with a long half-life, and therefore only requires once-daily dosing.[6 – 8] The efficacy of barnidipine in treating patients with hypertension has been demonstrated in oriental people[9 – 11] as well as in Caucasians.[12 – 17]

We conducted this clinical trial to compare the efficacy and the safety profile of barnidipine with felodipine in the treatment of hypertension in Chinese patients.

Felodipine was chosen as the comparator drug because of its common usage in Taiwan, its established effectiveness in the treatment of hypertension, and the similarity in the half-life of these two drugs.

Patients and methods

Chinese people living in Taiwan with mild-to-moderate hypertension were recruited to this trial. The inclusion criteria were: Chinese nationality; age 30 – 75 years; essential hypertension with systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg but ≤ 110 mmHg; and no severe systemic diseases (as listed in exclusion criteria). Patients with any of the following conditions were excluded from the trial: diastolic blood pressure > 110 mmHg; secondary hypertension; severe heart failure; significant arrhythmias; severe dysfunction involving respiratory system, liver, kidney, gastrointestinal system, neurological system, endocrine system or cardiovascular system; and significant metabolic abnormalities.

Eligible patients who provided informed consent were assigned randomly to receive a starting dose of either 5 mg barnidipine (Hypoca®, Yamanouchi, Tokyo, Japan) once daily or 5 mg felodipine (Plendil®, AstraZeneca, Bedfordshire, UK) once daily for 12 weeks. Other anti-hypertensive drugs and any other drugs that might affect blood pressure were prohibited during the trial period. Patients were followed up regularly in the out-patient clinic every 4 weeks to check blood pressure changes after treatment, compliance and adverse events. At each follow-up visit, if blood pressure did not reach 'adequate control' (defined below), the drug dose was titrated up by an increment of 5 mg each time.

Blood pressure changes after treatment were classified as 'marked decrease' if the decrease in systolic blood pressure was ≥ 30 mmHg and/or in diastolic blood pressure ≥ 15 mmHg. When the decrease of systolic blood pressure was 20 – 29 mmHg and/or the decrease of diastolic blood pressure 10 – 14 mmHg, the change of blood pressure was considered a 'moderate decrease'. Either marked or moderate decrease of blood pressure after treatment was considered as 'adequate control' of hypertension. A lesser reduction in blood pressure and/or no reduction was defined as 'inadequate control' of hypertension.

Laboratory examinations performed before and after the trial included electrocardiography, chest radiography, blood chemistry determinations (fasting glucose, aspartate aminotransferase, alanine aminotransferase, urea nitrogen, creatinine, uric acid, cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, sodium, potassium, chloride and calcium), complete blood count and urinalysis.

All data were collected and analysed according to the intention-to-treat model and also the per-protocol model. The blood pressure changes before and after treatment in the two treatment groups were compared using Student's paired *t*-test. The categories of blood pressure change were presented with a contingency table and compared using the χ^2 test. The incidence of adverse events was analysed with Fisher's exact test. $P < 0.05$ was defined as statistically significant.

Results

A total of 63 hypertensive patients were included in this trial, 31 in the barnidipine group and 32 in the felodipine group. Four patients, three in the barnidipine group and one in the felodipine group, were lost to follow-up after the first course of medication was dispensed. The remaining patients received at least 2 weeks' treatment with the

trial medicine: 28 patients in the barnidipine group and 31 patients in the felodipine group. Data from these 59 patients were analysed.

Among the patients in the barnidipine group, 12 were male and 16 female. In the felodipine group, the numbers of male and female patients were 15 and 16, respectively. The mean age of the patients in the barnidipine group was 54.0 ± 11.9 years, and in the felodipine group, 53.4 ± 10.5 years.

A total of 20 patients did not complete the trial, but received at least 2 weeks of barnidipine (nine patients) or felodipine (11 patients). The most frequent cause of early withdrawal from the trial was the occurrence of adverse effects (three in the barnidipine group and five in the felodipine group). Other reasons for withdrawal included inadequate blood pressure control in two cases, unrelated disease or injury in a further two cases, and, in four patients, difficulty in attending the clinic at 4-week intervals. In the remaining four patients, the cause of withdrawal was not specified. Table 1 shows the doses of the anti-hypertensive drugs administered to patients. The doses of felodipine used were lower than those of barnidipine (P = 0.066 for the intention-to-treat model; P = 0.056 for the per-protocol model).

Using both the intention-to-treat model (Table 2) and the per-protocol model (Table 3) for analysis, both barnidipine and felodipine reduced systolic and diastolic blood pressures significantly (P < 0.001). There was no significant difference between these two groups of patients in baseline blood pressure, blood pressure after

TABLE 1:
Doses of barnidipine and felodipine in a comparative trial of efficacy and safety in Chinese patients

	Barnidipine (patient numbers)		Felodipine (patient numbers)	
Dose (mg)	**ITT**	**PP**	**ITT**	**PP**
5	17	9	26	16
10	8	7	5	4
15	3	3	0	0
Total	28	19	31	20

ITT, intention-to-treat; PP, per-protocol

TABLE 2:
Systolic and diastolic blood pressures before and after treatment with barnidipine (5 – 15 mg once daily) or felodipine (5 – 10 mg once daily) in Chinese patients with hypertension who completed the study according to the intention-to-treat model

Group	Parameter	Baseline (mmHg)	After 12 weeks of treatment[a] (mmHg)	Difference (mmHg)
Barnidipine	SBP	164.8 ± 13.4	141.1 ± 14.0	–23.7 ± 13.5
(n = 28)	DBP	97.3 ± 8.1	84.6 ± 9.6	–12.7 ± 7.9
Felodipine	SBP	160.0 ± 12.8	135.7 ± 15.0	–24.3 ± 18.4
(n = 31)	DBP	100.7 ± 4.7	86.2 ± 9.5	–14.5 ± 10.0

All data are expressed as means ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Comparing blood pressure in the two treatment groups at baseline with that after 12 weeks' treatment, P < 0.001; comparing blood pressure between the barnidipine group and felodipine group, no significant difference.

treatment, and changes in both systolic and diastolic blood pressures after treatment (Tables 4 and 5). There was no significant difference between the two treatment groups in heart rate before and after treatment, and heart rate did not change significantly after treatment in either group.

In this trial, no severe adverse effects were

TABLE 3:
Mean blood pressures before and after treatment with barnidipine (5 – 15 mg once daily) or felodipine (5 – 10 mg once daily) in Chinese patients with hypertension who completed the study according to the per-protocol model

Group	Parameter	Baseline (mmHg)	After 12 weeks of treatment[a] (mmHg)	Difference (mmHg)
Barnidipine	SBP	166.3 ± 15.7	139.5 ± 15.0	–26.8 ± 13.4
(*n* = 19)	DBP	98.1 ± 6.7	83.7 ± 9.2	–14.4 ± 8.2
Felodipine	SBP	162.5 ± 13.3	131.6 ± 11.6	–30.9 ± 14.1
(*n* = 20)	DBP	101.5 ± 3.9	83.9 ± 7.7	–17.6 ± 8.7

All data are expressed as means ± SD.
SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Comparing blood pressure in the two treatment groups at baseline with that after 12 weeks' treatment, $P < 0.001$; comparing blood pressure between the barnidipine group and felodipine group, no significant difference.

TABLE 4:
Adequacy of blood pressure control after treatment with barnidipine (5 – 15 mg once daily) or felodipine (5 – 10 mg once daily) in Chinese patients with hypertension according to the intention-to-treat model

Group	Parameter	Adequate control (*n*)	Inadequate control (*n*)
Barnidipine	SBP	19	9
(*n* = 28)	DBP	22	6
Felodipine	SBP	23	8
(*n* = 31)	DBP	21	10

SBP, systolic blood pressure; DBP, diastolic blood pressure.
No statistically significant difference between barnidipine and felodipine groups.

TABLE 5:
Adequacy of blood pressure control after treatment with barnidipine (5 – 15 mg once daily) or felodipine (5 – 10 mg once daily) in Chinese patients with hypertension according to the per-protocol model

Group	Parameter	Adequate control (*n*)	Inadequate control (*n*)
Barnidipine	SBP	15	4
(*n* = 19)	DBP	16	3
Felodipine	SBP	17	3
(*n* = 20)	DBP	17	3

SBP, systolic blood pressure; DBP, diastolic blood pressure.
No statistically significant difference between barnidipine and felodipine groups.

TABLE 6:
Adverse effects experienced by Chinese patients with hypertension after 12 weeks' treatment with barnidipine (5 – 15 mg once daily) or felodipine (5 – 10 mg once daily)

	Number of adverse events	
Effect	**Barnidipine**	**Felodipine**
Palpitations	2	7[a]
Facial flushing	2	6
Headache	3	5
Chest tightness	2	1
Oedema	2	2
Weakness	4	4
Dizziness	1	4
Constipation	1	0
Rash	0	2
Total episodes	17	31[b]

[a]$P = 0.01$.
[b]$P = 0.083$.

observed, and only some mild unwanted reactions were reported (Table 6). There was no difference between the two treatment groups, except that more patients treated with felodipine experienced palpitations ($P < 0.01$). Overall, there were 31 episodes of adverse reactions in the felodipine group and 17 episodes in the barnidipine group ($P = 0.083$). Laboratory tests showed no significant changes after drug treatment with the exception of an elevation in high-density lipoprotein cholesterol level in barnidipine-treated patients (43.7 ± 9.2 mg/dl versus 48.6 ± 9.4 mg/dl [$P = 0.042$]).

Discussion

Calcium channel blockers have been recommended as a class of anti-hypertensive drug for the initial treatment of hypertension in some guidelines.[4,18] Calcium channel blockers have been proven to be effective and have a good safety profile for the treatment of hypertension.[18] The long-acting, once-daily preparations are preferred, and it has been suggested that short-acting dihydropyridines, such as immediate-release nifedipine, be avoided or used only with caution.[4,18]

Barnidipine is a long-acting calcium channel blocker with a long half-life after oral intake.[6 – 8] The efficacy and safety profiles of barnidipine have been well demonstrated in clinical studies.[9 – 17] In this trial, we showed that once-daily administration of barnidipine in Chinese patients with mild-to-moderate hypertension was highly effective and well tolerated. The efficacy of barnidipine was comparable to that of felodipine for the reduction of both systolic and diastolic blood pressures. It can be proposed, as shown in Table 1, that a 10 – 15-mg dose of barnidipine may have equivalent efficacy to 5 – 10 mg felodipine when used to treat Chinese patients with mild-to-moderate hypertension.

The safety analysis showed that neither barnidipine nor felodipine induced severe adverse events in the study patients. Side-effects were mild. It is interesting to note that palpitations were more frequently experienced by patients taking felodipine than by patients taking barnidipine ($P = 0.01$). The cause for this difference is not known. Argenziano *et al.*[12] demonstrated that barnidipine did not induce reflex neurohormonal activation, which may offer

a partial explanation for our observation that fewer patients taking barnidipine experienced palpitations. There were no significant changes in laboratory examination findings in patients taking these two drugs. The effect of significant elevation of serum high-density lipoprotein cholesterol level after barnidipine administration may require further study. A similar observation was reported by Horiuchi *et al.*,[19] but not by Kurihara *et al.*[20]

In conclusion, barnidipine, a long-acting dihydropyridine calcium channel blocker, has been shown in this study to be effective with a good safety profile in the treatment of Chinese patients with mild-to-moderate hypertension. This preparation was well tolerated and did not cause severe adverse effects. The long-acting, once-daily preparation of barnidipine provides another option for physicians in the clinical management of hypertensive patients.

Acknowledgement

This trial was supported by Yamanouchi Pharmaceutical Co. Ltd, Taiwan.

• Received for publication 19 February 2002 • Accepted 27 February 2002

References

1 Lee Y, Lin RS, Sung FC, Yang CY, Chien K, Chen W, *et al*: Chin-San Cardiovascular Cohort in Taiwan – baseline data and five-year follow-up morbidity and mortality. *J Clin Epidemiol* 2000; **53:** 838 – 846.
2 Liau CS, Tseng YZ, Lee TK: The prevalence of cardiovascular diseases in elderly Chinese people in Taiwan. *Int J Cardiol* 1998; **67:** 177 – 181.
3 Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, *et al*: Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 1995; **25:** 305 – 313.
4 Joint National Committee: The sixth report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med* 1997; **157:** 2413 – 2446.
5 Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przyeck TR: The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990; **150:** 1881 – 1884.
6 Hashimoto K, Motomura S, Tsujimoto G, Higuchi S, Teramura T: Phase I study of a calcium antagonist, YM730 (mepirodipine hydrochloride) (in Japanese). *Jpn J Clin Rep* 1990; **24:** 4443 – 4458.
7 Saruta T, Suzuki H: Single dose study of barnidipine hydrochloride (YM730) in essential hypertension. *J Med Pharm Sci* 1992; **28:** 178 – 185.
8 Korstanje C: Barnidipine, a long-acting slow onset calcium antagonist. *Intl J Clin Pract* 2000; **114** (Suppl): 2 – 5.
9 Suzuki S, Matsuoka H, Toda G: Effect of long-term administration of mepirodipine hydrochloride (YM730), a long-acting calcium antagonist, on blood pressure, serum lipids and carbohydrate metabolism in patients with essential hypertension (in Japanese). *Jpn J Clin Exp Med* 1990; **67:** 3589 – 3596.
10 Imai Y, Abe K, Nishiyama A, Sekino M, Yoshinaga K: Evaluation of the antihypertensive effect of barnidipine, a dihydropyridine calcium entry blocker, as determined by the ambulatory blood pressure level averaged for 24 h, daytime, and night-time. *Am J Hypertens* 1997; **10:** 1415 – 1419.
11 Bae JH, Lee JJ, Kwon SH, Kang HS, Choue CW, Kim KS, *et al*: An open-label, uncontrolled, 8-week clinical trial of barnidipine hydrochloride, a once-daily calcium channel blocker, in Korean patients with essential hypertension. *Curr Ther Res* 1997; **58:** 382 – 389.
12 Argenziano L, Izzo R, Iovino G, De Luca N, Parella L, Morisco C, *et al*: Distinct vasodilation, without reflex neurohormonal activation, induced by barnidipine in hypertensive patients. *Blood Press Suppl* 1998; **1:** 9 – 14.
13 Spieker C: Efficacy and tolerability of once-daily barnidipine in the clinical management of patients with mild to moderate essential hypertension. *Blood Press Suppl* 1998; **1:** 15 – 21.
14 van der Valden J, Beudeker HJ, Nishi M: Diversity and intensity of adverse events in the treatment of hypertension with barnidipine. *Blood Press Suppl* 1998; **1:** 27 – 29.
15 Otterstad JE, Ruilope LN: Treatment of hypertension in the very old. *Int J Clin Pract* 2000; **114** (Suppl): 10 – 19.
16 Smilde JG: The long-term efficacy and safety profile of barnidipine. *Int J Clin Pract* 2000; **114** (Suppl): 20 – 26.
17 Naber FB, Hage R, Mortelmans J: Barnidipine

monotherapy and combination therapy in older patients with essential hypertension: a long-term study. *Int J Clin Pract* 2000; **114** (Suppl): 27 – 35.
18 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 1999; **17:** 151 – 183.
19 Horiuchi I, Matsuura H, Hayashi K, Okamoto M, Inoue I, Mizuno T, *et al*: Antihypertensive effect on serum lipid of mepirodipine hydrochloride (YM730) in patients with essential hypertension (in Japanese). *Jpn J Med Consult New Remed* 1990; **27:** 1135 – 1145.
20 Kurihara H, Nakajima H, Hamaguchi T, Miyagawa J, Nanba M, Hanabusa T: Effect of barnidipine hydrochloride (Hypoca) on uric acid metabolism in patients with diabetes (in Japanese). *Jpn J Med Consult New Remed* 1998; **35:** 61 – 64.

Address for correspondence
CS Liau, MD
Department of Internal Medicine, National Taiwan University Hospital,
Taipei, Taiwan 100, Republic of China.
E-mail: csliau@ha.mc.ntu.edu.tw