Efficacy of a Very-low-dose Combination of Perindopril and Indapamide—Preterax Compared with Cilazapril Monotherapy in Patients with Inadequate Blood Pressure Control—A Randomized, Double-blind, Add-on Study

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Background: Combined regimen may be superior to monotherapy in blood pressure (BP) control. Since BP control is critically related to cardiovascular mortality and morbidity in hypertensive patients, this study aimed to evaluate the efficacy and safety of a low-dose combined regimen of preterax compared with cilazapril monotherapy for better BP control in treated hypertensive patients.

Methods: Stable hypertensive patients were evaluated if their systolic BP (SBP) was >130 mmHg and/or diastolic BP (DBP) was >85 mmHg even with up to 2 antihypertensive drugs. Patients were excluded if they were on angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers or a diuretic. They were then randomized to receive either preterax (perindopril 2 mg and indapamide 0.625 mg) or cilazapril 2.5 mg once daily in a double-blind fashion for a period of 12 weeks after a 2-week placebo run-in phase. Sitting BP was recorded and the safety and efficacy were evaluated at each visit every 4 weeks. Response was defined as positive if SBP was ≤140 mmHg and DBP was ≤90 mmHg at the last visit or there was >20 mmHg reduction in SBP and/or >10 mmHg reduction in DBP using either treatment. Plasma biochemical analysis was performed both before and after the treatment.

Results: Among the 47 patients initially enrolled, 41 completed the study (21 in the preterax group, 20 in the cilazapril group). There was no difference in the number of adverse events between the 2 groups. SBP was significantly reduced by preterax (13.43±12.48 mmHg, $p<0.0001$) and cilazapril (9.00±13.75 mmHg, $p<0.05$). However, DBP was significantly reduced only by preterax (7.67±9.40 mmHg, $p=0.0009$) but not by cilazapril (3.60±8.37 mmHg, $p>0.05$). The response rate was significantly higher to preterax (100%) than to cilazapril (70%) ($p=0.0086$).

Conclusion: Though similar in safety, combined regimen preterax was more effective than cilazapril to facilitate adequate BP control in already-treated hypertensives. It can be added on to other antihypertensives for better BP control in clinical hypertension. [*J Chin Med Assoc* 2008;71(5):247–253]

Key Words: combination therapy, hypertension, indapamide, perindopril

Introduction

Hypertension is a major cause of cardiovascular mortality and morbidity worldwide. In past decades, we have witnessed the dramatic effects of blood pressure (BP) lowering in the reduction of mortality and morbidity in patients with diabetes, stroke, heart failure, and myocardial infarction.[1] Unfortunately, BP in the majority of diagnosed hypertensive patients is still inadequately controlled.[2,3]

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A number of studies indicated that most patients required more than 2 kinds of antihypertensive agents to reach their target BP.[4,5] Therefore, a fixed very-low-dose combination of 2 antihypertensive drugs has become a popular approach in the initiation of hypertension treatment. Each drug in the combination therapy is given at an infra-therapeutic level but can act synergistically to offer the advantages of increased efficacy and fewer adverse effects.[6] The reduction in the number of tablets required also improves patient compliance with their antihypertensive treatment. To control BP with a minimal number of drug tablets may be particularly important when patients' BP cannot be adequately controlled with current antihypertensives.

The thiazide diuretics, recommended as first-line antihypertensive therapy in the Seventh Report of the Joint National Committee (JNC-VII), have metabolic side effects that can be abolished by combining them with angiotensin-converting enzyme inhibitors (ACEIs). Indapamide, a newly designed thiazide-like diuretic, may minimize the traditional adverse effects of diuretics on lipoprotein or glucose metabolism and reduces left ventricular mass in patients with left ventricular hypertrophy. Therefore, preterax, a combination of perindopril 2 mg and indapamide 0.625 mg, has been suggested as a better antihypertensive regimen. In fact, it was demonstrated in the PREMIER study that preterax could provide significantly better BP control and less albumin excretion than enalapril monotherapy.[7] However, it is not known whether its benefit continues beyond that of other current antihypertensive treatment that the patient may be on. This study was therefore conducted to evaluate the add-on efficacy and safety of preterax in patients with poor BP control by other antihypertensive treatment.

Methods

Study population

This was a randomized, double-blind, parallel-control study conducted in the hypertensive outpatient clinics of a single medical center between October 2005 and January 2007. Eligible patients were those aged from 25 to 75 years old who were on 1 or 2 antihypertensive agents, whatever the pharmacologic class, excluding ACEIs, angiotensin II receptor blockers and/or a diuretic, for at least 8 weeks before the outpatient visit. Seated SBP and DBP were the means of 3 measurements at 2-minute intervals taken with an electronic sphygmomanometer. Subjects with body mass index $< 30\ kg/m^2$ and BP within the ranges of $130 < SBP < 170$ mmHg and/or $80 < DBP < 105$ mmHg were enrolled.

Exclusion criteria were: allergy to perindopril or indapamide or cilazapril; pregnancy; breast feeding; secondary hypertension; complicated hypertension with target organ damage; participation in a drug trial within the last 1 month; history of unstable angina, percutaneous coronary angioplasty, coronary bypass surgery or arterial surgery within the last 3 months; deep vein thrombosis or pulmonary embolism within the last 6 months; acute infection; cancer; AIDS; alcoholism; drug abuse; heart rate < 50 bpm; pacemaker; hemoglobin < 10 g/dL; creatinine > 2 mg/dL; electrolyte imbalance (serum sodium level < 110 or > 180 mmol/L or serum potassium level < 3.5 or > 5.5 mmol/L).

Study design

The study protocol was reviewed by the institutional committee. After giving written informed consent, potential eligible individuals commenced a run-in period with 1 capsule of placebo orally per day and underwent detailed history-taking, demographic data measurement, physical examination, chest roentgenography, electrocardiography, and a series of biologic tests including electrolytes, renal function, liver function, lipid profiles, uric acid, fasting glucose and blood cell counts. After 2 weeks, the patients, who were confirmed to be enrolled, were randomly allocated to 2 active treatment groups: a double-blind comparison of preterax (perindopril 2 mg + indapamide 0.625 mg) and cilazapril 2.5 mg once daily for 12 weeks. Each individual had to maintain his/her original antihypertensive regimen, what he/she took before enrolment without additional antihypertensive agents except the study treatment, during the whole course of the study.

Participants were scheduled to visit the physicians in the outpatient clinics every 4 weeks until the end of the study. Three measurements of SBP and DBP of the same arm were taken using an electronic sphygmomanometer and with subjects in a sitting position; the mean of the 3 readings was calculated at all visits, prior to drug intake. All participants were instructed to refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurements. Once SBP was noted to be < 105 mmHg or DBP < 65 mmHg at any visit, the investigator would be alerted to consider if withdrawal of the subject from the study was necessary.

Treatment was prematurely and definitively discontinued for a participant for any of the following reasons: pregnancy; personal wish; adverse event

requiring study treatment cessation; detection of sodium level < 110 mmol/L; loss to follow-up; severe hypertension with SBP > 190 mmHg and/or DBP > 110 mmHg.

Efficacy evaluation

Responders were defined as individuals in whom SBP was ≤ 140 mmHg and DBP was ≤ 90 mmHg at the last visit, or whose BP had dropped by > 20 mmHg in SBP or 10 mmHg in DBP when comparing the selection visit with the final visit. The primary efficacy endpoint was the response rate in each group. The secondary endpoints were the range of reductions in SBP and DBP.

Safety evaluation

All patients were evaluated for safety and compliance at every visit. The frequencies of adverse effects and mean variation in heart rate were evaluated. Electrocardiography was repeated at the final visit in an attempt to discover if there were any newly developed abnormalities. Another series of biologic tests was also performed at the last visit to check for the presence of any clinically significant laboratory abnormalities.

Statistical analysis

The analysis was performed in terms of variation between baseline and the final visit with Wilcoxon signed rank test. Variation between baseline values and the final recorded values of BP measured was adjusted for baseline demographic data. Because the sample size in each group was less than 30 and the variables of BP were not normally distributed, the difference in BP between groups was analyzed using Wilcoxon rank sum test. After adjusting for the baseline characteristics, response rates were compared by using logistic regression; 95% confidence intervals associated with between-group differences are given. Statistical significance was set at $p < 0.05$.

Results

A total of 56 potentially eligible patients entered the open-label run-in phase, and 47 (27 men, 57.4%) of them were subsequently randomized. Twenty-three patients were treated with preterax, and 24 were treated with cilazapril. There were 2 patients in the preterax group (8.7%) and 4 in the cilazapril group (16.67%) who withdrew from the study due to adverse effects. The main reasons cited for withdrawal were malaise (1 in the preterax group), cough (1 in the preterax group and 2 in the cilazapril group), headache (1 in the cilazapril group) and dizziness (1 in the cilazapril group). The baseline characteristics of each group are shown in Table 1. In brief, there were no significant differences between groups in age, body mass index, SBP and DBP, but there were more men in the preterax group than in the cilazapril group.

BP reduction

The serial changes in SBP and DBP at each visit are illustrated in Figure 1. Only preterax, but not cilazapril, could lower both SBP and DBP consistently at each visit.

There were 21 patients in the preterax group and 20 in the cilazapril group who completed the study. Baseline SBP was 137.73 ± 13 mmHg in the preterax group and 139.8 ± 12.27 mmHg in the cilazapril group. Baseline DBP was 86.9 ± 8.06 mmHg in the preterax group and 86.95 ± 5.67 mmHg in the cilazapril group.

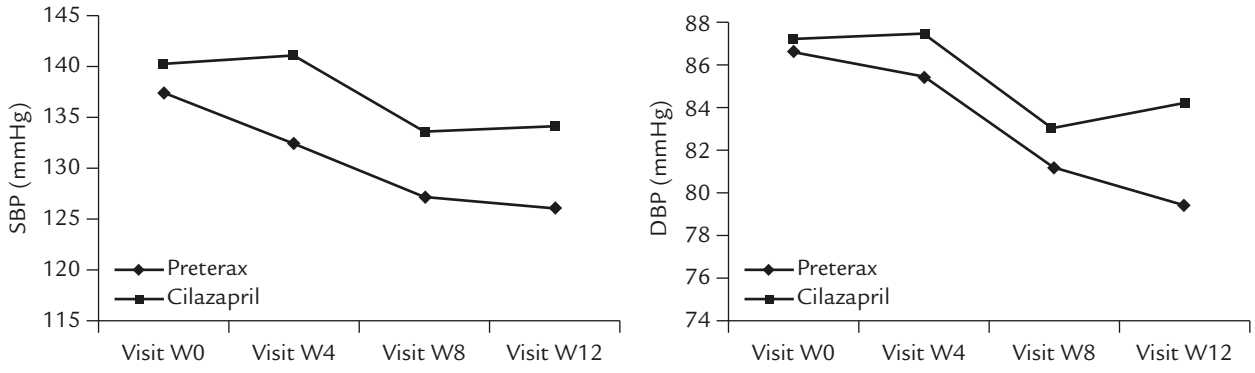
The change in SBP in the cilazapril group ranged from +14 to −36 mmHg (mean, −9 mmHg) and from +11 to −37 mmHg (mean, −13.47 mmHg) in the preterax group. Significant reductions in SBP at the end of the study were demonstrated in both groups ($p < 0.0001$ in the preterax group and $p = 0.0109$ in the cilazapril group).

The change in DBP in the cilazapril group ranged from +16 to −23 mmHg (mean, −3.6 mmHg) and

Table 1. Baseline patient characteristics*

	Preterax ($n = 23$)	Cilazapril ($n = 24$)	p
Age (yr)	50.26 ± 14.85	56.38 ± 11.92	0.1895†
Sex			0.0254‡
Male	17 (73.91)	10 (41.67)	
Female	6 (26.09)	14 (58.33)	
Body mass index (kg/m^2)	27.02 ± 3.70	26.20 ± 3.95	0.2785†
Blood pressure (mmHg)			
Systolic	137.48 ± 12.61	140.21 ± 12.27	0.3536†
Diastolic	86.61 ± 7.92	87.25 ± 6.07	0.8156†

**Data presented as mean ± standard deviation or n (%); †Wilcoxon rank sum test; ‡χ^2 test.*



	Sample size			
	W0	W4	W8	W12
Cilazapril	24	22	21	20
Preterax	23	23	23	21

Figure 1. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) at each visit.

Table 2. Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline (visit W0) to the last visit (visit W12)*

	Preterax ($n=21$)	Cilazapril ($n=20$)	$p^{\dagger}$
SBP (mmHg)			
Baseline	137.71 ± 13.00	139.80 ± 12.27	0.4613
W12	124.29 ± 9.14	130.80 ± 14.55	0.1481
Change	–13.43 ± 12.48	–9.00 ± 13.75	0.2413
$p^{\ddagger}$	< 0.0001	0.0109	
Difference in mean reduction (95% CI)	4.43 (–3.86, 12.72)		
DBP (mmHg)			
Baseline	86.90 ± 8.06	86.95 ± 5.67	0.9586
W12	79.24 ± 7.92	83.35 ± 8.42	0.2517
Change	–7.67 ± 9.40	–3.60 ± 8.37	0.2413
$p^{\ddagger}$	0.0009	0.0594	
Difference in mean reduction (95% CI)	4.07 (–1.57, 9.70)		

**Data presented as mean ± standard deviation; †Wilcoxon rank sum test; ‡Wilcoxon signed rank test. CI = confidence interval.*

from +4 to –30 mmHg (mean, –7.67 mmHg) in the preterax group. There was a significant reduction in DBP in the preterax group ($p=0.0009$) but not in the cilazapril group ($p=0.0594$) (Table 2). Between the 2 groups, there was no significant difference in BP at baseline or at the final visit, and none in the range of reduction of BP (Table 2).

Response rate

For the entire enrolled population ($n=47$), the response rates were 95.65% in the preterax group and 66.67% in the cilazapril group ($p=0.0226$). After adjusting for sex, the response rate was still higher in the preterax group than in the cilazapril group ($p=0.037$). For the subjects who completed the study ($n=41$), the response rates were 100% in the preterax group ($n=21$) and 70% in the cilazapril group ($n=20$; $p=0.0086$). However, the sex was not different between the 2 groups in this setting.

Safety and adverse events

All adverse events were recognized, including dizziness (nervous system), cough, respiratory distress (respiratory system), pain, malaise (body as a whole), and hematuria (urogenital system). Eleven patients (47.83%) treated with preterax and 17 (70.83%) with cilazapril encountered adverse events. There was no statistically significant difference in the incidence of adverse events between the 2 groups. The details of adverse events are shown in Table 3. There were no serious adverse events and no clinically significant findings detected on electrocardiography in the overall population. There were no significant differences in biochemistry data between the 2 groups except for

Table 3. Adverse events*

	Preterax ($n=23$)	Cilazapril ($n=24$)	p
Number of patients with adverse events	11 (47.83)	17 (70.83)	0.1081†
Body as a whole	4 (17.39)	3 (12.50)	0.6378‡
Cardiovascular system	4 (17.39)	3 (12.50)	0.6378‡
Digestive system	0 (0)	3 (12.50)	0.2340‡
Metabolic and nutritional disorders	0 (0)	1 (4.17)	1.0000‡
Nervous system	4 (17.39)	6 (25.00)	0.7238‡
Respiratory system	4 (17.39)	7 (29.17)	0.3405†
Skin and appendages	0 (0)	1 (4.17)	1.0000‡
Urogenital system	1 (4.35)	1 (4.17)	1.0000‡

Data presented as n (%); †χ^2 test; ‡Fisher's exact test.

Table 4. Blood biochemistry tests at baseline and at the final visit*

	Preterax		Cilazapril	
	Baseline ($n=23$)	Final visit ($n=21$)	Baseline ($n=24$)	Final visit ($n=20$)
Hemoglobin (g/dL)	14.88±1.19	14.50±1.25	14.50±1.16	14.21±1.47†
White cell count ($10^3/\mu L$)	5.67±0.88	6.42±2.05	6.32±1.38	6.10±1.18‡
Platelets ($10^3/\mu L$)	252.52±55.81	260.24±63.00	267.63±73.26	260.05±76.04
Sodium (mmol/L)	141.35±1.43	141.14±1.53	141.42±1.69	140.80±1.67
Potassium (mmol/L)	4.17±0.35	3.89±0.41†	4.24±0.33	4.27±0.32‡
Creatinine (mg/dL)	0.93±0.22	0.95±0.22	0.93±0.25	0.96±0.26
AST (U/L)	23.96±6.22	23.81±4.24	23.13±8.42	24.10±8.92‡
ALT (U/L)	29.00±16.54	27.71±14.38	33.21±17.59	27.30±19.45†
Blood glucose (mg/dL)	98.22±13.76	96.52±9.99	105.29±13.47	104.40±15.86
Total cholesterol (mg/dL)	175.52±24.18	181.43±33.54	223.21±38.69	217.35±29.81
Triglycerides (mg/dL)	112.22±48.09	140.29±105.34	149.96±120.64	125.05±73.61
HDL cholesterol (mg/dL)	38.30±9.11	38.76±7.70	45.17±10.11	44.70±10.03
LDL cholesterol (mg/dL)	122.52±26.35	123.53±36.51	150.71±51.49	157.35±33.69
Uric acid (mg/dL)	6.49±1.21	6.65±1.59	6.49±1.58	6.22±1.38‡

Data presented as mean±standard deviation; †Wilcoxon signed rank test was used for within-group analysis, significant difference ($p<0.05$) when comparing the mean values of the baseline and the last visit; ‡Wilcoxon rank sum test was used for between-group analysis, significant difference ($p<0.05$) when comparing the change between the mean values of the baseline and the last visit in the 2 groups.

a lower plasma potassium level and a higher uric acid level in the preterax group compared with the cilazapril group ($p=0.007$ and 0.036, respectively) (Table 4).

Discussion

The major findings of the present study indicated that a fixed low-dose combination of perindopril 2 mg and indapamide 0.625 mg (preterax) could be effective and safe as a therapeutic add-on strategy to achieve better BP control in hypertensive patients who are already being treated. Further, preterax was shown to effectively lower BP, particularly DBP. Compared with cilazapril, an ACEI, preterax resulted in a significantly increased response rate in BP reduction in patients with mild to moderate hypertension whose BP was not well controlled by their current medications.

Pharmacology and pathophysiology of combination therapy

Diuretics, particularly thiazides, exert a gradual and stable hypotensive effect, especially in the elderly and in patients with poor renal function. They facilitate the excretion of serum sodium accompanied with a reduction in body fluid volume and blood pressure.[8] However, the causes of hypertension are multifactorial, including sympathetic activity, renin–angiotensin activation, fluid accumulation and hereditary genes. Once you block 1 mechanism, others might be compensatorily activated. Accordingly, as BP goes down, the glomerular capillary pressure drops and glomerular filtration rate decreases.[9] Thereafter follows activation

of the sympathetic nerve and renin–angiotensin system, which are responsible for the vast majority of diuretic-resistant hypertension cases.[10] Therefore, the concomitant administration of ACEIs will further promote the natriuretic and hypotensive effects of diuretics. This might be the reason why cilazapril lowered neither SBP nor DBP consistently at the final visit, but preterax did. Further, combination therapy with indapamide and perindopril has been proven to be effective in reducing arterial stiffness, albuminuria, recurrent stroke, and left ventricular hypertrophy,[7,11–16] and it would be reasonable to include it as a first-line or add-on therapy in clinics.

Response rate to combination therapy

In the Framingham Heart Study, it was found that even high-normal BP (SBP, 130–139 mmHg; DBP, 85–89 mmHg; or both) augmented the risk of cardiovascular disease 2-fold compared with lower levels.[17] In our study, aggressive treatment using add-on therapy with preterax resulted in a higher response rate than to cilazapril, both in the overall study population (96.65% *vs.* 66.67%, $p=0.0226$) and in the subgroup who completed the study (100% *vs.* 70%, $p=0.0086$). Also, mean DBP was significantly reduced in the preterax group rather than in the cilazapril group between the baseline visit and final visit. Elevated SBP and DBP are common in young hypertensives, compared to isolated systolic hypertension in the elderly. Preterax, which can lower both SBP and DBP significantly, might be more suitable for young hypertensives than cilazapril.

Tolerability of combination therapy

Due to the low dosage of both components of preterax, good efficacy is accompanied by excellent tolerability and safety. In previous studies, the safety of combination therapy with indapamide and perindopril was comparable or superior to that of other common antihypertensive drugs.[7,12,15,18] In our study, we also demonstrated that there was a trend of lower withdrawal rate in the preterax than in the cilazapril group (8.7% *vs.* 16.67%). As drug compliance is a key factor for efficacious treatment in hypertension as well as for other diseases, the impact of preterax on patient compliance and safety needs to be confirmed in future research.

In conclusion, the importance of a fixed very-low-dose combination therapy has been emphasized as first-line treatment of hypertension. Though similar in safety, combined regimen such as preterax, rather than cilazapril, could be more effective to achieve adequate BP control by being added to already existing antihypertensive medications. Accordingly, preterax could be used safely and effectively as an add-on regimen for further BP reduction in patients without adequate BP control by other classes of antihypertensive medications.

Combination therapy has been recommended as the initial treatment of hypertension in recent trials. This study demonstrated that combination therapy, instead of administering a single drug step by step, constitutes a superior choice for add-on therapy.

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