Efficacy and Acceptability of Perindopril in Essential Hypertension

APICHARD SUKONTHASARN, M.D.*, RANGSON RATANAPRAKARN, M.D.**,
BANHAN KOANANTAKUL, M.D.***, PUNGCHAI NGAM-UKOS, M.D.****

It was reported in 1988 by the Joint National Committee on the detection, evaluation and treatment of high blood pressure in the U.S.A. that angiotensin converting enzyme (ACE) inhibitors were among the first drugs of choice in the treatment of essential hypertension[1]. In cases where the response to initial therapy is inadequate, one of the options in the stepped care approach is to add another antihypertensive agent with a different mode of action. This will often allow the use of low doses of antihypertensive drugs to achieve blood pressure control whilst minimising the potential for dose-dependent side effects. In the case of ACE inhibitors, the antihypertensive effect has been shown to be augmented by the addition of thiazide diuretic therapy[2-5]. This combination with diuretic has proved to be superior to that with beta-blocker and at the same time it can compensate for the effect on plasma potassium levels.

Perindopril is a prodrug, nonsulfhydryl ACE inhibitor which is rapidly hydrolysed to its active, long-acting metabolite, perindoprilat after oral administration. Single oral doses of 1-16 mg cause dose-dependent inhibition of plasma ACE with a peak effect at 4-6 hours after administration and significant inhibition remaining longer than 24 hours after a dose of 4 mg or above[6]. In patients with essential hypertension, perindopril has significant antihypertensive activity at doses of 4 to 8 mg daily[7-9]. It has also been shown in these studies that the antihypertensive effect of perindopril given at 8 mg daily can be augmented by the addition of hydrochlorothiazide. It is, therefore, of interest to conduct a clinical trial to assess the clinical efficacy and acceptability of perindopril and the additive effect of hydrochlorothiazide in the Thai population.

METHODS

Patient selection

Men and women (not of child bearing potential) aged between 18 and 70 years were recruited from patients attending the Cardiology Clinic at Bhumibol, Maharaj N' Chiang Mai, Chulalongkorn and Ramathibodi Hospitals respectively. They had mild to moderate stable essential hypertension with supine diastolic blood pressure (DBP) of 95-115 mmHg after a minimum of 2 weeks placebo run-in period.

Patients were excluded if they had secondary or accelerated hypertension, evidence of strokes, unstable angina or myocardial infarction in the previous 3 months, acute or chronic heart failure, and/or any other severe concomitant diseases e.g. hepatic or renal failure.

* Division of Cardiology, Department of Medicine, Faculty of Medicine, Maharaj Nakhon Chiang Mai Hospital, Chiang Mai 50200,
** Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400,
*** Department of Medicine, Bhumibol Adulyadej Hospital, Bangkok 10220,
**** Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Study design

The study was an open, self-controlled study with a minimum of 2 weeks placebo run-in period followed by 3 months of active treatment with 4 to 8 mg perindopril with or without addition of 50 mg hydrochlorothiazide in the third month. On entry to the study, BP was measured using an arm cuff and a mercury sphygmomanometer after 10 minutes of supine rest and 2 minutes after standing. The mean of 3 measurements was recorded and the conditions of measurements for all visits were maintained throughout the study.

After general assessment, fundoscopic and electrocardiographic examinations, and all previous antihypertensive medications stopped, patients then received 2 to 4 weeks of placebo therapy.

After the run-in period, patients who fulfilled all inclusion criteria were administered with 4 mg of perindopril once daily for 1 month. If adequate BP control was not achieved (i.e., supine DBP > 90 mmHg), the dose of perindopril was increased to 8 mg once daily in the second month. If supine DBP was still greater than 90 mmHg, 50 mg hydrochlorothiazide once daily was added in the third month. At the end of this 3-month treatment, the patients might or might not continue the treatment with perindopril depending on individual judgement.

Therapeutic activity and evaluation criteria

Blood pressure (BP) and heart rate (HR) were recorded at each visit and dosage of perindopril was adjusted during the course of treatment. The changes in BP and HR and number of patients with normalisation of the supine DBP (DBP $\leq$ 90 mmHg) were calculated for each possible therapeutic combination after 3 months of treatment.

Evaluation of clinical acceptability

During all these periods, patients were thoroughly monitored for any change in weight, haemodynamic and laboratory parameters. Any side effect, concomitant medication and compliance were also recorded monthly throughout the study.

Statistical analysis

The changes in supine and standing BP and HR were subjected to two-way (time x subject) analysis of variance (ANOVA). The measurements at entry, after placebo treatment and at monthly visits of active treatment were compared using student's paired *t*-test.

The laboratory parameters between MO and M3 were also studied by student's paired *t*-test.

The results were expressed as percentage and mean ± SEM and the threshold of significance was fixed at 0.05.

RESULTS

Patients

One hundred and nine patients (55 men, 54 women) with a mean age of 52.1 years were initially included into the study. Demographic data are shown in Table 1.

Table 1. Characteristics of patients

Total number	109
Male : Female	55 : 54
Mean age ± SEM (yrs)	52.1 ± 0.9
Mean weight ± SEM (kgs)	66.7 ± 3.28
Mean height ± SEM (cms)	159.0 ± 0.87
Mean duration of HT ± SEM (months)	36.9 ± 4.53
Severity of HT, mild : moderate	67 : 42
Treatment status, newly untreated : treated	47 : 62
Mean duration of stopping treatment ± SEM (months)	1.3 ± 0.24
Sodium diet, normal : restricted	96 : 13

Seven patients were excluded due to rising of supine DBP > 115 mmHg, 3 patients were lost to follow-up, 4 patients were withdrawn during the first month of active treatment due to adverse reactions of nausea/vomiting, severe cough and drug rash[1,2]. Hence a total of 95 patients were studied for therapeutic efficacy at the end of the study.

Changes in BP and HR

The supine and standing BP and HR of all 95 patients at each visit are displayed in Fig. 1 and Table 2 respectively.

From Table 2, perindopril significantly reduced the mean BP throughout the study without significantly affecting the heart rate. The mean reductions in supine systolic and diastolic blood pressure at 1, 2 and 3 months after active treatment were of 10.3 ± 1.9 / 8.0 ± 0.9, 13.2 ± 2.1 / 8.7 ± 1 and 19.1 ± 2.3 / 13.7 ± 1 mmHg respectively.

The number of patients with different degrees of severity of hypertension whose blood pressure was controlled after treatment (supine DBP $\leq$ 90 mmHg) by different regimens at each visit are disclosed in Table 3.

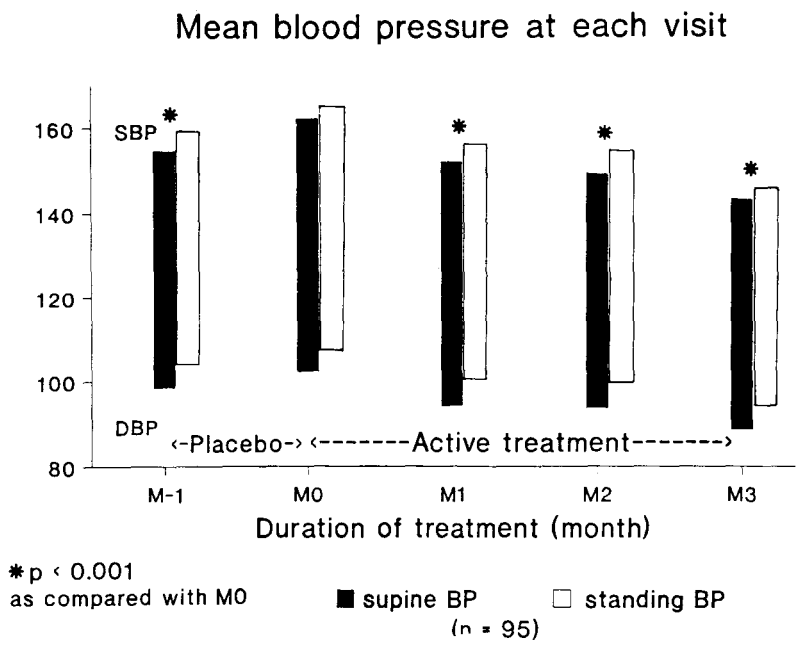

Fig. 1 Mean blood pressure before and after treatment with perindopril.

Table 2. Changes in blood pressure and heart rate

	Duration of treatment (months)					ANOVA
	<----------Run-in---------->		<----------Active treatment---------->			
	M-1	M0	M1	M2	M3	Statistical p value
Supine						
Reduction of SBP (mmHg)			10.3±1.91	13.2±2.08	19.1±2.3	<0.001
Reduction of DBP (mmHg)			8.0±0.9	8.7±1.0	13.7±1.0	<0.001
HR (beat/min)	78.4±1.21	76.7±1.02	77.4±0.97	76.9±0.99	76.8±1.19	NS
Standing						
Reduction of SBP (mmHg)			8.8±1.6	10.0±2.2	17.6±2.2	<0.001
Reduction of DBP (mmHg)			6.9±1.3	7.6±1.4	12.2±1.6	<0.001
HR (beat/min)	82.0±1.3	80.5±1.0	80.2±1.0	79.8±1.0	79.9±1.1	NS

Remarks The results are expressed as mean ± SEM.

Table 3. Percentage and number of patients with normalisation of the supine DBP (≤ 90 mmHg) by different regimens

	Number of patients	Percentage of patients with normalised DBP at each visit (number of patients controlled by each regimen) (Per 4 mg : Per 8 mg : Per 8 mg + HCTZ)		
		M1	M2	M3
Mild HT	63	57.1 (36:0:0)	63.5 (27:13:0)	85.7 (24:17:13)
Moderate HT	32	15.6 (5:0:0)	25.0 (1:7:0)	68.8 (2:4:16)
Total	95	43.2 (41:0:0)	50.5 (28:20:0)	80.0 (26:21:29)

Remarks Per = perindopril, HCTZ = hydrochlorothiazide

Perindopril monotherapy for 3 months (4-8 mg once daily) was able to normalise supine DBP to be equal to or lower than 90 mmHg in about 50 per cent of all cases (65.1% in mild HT and 18.8% in moderate HT) as demonstrated in Table 3. An additional 30 per cent of the patients were successfully controlled by combined antihypertensive therapy of perindopril and hydrochlorothiazide. Hence, a total of 80 per cent of the patients were successfully controlled at the end of the study.

Acceptability profiles

Table 4 shows the number of patients and the adverse events reported at each visit throughout the study. A total of 13 cases developed cough with 1 case having persistent cough even before receiving perindopril, 3 cases had cough after initiation of active treatment (treatment was withdrawn in 1 case due to severe cough). An additional 4 and 5 patients developed chronic cough after increasing dosage of perindopril to 8 mg in the second and third month of treatment.

Table 4. Adverse events reported during each period of the study

Symptoms	Run-in	Period M0-M1	M1-M2	M2-M3
Cough	1	4*	8	13
Neurosensory symptoms				
Headache	2	4	7	3
Dizziness	1	3	2	3
Tinnitus	-	1	-	-
Blurring of vision	-	-	1	-
Insomnia	-	1	-	-
Numbness	-	-	-	1
Cardiovascular symptoms				
Palpitation	1	3	2	1
Chest pain	1	1	-	-
GI symptoms				
Nausea/vomiting	-	4**	-	-
GI discomfort	-	1	-	-
Others				
Drug rash	-	1***	-	-
Myalgia	-	-	1	-
Back pain	-	-	-	1

N.B. * One case had so severe cough that the treatment was withdrawn.
** Treatment was withdrawn in 2 cases.
*** Treatment was withdrawn.

Concerning GI symptoms, 2 out of 4 patients who developed nausea and vomitting were withdrawn from the treatment after a month of active treatment. Treatment was withdrawn in another patient who developed drug rash after 1 month of perindopril. All the other events were minor complaints and spontaneously recovered without clinical relevance.

With respect to the evolution of important laboratory parameters linked with cardiovascular risks (i.e. renal function, electrolytes, lipid profiles, uric acid and glucose levels), the patients receiving perindopril monotherapy did not show significant change of the blood urea nitrogen or creatinine levels. In spite of better control of HT, those treated with 8 mg/day perindopril and 50 mg/day HCTZ showed significant increase ($p < 0.01$) of BUN and creatinine. Nevertheless, all the parameters were still in normal ranges as displayed in Table 5.

Perindopril at a dose of 4 mg/day did not significantly alter blood potassium. Increase of the dosage to 8 mg/day resulted in significant increase ($p<0.01$) of kalemia (Table 6). However, they were still in the normal ranges. The addition of HCTZ compensated this change back to the initial level.

Perindopril did not significantly change the blood sodium levels. The addition of HCTZ slightly but significantly ($p = 0.038$) reduced the sodium levels (Table 6).

Lipid metabolism

Perindopril did not significantly affect the plasma levels of total cholesterol, triglycerides or HDL-cholesterol. However, the addition of hydrochlorothiazide to 8 mg of perindopril significantly ($p = 0.014$) increased the total cholesterol levels from 5.62 ± 0.15 mmol/l at MO to 5.92 ± 0.17 mmol/l at M3 without significant effect on triglycerides or HDL-cholesterol.

Uric acid metabolism

Perindopril 4 mg once daily significantly ($p = 0.0205$) reduced serum levels of uric acid from 377.4 mmol/l at MO to 353.2 mmol/l at M3. However, increased dosage of perindopril and addition of 50 mg/day HCTZ reversed the effect (Data not shown).

Glucose metabolism

There was no statistical change of fasting blood glucose levels before and after treatment by

Table 5. Renal function before and after treatment

Regimens	BUN (mmol/l)			Creatinine (μmol/l)		
	M0	M3	Significant change (p)	M0	M3	Significant change (p)
Per 4 mg	4.22±0.21 (29)	4.74±0.26 (28)	NS	83.9±3.43 (30)	89.0±4.09 (29)	NS
Per 8 mg	5.01±0.36 (20)	5.17±0.44 (24)	NS	92.8±4.55 (28)	89.8±4.97 (28)	NS
Per 8 mg +HCTZ	4.95±0.34 (31)	6.47±0.47 (34)	<0.001	91.2±3.76 (41)	98.8±7.98 (43)	<0.01

Remarks: Per = perindopril, HCTZ = hydrochlorothiazide 50 mg/day.
The results are expressed as mean ± SEM. Number of patients are shown in the brackets.

Table 6. Changes of blood electrolyte levels in patients receiving different antihypertensive regimens

Regiments	Potassium (mmol/l)			Sodium (mmol/l)		
	M0	M3	Significant change (p)	M0	M3	Significant change (p)
Per 4 mg	4.42±0.01 (30)	4.33±0.1 (29)	NS	142.5±0.78 (30)	142.6±0.64 (29)	NS
Per 8 mg	4.08±0.01 (28)	4.33±0.01 (28)	<0.01	143.4±0.66 (28)	144.2±0.71 (28)	NS
Per 8 mg +HCTZ	4.19±0.01 (43)	4.21±0.02 (42)	NS	141.9±0.6 (43)	140.6±0.64 (42)	0.038

Remarks: Per = perindopril, HCTZ = hydrochlorothiazide 50 mg/day
The results are expressed as mean ± SEM. Number of patients are shown in the brackets.

any regimen in this study.

All the other biochemical parameters remained unchanged. There was no significant change of the haematological parameters except for platelet count which showed slight but significant ($p < 0.001$) reduction from 310.5 ± 7.05 x 10^9/l at MO to 292 ± 6.88 x 10^9/l at M3.

The compliance was higher than 95 per cent in every period of the study.

DISCUSSION

The results of this study were comparable to those previously reported that the overall response rates on perindopril monotherapy and in combination with a diuretic were approximately 50-55 per cent and 75-85 per cent respectively[5-9]. It also demonstrated that perindopril monotherapy (4-8 mg once daily) showed higher antihypertensive efficacy on supine BP than standing BP. The antihypertensive effects of 50 mg/day hydrochlorothiazide were synergistic to perindopril for both supine and standing BP. In addition, the analysis of the subgroups of patients according to the severity of HT, those with mild HT showed better response to perindopril than those with moderate HT. The addition of hydrochlorothiazide boosted the percentage of patients with normalised supine DBP (≤90 mmHg) in latter group from 25 to 68.8 per cent. This confirmed the synergistic effect of perindopril and hydrochlorothiazide as previously reported by other investigators[5-9]. Lees et al have shown that either captopril or perindopril monotherapy was equally effective in normalisation of the supine DBP in about 49 per cent of each group[8]. However, after the addition of hydrochlorothiazide, the final control rate was higher with perindopril than captopril (*75% vs 57%*).

Unlike beta-blocker, ACE inhibitor had no effect on the heart rate[1,9]. Similar results have been obtained in this study.

Perindopril monotherapy possesses a good biological safety profile with no significant effects on the renal function, lipid and glucose metabolism.

A dose of 4 mg daily of perindopril also significantly (p=0.0205) reduced the levels of uric acid. All these parameters confirm the benefit of perindopril in terms of cardiovascular risks.

The addition of hydrochlorothiazide resulted in better response and control of supine DBP. However, it has raised several cardiovascular risks i.e., mild but significant increase of BUN and creatinine, increased total cholesterol levels and increased uric acid levels. Therefore, one must carefully consider the benefit of combining thiazide diuretic and ACE inhibitor in the treatment of hypertension whether the additional antihypertensive efficacy outweighs the increase of cardiovascular risks. ACE inhibitors have been shown to increase serum potassium levels[1]. The results of this study show an significant increase of serum potassium although remaining in normal values after high doses (8 mg) of perindopril. It did not affect the serum sodium. Hydrochlorothiazide led to a slight but significant (p=0.038) decrease of sodium and compensated for the effect of perindopril on kalemia resulting in retaining the initial potassium levels.

Perindopril was well tolerated with only 4 patients being withdrawn from treatment due to adverse effects of nausea/vomiting, cough and drug rash in this study[1,2].

Although cough was most commonly complained of by 13 patients, it was tolerable and only 1 case withdrew from treatment due to this side effect. One patient had developed persistent cough even before initiation of perindopril treatment, 3 had dry cough from the first month, 4 after the second month and 5 only in the last month of active treatment. Those who developed cough in the last month of the study should be reevaluated for persistency and severity of cough. Therefore, fewer than 10 per cent of the patients actually had persistent dry cough after perindopril therapy. In addition, some of them, apart from perindopril-related, were also associated with other causes e.g. respiratory tract infection, smoking or bronchial allergy. Other side effects were trivial and nonspecific and they were no more frequent in the group receiving monotherapy or combined treatment.

It is therefore concluded that once-daily treatment with perindopril appears to be an effective and safe antihypertensive agent used for the treatment of mild to moderate essential hypertension in the Thai population.

SUMMARY

The clinical efficacy and acceptability of once-daily perindopril (4 to 8 mg) monotherapy and in combination with hydrochlorothiazide (50 mg/day) was studied in mild to moderate stable essential hypertensive patients in 4 centres in Thailand. After 2-4 weeks of placebo run-in period, patients received active treatment for 3 months starting with 4 mg perindopril once daily. Dose titration was at second and third month of active treatment if the supine DBP was > 90 mmHg. The dose was doubled and if necessary, 50 mg/day hydrochlorothiazide was added in the last month. The results in 95 patients showed that the mean reduction in supine SBP/DBP at 1, 2 and 3 months of treatment was 10.3/8.0, 13.2/8.7 and 19.1/13.7 mmHg respectively. At the end of the study, 80 per cent of the patients showed normalisation of the supine diastolic blood pressure (supine DBP ≤ 90 mmHg) with 30 per cent receiving combined therapy of perindopril and hydrochlorothiazide. There was no significant change in routine haematology or serum biochemistry except for slight increase of potassium levels in patients receiving 8 mg perindopril monotherapy.

The incidence of side effects and withdrawal from treatment were quite low. Cough was the major side effect reported comprising 13.6 per cent with only 1 case withdrawn. The study comfirms the previous studies that perindopril had satisfactory antihypertensive efficacy and acceptability profiles.

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ประสิทธิภาพและการยอมรับยาเพรินโดพริลในผู้ป่วยความดันโลหิตสูงชนิดไม่ทราบสาเหตุ

อภิชาต สุคนธสรรพ์, พ.บ., รังสรรค์ รัตนประการ, พ.บ.**, บรรหาร กออนันตกูร, พ.บ.***, พึงใจ งามอุโฆษ, พ.บ.*****

ได้ทำการศึกษาประสิทธิภาพและการยอมรับยา Perindopril (Coversyl®) ในการรักษาผู้ป่วยความดันโลหิตสูงชนิดไม่ทราบสาเหตุที่มีความดันโลหิตสูงน้อยและปานกลางและไม่มีโรคแทรกซ้อนอื่นๆ โดยใช้ Perindopril เพียงอย่างเดียว ขนาด 4–8 มก.ต่อวัน หรือร่วมกับยาขับปัสสาวะชนิด hydrochlorothiazide ขนาด 50 มก.ต่อวันเป็นเวลานาน 3 เดือน ในการทดลองผู้ป่วยได้รับยาหลอกเป็นเวลา 2–4 สัปดาห์จากนั้นจึงได้รับการรักษาด้วย Perindopril 4 มก.ต่อวันเป็นเวลา 1 เดือน ถ้าความดันโลหิตไดแอสโตลในท่านอนยังสูงกว่า 90 มม.ปรอท หลังจากรักษาไปแล้ว 1 และ 2 เดือนจะเพิ่มยาเป็น 8 มก.ต่อวัน และให้ hydrochlorothiazide ขนาด 50 มก.ต่อวันร่วมด้วยตามลำดับ ผลการทดลองในผู้ป่วย 95 คนพบว่าความดันโลหิตซิสโตลและไดแอสโตล หลังการรักษา 1, 2 และ 3 เดือนลดลง มีค่าเฉลี่ยเท่ากับ 10.3/8.0, 13.2/8.7, และ 19.1/13.7 มม.ปรอท ตามลำดับ เมื่อจบการศึกษาผู้ป่วยร้อยละ 80 มีค่าความดันโลหิตอยู่ในเกณฑ์ปกติ (ค่าความดันไดแอสโตลน้อยกว่า 90 มม.ปรอท) โดยที่ร้อยละ 30 ของผู้ป่วยได้รับยา Perindopril ร่วมกับ hydrochlorothiazide

ไม่พบว่ามีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางโลหิตวิทยาหรือชีวเคมี ฤทธิ์แทรกซ้อนและผลข้างเคียงของยามีน้อย ผลการศึกษานี้ยืนยันการศึกษาอื่นๆ ว่า Perindopril เป็นยารักษาโรคความดันโลหิตที่มีประสิทธิภาพและการยอมรับดี

* หน่วยโรคหัวใจ, ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์, โรงพยาบาลมหาราชนครเชียงใหม่, เชียงใหม่ 50200,

** ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพฯ 10400,

*** ฝ่ายอายุรกรรม, โรงพยาบาลภูมิพลอดุลยเดช, กรุงเทพฯ 10220,

**** ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพฯ 10330