นิพนธ์ต้นฉบับ • **Original Article**

การรักษาผู้ป่วยโรคความดันโลหิตสูงในเวชปฏิบัติทั่วไป : การประเมินความปลอดภัย อาการไม่พึงประสงค์ และประสิทธิภาพในการใช้ยาสูตรผสมแบบคงที่ของเพอรินโดพริลและอินดาปาไมด์

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Management of Hypertension in the General Practice Clinic : Post-Marketing Surveillance with a fixed Combination of Perindopril and Indapamide

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หลักการและวัตถุประสงค์: ยาลดความดันโลหิตสูตรผสมแบบคงที่ของเพอรินโดพริลและอินดาปาไมด์เป็นยาที่มีการใช้กันทั่วไป คณะผู้ศึกษาต้องการประเมินประสิทธิภาพและความปลอดภัยจากการใช้ยาสูตรผสมดังกล่าวช่วงระยะสั้นในผู้ป่วยคนไทย

วิธีการศึกษา: เป็นการศึกษาแบบพรรณาเพื่อประเมินประสิทธิภาพและความทนต่อยาลดความดันโลหิตสูตรผสมแบบคงที่เพอรินโดพริล/อินดาปาไมด์ (4/1.25 มิลลิกรัม) จากผู้ป่วยนอกจำนวน 476 รายจากโรงพยาบาล 18 แห่งในประเทศไทยระหว่างเดือนตุลาคม 2551 ถึงเดือนพฤษภาคม 2552

ผลการศึกษา: ผู้ป่วยความดันโลหิตสูง 476 ราย เมื่อแยกตามระดับความดันโลหิตจะแบ่งได้เป็น 3 กลุ่ม ได้แก่ ระยะที่หนึ่ง (ร้อยละ 39.3) มีระดับความดันโลหิตที่ 145.7/86.1 มม.ปรอท ระยะที่สอง (ร้อยละ 51.5) มีระดับความดันโลหิตที่ 167.5/98.7 มม.ปรอท และกลุ่ม prehypertension (ร้อยละ 9.2) ผู้ป่วยทั้งหมดได้รับยาสูตรผสมแบบคงที่เพอรินโดพริล/อินดาปาไมด์ (4/1.25 มิลลิกรัม) และประเมินประสิทธิภาพที่ 1 และ 3 เดือน หลังได้รับยา ร้อยละ 86.6 ของผู้ป่วยที่มีความดันโลหิตสูงระยะที่หนึ่ง สามารถควบคุมความดันโลหิตได้ภายในเดือนที่ 1 และ 3 โดยความดันโลหิตลดลง [p<0.001] 15.8/7.7 และ 12.1/5.7 มม.ปรอท ตามลำดับ ร้อยละ 88.5 ของผู้ป่วยระยะที่สอง สามารถควบคุมความดันโลหิตได้ภายใน

Background and objectives: A fixed-dose combination of perindopril and indapamide (FCPI) is currently used as antihypertensive agent. We studied the short-term efficacy and safety of FCPI in Thai hypertensive patients.

Methods: The study was a post-marketing surveillance and safety monitoring in a prospective, observational, multicenter trial in ambulatory hypertensive patients recruited in daily hypertension and diabetes clinics in 18 hospitals in Thailand. The study assessed the efficacy and tolerability of FCPI (4/1.25 mg) given once daily for 3 months during October 2008 to May 2009.

Results: Of the 476 hypertensive patients, 39.3 % had stage 1 hypertension with mean baseline BP of 145.7/86.1 mmHg and 51.5 % had stage 2 hypertension with mean baseline BP of 167.5/98.7 mmHg and 9.2 % were prehypertensive. In stage 1 hypertension, BP control was achieved in 86.6% of patients by month 3, and BP reduction was significant at month 1 (12.1/5.7 mmHg [p<0.001]) and at month 3 (15.8/7.7 mmHg [p<0.001]), respectively, compared with baseline. In stage 2 hypertension, BP control was achieved in 88.5% patients by month 3 (132.9/78.8 mmHg), and BP reduction was significant at month 1 (25.6/14.1 mmHg [p<0.001]) and at month 3 (34.6/19.9 mmHg [p<0.001]), respectively, compared with baseline. Overall, blood pressure was

เดือนที่ 1 และ 3 โดยความดันโลหิตลดลง [p<0.001] 25.6/14.1 และ 34.6/19.9 มม.ปรอท ตามลำดับ อาการไม่พึงประสงค์จากยาที่พบได้ประมาณร้อยละ 0.2 ได้แก่อาการไอแห้ง มึนงง และภาวะโปแทสเซียมในเลือดต่ำ

สรุป: การลดความดันโลหิตด้วยยาสูตรผสมแบบคงที่เพอรินโดพริล/อินดาปาไมด์(4/1.25 มิลลิกรัม) มีประสิทธิภาพดีในการนำมารักษาผู้ป่วยคนไทยที่มีความดันโลหิตสูงในเวชปฏิบัติทั่วไป โดยผู้ป่วยสามารถทนต่อยาได้ดี

คำสำคัญ: ยาลดความดันโลหิตชนิดสูตรผสมแบบคงที่เพอรินโดพริล/อินดาปาไมด์ (4/1.25 มิลลิกรัม) (FCPI), ยาลดความดันโลหิตสูง, โรคความดันโลหิตสูง, ความดันโลหิตสูงระยะที่หนึ่ง, ความดันโลหิตสูงระยะที่สอง

below 140/90 mmHg in 74% of patients at month 1. Adverse drug reactions reported in about 0.2 % of patients were dry cough, dizziness and hypokalemia.

Conclusion: The fixed-dose combination of perindopril and indapamide (4/1.25 mg) was effective and well tolerated in daily clinical use for BP control in Thai hypertensive patients.

Key words: Fixed-dose combination of perindopril and indapamide (FCPI); antihypertensive; hypertension; stage 1 hypertension; stage 2 hypertension

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Introduction

Hypertension and diabetes are a major chronic health burden and contribute greatly to chronic kidney disease in Thailand.[1] Hypertension, the major treatable cardiovascular (CV) disease, usually occurs in association with other major risk factors, especially diabetes. Two third of diabetes and hypertension patients have a blood pressure (BP) of 130/80 mmHg or above. Up to 80% of people with diabetes died of cardiovascular complications and up to three-quarters of specific diabetes complications can be attributed to high BP. In people with diabetes and hypertension, reducing BP greatly reduces death and disability.[2-4] Effective BP goal should therefore provide long-term benefits, such as reduction of CV events, which can be anticipated in a wide range of hypertensive patients.[2-12] However, effective short-term BP reduction in daily clinical practice should be a major goal if long-term compliance is to be achieved. For this reason, a combination of an angiotensin-converting enzyme (ACE) inhibitor (perindopril) and a diuretic (indapamide), which has been investigated for its antihypertensive efficacy and tolerability in the ADVANCE trial, is a promising antihypertensive medication.[5,7,12] In Thailand, a fixed-dose combination of perindopril/indapamide (4 mg/1.25 mg) (FCPI) is limited by the Thai Food and Drug Administration (FDA) to hospital use, and prescribers must report on its safety and tolerability. Therefore, we initiated safety monitoring by using reports of short-term efficacy and post-marketing surveillance reports.

Methods

Safety monitoring data on the BP-lowering efficacy and tolerability of FCPI were gathered from 18 hospitals. This 3-month, prospective, open-label, observational, phase IV study was carried out as post-marketing surveillance. Patients were recruited from hospitals where FCPI was being evaluated in the safety monitoring program required by the Thai FDA. All 25 physicians from 18 hospitals were well aware of the benefits and risks of FCPI. All physicians were informed about the status of the safety monitoring program inclusive of short-term monitoring of BP. Hospitals involved in the evaluation program completed safety monitoring report forms, which were collected and sent to the Thai FDA as quarterly reports. Physicians were advised to monitor patients closely, and those who showed good compliance were asked to make follow-up visits at the end of month 1 and month 3.

Patient characteristics

Male and female patients aged 39-88 years with any of the following categories of hypertension: (i) newly diagnosed and untreated stage 1 and stage 2 hypertension; (ii) uncontrolled stage 1 and stage 2 hypertension, (iii) newly diagnosed and untreated stage 1 and stage 2 hypertension with diabetes, (iv) uncontrolled stage 1 and stage 2 hypertension with diabetes. Blood pressure levels at baseline

were classified as stage 1 or stage 2 hypertension as per the Seventh Report of the Joint National Committee for Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC VII) classification.

Intervention

Ambulatory patients recruited in the usual clinical practice setting when diagnosed with hypertension at each monthly examination were given FCPI, and as per the follow-up monthly visit. When hypertension was newly diagnosed, the patient was told to take FCPI daily. If hypertension was uncontrolled, whatever the BP, the patient was told to stop from his or her current antihypertensive agent and then switch to FCPI, or continued his or her current antihypertensive treatment and plus daily FCPI as added-on therapy. Patients with uncontrolled hypertension receiving thiazide diuretics were switched to FCPI. In patients with uncontrolled hypertension receiving other antihypertensive drugs, addition of FCPI was voluntary. All antihypertensive medication, past and present, was recorded. No other antihypertensive agents were allowed during the 3-month safety monitoring to avoid possible additional BP-lowering effects.

Assessment

Our BP target was $\leq$140/90 mmHg, or 130/80 mmHg in diabetics, as stipulated in the JNC VII guidelines. BP (average of three measurements) was determined with the patient in the seated position, as defined in the JNC VII guidelines, using a calibrated manual sphygmomanometer, at baseline and at the follow-up visits at months 1 and 3. If targeted BP was not achieved, patients continued on the same medication until the second and third follow-up visits. Physicians asked patients open-ended questions to establish whether any adverse events had occurred between visits. An adverse event was defined as any experience that resulted in death, required hospitalization or a prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity. Patients were free to withdraw at any time if they experienced adverse effects, and this was recorded as noncompliance. Compliance with treatment was evaluated at each the month 1 and month 3 follow-up visits, by questioning the patient and checking for missed doses.

Statistical analysis

The SPSS Program version 13 was used for analysis of short-term efficacy and safety. Data are expressed as mean (SD), number and proportion of patients (%). The significance of changes in quantitative variables was tested using the one sample *t*-test for difference of mean for both BP reductions (in mmHg) at baseline, during 1 and 3 month follow up respectively. Significant differences were defined as a 95% confidence interval at a p-value of <0.05.

Results

Baseline patient characteristics

Table 1 presents the baseline characteristics of the 476 patients included in the study. There were 187 patients who had stage 1 hypertension (mean BP 144.9/86.1 mmHg) and 245 had stage 2 hypertension (mean BP 168.5/98.7 mmHg). Hypertension was newly diagnosed in 241 patients (50.5%) and uncontrolled in 236 (49.5%). Among hypertensive patients, 192 (40.3%) also had diabetes. Among patients with uncontrolled hypertension, 213 (90.3%) were switched to FCPI and 28 patients (9.7%) were given FCPI as add-on therapy.

Table 1 Baseline patient characteristics

Patient Characteristics	Overall
Numbers of patients	476
Male	257
Female	219
Age average in years (SD)	59.9 (9.9)
Patients with prehypertensive (%)	44 (9.2)
Patients with stage 1 hypertension (%)	
BP criteria (BP) in mmHg $\geq$140-159 / $\geq$90-99	187 (39.3)
Patients with stage 2 hypertension (%)	245 (51.5)
BP criteria (BP) in mmHg $\geq$160 / $\geq$100	
Patients with type 2 diabetes (%)	192 (40.3)
Patients with newly diagnosed hypertension (%)	241 (50.5%)
Patients with uncontrolled hypertension (%)	236 (49.5%)

Effects of FCPI treatment on blood pressure

Of the 476 hypertensive patients, baseline BP was 156 (SD 10.6)/92 (SD 9.0) mmHg. Stage 1 hypertensive patients had a mean baseline BP of 145.7 (SD 6.1)/86.1 (SD 6.6) mmHg and stage 2 hypertensive patients had a mean baseline BP of 167.5 (SD 14.4)/98.7 (SD 10.9) mmHg (Table 2). Of these, 44 patients (9.2%) were prehypertensive. All hypertensive patients received FCPI for 3 months. In stage 1 hypertensive patients, BP control was achieved in 86.6% of patients (N=162) by month 3 (129.9 mmHg [SD 5.5]/78.8 mmHg [SD 6.7], and BP reduction was significant at month 1 (12.1/5.7 mmHg [p<0.001]) and at month 3 (15.8/7.7 mmHg [p<0.001]), respectively, compared with baseline. In stage 2 hypertension, BP control was achieved in 88.5% patients (N=217) by month 3 (132.9 mmHg [SD 8.2]/78.8 mmHg [SD 6.7]), and BP reduction was significant at month 1 (25.6/14.1 mmHg [p<0.001]) and at month 3 (34.6/19.9 mmHg [p<0.001]), respectively, compared with baseline (Figures 1 and 2). Overall, blood pressure was below 140/90 mmHg in 74% of patients at month 1.

Table 2 Effects of FCPI treatment on blood pressure

Blood pressure All hypertensive patients	Baseline N = 476	Month 1 N = 432	Month 3 N = 432
Mean SBP mmHg (SD)	156 (10.6)	137.5 (9.6)	131.3 (7.0)
Mean DBP mmHg (SD)	92 (9.0)	82.2 (6.8)	78.5 (6.0)

Blood pressure Stage 1 hypertensive patients	Baseline N = 187	Month 1 N =187	Month 3 N =187
Mean SBP mmHg (SD)	145.7 (6.1)	133.6 (6.7)	129.9 (5.5)
Mean DBP mmHg (SD)	86.1 (6.6)	80.4 (5.7)	78.4 (5.1)

Blood pressure Stage 2 hypertensive patients	Baseline N = 245	Month 1 N = 245	Month 3 N = 245
Mean SBP mmHg (SD)	167.5 (14.4)	141.9 (12.0)	133 (8.2)
Mean DBP mmHg (SD)	98.7 (10.9)	84.6 (7.9)	78.8 (6.7)

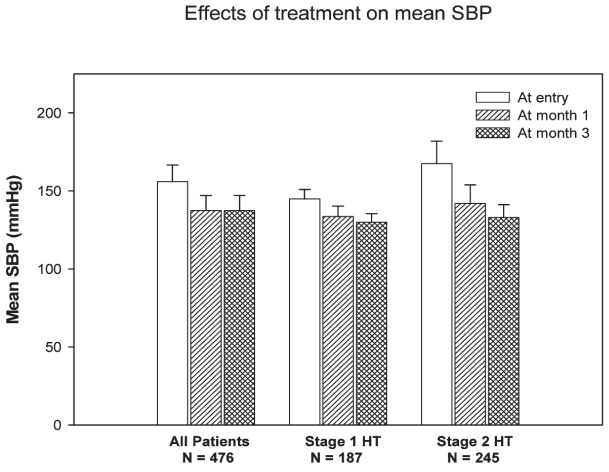

Figure 1 Effects of a FCPI on mean SBP

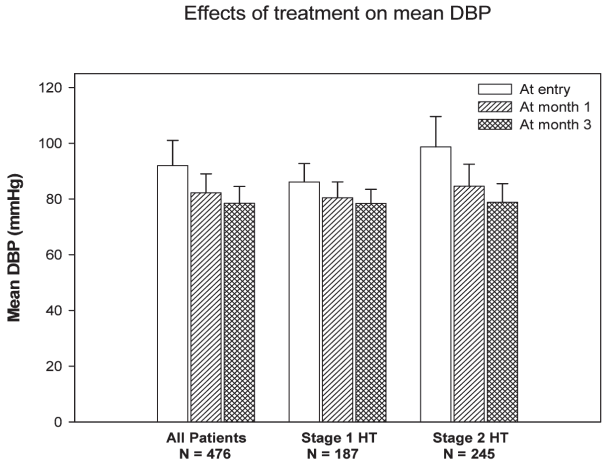

Figure 2 Effects of a FCPI on mean DBP

During 3 months period of the treatment, adverse drug reactions reported by patients included dry cough 0.2% (N=1), dizziness 0.2% (N=1) and hypokalemia 0.2% (N=1).

Discussion

Hypertension and its cardiovascular risks are preventable as well as treatable. The long-term clinical benefits of antihypertensive treatment are encouraging. In spite of the availability of a variety of classes of antihypertensive drugs, most hypertensive patients need two or more drugs to control BP to target level. The angiotensin-converting enzyme inhibitor perindopril is well established in its class with an extensive series of landmark trials. Indapamide is an established diuretic of excellent tolerability whose clinical efficacy as the antihypertensive of choice in very elderly hypertensives was well documented.[6,10] Although some adverse reactions concerning the use of FCPI has been reported such as dry cough and hypokalemia[9,11], no impact on the safety profile of perindopril/indapamide had been noted. In this study, the most frequent adverse events reported by the patients (0.2%) were dry cough, dizziness and hypokalemia. There is then a good rationale for using a fixed-dose combination of perindopril (4 mg) and indapamide (1.25 mg). Our findings confirm that treatment of hypertension with a fixed-dose combination of perindopril/indapamide is effective, safe and well tolerated and should be considered an alternative treatment of choice for all hypertensive patients.

Conclusion

Post-marketing surveillance in the context of safety monitoring shows that a fixed-dose combination of perindopril/indapamide (4/1.25 mg) is an effective antihypertensive for all types of primary hypertension, whatever the risk factors, especially in patients with diabetes. It effectively lowers BP in both for stage 1 and stage 2 hypertension, and is a promising antihypertensive of choice for both newly diagnosed and uncontrolled hypertension. It is well tolerated and rapidly controlled BP in this 3-month safety monitoring program in Thai hypertensive patients.

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