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A DOSE-RESPONSE STUDY OF PERINDOPRIL IN ITS HYPOTENSIVE EFFECTS ON BLOOD PRESSURE 6 AND 24 H AT THE TROUGH

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ABSTRACT

Angiotensin-converting enzyme (ACE) inhibitors have achieved wide acceptance in the treatment of hypertension both as monotherapy and in combination with other agents. The antihypertensive effects of different doses of perindopril were compared using a randomized placebo-controlled parallel design. All patients initially entered a four-week single-blind placebo run-in period. The mean supine diastolic blood pressure was between 95 and 114 mmHg. After four weeks, patients were randomized to 12 weeks of therapy with perindopril 2, 4, 8 or 16 mg or matching placebo, each given once daily in the morning. Patients were seen weekly for four weeks and then every two weeks for the last eight weeks of the double-blind phase.

Of a total of 508 patients entered into the study, 249 were eligible for randomization to perindopril 2, 4, 8 or 16 mg or placebo at the end of the four-week placebo run-in period. All five groups (perindopril 2, 4, 8 and 16 mg and placebo) had similar characteristics at baseline. Randomization of patients to four different doses of perindopril or to placebo resulted in similar mean supine and diastolic blood pressure values at baseline for each subgroup. At the four visit, perindopril 2 mg once daily significantly ($P<0.05$) lowered diastolic blood pressure versus baseline 24 h after tablet administration. Doses of perindopril 4 mg daily or greater also lowered blood pressure significantly ($P<0.05$) more than did placebo (Table 2). Doses of perindopril up to 8 mg caused a progressive decrease in placebo-corrected blood pressure at 24 h, with changes at the 16 mg dose exerting no additional effect.

Changes in blood pressure at 6 h, the time of perindopril's peak antihypertensive effect, were similar in magnitude to those noted at 24 h. Perindopril 2 mg significantly reduced diastolic blood pressure versus baseline, with higher doses up to 8 mg daily causing a further reduction in diastolic blood pressure, which was significantly different from placebo.

INTRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors have achieved wide acceptance in the treatment of hypertension both as monotherapy and in combination with other agents. Current national and international guidelines for treating uncomplicated essential hypertension recommend ACE inhibitors either as second-line therapy after thiazide diuretics and beta-blockers or as alternate first-line monotherapy under special circumstances[1-3]. Unlike many other antihypertensive agents, ACE inhibitors tend to have a similar side effect profile at both lower and higher doses. The one exception may be captopril, which was associated with dose-related adverse effects including skin rash and dysgeusia presumably as a consequence of the sulfhydril moiety in its chemical structure. When ACE inhibitors are used as alternate first-line therapy, patients are often unable to take thiazide diuretics or beta-blockers because of biochemical abnormalities or concurrent conditions. In such instances, it would be advantageous to achieve the maximum antihypertensive effect from ACE inhibitor monotherapy.

Lees[4] has reported the dose-response relationships of various ACE inhibitors based upon a review of the literature. For some drugs such as captopril and benazepril, recommended doses appear to lie at the top of the dose-response curve, whereas for others the doses are on the more linear part of the curve. The review of the available data provides only preliminary information for some agents because proper parallel design dose-response studies have not always been performed. For example, Lees[4] reported that perindopril exhibited a linear dose-response relationship at the time of its peak and trough effects. However, the data were based primarily on studies in normotensive subjects or in small numbers of hypertensive patients.

Thus, we do not yet know whether high dose perindopril monotherapy provides an additional antihypertensive effect beyond that achieved by currently recommended doses. Accordingly, the present study was undertaken to examine the dose-response characteristics of perindopril over an eightfold dose range with data being collected during both peak and trough antihypertensive effects of the drug.

PATIENTS AND METHODS

Study design: The antihypertensive effects of different doses of perindopril were compared using a randomized placebo-controlled parallel design. All patients initially entered a four-week single-blind placebo run-in period. The mean supine diastolic blood pressure was between 95 and 114 mmHg. After four weeks, patients were randomized to 12 weeks of therapy with perindopril 2, 4, 8 or 16 mg or matching placebo, each given once daily in the morning. Patients were seen weekly for four weeks and then every two weeks for the last eight weeks of the double-blind phase. Patient population: Patients 18 years of age and older of either sex were eligible for entry if their mean supine diastolic blood pressure was between 95 and 114

mmHg off antihypertensive therapy. Patients with any of the following were excluded from participation: secondary cause for hypertension; presence of clinically important cardiac, renal or hepatic disease; history of myocardial infarction, congestive heart failure or stroke within the previous six months; drug or ethanol abuse; poorly controlled diabetes mellitus; collagen vascular disease; concurrent use of antipsychotic or major tranquillizer therapy; or any serious concurrent illness that would affect participation in the study. Eligible patients were free of any known sensitivity to ACE inhibitors and were not receiving any medication that might affect blood pressure. Written informed consent was obtained from all participants before enrolment.

Of a total of 300 patients entered into the study, 249 were eligible for randomization to perindopril 2, 4, 8 or 16 mg or placebo at the end of the four-week placebo run-in period. All five groups (perindopril 2, 4, 8 and 16 mg and placebo) had similar characteristics at baseline (Table1).

Table 1: Characteristics of all patients randomized to perindopril or placebo therapy

	Total (n=249)	Placebo (n=50)	2 mg (n = 50)	Treatment group Perindopril 4 mg (n=49) 8 mg (n=48)		16 mg (n=52)
Sex						
Male	138	25	30	30	25	30
Female	111	25	20	20	23	22
Age		53±2	51±2	56±2*	51±2	51±2
Weight						
Male		98±3	89±2	91r2	92±2	95-3
Female		82±4	77±4	79r3	82±3	83±3

*Statistically significantly greater (P<0.05) than each of the other treatment group means. Age and weight data are mean ± SEM.

Procedures: Before entry, all patients received a complete evaluation including history taking and physical examination, electro-cardiogram, urinalysis, and hematological and biochemical laboratory tests to exclude any clinically important underlying medical conditions. Blood pressure was measured using a standard mercury sphygmomanometer in triplicate after 10 min of resting in the supine position, with readings taken 2 min apart. The primary outcome measure was the mean of the three supine blood pressure readings. Korotkoff phase 5 was used to determine the diastolic blood pressure. Blood pressure was measured by specially trained research nurses in the morning before that day's dose of medication in order to obtain the minimum (trough) blood pressure value. Patients were asked to return approximately 6 h after tablet administration for an afternoon blood pressure measurement in order to obtain an estimate of the drug's peak antihypertensive effect. Data analysis: The primary outcome measure was the placebo-corrected change in diastolic blood pressure for each dose of perindopril at 6 and 24 h after tablet administration. Data for changes in systolic blood pressure were also analyzed. End-point data from all eligible patients were included in the efficacy analysis.

Table 2: Mean (± SEM) baseline diastolic and systolic blood pressure (BP) and changes from baseline at first visit for placebo and each perindopril dose group at 6 and 24 h after dosing

	BP at 6 h			BP at 24 h	
Supine diastolic BP	Mean BP at baseline	Change at final visit	Mean BP at baseline	Change at final visit	BP ratio (24:6 h)*
Placebo	99.6 ±0.6	-4.8*	99.5 ±0.9	-1.8	
Perindopril					
2mg	100.4 ±0.6	-7.2*	99.3 ±0.9	- 4.5*	1.00
4 mg	99.8 ±0.6	- 8.4**	101.2 ±0.7	- 5.9**	1.00
8 mg	100.1 ±0.7	- 11.1**	100.2±0 .7	-7 9**	0.97
16 mg	99.1 ±0.6	- 12.2**	100.0 ±0.7	-7 3**	0.74
Supine systolic BP					
Placebo	153.8 ±2.3	- 2.9	151.5 ±2.5	- 0.7	
Perindopril					
2 mg	154.7 ±2.1	-7.5*	153.6 ±2.5	- 2.7	0.43
4 mg	154.1 ±2.1	- 9. 2**	153.8 ±2.1	- 4.7*	0.63
8 mg	153.0 ±2.1	-15. 9**	152.5 ±2.0	- 11.2* *	0.81
16 mg	154.6±1 .9	- 15.5**	154.2 ±2.0	- 9.6**	0.71

'Ratio of placebo-corrected reduction in BP at 24 versus 6 h; *Significant change from baseline (P<0.05); **Significant change from placebo (P<0.05)

Differences among treatment groups in baseline values or changes from baseline for continuous variables were analyzed using two-way analysis of variance. Pair wise comparisons with placebo were by Dunnett's test. Categorical data were analyzed using the x2 statistic. All

data are expressed as mean ± SEM. $P<0.05$ was denoted as the minimum level of statistical significance.

RESULTS

Randomization of patients to four different doses of perindopril or to placebo resulted in similar mean systolic and diastolic blood pressure values at baseline for each subgroup (Table 2). At the final visit, perindopril 2 mg once daily significantly ($P<0.05$) lowered diastolic blood pressure versus baseline 24 h after tablet administration (Table 2). Doses of perindopril 4 mg daily or greater also lowered blood pressure significantly ($P<0.05$) more than did placebo (Table 2). Doses of perindopril up to 8 mg caused a progressive decrease in placebo-corrected blood pressure at 24 h, with changes at the 16 mg dose exerting no additional effect (Table 2).

Changes in blood pressure at 6 h, the time of perindopril's peak antihypertensive effect, were similar in magnitude to those noted at 24 h (Table 2). Perindopril 2 mg significantly reduced diastolic blood pressure versus baseline, with higher doses up to 8 mg daily causing a further reduction in diastolic blood pressure, which was significantly different from placebo (Table 2).

Placebo-corrected changes in systolic and diastolic blood pressure (BP) 6 and 24 h after tablet administration on the final visit are shown in (Table 2) for perindopril at doses between 2 mg and 16 mg once daily. Significant ($P<0.05$) change in BP from baseline placebo. Progressive decreases in systolic blood pressure were also seen up to the 8 mg dose.

At both 6 and 24 h post-dosing, perindopril 16 mg did not exert any additional antihypertensive effect compared with the 8 mg dose. At the final visit, perindopril 16 mg reduced blood pressure at 6 and 24 h by 15.5/12.2 and 9.6/7.3 mmHg, respectively, compared with reductions of 15.9/11.1 and 11.2/7.9 mmHg at 6 and 24 h, respectively, after the 8 mg dose. There were no differences in the placebo-corrected changes in blood pressure after perindopril 8 mg versus 16 mg with the exception of the diastolic blood pressure at 6 h, which was 1.1 mmHg greater after perindopril 16 mg versus perindopril 8 mg. Placebo-corrected changes in mean supine blood pressure for each dose at 6 and 24 h are shown in (Table 2). Similar reductions in blood pressure were noted for perindopril 2, 4 and 8 mg, with the ratio of changes in the primary outcome measure, diastolic blood pressure, at 24 h (trough effect) versus 6 h (estimated peak effect) being 1.0, 1.0 and 0.97 for perindopril 2, 4 and 8 mg, respectively (Table 2). Perindopril 16 mg exerted a somewhat greater effect on blood pressure at 6 h versus 24 h, with the ratio being 0.74. The ratio of changes in systolic blood pressure at 24 to 6 h for perindopril 2, 4 and 8 mg was 0.43, 0.63 and 0.81, respectively.

DISCUSSION

This dose-response study of perindopril in patients with mild to moderate essential hypertension clearly demonstrates a linear relationship between the dose of perindopril and the reduction in blood pressure over the range of 2 mg to 8 mg once daily. Increasing the dose of perindopril further to 16 mg once daily provides no additional depressor response, with placebo-corrected decreases in trough blood pressures not significantly different at 16 mg versus 8 mg. These findings differ from data reported in the review by Lees (3), which noted a linear dose-response relationship for perindopril from 2 mg to 16 mg daily. In contrast, Chrysant et al [4] showed little additional effect for perindopril 16 mg versus 8 mg on trough blood pressure in a forced dose-titration study with perindopril given either once or twice daily.

In the present study, we examined the blood pressure responses to increasing doses of perindopril using a randomized, parallel study design at both 6 and 24 h after dosing. The time of the peak effect at 6 h is based upon several studies[5-7] showing maximum ACE inhibition between 4 and 8 h. Similarly, Luccioni et al. [8] reported that the maximum decrease in blood pressure with perindopril occurs between 6 and 7 h, whereas Lees and Reid[7] found the maximum depressor response between 4 and 8 h. These findings suggest that the maximum antihypertensive effect of perindopril generally occurs about 6 h after dosing. It would have been preferable to obtain either repeated office readings over the first 12 h or 24 h ambulatory blood pressure recordings in order to determine the precise time of maximum effect for each individual patient.

From our data, it is evident that perindopril reduces the diastolic blood pressure after both 6 and 24 h equally over the dose range between 2 mg and 8 mg daily. Over the recommended dose range of perindopril, between 4 mg and 8 mg once daily, the placebo-corrected ratios of changes in blood pressure after 24 versus after 6 h were 1.0 for the diastolic blood pressure. The ratios of 0.63 and 0.81 for perindopril 4 mg and 8 mg for systolic blood pressure are slightly less. Overall, the reductions in blood pressure following perindopril 8 mg and 16 mg were of a similar magnitude. Thus, perindopril appears to exert a similar decrease in blood pressure at the time of its maximum ACE inhibition compared with the end of the dosing interval, particularly

at recommended doses of 4 mg and 8 mg once daily. Increasing the dose further to 16 mg does not appear to offer any advantage by Gomez[9].

However, changes in systolic blood pressure with increasing doses of perindopril tend to be more sigmoidal if one compares the effects of the drug at 6 versus 24 h. Using these data, the estimated trough to peak ratio for systolic blood pressure progressively increases to 0.81 for perindopril 8 mg.

As opposed to a recent report by Zannad[10], this double-blind placebo controlled study clearly shows that perindopril at doses between 2 mg and 8 mg once daily maintains consistent blood pressure control at both 6 and 24 h after dosing. Although this study did not employ ambulatory blood pressure monitoring, the reduction in diastolic blood pressure at 24 h was between 97% and 100% of that recorded 6 h after taking the drug, the estimated time of its maximum pharmacologic effect. In contrast, Zannad et al[10] reported trough to peak ratios for perindopril in the range of 30%, but his findings were derived from calculations that do not meet current criteria for estimating trough to peak ratio[9-10].

CONCLUSIONS

Monotherapy with perindopril can achieve clinically useful reductions in blood pressure within a relatively narrow dose range of 4 mg to 8 mg once daily. Similar reductions in diastolic blood pressure were seen at the time of the drug's peak and trough effects. In contrast, systolic blood pressure changes after perindopril, with the ratio of its effects at 6 versus 24 h becoming similar at higher doses. As with previous studies, the higher doses of perindopril were not associated with an increased incidence of adverse effects. To date, very few properly designed studies have examined the 24 h antihypertensive profile of ACE inhibitors (11-13). Forthcoming studies using standardized methodology to assess data derived from ambulatory blood pressure recordings should clarify the extent to which the different ACE inhibitors control blood pressure over a 24 h dosing interval.

Appendix 1. Study sites

Asser central hospital

Abha general hospital

Abha private hospital

Alahly khamis meshat hospital

Saudi German hospital, Abha

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دراسة العلاقة بين الجرعة والاستجابة لعقار البرندوبريل في ارتفاع ضغط الدم ومدي هذا التاثير بعد مرور ٦ ساعات و٢٤ ساعة

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ان كوابح محولات انزيم الانجوتنسين فى علاج ضغط الدم المرتفع وهى حاليا تستخدم كعلاج منفرد او تضاف الى عقاقير اخرى وقد تم مقارنة تاثير الجرعات المختلفة لعقار البرندوبريل باستخدام نظام عشوائى ومقارنته بجرعات خالية من الدواء متوازية مع مجموعات اخرى من المرضى اولاً تم اعطاء جميع المرضى جرعات خالية من الدواء لمدة ٤ اسابيع فاذا كان معدل ضغط الدم الانبساطى بين ٩٥- ١١٤ ملم زئبق فيتم توزيع المرضى للعلاج بالبندوبريل بجرعات ٢و٤و٨و١٦ وخالية من الدواء عشوائيا لمدة ١٢ أسبوع جرعة واحدة يوميا فى الصباح وقد تم متابعة المرضى اسبوعيا لمدة ٤ اسابيع ثم كل اسبوعين بعد ذلك.

هذا ومن ٣٠٠ مريض تم تسجيلهم لهذة الدراسة تم الاستعانة ب ٢٤٩ مريض فقط وقد تميزت المجموعات الخمس بنفس الصفات عند بداية العلاج وكذلك متوسط الضغط الانبساطى والانقباضى

فى الزيارة الأخيرة كانت النتائج كما تلى: جرعة البندوبريل ٢ ملجم مرة واحدة بمقارنة القراءة الأولية قد خفضت ضغط الدم الانبساطى ($p<0.05$) وكذلك جميع الجرعات الأخرى ٤-٨-١٦ خفضت ضغط الدم ($p<0.05$) أكثر من الجرعات الخالية من الدواء وتم ملاحظة أن زيادة الجرعة من ٤ الى ٨ كان لها أكبر الاثر تقدما أما الجرعة ١٦ ملجم فلم يكن لها زيادة فى التاثير. يكون ذروة معدل التغير فى ضغط الدم باستخدام البرندوبريل بعد مرور ٦ ساعات ولكنها كانت متساوية مع القيم التى تم رصدها بعد ٢٤ ساعة.