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ORIGINAL ARTICLE

Antihypertensive efficacy of the ACE-inhibitor perindopril in the elderly

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To assess the antihypertensive efficacy of the angiotensin-converting enzyme (ACE)-inhibitor, perindopril, in the elderly, patients >65 years of age with supine diastolic blood pressure (BP) ⩾90 and ⩽110 mm Hg at the end of a 4-week placebo washout period were treated with perindopril 4–8 mg/daily *vs* placebo using a multicentre, randomised, double-blind, parallel group design. Of the 191 patients entered, 183 completed 8 weeks of double-blind therapy. Average age was 72–73 years. Supine and standing BP at the end of the placebo run-in period were 173/96 *vs* 168/96 mm Hg. BPs were measured in the morning, 20–25 h after the previous day's dose (ie, at the end of the dosing interval). In the placebo group, supine and standing diastolic BP decreased by 3–4 mm Hg, and systolic BP by 6–7 mm Hg. In the perindopril-group, diastolic BP decreased by 6–7 mm Hg and systolic BP by 10–13 mm Hg (both $P < 0.01$ *vs* placebo). These data indicate a substantial placebo response of particularly systolic BP in older hypertensives and indicate the importance of a parallel placebo-group to assess the extent of the actual drug's effect. Perindopril caused additional decreases in diastolic BP by about 2 mm Hg, and in systolic BP by 4–5 mm Hg. The extent of this drug-effect may be less in older *vs* middle-aged hypertensives.
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Introduction

Hypertension in the elderly is no longer considered an 'innocent' consequence of aging. On the contrary, it is now recognised as a powerful determinant of coronary events and stroke. Moreover, large-scale clinical trials have demonstrated that elderly patients actually show the greatest absolute benefits from antihypertensive drug therapy.[1,2] Aging is also associated with changes in a number of control mechanisms involved in cardiovascular homeostasis. These may make the blood pressure (BP) more responsive to diuretics and calcium-antagonists, and less to beta-blockers. Regarding blockers of the renin-angiotensin system (RAS), a decrease in antihypertensive efficacy of ACE-inhibitors or AT_1-receptor blockers in the elderly could be postulated[3] because of the decrease in plasma renin associated with aging.[4] However, a recent review by Israili and Hall[5] concludes 'the BP lowering efficacy of angiotensin-converting enzyme (ACE)-inhibitors is the same in elderly as it is in young patients, despite lower plasma renin activity (PRA)'. However, a number of the studies included in this review had either small sample sizes or reflected open studies without proper placebo-controls. For example, the ACE-inhibitor perindopril has been studied extensively in Europe and North America, is well tolerated[6,7] and demonstrates consistent antihypertensive efficacy over a 24-h dosing interval.[8,9] However, the data on its use in the elderly population is limited to open studies only.[10,11] Accordingly, the present study was designed to evaluate the antihypertensive efficacy of perindopril in an elderly hypertensive population, using a double-blind, placebo controlled, parallel-group design.

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Methods

Patients

Hypertensive men and women, 65 years or older, were eligible to enter a 4-week single-blind placebo washout period. Inclusion criteria included newly diagnosed hypertension or hypertension previously treated with monotherapy or low dose two-drug therapy, and stable renal and hepatic function. Exclusion criteria were limited to recent use of experimental drugs, significant cardiovascular disease, malignancy, a history of substance abuse or mental incapacity. Prior antihypertensive drug therapy was discontinued 1 to 2 weeks before the screening visit after written informed consent had been obtained. The study was approved by research ethics review boards of relevant institutions.

Study design

The study used a multicentre, randomised, placebo-controlled, parallel group design, and was conducted in 15 centres in Ontario, Canada, in 1995/1996. The study consisted of a 4-week single-blind placebo

washout period followed by an 8-week double-blind treatment period. Patients with a supine diastolic BP ⩾90 and ⩽110 mm Hg as well as a supine systolic BP ⩾160 and ⩽220 mm Hg at the end of the 4-week placebo washout period were eligible to be randomised to double-blind treatment with either perindopril 4 mg or placebo, both one capsule daily. After 2, 4 or 6 weeks of double-blind treatment, the dose of study-medication was increased to two capsules in the morning, if the supine systolic or diastolic BP was >160 or 90 mm Hg, respectively. Patients were discontinued from the study, if the diastolic BP increased above 110 mm Hg, or above 105 mm Hg at two visits while taking the highest dose of medication. Study medication was provided in blister cards for each 2-week period. Patients were instructed to take one (or two) capsules in the morning between 07.00 and 09.00, except on the days of their clinic visits, and return the blister card(s) with unused capsules at each visit for assessment of compliance by 'pill-count'.

Patients were seen at 2-week intervals throughout the study, ie, week −4, −2 and 0 of the placebo run-in period, and at +2, +4, +6 and +8 weeks of double-blind treatments. Visits were scheduled between 06.00 and 10.00 in the morning (20–25 h after the previous day's dose). Blood pressures were measured at each visit before that day's dose. In a given patient, the BP was measured by the same person at the same arm (with the highest reading), and the same appropriate cuff size, using a mercury sphygmomanometer. Three BP readings were obtained after a 5-min rest in supine position, and two after standing for 1 min. Average values were used for the statistical analysis. The pulse rate was obtained once in supine and standing positions. Patients were instructed not to talk during this time. Body weight was obtained at week 0 and +8. Possible side-effects were noted at each visit. Laboratory assessments were performed at week −4 and 0 and +8 of the double-blind period.

Sample size and statistical analysis

Assuming a standard deviation of 7.0 mm Hg for changes in supine diastolic BP from baseline, 82 evaluable patients per treatment arm would provide 90% power to detect a difference between treatments of 3.5 mm Hg in the change from baseline in supine diastolic BP using a two-tailed test at $\alpha = 0.05$. To allow for a non-evaluability rate of up to 20%, the goal for enrolment was up to 200 patients.

The primary efficacy parameter for the study was the change in supine diastolic BP from baseline (week 0) to the end of 8 weeks of therapy. Secondary efficacy parameters included the proportion of patients achieving a supine diastolic BP of ⩽90 mm Hg, or a reduction of at least 10 mm Hg, and the change in supine systolic BP from baseline to the last study assessment. Both an intention-to-treat (patients who had entered the double-blind phase) and efficacy (only patients who finished the 8-week double-blind phase) analysis was performed for the primary and secondary efficacy parameters. No meaningful differences were found between the two analyses, and therefore only the intent-to-treat analyses will be presented. Analysis of safety parameters included all patients who received at least one dose of double-blind study medication. Mean changes from baseline were analysed using ANOVA with factors for treatment, centre, and treatment by centre interaction. The latter was not significant for any of the BP measurements. The percent of patients with a diastolic BP <90 mm Hg or with a >10 mm Hg decrease from baseline at the end of treatment and the percent of patients experiencing one or more adverse reactions were analysed using Cochran–Mantel–Haenszel χ^2 controlling for centres.

Results

Patients

A total of 193 patients were randomised, 183 patients completed 8 weeks of double-blind therapy (91 in the placebo-arm *vs* 92 in the perindopril-arm). Of the 193, 191 were included in the statistical analysis with two patients being excluded from the efficacy analyses: one patient had no BP measurements after the placebo run-in period and another patients was not eligible (BP 176/89 mm Hg at the end of the placebo run-in period).

General characteristics for the 191 patients are shown in Table 1. The treatment groups were comparable for age, height, weight, gender and race. The mean age was 72–73 years, about 65% of the patients were female and 80% were white. Most patients took antihypertensive drug therapy before entering the study.

Baseline blood pressures

As shown in Table 2, consistent with the age of the patient-population, clear systolic hypertension was present with more mild diastolic hypertension at the

Table 1 General demographic characteristics of patients randomised to the double-blind treatment phase of the study

	Placebo		*Perindopril*	
	No.	*mean ± s.d. or %*	*No.*	*mean ± s.d. or %*
Age (years)	95	72.4 ± 5.5	96	72.8 ± 5.3
Height (cm)	97	163 ± 9	95	163 ± 9
Weight (kg)	97	65 ± 13	96	67 ± 12
Gender				
female	63	65	62	65
male	34	35	34	35
Race				
white	79	81	78	81
black	14	14	17	18
other	4	4	1	1
Prior antihypertensive therapy	96	99	91	95

Demographic information was collected at the screening visit. Some information was not collected for some patients, and number of patients may therefore vary.

Table 2 Supine and standing blood pressure (mm Hg) at the end of the placebo run-in period and end of double-blind treatment period

	Placebo-group (n = 95)		*Perindopril-group (n = 96)*	
	End of placebo run-in	*End of double-blind placebo*	*End of placebo run-in*	*End of double-blind active*
Supine				
systolic BP	173 ± 10.6	165 ± 14.7	173 ± 10.7	160 ± 15.5
diastolic BP	96 ± 4.8	92 ± 8.3	96 ± 4.7	90 ± 8.1
Standing				
systolic BP	168 ± 13.8	161 ± 15.4	167 ± 13.6	158 ± 16.6
diastolic BP	96 ± 6.2	93 ± 8.7	96 ± 7.1	90 ± 9.1

Values are mean ± s.d.

end of the 4-week placebo run-in period. The two treatment groups were very close for all BP parameters.

Double-blind treatment

Most patients were titrated up to two capsules daily. This occurred in up to 80% of patients on placebo and 66% in patients on perindopril ($P \leqslant 0.05$ at week +6 and +8). All patients, except two, were compliant with dosing instructions. These two (one placebo and one on perindopril) stopped taking double-blind medication between weeks +2 and +4. Compliance as assessed by counts of medication dispensed and returned at each visit ranged from 85 to 109%, and averaged around the 95% for the two groups.

Figure 1 shows the changes in systolic and diastolic BP for perindopril *vs* placebo. Perindopril was significantly more effective than placebo in decreasing supine BP, both diastolic and systolic at all visits on double-blind treatment. For the standing BP, this was also the case for the diastolic BP at weeks +6 and +8, but not for the systolic BP. Sub-analysis based on gender or on race showed similar patterns of changes in females *vs* males and whites *vs* non-whites (data not shown).

Successful treatment, defined as supine diastolic BP <90 mm Hg or >10 mm Hg decrease from baseline at end of treatment was significantly ($P = 0.014$) higher on perindopril (58/96 = 60%) compared to placebo (42/95 = 44%).

Possible side effects were reported by 34% of placebo patients and 47% perindopril patients during the single-blind placebo washout period and by 54% and 50% respectively during the double-blind period. The type and severity and the side effects were similar between treatments, except for cough, reported by 13% of patients on perindopril *vs* 2% on placebo. Three patients in each treatment arm discontinued the study due to adverse events, which did not appear study-drug related. One patient (71 year old female) who had been on perindopril during the study, and subsequently was re-started on indapamide 2.5 mg once daily, was admitted to hospital 8 days later and a CT scan showed a large communicating artery aneurysm, a left frontal intracerebral haematoma and an acute left subdural haematoma. She died the next day.

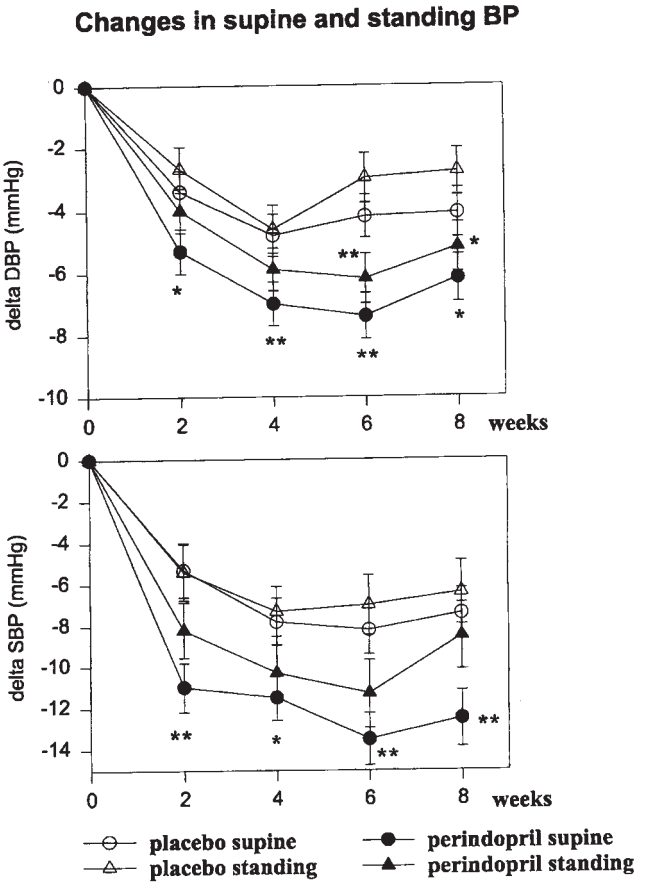

Figure 1 Changes in supine and standing systolic (bottom panel) and diastolic (top panel) BP at trough (ie, at the end of the dosing-interval) during 8-week double-blind treatment on placebo *vs* perindopril. Values are means ± s.e.m. Last BP values were carried forward. $^{*}P < 0.05$, $^{**}P < 0.01$ for change in BP on placebo *vs* perindopril.

Laboratory screening showed no changes in haematology, serum electrolytes, lipids or urinalysis during the study. Serum creatinine showed a small increase (+0.8 ± 7.5 μmol/L) on perindopril *vs* a

small decrease (–2.3 ± 8.9 μmol/L) on placebo, *P*-value = 0.012 for the difference.

Discussion

The benefits of antihypertensive drug therapy in the elderly for decreasing cardiovascular morbidity and mortality have become increasingly apparent in the past decade. Diuretics are generally recommended as the first approach to the treatment of older hypertensive patients.[12] However, in many patients a diuretic is either not sufficient for BP control, or causes side effects. Open-label studies or studies without a proper placebo-control group will generally overestimate the actual extent of the antihypertensive effect. In the present study, during the double-blind period placebo caused clear decreases in systolic (7–8 mm Hg) as well as diastolic (4–5 mm Hg) BP. In other recent studies[9,13,14] using a similar study-design in middle-aged patients (mean age 50–55 years) and less systolic hypertension (150–155 mm Hg) the placebo response for the diastolic BP (2–5 mm Hg) was fairly similar as observed in the present study, but clearly less (2–4 mm Hg only) for the systolic BP. Both older age and the more marked systolic hypertension may contribute to a larger placebo-response of the systolic BP. In a recent VA Cooperative study, older subjects showed a 38% response rate to placebo, *vs* 23–27% in younger subjects.[15]

ACE-inhibitors are in general well tolerated, and in many double-blind, placebo-controlled trials, perindopril has been shown to lower BP of middle-aged to older patients.[9,13] However, the mechanisms controlling BP change with aging, and the extent of such BP lowering cannot be assumed to be similar in the older hypertensive population. Relative to baseline, perindopril as monotherapy lowered diastolic BP by about 6 mm Hg, and systolic BP by about 10–11 mm Hg, similar to decreases caused by, for example, quinapril in older hypertensives.[16] Correcting for the placebo-response, perindopril still lowered systolic and diastolic BP significantly, but the magnitude is clearly less: the actual drug effect at the end of the dosing interval amounted to decreases in diastolic BP by about 2 mm Hg, and in systolic BP by 4–5 mm Hg. These decreases are statistically significant with the sample size of 90–95 patients/treatment arm and are clinically significant relative to outcome. However, the magnitude of the antihypertensive effect of perindopril in this older population (average age 72 years) appears to be substantially less than previously observed in a middle-aged population (mean age 50–55 years) showing placebo-corrected decreases of 6 mm Hg in diastolic BP and of 10 mm Hg in systolic BP for perindopril[9,13] or the AT_1-receptor blocker, irbesartan.[14] The latter studies used a similar study-design as the present study and studied 60–140 patients/treatment arm. These findings may therefore indicate that older hypertensives indeed exhibit smaller placebo-corrected antihypertensive responses to blockers of the RAS than middle-aged subjects. It is likely that older hypertensives will respond better in combination with a diuretic,[17] making the BP more renin-dependent. Further studies including a placebo-arm and appropriate numbers of both middle-aged and older hypertensives are clearly important in this regard.

Over the 8-weeks of double-blind treatment, placebo and perindopril were equally well tolerated, and the only relevant side effect attributable to perindopril was a cough in 13% of patients (*vs* 2% on placebo).

In summary, the present double-blind, placebo-controlled study shows a significant antihypertensive effect of placebo, and additional effect of perindopril in an elderly population. The extent of this effect may be less than observed in middle-aged hypertensives.

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Appendix I

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