Twenty-Four-Hour Ambulatory Blood Pressure Monitoring Efficacy of Perindopril/Indapamide First-Line Combination in Hypertensive Patients: The REASON Study

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Background: Circadian blood pressure (BP) measurements provide more information on hypertensive complications than office BP measurements. The purpose of this study was to analyze the efficacy of the first-line combination of perindopril 2 mg plus indapamide 0.625 mg versus atenolol 50 mg on BP parameters and variability over 24 h in patients with hypertension.

Methods: A double-blind, randomized, controlled, 12-month study comparing perindopril/indapamide and atenolol was performed in 201 patients (age 55.0 years) with uncomplicated sustained essential hypertension. Ambulatory BP measurements (ABPM) were done every 15 min over 24 h.

Results: After 1 year of treatment, the decrease in systolic BP was significantly greater for perindopril/indapamide than for atenolol during the entire 24-h period (-13.8 *v* −9.2 mm Hg), the daytime and the nighttime periods ($P < .01$). Diastolic blood pressure (DBP) variations were comparable for the two groups (−7.2 *v* −8.3 mm Hg, NS). Pulse pressure (PP) reduction was also significantly greater for perindopril/indapamide than for atenolol (for the whole 24 h, −6.6 *v* −0.9 mm Hg, $P <$ .001). The through to peak (T/P) BP ratio and the smoothness index were comparable in the two groups for DBP. For systolic blood pressure (SBP), higher values of the T/P ratio (0.80 *v* 0.59) and the smoothness index (1.45 *v* 0.98; $P < .02$) were achieved for the perindopril/indapamide combination than for atenolol.

Conclusions: The perindopril/indapamide first-line combination decreased SBP and PP more effectively than atenolol. Moreover, the BP control effect was smooth and consistent throughout the 24-h dosing interval and BP reduction variability was lower than the one induced by atenolol. Am J Hypertens 2004;17:245–251 © 2004 American Journal of Hypertension, Ltd.

Key Words: Antihypertensive drug treatment, ambulatory blood pressure measurement, blood pressure variability, smoothness index, trough/peak ratio, perindopril/indapamide combination.

Hypertensive subjects are at increased risk for myocardial infarction, heart failure, stroke, peripheral arterial disease, and renal impairment. Blood pressure (BP) fluctuates constantly over time. This variability, either spontaneous or related to exercise or stress, is of major clinical and therapeutic importance. Many studies have confirmed the primary observation by Mancia et al[1] that BP varies more widely in hypertensive

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A list of the participants in the REASON Project is given in the Appendix.

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than in normotensive subjects and that variability contributes to end-organ damage. Similar observations have been made in animal models of hypertension, particularly in strains of spontaneously hypertensive rats.[2]

The relationship between BP variability and the alterations of end-organ damage has been studied in hypertensive patients by Parati et al[3] and Frattola et al.[4] Several investigations have provided consistent evidence of the prognostic value of ambulatory BP monitoring (ABPM) for cardiovascular risk[5–9] and have shown that ABPM is superior to office BP in predicting cardiovascular outcome.[5,7,8] Moreover, nighttime systolic BP (SBP) has been shown to be a better predictor of cardiovascular events than the average daytime BP.[10]

Another goal for innovative antihypertensive drug treatment is not only to reduce BP but also to "smooth" the pressure profile over 24 h and to attenuate BP fluctuations, particularly those related to SBP.[11] Although office BP measurement has been used traditionally for the evaluation of antihypertensive drugs, ABPM has the advantage of providing sensitive and reliable BP evaluations over 24 h.

The combinaton of perindopril 2 mg and indapamide 0.625 mg, which contains one half the dose the angiotensin-converting enzyme (ACE) inhibitor perindopril and one quarter the dose of the diuretic indapamide used for usual treatment, has been shown to be effective as first-line treatment of hypertension and to have a superior antihypertensive efficacy in comparison with atenolol, enalapril, losartan, and irbesartan.[12–19] When compared with atenolol in hypertensive subjects, the perindopril/indapamide combination effected a greater reduction in SBP for the same reduction of diastolic BP (DBP) at both the brachial and central (thoracic aorta) arterial levels.[18,19]

The aim of the present study was to determine whether the first-line combination perindopril/indapamide would be able to control BP, and mainly SBP, over 24 h and to buffer the BP variability assessed by ABPM, in comparison with the β-blocker atenolol used as reference.

Methods

Study Population

The ABPM investigation was an ancillary study of the PREterax in regression of Arterial Stiffness in a contrOlled double-bliNd study (REASON). REASON is a multicenter, controlled, randomized, double-blind, two parallel group study conducted in 13 countries.[18,19] ABPM was carried out only in the centers able to perform this examination (32 of 52). Among the 471 hypertensive patients randomized in REASON, 269 underwent 24-h ABPM. Of the patients, 68 were excluded from the final analysis because of a lack of valid ABPM data before or after 1 year of treatment, as described later here. Finally, 201 patients were analyzed in the ABPM study (perindopril/indapamide group, 107 patients; atenolol group, 94 patients). These 201 patients were from nine countries (France, $n = 52$; Australia, $n = 50$; Spain, $n = 38$; Ireland, $n = 22$; Germany, $n = 16$; Switzerland, $n = 7$; Belgium, $n = 6$; Austria, $n = 5$; The Netherlands, $n = 5$).

The inclusion criteria were uncomplicated essential arterial hypertension ($160 \leq$ SBP < 210 mm Hg or $95 \leq$ DBP < 110 mm Hg) measured in the supine position with a mercury sphygmomanometer without intake of any antidiabetic, cardiovascular, or cholesterol-lowering drugs. Informed written consent was obtained from each patient. The protocol was approved by the Ethics Committees according to national regulations. The study was conducted in accordance with the Declaration of Helsinki.

Treatments

After a 4-week placebo washout period, the patients were randomly assigned to receive either perindopril 2 mg plus indapamide 0.625 mg, or atenolol 50 mg for 1 year. The medication was taken orally each morning. After 3, 6, or 9 months of treatment, the dose could be adjusted according to the conventional BP. In the event of SBP >160 mm Hg or DBP >90 mm Hg, the dose was increased to two tablets each morning. Other antihypertensive drugs were not allowed during the study follow-up.

ABPM

We performed ABPM with equipment validated as class A or B by the protocols of the British Hypertension Society or of the Association for the Advancement of Medical Instrumentation.[20,21]

A cuff size suitable for the patient's arm circumference was selected. The ABPM device was set up during a normal activity day, just before the drug intake (from 8 to 10 AM), at the end of the washout period and after one year of treatment. At the second set-up, the same device was used for a given patient and was installed by the same investigator on the same arm; the difference between the first set-up times did not exceed one hour.

The DBP, SBP, and heart rate (HR) measurements were recorded every 15 min over 24 h and while the patients continued their normal daily activities. To be valid, an ABPM recording had to have at least 48 adequate measurements during 24 h and no more than 1 h of missing data during the day or night.

Efficacy

The mean ABPM-derived SBP, DBP, PP (calculated from individuals values of SBP and DBP), and HR values were calculated for the whole 24-h period, the daytime period (from 7 AM to 10 PM) and the nighttime period (from 10 PM to 7 AM).

Trough (T) and peak (P) BP changes (M12–M0) were calculated by considering the 2-h means of respectively minimal drug efficacy (just before the next dose) or of maximal drug effect. The ratios T/P were then analyzed.[22–25] The T and P were evaluated only in patients who responded to therapy, defined as subjects with a clinic

SBP decrease ≥15 mm Hg or clinic DBP decrease ≥10 mm Hg from M0 to M12.

In addition, the smoothness index (SI) was calculated.[26,27] The SI is equal to $\Delta H/SD_{\Delta H}$, where ΔH is the mean treatment-induced BP reduction for each hour during the 24-h period and $SD_{\Delta H}$ is the standard deviation of that mean. This parameter takes into account all BP measurements over 24 h and integrates their possible fluctuations. For a given BP reduction, a high SI indicates that the treatment decreases the BP with low hourly variations around the mean value. The SI was calculated on the whole population.

The peak efficacy slope (PES, expressed as mm Hg/h) was calculated by dividing the difference between the set-up and the peak values for a given variable by the time to reach peak efficacy (Δ_t). The PES was calculated only for responder subjects as defined previously.

Safety

Safety assessment was based on the incidence of adverse events among all the patients participating to the REASON study.

Statistical Analyses

Data are expressed as mean ± SD or percentages. The comparability of the groups at baseline was assessed with the Student *t* test for quantitative variables and the χ^2 test for qualitative variables. The comparison of variation of BP and heart rate between treatments was performed by ANOVA or the Mann-Whitney *U* test when ANOVA was not valid. The comparison of the smoothness index was assessed with the Student *t* test and the comparison of PES with Kruskal-Wallis test. *P* values $< .05$ were considered to be significant.

Results

Efficacy

Among the 471 patients randomized in the REASON trial,[18,19] 201 were analyzed in the ABPM study (107 in the perindopril/indapamide group and 94 in the atenolol group). The characteristics of the patients assigned to the two arms did not differ significantly for the different parameters considered (Table 1) and did not differ from those of the whole population.[18,19] Dose adjustment was similar in the two treatment groups (51/107 *v* 36/94). More than 70% of dose titration was performed at the 3-month visit. At inclusion, SBP, DBP, PP, and HR measured by ABPM were comparable in the two groups (Table 2).

After 1 year of perindopril/indapamide treatment, the decreases of 24-h SBP, DBP, and PP were significant, without significant reduction in the HR. In the atenolol group, the decreases in 24-h SBP, DBP, and HR were significant but the PP decrease was not significant. Analyses performed on the daytime and nighttime monitoring periods led to the same conclusions (Table 2, Figs. 1 to 3).

Table 1. Characteristics of the patients at inclusion

Characteristic	Perindopril/indapamide (*n* = 107)	Atenolol (*n* = 94)	*P**
Age (y)	53.9 ± 11.4	56.2 ± 13.4	0.20
Range	25–77	26–82	
Sex (male)	70%	67%	0.64
Body mass index (kg/m^2)	26.9 ± 2.8	26.8 ± 2.5	0.62
Office BP (mm Hg)			
SBP	162.1 ± 13.1	160.9 ± 15.3	0.54
DBP	97.8 ± 7.5	97.6 ± 8.1	0.88
PP	64.3 ± 16.2	63.2 ± 17.6	0.66

Values are mean ± SD, unless indicated otherwise.
BP = blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; SBP = systolic blood pressure.
* Student *t* test or χ^2 test.

For the whole 24-h period, the daytime period and the nighttime period, the SBP reduction was significantly greater for the perindopril/indapamide group than for the atenolol group (for the whole 24 h, −13.8 ± 11.9 *v* −9.2 ± 13.2 mm Hg; $P < .01$, respectively). For the three periods, the PP reduction was also significantly greater for the perindopril/indapamide group than for the atenolol group (for the whole 24 h, −6.6 ± 6.6 *v* −0.9 ± 7.5 mm Hg; $P < .001$). The SBP and PP reduction remain significantly different between perindopril/indapamide and atenolol after adjustment on treatment adaptation. The DBP declines were comparable for the two treatment arms (−7.2 ± 7.3 for *v* −8.3 ± 7.8 mm Hg; $P = .30$, respectively). As expected, the HR was lowered significantly by the β-blocker, and not by perindopril/indapamide (−11.0 ± 7.9 *v* 0.4 ± 5.5 beats/min; $P < .001$).

The T/P ratios were calculated for all patients who responded to treatment (as defined under Methods): 90 patients treated with perindopril/indapamide and 78 patients treated with atenolol. For SBP, the efficacy profile was significantly better with perindopril/indapamide than with atenolol, as the T/P ratio was higher (respectively 0.80 and 0.59). In contrast, the T/P ratio was similar between the two groups for DBP (respectively, 0.67 and 0.69; Table 3).

The SI were calculated on the whole population of 201 patients (Table 3). For SBP, the SI was significantly higher with perindopril/indapamide than with atenolol (respectively, 1.45 ± 1.24 *v* 0.98 ± 1.42; $P < .02$). The DBP SI of the two groups did not differ significantly (1.07 ± 1.11 *v* 1.20 ± 1.23; $P = .47$, respectively).

The PES was calculated for all patients who responded to treatment ($n = 168$). The PES was lower with perindopril/indapamide than with atenolol but the difference was not statistically significant (respectively, −3.76 *v* −471 mm Hg/h; $P = .31$). The DBP PES was similar in the two groups (−2.73 *v* −2.70 mm Hg/h; Table 3).

Table 2. Effects of perindopril/indapamide or atenolol on ABPM after 12 months of treatment

Monitoring period (Parameters, mm Hg)	Perindopril/indapamide (*n* = *107*)				Atenolol (*n* = *94*)				
	M0	M12	M12 - M0	*P**	M0	M12	M12 - M0	*P**	*P*†
24h									
SBP	143.7 ± 14.6	130.0 ± 13.7	−13.8 ± 11.9	0.001	143.0 ± 14.9	133.8 ± 16.6	−9.2 ± 13.2	0.001	0.01
DBP	87.9 ± 10.2	80.7 ± 9.7	−7.2 ± 7.3	0.001	86.7 ± 10.0	78.4 ± 9.0	−8.3 ± 7.8	0.001	0.30
PP	55.8 ± 11.7	49.2 ± 9.6	−6.6 ± 6.6	0.001	56.3 ± 12.2	55.5 ± 13.1	−0.9 ± 7.5	0.26	0.001
Day (7 AM to 10 PM)									
SBP	150.4 ± 14.7	135.8 ± 13.4	−14.7 ± 12.4	0.001	149.1 ± 15.0	138.6 ± 16.7	−10.4 ± 13.8	0.001	0.02
DBP	93.0 ± 10.7	85.2 ± 10.1	−7.9 ± 7.4	0.001	91.4 ± 10.9	82.4 ± 9.4	−9.0 ± 8.5	0.001	0.32
PP	57.4 ± 12.3	50.6 ± 10.0	−6.8 ± 7.1	0.001	57.7 ± 12.5	56.2 ± 13.3	−1.5 ± 7.9	0.08	0.001
Night (10 PM to 7 AM)									
SBP	132.5 ± 15.6	120.0 ± 15.0	−12.5 ± 12.8	0.001	132.5 ± 16.2	125.5 ± 18.0	−7.0 ± 13.6	0.001	0.003
DBP	79.4 ± 10.4	73.2 ± 9.9	−6.2 ± 8.5	0.001	78.5 ± 9.9	71.3 ± 9.6	−7.2 ± 8.2	0.001	0.41
PP	53.1 ± 11.2	46.8 ± 10.0	−6.3 ± 7.3	0.001	54.0 ± 12.2	54.2 ± 13.1	0.2 ± 7.8	0.78	0.001

Results are expressed as mean ± SD.

* *P* intragroup Student *t* test.

† *P* intergroup, ANOVA, or Mann-Whitney *U* test when ANOVA was not valid.

M0, M12, months 0 (inclusion) and 12 (end) of the study; other abbreviations as in Table 1.

FIG. 1. Effects (Δ) of the perindopril/indapamide combination versus atenolol on 24-h systolic blood pressure (SBP) measured by ambulatory blood pressure monitoring. **Dotted bars** indicate two hourly means retained for the trough and peak determinations. SI = smoothness index; T/P = trough to peak ratio.

Safety

The incidence of adverse events was similar in both groups. The most classic emergent adverse events were expected in each group, involving tiredness or lethargy (5.1%) and vertigo (3.8%) in the atenolol group, and cough (5.5%) and tiredness or lethargy (3.0%) in the

FIG. 2. Effects (Δ) of the perindopril/indapamide combination versus atenolol on 24-h diastolic blood pressure (DBP) measured by ambulatory blood pressure monitoring. **Dotted bars** indicate two hourly means retained for the trough and peak determinations. Other abbreviations as in Fig 1.

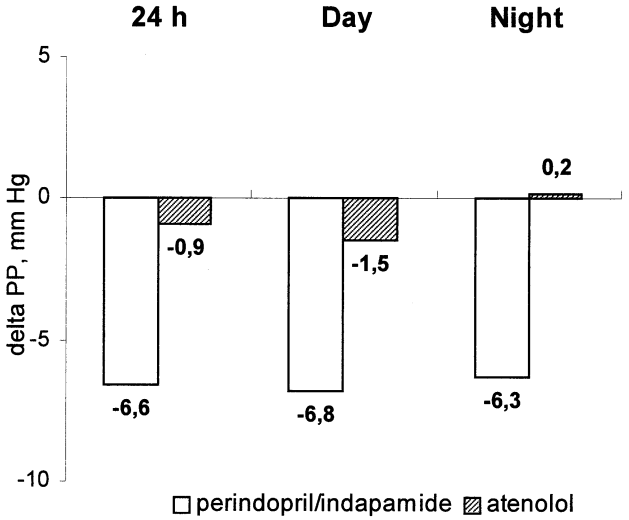

FIG. 3. Effects (Δ) of perindopril/indapamide and atenolol on 24-h pulse pressure (PP).

perindopril/indapamide group. The incidence of hypokalemia (<3.4 mmol/L) was 1.3% with atenolol and 3.0% with perindopril/indapamide. No relevant changes over time were detected for the other laboratory parameters.

Discussion

In the present study, the antihypertensive effects of the perindopril/indapamide first-line combination were compared to those of the β-blocking agent atenolol. After 12 months of perindopril/indapamide treatment, SBP and PP were decreased significantly more during the day, the night, and over 24 h as compared to atenolol. No significant difference was observed for DBP between the two treatments regardless of the period analyzed (entire 24 h, day or night). As would be expected with a β-blocker, the HR was lowered significantly by atenolol but not by the perindopril/indapamide combination. Finally, PP was significantly reduced by the perindopril/indapamide combination during the whole 24 h, whereas it was unaffected by atenolol.

These results from ABPM investigation are consistent with the results from the main REASON study, in which the effects of atenolol and perindopril/indapamide on arterial pressure were assessed by mercury sphygmomanometer measurements.[18] Indeed, in the latter study, a greater decrease in brachial artery SBP and PP was achieved with perindopril/indapamide than with atenolol. A similar finding was also observed using noninvasive central (thoracic aorta, carotid artery) BP measurements.[18,19] Thus, the selective reduction in SBP and PP under the perindopril/indapamide combination was demonstrated using three independent methods of BP measurements (brachial artery using conventional mercury sphygmomanometer, central arteries with noninvasive measurements, and ABPM). Regarding PP, the difference between the two drug regimens could be attributed to specific and independent effect of each regimen on arterial stiffness and wave reflections. More distant reflecting sites or change in the reflective properties of these sites induced by the perindopril/ indapamide combination but not by atenolol might be an explanation for differential patterns of wave reflections with a more substantial reduction of SBP and PP on perindopril/indapamide than on atenolol.[18,19] The combination of the two drugs perindopril and indapamide and not the ACE inhibitor treatment alone was responsible for the selective SBP and PP reduction.[27,28]

The more marked effect of perindopril/indapamide on SBP and PP as compared to the reference treatment merits consideration because SBP and PP in patients >50 years of age are the most relevant mechanical factors predicting cardiovascular risk.[8,10,29–32] The predictive value of PP is known to be superior for ABPM than for clinic PP.[8] The PP measurements are poorly modified by placebo, whatever the device.[33] In the SystEur trial, Staessen et al[34] have shown that an increased nocturnal PP with ABPM is a very sensitive predictor of cardiovascular complications in treated patients. It is noteworthy that the perindopril/indapamide combination in our study was shown to normalize PP even during the nocturnal period.

There is considerable evidence that high BP should be reduced by antihypertensive drug treatment in a smooth and consistent fashion.[3–11] The T/P ratio has been proposed as an index to assess the ability of a drug to induce smooth or irregular BP decreases.[21–23] In our study, the efficacy at trough SBP was significantly better with perindopril/indapamide than with atenolol. The T/P ratio has some limitations, however, particularly with regard to the nongaussian distribution of the values and its poor reproducibility. The latter finding can essentially be explained by the use of only two short segments of the whole recording to calculate the index. Thus, it is possible that the BP measurement retained are more representative of BP fluctuations than of the effect of treatment.

Table 3. Calculated parameters: trough/peak (T/P) ratio, smoothness index (SI) and peak efficacy slope (PES) after 12-month treatment

	Perindopril/ indapamide	Atenolol	*P**
T/P ratio (%)	(*n* = 90)†	(*n* = 78)†	
SBP	80%	59%	NA
DBP	67%	69%	NA
SI	(*n* = 107)	(*n* = 94)	
SBP	1.45 ± 1.24	0.98 ± 1.42	0.02
DBP	1.07 ± 1.11	1.20 ± 1.23	0.47
PES (mm Hg/h)	(*n* = 90)†	(*n* = 78)†	
SBP	−3.76 ± 4.44	−4.71 ± 5.23	0.31
DBP	−2.73 ± 2.96	−2.70 ± 3.18	0.78

Results are expressed as mean ± SD, unless otherwise indicated.

* Student *t* test for comparison of SI; Kruskal-Wallis test for comparison of PES.

† T/P ratio and PES were calculated for responding patients.

NA = not applicable; other abbreviations as in Table 1.

As an alternative to the T/P ratio, the SI has been proposed as a more reproducible measure of the evenness of BP reduction. In addition, the SI has been shown to predict better the regression in left ventricular hypertrophy in treated hypertensive patients than the T/P ratio.[25] In the REASON study it has been shown that cardiac mass was significantly more reduced by perindopril/indapamide than by atenolol.[35] More recently, Rizzoni et al[26] showed the superiority of SI over the T/P ratio for predicting changes of carotid wall thickness during antihypertensive drug therapy. Therefore, the finding that the SBP SI of the perindopril/indapamide group was significantly higher than that of the atenolol group suggests that BP reduction in the former group occurred with fewer fluctuations in BP.

In conclusion, in this 1-year clinical study, the perindopril/indapamide first-line combination decreased SBP and PP more effectively than atenolol. Moreover, with the perindopril/indapamide combination the BP control effect was smooth and consistent throughout the 24-h dosing interval, and variability in BP reduction was less than that induced by atenolol.

Appendix

The REASON project involves the following participants:

Main co-ordinator M.E. Safar (Paris, France).

Ambulatory Blood Pressure co-ordinator J.M. Mallion (Grenoble, France).

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