Spectral analysis of 24 h blood pressure monitoring in the assessment of trough: peak ratio. A randomized, placebo-controlled,

Spectral analysis of 24 h blood pressure monitoring in the assessment of trough : peak ratio. A randomized, placebo-controlled, cross-over comparison of ramipril and enalapril

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Background The ratio between the magnitude of blood pressure reduction during the steady-state dosage interval (trough) and the maximum blood pressure reduction (peak) is an integrated in-vivo index both of the pharmacokinetic properties and of pharmacodynamic activity of an antihypertensive drug. Angiotensin converting enzyme inhibitors are often characterized by a low (often lower than 50%) trough : peak ratio but no direct drug comparisons are available.

Objective To compare the absolute blood pressure reduction and the trough : peak ratio of daily doses of two angiotensin converting enzyme inhibitors, 5 mg ramipril and 10 mg enalapril.

Method After a 1-month wash-out and a 2-week placebo run-in, 25 mild hypertensives aged 47 ± 4 years (17 men and eight women) were randomly assigned to treatments separated by a 2-week interval. Ambulatory blood pressure monitoring was performed and trough : peak ratio was calculated by the fast Fourier transform analysis of placebo-effect-subtracted data.

Results After 1 month of ramipril treatment, 24 h blood pressure decreased from 139 ± 10 to 129 ± 11 mmHg for systolic ($P < 0.05$) and from 89 ± 8 to 81 ± 5 mmHg for diastolic blood pressure ($P < 0.01$). Also enalapril treatment caused a significant 24 h reduction in blood pressure both for systolic (to 132 ± 7 mmHg, $P < 0.05$) and for diastolic blood pressure (to 84 ± 5 mmHg, $P < 0.05$). Placebo caused a 24 h reduction in blood pressure (to 136 ± 8 mmHg for systolic and 87 ± 5 mmHg for diastolic blood pressure, NS, versus wash-out period). The two drugs were equally effective in reducing ambulatory blood pressure, but ramipril produced a trough : peak ratio significantly higher than that with enalapril both for systolic (48 ± 11%, range 34–74%, versus 38 ± 11%, range 21–67%, $P < 0.005$) and for diastolic blood pressure (47 ± 11%, range 30–79%, versus 37 ± 12%, range 21–68%, $P < 0.05$).

Conclusion The low trough : peak ratios could have been due to the daily pattern of blood pressure of mild hypertensives, many of whom are normotensives at night-time, so that the main antihypertensive effect is exerted during daytime rather than during the night or early morning.

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Keywords: blood pressure, trough : peak ratio, antihypertensive treatment, ambulatory monitoring, spectral analysis

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Introduction

The persistence of a blood-pressure-lowering effect rather than merely an absolute reduction in blood pressure, is an important parameter for the evaluation of antihypertensive drug treatments [1,2]. The calculation of the ratio between the magnitude of the blood pressure reduction at the end of the steady-state dosage interval (trough) and the maximum reduction in blood pressure (peak; the trough : peak ratio) was proposed by the United States Food and Drug Administration as an integrated in-vivo index both of the pharmacokinetic properties and of the pharmacodynamic activity of a drug.

However, the methodologic approaches used in the calculation of trough : peak ratios are often questionable and differ from paper to paper, thus also invalidating the comparison among results reported for the same drug. The use of ambulatory blood pressure monitoring, which allows daily changes in blood pressure to be followed, has been questioned mainly due to the lack of standardization of external activities [3]. Other methodologically questionable aspects are the lack of assessment of the circadian fluctuations of the blood pressure profile and of the placebo effect [3,4].

In the present study we calculated the trough : peak ratios for ramipril and enalapril in a randomized, placebo-controlled, double cross-over study using data obtained from ambulatory blood pressure monitoring under well-standardized conditions. To better define the pattern in time of the antihypertensive effect and to obtain a clear definition of the peak effect, smoothing of 24 h blood pressure curves was performed with fast Fourier trans-

form analysis. Enalapril and ramipril are two angiotensin converting enzyme inhibitor drugs whose antihypertensive activity had been demonstrated by previous studies [5,6], but no direct comparison between the trough : peak ratios for these two drugs had previously been performed.

Patients and methods

Subjects investigated

Twenty-five outpatients (17 men and eight women, aged 47 ± 4 years) were recruited from mild hypertensive patients referred to our hypertension unit, who had recently been diagnosed according to Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure criteria [7] or were undergoing wash-out from previous medical treatment. No patients had previously been subjected to ambulatory blood pressure monitoring. Basal blood pressure values were measured in the sitting patients by a physician on two occasions with a 1-day interval between measurements, using a mercury sphygmomanometer according to the recommendations of the American Society of Hypertension [8]. The mean values of the two office measurements of blood pressure were used in the analysis. Patients with a mean office diastolic blood pressure (DBP) in the range 95–110 mmHg after the 1-month run-in phase were enroled and allocated randomly to treatment. Systolic blood pressure (SBP) and DBP at enrolment were 149 ± 12 and 102 ± 4 mmHg, respectively. Patients were excluded from the study if they had angina pectoris, had recently (within 6 months) had a myocardial infarction, had had heart failure, had suffered cerebrovascular accidents, had diabetes, had clinically important renal, hepatic, or hematologic disorders, had secondary hypertension, or had hyperkalemia or hypokalemia. All patients gave their informed consent to participate in the study.

Study design

This study began with a 2-week, single-blind, placebo run-in phase, and then the double-blind treatment phase was performed according to a double cross-over design. After a preliminary 1-month wash-out period (WOP) patients were subjected to two 24 h ambulatory blood pressure monitorings separated by a 2-week interval (WOP1 and WOP2). Patients were then randomly assigned to administration either of 5 mg ramipril or of 10 mg enalapril at 0800 h. After 4 weeks of treatment ambulatory blood pressure monitoring was repeated (treatment A) and the drug discontinued for a 2-week WOP. Patients were then assigned to the other treatment for an additional 4 weeks (treatment B).

Blood pressure monitoring

Blood pressure monitoring was performed using a portable, automatic, noninvasive device (Quiet-track, Welch-Allyn, New Jersey, USA), which measured and recorded blood pressure and heart rate at programmable time intervals [9,10]. Patients arose from bed at 0700 h, monitoring procedure was started at 0800 h and continued to 0800 h of the following morning with blood pressure measurements programmed to occur at 15 min intervals. During the monitoring days patients performed their usual clerical work in the morning and during the first hours of the afternoon, having lunch between 1200 and 1300 h. Then subjects performed recreational activities at home, and had dinner between 1900 and 2000 h. All physical activities (sport, physical work, and car driving) were avoided. Daytime and night-time were taken to be between 0800 and 2300 h and between 2300 and 0800 h, respectively. Data were automatically edited. Briefly, SBP readings greater than 260 mmHg or less than 70 mmHg, DBP readings greater than 150 mmHg or less than 40 mmHg, and pulse pressure readings greater than 150 mmHg or less than 20 mmHg were automatically discarded.

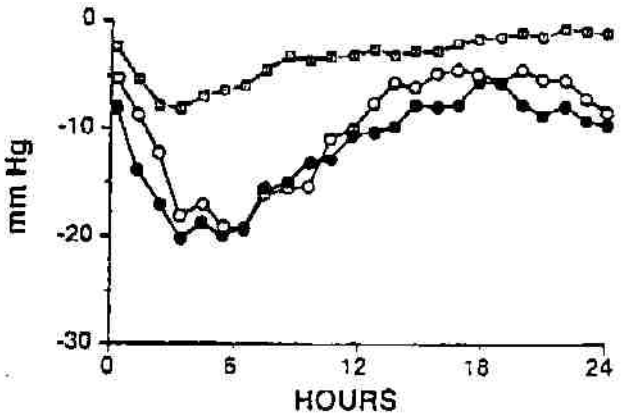
Calculation of the trough : peak ratio

The trough : peak ratio was calculated for both drugs (versus WOP2) and for the placebo effect (WOP2 versus WOP1). Fast Fourier transform analysis of the raw 24 h blood pressure data was performed and a smoothed curve was then plotted. The Fourier transformation was based on complex regression analysis of the curve, which defined the high and low spans over time. An order of five was used to transform the ambulatory blood pressure monitoring data, so that the resulting curve was smoothed but remained mathematically similar to the original one, which could aid the evaluation of peak and trough activities [2] (see appendix). The effects of treatments were calculated by subtracting hourly values from values of corresponding times on the baseline curve (WOP2). The trough response was timed for the end of the dose interval (immediately before the next drug dose). The peak response was sought in a series of blood pressure measurements across the dose interval. The peak effect was measured by averaging measurements obtained during a 2 h period around the time of maximum net reduction of blood pressure. Maximum net reduction was determined by fast Fourier transform analysis. The trough : peak ratio was calculated for each individual patient. To calculate whether a 'placebo' effect is detectable also for 24 h blood pressure monitoring, the same calculation was performed for differences between WOP1 and WOP2.

Statistical analysis

Data are reported as means ± SD. Changes in ambulatory blood pressure monitoring daily curves were assessed by multivariate analysis of variance. Student's paired t test was used to compare the baselines and treatment. Two-tailed P values were used to express the significance of the tests. Comparisons of trough : peak values of the two drugs were performed by using a nonparametric test (Wilcoxon signed-rank test). All tests were performed using BMDP statistical software (BMDP Statistical Software, Los Angeles, California, USA).

Fig. 1



Hourly differences in blood pressure between the ambulatory blood pressure monitorings and ambulatory blood pressure monitorings performed during placebo (□) and active (●, ramipril; ○, enalapril) treatments.

Results

The percentage of valid readings was always higher than 90% for all subjects investigated and no more than one invalid reading hourly was recorded. At the end of the WOP1 (first blood pressure monitoring) the 24 h blood pressure was 139 ± 10 and 89 ± 8 mmHg for SBP and DBP, respectively.

When 24 h ambulatory blood pressure monitoring was repeated (WOP2), 24 h reduction in blood pressure was not significantly changed (136 ± 8 mmHg for SBP and 87 ± 5 mmHg for DBP, NS for both). However, blood pressure values measured during the 2 h immediately after the application of the instruments were significantly lower, so that a sort of 'placebo effect' was detectable (Fig. 1). The peak effect was a decrease by 12.9 ± 2.5 and 6.5 ± 1.3 mmHg for SBP and DBP, respectively, whereas the trough response was absent (increases by 0.9 ± 0.8 and 0.4 ± 0.4 mmHg for SBP and DBP, respectively). The resulting trough : peak ratios for 'placebo' were 6.9 ± 4.8% (range 3–19%) for SBP and 5.7 ± 6.1% (range 0–17%) for DBP (Table 1).

After 1 month of ramipril treatment, 24 h blood pressure decreased to 129 ± 11 mmHg for SBP ($P < 0.05$, versus placebo) and to 81 ± 5 mmHg for DBP ($P < 0.001$, versus placebo). SBP and DBP were significantly reduced both during daytime and during night-time (Table 1). The study of the daily pattern of reduction in blood pressure revealed a time to peak of 5.0 ± 1.6 h with a peak response

Table 1 Ambulatory blood pressure values at the end of the preliminary wash-out, after the 2-week placebo period, and after the two 4-week periods of treatment with ramipril and enalapril

	WOP1	WOP2 (placebo)	Ramipril treatment	Enalapril treatment
Systolic blood pressure				
24 h (mmHg)	139 ± 10	136 ± 8	129 ± 11*	132 ± 7*
Daytime (mmHg)	143 ± 11	142 ± 8	133 ± 11*	136 ± 7*
Night-time (mmHg)	131 ± 12	128 ± 9	123 ± 10*	125 ± 9*
Peak effect (mmHg decrease)				
Versus WOP1		12.9 ± 2.5	22.9 ± 7.3	23.7 ± 9.3
Versus WOP2			19.4 ± 8.1	19.8 ± 9.8
Trough effect (mmHg decrease)				
Versus WOP1		0.9 ± 0.8	9.2 ± 3.5	7.0 ± 3.3
Versus WOP2			8.9 ± 3.6	7.1 ± 3.3
Trough : peak ratio (%)				
Versus WOP1		6.9 ± 4.8	41 ± 9**	30 ± 10
Versus WOP2			48 ± 11**	38 ± 11
Diastolic blood pressure				
24 h (mmHg)	89 ± 8	87 ± 5	81 ± 5**	84 ± 5*
Daytime (mmHg)	94 ± 9	92 ± 5	86 ± 7*	88 ± 6*
Night-time (mmHg)	80 ± 8	79 ± 7	74 ± 5*	77 ± 6*
Peak effect (mmHg decrease)				
Versus WOP1		6.5 ± 1.3	16.7 ± 3.8	16.0 ± 3.9
Versus WOP2			14.7 ± 4.2	14.2 ± 4.8
Trough effect (mmHg decrease)				
Versus WOP1		0.4 ± 0.4	7.0 ± 2.0	4.7 ± 2.1
Versus WOP2			6.8 ± 1.9	4.9 ± 1.8
Trough : peak ratio (%)				
Versus WOP1		5.7 ± 6.1	42 ± 10*	30 ± 12
Versus WOP2			47 ± 11*	37 ± 12
Heart rate (beats/min)				
24 h	84 ± 12	81 ± 14	81 ± 11	81 ± 12
Daytime	85 ± 13	82 ± 15	81 ± 11	81 ± 13
Night-time	82 ± 11	80 ± 14	82 ± 14	79 ± 12

Values are expressed as means ± SD. WOP, wash-out period. *$P < 0.05$, **$P < 0.001$, versus placebo; †$P < 0.05$, ††$P < 0.005$, versus enalapril treatment.

of decreases by 22.9 ± 7.3 and 16.7 ± 3.8 mmHg for SBP and DBP, respectively, and a trough response of decreases by 9.2 ± 3.5 mmHg for SBP and by 7.0 ± 2.0 mmHg for DBP. In comparison with the WOP2, the peak responses were 19.4 ± 8.1 and 14.7 ± 4.2 mmHg for SBP and DBP, respectively, and the trough responses were 8.9 ± 3.5 and 6.8 ± 1.9 mmHg, respectively. The resulting trough : peak ratios were 48 ± 11 (range 34–74) for SBP and 47 ± 11 (range 30–79) for DBP.

Enalapril treatment caused a significant reduction in blood pressure both for the 24 h values (132 ± 7 mmHg for SBP and 84 ± 5 mmHg for DBP, $P < 0.05$, versus placebo for both) and for the daytime and night-time values (Table 1). The maximal reduction in blood pressure occurred 5.0 ± 2.0 h after dosing with peak reductions of 23.7 ± 9.3 and 16.0 ± 3.9 mmHg for SBP and DBP, respectively, and a trough response of decreases by 7.0 ± 3.3 and 4.7 ± 2.1 mmHg for SBP and DBP, respectively. In comparison with WOP2 the peak reductions were 19.6 ± 9.8 mmHg for SBP and 14.2 ± 4.8 mmHg for DBP with trough responses of 7.1 ± 3.3 and 4.9 ± 1.8 mmHg, respectively. Trough : peak ratios were significantly lower than values calculated during ramipril treatment with 38 ± 11% (range 21–67%) for SBP ($P < 0.005$, versus ramipril treatment by Wilcoxon signed-rank test) and 37 ± 12% (range 21–68%) for SBP ($P < 0.05$, versus ramipril treatment).

Discussion

The present findings show that ramipril and enalapril are similarly effective in reducing the 24 h blood pressure but their antihypertensive effects have different durations, ramipril presenting a trough : peak ratio slightly but significantly better than the enalapril one. Present findings confirm also previous observations of an alerting reaction to ambulatory blood pressure monitoring which has to be considered when calculating the placebo effect [11,12].

According to the Food and Drug Administration recommendations an antihypertensive drug should have an effect at trough of at least half of the peak effect (trough · peak ratio > 50%). A very large range of values (30–90%) has been quoted not only for different drugs but also for the same angiotensin converting enzyme inhibitor [13,14]. The disparity of trough : peak ratio values for an individual angiotensin converting enzyme inhibitor in previous studies might reflect a bias in the assessment of one or more of five factors, namely placebo effect, circadian variability, standardized conditions, individual calculations, and multiple blood pressure readings.

A point that is often disregarded is the placebo effect, which does not significantly affect the 24 h mean blood pressure but is particularly evident during the first few hours of the first ambulatory blood pressure monitoring period, such that it could mimic the effect of a mild, short-lasting, hypotensive treatment [11,12]. An accurate assessment of the placebo effect and its subtraction from the peak effect is necessary to correctly calculate the trough : peak ratio [11,12]. A second point that should be considered in the assessment of time response of blood pressure to treatment is daily changes in blood pressure. In fact, blood pressure readings are usually higher, especially for mild hypertensives, during hours of activity rather than during sleep. Thus, because blood pressure continuously changes during the day, the baseline value to calculate peak blood-pressure-lowering effect of a drug administered during the morning should not be considered the value measured before drug administration but rather ought to be dynamically considered in terms of values obtained for the same hours on a separate day during administration of placebo [15]. Furthermore, 24 h blood pressure monitoring has to be performed under standardized conditions to study drug efficacy independently from background factors, such as physical activities, mental stress, and mealtimes, which may modify the daily blood pressure curve regardless of drug treatment. The fourth point is the need to calculate the trough : peak ratio on an individual basis, not only to allow the full range of values to be investigated but also because trough : peak values calculated from individual 24 h curves are usually lower than those calculated from the mean of curves of different patients. The use of mean values, instead of individual data, could lead to underestimation of the peak effect, with consequent overestimation of trough : peak ratios [16]. Finally, the use of multiple blood pressure readings is essential to correctly define the shape of daily blood pressure curves and the times to peak effect [12].

In the present study we tried to avoid all these biases by performing ambulatory blood pressure monitoring under controlled conditions with patients avoiding physical activities in order to exclude circadian variability, and we excluded the placebo effect of repeated ambulatory blood pressure monitoring by performing a preliminary ambulatory blood pressure monitoring session.

The use of fast Fourier transformation to smooth the ambulatory blood pressure monitoring curve allowed a better evaluation of the peak antihypertensive effect [2].

The selected fixed once-daily dosage was chosen on the basis of reports from previous studies that administrations of 5–10 mg ramipril and 10–20 mg enalapril had comparable antihypertensive efficacies [17]. The ranges of trough : peak ratio values observed in the present study for ramipril (30–79%) and enalapril (21–68%) are in the lower range of values recommended by the Food and Drug Administration guidelines, such as have usually been reported also for other angiotensin converting enzyme inhibitors that usually produce a low trough : peak ratio when they are administered once a day [13,16]. In

conclusion, a similar reduction in blood pressure was obtained with both agents but, although statistical comparison of trough : peak ratios between different drugs is unusual [18], ramipril presented a trough : peak ratio slightly better than the enalapril one.

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Appendix

Spectral analysis is employed to discriminate and evaluate different frequencies otherwise not immediately recognizable inside a signal. It basically consists in transforming a signal originated in the time domain, s(t), to a signal, S(f), that is a function of a new variable and vice versa according to the relations

$$S(f) = \int s(t) \exp(-j2ft)\, dt \qquad (1)$$

$$S(t) = \int S(f) \exp(-j2ft)\, df \qquad (2)$$

S(f) represents the Fourier transform of the signal s(t), t is time, and j is square root of −1. Relation (2) in particular allows direct interpretation of the significance of S(f) to be performed. Here s(t) is in fact represented as being constituted by the summation of infinite oscillations, S(f) exp (−j2ft), each with its own proper frequency f and amplitude S(f). The knowledge of S(f), which can be calculated through the relation (1), therefore corresponds to the knowledge of the strength of each frequency component into which the signal can be decomposed. Spectral analysis thus allows periodicities that are not immediately evident in time domain to be recognized in the frequency domain. When the input signal s(t) is known just at equispaced time instants kt, the relation (1) can be written in discrete form as

$$S(n\ f) = s(kt) \exp(-j2knf) \qquad (3)$$

The computer calculation of this formula then embroils one into considering the signal s(t) during a finite period of duration T. For that reason, N=T/t samples of s(t) are available to perform the Fourier transform, and in the frequency dominion N values of the corresponding spectral analysis S(f) are equispaced in the range of $-F_c$ where the sample frequency F_c is equal to 1/t. The frequency resolution f is given by the inverse of the signal length T:

$$f = F_c/N = 1/(Nt) = 1/T$$

In other terms this means that two frequency components of S(t) can not be distinguished if they are closer than 1/T to one another. The contribution to the spectral distribution of all the frequencies included between two consecutive multiplies of f is represented in correspondence of the two frequencies themselves. For example in the cases reported in present paper the blood pressure of each subject was mensured over a 24 h period. Correspondingly, spectral samples were obtained spaced (1/24) h apart. First sample (n = 0), A(0), gives a measure of the signal spectral content at 0 frequency (i.e. of the signal's mean value over the considered time period). The next sample (n = 1), A(1), is proportional to the signal component with a periodicity of 1 day (24 h). It thus gives a measure of the weight of the periodicity of 1 day and, similarly to that, of how the detected pressure values evolve during the observation period. In the present paper the curve was replotted using the first five harmonics.