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ORIGINAL ARTICLE

Lisinopril versus enalapril: evaluation of trough:peak ratio by ambulatory blood pressure monitoring

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In 34 out-patients with essential hypertension, the antihypertensive effect and the trough-to-peak ratios of once-daily enalapril or lisinopril were compared by ambulatory blood pressure monitoring (ABPM) according to a crossover design. The drug dose was titrated and a thiazide diuretic was added if necessary to attain a target office BP of less than 140/90 mm Hg. Both drugs significantly lowered BP but the effect of lisinopril was greater ($P < 0.009$): day- and night-time mean BP fell from 152/98 and 135/84 mm Hg, respectively to 133/85 and 118/74 mm Hg with enalapril and to 129/83 and 116/70 mm Hg with lisinopril. BP goal was reached with an average dose of 18 mg enalapril with 8 mg hydrochlorothiazide and with 17 mg lisinopril combined with 6 mg diuretic. Trough:peak ratio values, which were calculated after Fourier analysis of ABPM data in individual patients, were independent of drug dose. The combination with the diuretic resulted in slightly higher trough:peak ratios than with ACE inhibitor monotherapy, but the difference was not significant. The median trough:peak ratio in patients when using enalapril-based therapy was 0.48 and, when taking lisinopril-based treatment, it was 0.65 ($n = 28$, $P < 0.005$). A significant correlation was found between trough:peak ratio and changes in daytime mean arterial pressure (MAP; Spearman $r = 0.43$) and night-time MAP ($r = 0.66$). When 24-h ABPM was performed starting 24 h after last drug intake, both ACE inhibitors still had a significant antihypertensive effect ($P < 0.001$), which was similar for both drugs. Eleven patients reported minor side effects. Four patients stopped ACE-inhibitor treatment because of cough. The data show that lisinopril has a longer duration of action than enalapril.

Keywords: ambulatory blood pressure monitoring; trough:peak ratio; lisinopril; enalapril; Fourier analysis

Introduction

Enalapril and lisinopril are both moderate-acting angiotensin-converting enzyme (ACE) inhibitors used for the treatment of hypertension. Although various studies have demonstrated that both drugs are effective once-daily antihypertensive agents in similar dose ranges, differences have been observed with regard to duration of action. Plotquin *et al*[1] compared the antihypertensive effect of chronic treatment with once-daily enalapril and lisinopril 10–20 mg by ambulatory blood pressure montoring (ABPM) and estimated that the duration of effect was about 20 h for enalapril and over 30 h for lisinopril. Using ABPM, Enstrom *et al*[2] found no difference in BP-lowering efficacy between the two drugs. In contrast, others have found that 13–24 h after a single 10 mg-dose of both ACE inhibitors, only lisinopril had a BP-lowering effect greater than placebo.[3,4] Plasma renin activity did not predict the responses in either agent.[3–5]

In 1988, the USA Food and Drug Administration (FDA) has suggested that antihypertensive drugs may be licensed for once-daily administration if they provide at least 50% of their maximal BP-lowering effect 24 h after dosing, ie, if their 'trough to peak effect ratio' is at least 0.50.[6] In the absence of guidelines for methodology of trough:peak (T:P) ratio calculation, especially from data obtained from ABPM, different T:P ratio values have been reported for both enalapril and lisinopril.[7–14] Recent studies critically addressing methods of T:P ratio calculation for once-daily antihypertensive agents, indicate that T:P ratios may be dose-dependent and that in individual patients the 0.50 criterion may not be met.[14–19] Recently, we have found that T:P ratios can be reliably calculated from 24-h ABPM data after Fourier analysis with four harmonics.[20] Furthermore, to prevent erroneous T:P ratio values, peak- and trough-effect periods of 2 h each should be used and the peak effect should not be determined within a preset time window.[15,20] In the present study, using a crossover design, the possible differences in magnitude and duration of action of enalapril and lisinopril were further investigated in patients with essential hypertension by choosing the doses on the basis of the office BP response. The doses of the drugs were titrated until an office BP of less than

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140/90 mm Hg was achieved. We used ABPM and curve smoothing by Fourier analysis to calculate individual T:P ratios for both drugs.

Materials and methods

Patients and study design

Patients with essential hypertension, ie, systolic BP (SBP) between 160–200 mm Hg and/or diastolic BP (DBP) between 95–120 mm Hg entered the study. Patients with renal disease (serum creatinine >200 μmol/l) or liver disease, heart failure, angina pectoris or previous myocardial infarction, or secondary hypertension were excluded. Nightshift workers were excluded as well. All previous antihypertensive therapy was discontinued for 2 weeks at which time baseline 24-h BP measurements were made. The patients were then randomised to receive either enalapril 10 mg or lisinopril 10 mg, each administered once-daily for 4 weeks. At week 4, office BP was recorded 3–6 h after drug intake. If BP goal (SBP <140 mm Hg and DBP <90 mm Hg) was not reached, the drug dose was doubled (maximum dose of each drug was 20 mg once-daily). After another 4 weeks, 12.5 mg hydrochlorothiazide (HCTZ) was added if BP still exceeded 140/90 mm Hg. After a further 4-week period, office and ambulatory BP were measured, the latter covering 0–24 and 24–48 h after last drug ingestion. These measurements were made 1–2 weeks apart in random order. After 13–14 weeks, the patients were switched to the alternative drug and the same procedure was followed. The randomised crossover study design ensures that patients act as their own controls (Figure 1). The study was approved by the local Ethics Committee and written informed consent was obtained from all patients. Forty consecutive patients entered the study, five dropped out because their BP before treatment or during the titration phase exceeded preset limits. Finally, one patient dropped out because of protocol violation. Some patients completed the first phase of the study but were unwilling to proceed with the study (see under Results).

Blood pressure measurements and data processing

At each visit, seated office BP measurements were taken three times, with 1–2 min between each reading, after a period of 10-min rest with a conventional sphygmomanometer by a physician who was blinded to the study medication. The three readings were averaged.

ABPM was performed using the SpaceLabs 90207 BP monitor (SpaceLabs Inc, Redmond, WA, USA). Measurements were made every 15 min from 7.00 am to 11.00 pm (daytime) and every 30 min from 11.00 pm to 07.00 am (night-time). The following were automatically discarded: systolic readings <70 and >250 mm Hg; diastolic readings <40 and >150 mm Hg; pulse pressure readings <15 and >150 mm Hg, and heart rate <30 and >200 beats per min. Measurements were made on 'average' week-days and patients were discouraged to engage in excessive activities. They were instructed to rise at 07.00 am, take their medication at 08.00 am, report at the out-patient clinic before 09.00 am, and go to bed at 11.00 pm. Compliance with the instructions was verified by inspecting their diaries.

For the BP recording to be accepted, it had to span the full 24-h period and at least 80% of the readings had to be valid. The standard SpaceLabs software was used to obtain raw data and a Lotus-123 spread sheet program was used for calculation of hourly averages. Furthermore, Fourier analysis with four harmonics was applied to the raw data to obtain smoothed BP profiles.[20] The peak effect was defined as the maximal drop in pressure over any period of 2 h using moving averages. The trough effect was defined as the drop in pressure over the last 2 h before drug administration. The data were then synchronised and the mean pressures before and after treatment were subtracted to determine the peak and trough treatment effects. From these values, T:P ratios were calculated. With this method the maximal T:P ratio value is 1.00. When BP at trough after treatment was higher than at baseline (positive denominator divided by negative nominator), the T:P ratio value was negative. Negative values were converted to zero, indicating that the drug is no longer active.[20]

Statistical analysis

The required sample size was calculated as follows: assuming a clinically important difference in 24-h mean arterial pressure (MAP) of 5 mm Hg (standard deviation [s.d.]: 8 mm Hg) and a difference in T:P ratio of 5% (s.d. 8%) after 12 weeks of therapy

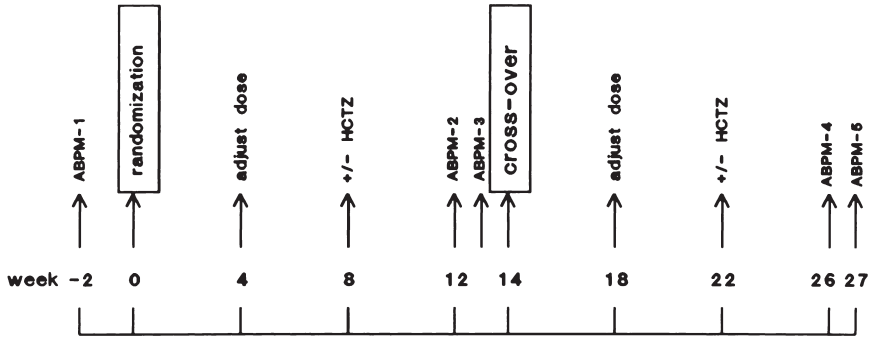

Figure 1 Study design for randomised crossover study of enalapril *vs* lisinopril. ABPM1–5: sequential ambulatory BP monitoring; HCTZ: hydrochlorothiazide.

(power 0.9, significance level 0.05), 14 patients were required on each treatment arm. Taken into account a drop-out rate of 40%, at least 20 patients in each group should be included. BP changes during the indicated periods are given as changes in either systolic, diastolic or MAP from base-line in mean ± s.d. mm Hg. The data were investigated for a period effect, ie, an effect of the order in which treatments were given on their efficacy, using analysis of variance (ANOVA). BP-lowering effects were analysed with respect to response/non-response using McNemar's test and when comparing BP-lowering effects, Student's *t*-test or ANOVA was used. Because of the non-normal distribution, T:P ratios are represented by median values and the 5th and 95th percentile interval (PI), and compared using Wilcoxon's signed rank test or Kruskal–Wallis test. Correlation between BP changes and T:P ratios was performed by Spearman rank correlation test. After separate analysis of the effect of drug dose on T:P ratio, data were pooled and reported as effects of either ACE inhibitor. Thus, unless otherwise stated, the effect of enalapril refers to any enalapril-based therapy, ie, 10 or 20 mg enalapril monotherapy or 20 mg enalapril plus 12.5 mg HCTZ. The same holds for lisinopril-based therapy. Adverse effects were evaluated with McNemar's test. Statistical analysis was performed with the PC-SAS for Windows program (version Orlando l) and SPSS 7.5.4 for Windows. Differences were considered to be statistically significant if $P < 0.05$.

Results

Patients and BP profiles at baseline and follow-up: pooled data

Data sets for both drugs were obtained from 28 patients, one patient completed evaluation of enalapril- and four patients lisinopril therapy only. From each of the latter groups, two patients dropped out because of cough (see below). Two patients discontinued the study without specific reasons. The 34 participants, 18 men and 16 women, were 47 ± 11 years old (range, 29–78 years). From the 18 patients on treatment before onset of the study, five were using an ACE inhibitor, four a beta-blocker, four a diuretic, three a calcium channel blocker and two used a combination of two of these drugs. Prior treatment had no influence on the study variables. At baseline, the office BP averaged 167 ± 18 mm Hg systolic and 104 ± 7 mm Hg diastolic. The 24-h BP were 145 ± 14/93 ± 8 (MAP 111 ± 10) mm Hg. All patients had normal diurnal BP and heart rate variations (night-time at least 10% below daytime values), and this was not affected by therapy (data not shown). Body mass index averaged 27.1 ± 3.2 kg/m^2 in men and 25.3 ± 4.5 kg/m^2 in women. In order to reach BP goal, the highest dose of the ACE inhibitors was needed in 25 out of 29 patients on enalapril and in 24 out of 32 on lisinopril (mean dose 18 *vs* 17 mg, respectively). HCTZ was added to 18 enalapril- and to 15 lisinopril patients. Finally, an office BP of <140/90 mm Hg and a daytime ambulatory BP of <135/85 mm Hg was achieved in 43% of patients when taking enalapril and in 56% when using lisinopril ($P < 0.05$), but 87% of the patients on either drug had an ambulatory daytime MAP of <105 mm Hg. After 12 weeks of treatment, office BP was slightly higher in patients on enalapril than in patients on lisinopril (SBP 143 ± 14 and 137 ± 15 mm Hg, $P = 0.06$; DBP 92 ± 9 and 87 ± 9 mm Hg, $P = 0.08$, respectively). During the trial no period effects were detected. Also, no statistical difference was found when patients who received either drug first were compared to those who received them in the second treatment period.

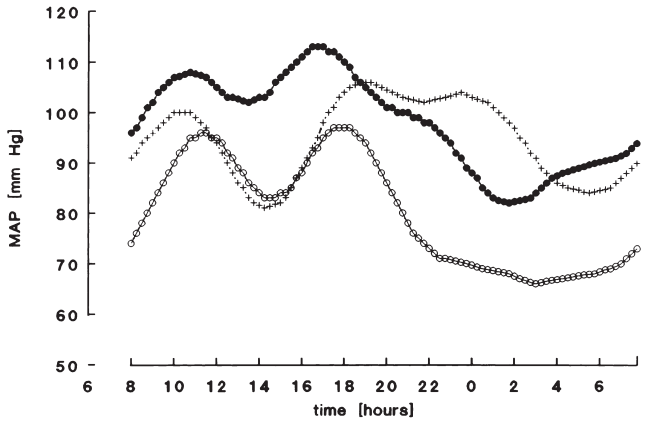

Figure 2 Twenty-four hour mean arterial pressure (MAP) profiles after Fourier analysis in a patient at baseline (●), after 12 weeks of treatment with enalapril (+) and lisinopril (○), respectively.

Typical examples of Fourier-smoothed 24-h BP curves at baseline, and after 12 weeks of enalapril and lisinopril are shown in Figure 2. When BP-lowering effects of both ACE inhibitors were compared in all patients, ie, irrespective of drug dose or addition of diuretic, both enalapril and lisinopril significantly lowered 24-h BP (SBP/DBP/MAP: 127 ± 9/81 ± 7/97 ± 7 and 124 ± 11/78 ± 8/94 ± 8 mm Hg, respectively; $P < 0.001$), but the antihypertensive effect of lisinopril was greater ($P < 0.01$). Also, both daytime and night-time BP were significantly reduced by both drugs (Figure 3, $P = 0.001$) and again, lisinopril was more effective (Figure 3, $P < 0.05$). Similarly, BP reduction at trough (22–24 h

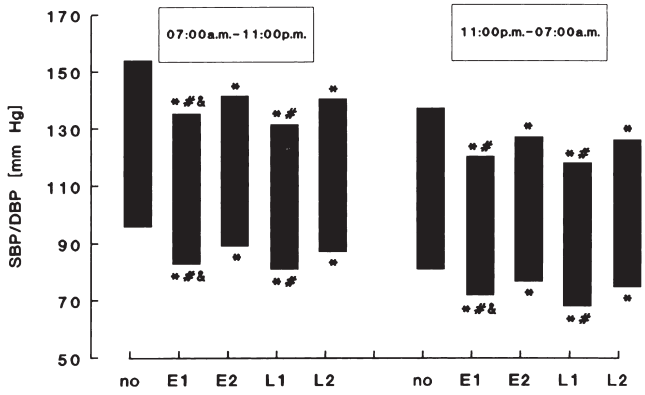

Figure 3 Mean day- and night-time systolic (SBP) and diastolic (DBP) blood pressure in untreated (no) patients and after treatment with enalapril (E) and lisinopril (L). For both drugs, ABPM was performed during 0–24 h (E1, L1) and 24–48 h (E2, L2) after drug intake. *$P < 0.05$ *vs* untreated; #$P < 0.05$ *vs* 24–48 h same drug; &$P < 0.05$ *vs* L1.

post-dose) after lisinopril was greater than after enalapril (–18 ± 13 and –14 ± 15 mm Hg, respectively; $P = 0.06$).

Trough:peak ratio

The frequency distribution of individual T:P ratios for both drugs is shown in Figure 4. Median T:P ratio values were significantly higher for lisinopril than for enalapril (0.65 (PI, 0–0.99) and 0.48 (PI, 0–0.98), respectively; $P < 0.005$). Enalapril, on average, exhibited an earlier maximum BP-lowering effect than lisinopril, although the difference was not significant (time-to-peak: 9 ± 5 h and 11 ± 5 h, respectively).

Figure 5A and 5B show the correlation between T:P ratio and the magnitude of the antihypertensive drug-effect. For both drugs, there was a weak, but significant correlation between the T:P ratio and changes in daytime MAP (Figure 5A; Spearman $r = 0.479$, $P < 0.01$ for enalapril and $r = 0.394$, $P < 0.03$ for lisinopril) but it was highly significant for changes in night-time MAP (Figure 5B; Spearman $r = 0.697$, $P < 0.0001$ for enalapril and $r = 0.630$, $P < 0.0001$ for lisinopril). There was no correlation with absolute BP values.

Although the number of patients is too small for further subgroup analysis, we looked at trough- and peak BP effects, the T:P ratios and the time-to-peak for the two doses of each ACE inhibitor and for combination therapy. These data are listed in Table 1. For enalapril, the number of patients treated with the 10 mg-dose was too small ($n = 4$) to allow definitive interpretation, but interestingly, from this group two patients had T:P ratios of zero, suggesting that the duration of action of the drug(dose) did not span the full 24 h. However, these patients were still classified as responders according to their office BP, which did not necessitate dose adjustment. The two other patients had T:P ratios of 0.57 and 0.91, respectively. This large variation in T:P ratio values explains the low median value. In patients using 20 mg enalapril, all T:P ratio values were greater than zero and the median was 0.46. In the combination group, two patients had T:P ratios of zero and the median was 0.49. Kruskal–Wallis test did not

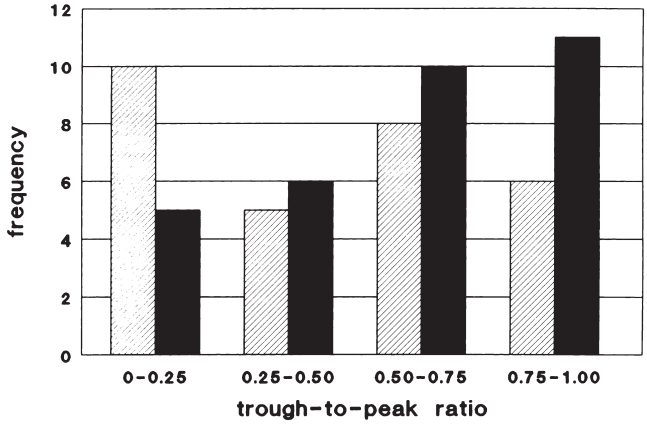

Figure 4 Frequency distribution of trough:peak ratio values for mean arterial pressure after once-daily enalapril (▨, $n = 29$) and lisinopril (■, $n = 32$).

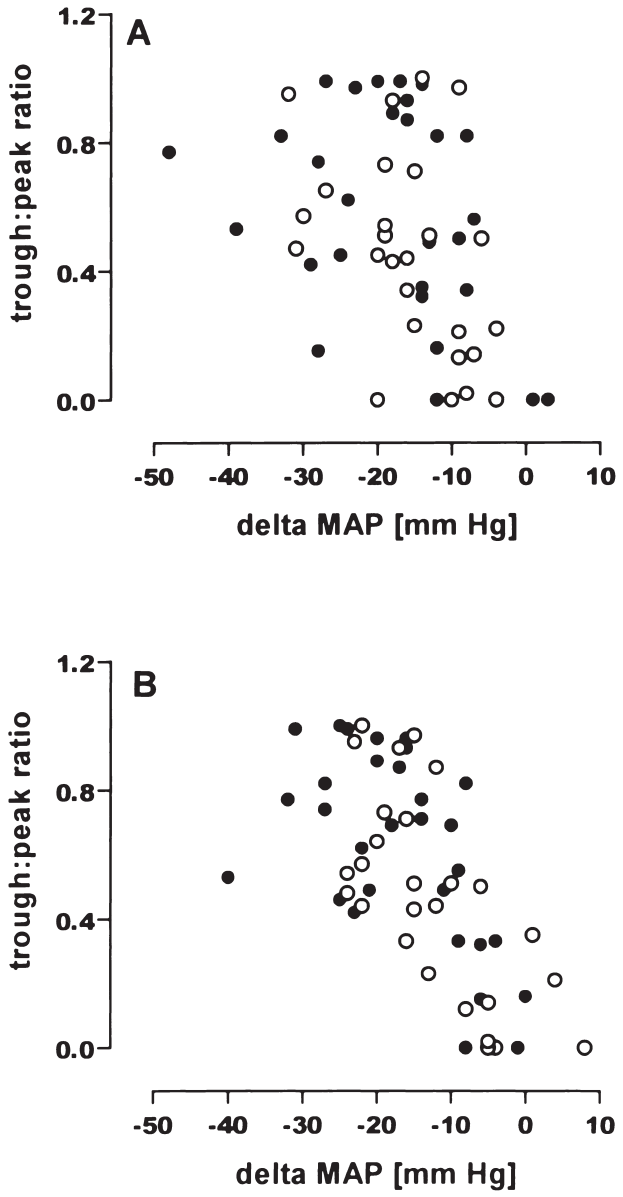

Figure 5 Relationship between trough:peak ratio values and changes in mean arterial pressure (delta MAP) during daytime (07.00 am to 11.00 pm (**A**), and night-time (11.00 pm to 07.00 am (**B**), after treatment with enalapril (○) and lisinopril (●). Panel A: Spearman $r = 0.479$, $P < 0.01$ for enalapril, $r = 0.394$, $P < 0.03$ for lisinopril; panel B: $r = 0.697$, $P < 0.0001$ for enalapril, $r = 0.630$, $P < 0.0001$ for lisinopril.

detect a significant effect of treatment on T:P ratios ($P = 0.758$). In this small group, for neither of the ACE inhibitors the fall in BP at peak and trough was dose-dependent. When patients were treated with lisinopril, three of them, each in every regimen group, had T:P ratios of zero. The median T:P ratio was 0.65 at 10 mg, and 0.50 at 20 mg of lisinopril. In patients using combination therapy the median T:P ratio was 0.69. Due to the large scatter no significant treatment effect was found. Also, there was a large variation of the timing of the peak effect and the time-to-peak was not dose-related (Table 1). Although dose-dependency cannot be definitively excluded, based on the above-mentioned data, it was assumed. Thus, for each ACE inhibitor, the T:P ratio values were pooled and further comparisons

Table 1 Effect of drug-dose and combination therapy on trough, peak, trough:peak ratio and time-to-peak

Drug	*Enalapril*			*Lisinopril*		
Dose/combination	*10 mg*	*20 mg*	*+HCTZ*	*10 mg*	*20 mg*	*+HCTZ*
Mean arterial pressure						
Peak (mm Hg)	−28 ± 13 (−43, −12)	−23 ± 6 (−33, −10)	−28 ± 9 (−46, −9)	−27 ± 9 (−39, −13)	−28 ± 15 (−58, −9)	−33 ± 9 (−60, −18)
Time-to-peak (h)	8 ± 2 (5, 10)	9 ± 5 (4, 16)	10 ± 5 (6, 16)	12 ± 7 (5, 18)	13 ± 6 (8, 18)	10 ± 5 (6, 17)
Trough (mm Hg)	−14 ± 15 (−34, +2)	−11 ± 6 (−18, −2)	−14 ± 14 (−44, +15)	−15 ± 12 (−35, +1)	−16 ± 15 (−45, +1)	−23 ± 10 (−37, +3)
Trough:peak ratio	0.29 (0.00–0.91)	0.46 (0.21–0.71)	0.49 (0.00–1.00)	0.65 (0.16–0.99)	0.50 (0.00–1.00)	0.69 (0.00–1.00)
Number	4	7	18	8	10	14

For each drug dose and combination, BP changes at peak and trough and time-to-peak are expressed as mean ± s.d. (maximum and minimum). T:P ratios are expressed as median (5th and 95th percentile interval). HCTZ: hydrochlorothiazide.

were made between enalapril- and lisinopril-based regimens and not between different doses or mono-*vs* combination therapy.

The effect of skipped dose on BP

To assess the effect of a skipped dose, ABPM was performed 24–48 h (day 2) after the last drug intake. On day 2, both drugs retained a significant antihypertensive effect (24-h MAP 102 ± 10 mm Hg for enalapril, 100 ± 9 mm Hg for lisinopril; $P < 0.001$), but there was no longer any difference between the two treatments ($P = 0.09$). Figure 3 depicts daytime and night-time SBP and DBP. When BP changes were assessed at trough on day 2, ie, from 46–48 h post-dose, the BP-lowering effect of lisinopril seemed more pronounced and of longer duration than after enalapril, but the difference was not significant, probably due to the large scatter (−12 ± 14 and −7 ± 12 mm Hg, respectively; $P = 0.09$). There was no relation between T:P ratio values and the magnitude of the antihypertensive effect between 24–48 h (data not shown).

Drug tolerability

Eleven patients reported side effects and four discontinued ACE inhibitor therapy because of cough. No relationship was found between T:P ratio and the incidence of side effects. Combination therapy did not cause an increase in side effects. Retrospective evaluation of overall BP control with respect to all parameters (target office and daytime BP, T:P ratio >0.50 and tolerability) revealed that 52% of the patients achieved better results with lisinopril-based treatment, while only 6% of patients was better off using any combination with enalapril ($P < 0.006$). For 42% of the patients, the outcome was unequivocal.

Discussion

The USA FDA has suggested that a T:P ratio of at least 0.50 is required to allow a drug to be registered for once-daily administration.[6] This rather arbitrary limit seems meaningless, however, unless the method by which the T:P ratio of a drug is determined is specified.[15,17–22] In the last years, many excellent reviews addressing the methodology of T:P ratio assessment, especially from 24-h ABPM data, have been published.[15–19,21,22] In these papers, many recommendations have been made for calculation of T:P ratios. Not only do these guidelines need validation in prospective studies, but also the value of the T:P ratio as an index of 24-h BP control still needs to be established, as there are no prospective studies showing a relation between T:P ratio and target organ damage.

In this study, we compared the duration of action of two moderate-acting ACE inhibitors, enalapril and lisinopril, by determining their T:P ratios from ABPM data in patients with essential hypertension. We found that the median T:P ratios were 0.65 for lisinopril and 0.48 for enalapril. The higher median T:P ratio value indicates a longer duration of action of lisinopril, as compared to enalapril, and this was also demonstrated by the reduction in BP after skipped dose which, although not significantly, was greater for lisinopril. These findings are in line with those reported by others.[1,3,4] Although the number of patients is too small, the data indicate that for enalapril, but not for lisinopril, T:P ratios may be dose-related. For enalapril, these findings are in line with those reported in other studies,[14,23] but for lisinopril, conflicting data have been described.[13,15,24] Staessen *et al*[15] found no difference in median T:P ratio values between 10 and 20 mg lisinopril. In contrast, Ménard *et al*[24] reported dose-dependent T:P ratios for the dose range of 10–80 mg of the drug. These authors found similar peak effects at each dose but a dose-dependent BP at trough. Although others observed similar dose-dependency for trough effects, the peak effects varied such that mean T:P ratios were not different (0.70 for 10 mg and 0.77 for 20 mg lisinopril).[13]

Only a few studies have investigated T:P ratios for drugs at more than one dose. T:P ratios of antihypertensive drugs with a linear dose-response curve are dose-independent whereas they are dose-dependent for agents with more complex concentration-effect relationships, such as ACE inhibitors and beta-blockers.[13,14,16] Interestingly, Ford *et al*[25] found that the ACE inhibitor, fosinopril, at once-daily doses of 10, 20 and 40 mg exhibited dose-dependent T:P

ratios with acute dosing, which appeared dose-independent with chronic therapy, illustrating the complexity of the issue. Also, for enalapril, when assessed only in responders, T:P ratios averaged 0.71,[26] as opposed to the average 0.30–0.50 found by others in an unselected population.[7,9,13,14] However, these studies calculate T:P ratios from group mean peak and trough effects, do not observe the non-normal distribution and do not show the scatter of the T:P ratio values which can be considerable for a given dose.[15,27] Thus, the differential results can largely be ascribed to differences in methodology for T:P ratio calculation.[15,18–21] We and others have suggested that T:P ratios should be calculated individually and interpreted together with the BP-lowering effect and the 24-h BP curve.[15,17,20] Then, it may even not be necessary for T:P ratios to reach the arbitrary value of 0.50 in order to represent a clinically relevant magnitude and duration of BP reduction, as was examplified in this study by enalapril. The 11 patients whose individual T:P ratio was less than 0.50, had a significant BP decrease on day 1. On day 2, ie, after the omitted dose, they showed a mean reduction in 24-h MAP of 8 mm Hg, in comparison to 12 mm Hg observed in patients with ratios higher than 0.50. Some authors claim that similar BP reduction may well be within the range of random BP fluctuations and circadian variations.[26] Although these BP changes remain after curve smoothing by Fourier analysis, which diminishes random variations,[20] we agree with others, that in individual cases, to improve 24-h BP control, enalapril should be given twice-daily.[14]

There are not many studies reporting T:P ratios for combination therapy,[28,29] Generally, one may expect the T:P ratio for combination therapy to be greater than that of either of the single components. As the two components of the combination do not induce their peak effect around the same time, the actual peak effect (nominator) is smaller than if the two maximum effects were reached at the same time. Also, addition of another drug is likely to extend the duration of action, resulting in a greater BP fall at trough (denominator). Thus, the value of T:P ratio was found increased for the combination of losartan and HCTZ,[28] and that of verapamil SR and trandolapril.[29] In our study, the addition of HCTZ to enalapril resulted in a nonsignificant increase in T:P ratio (0.46 to 0.49). In patients taking 20 mg lisinopril and HCTZ, the median T:P ratio was higher than in those on 20 mg lisinopril only (0.69 *vs* 0.50), but it did not differ from T:P ratios in patients taking 10 mg lisinopril. These findings indicate that patients treated with combination therapy have a hypertension that is more difficult to treat and only reach BP reduction similar to patients on monotherapy with more intensive treatment.

T:P ratios were introduced initially as a safety measure to prevent excessive BP falls.[6] In clinical practice the problem may be the reverse: as titration of drug dose is usually to office BP, which is measured around the time of peak response, the main question is whether BP control remains adequate until the next dose.[19] Plasma lisinopril concentrations peak within 6–8 h, plasma levels of enalapril reach a maximum within 1–2 h after administration.[30,31] In our patients, the peak BP response was reached on average 9 h and 11 h after intake of enalapril and lisinopril, respectively. Staessen *et al*[15] found similar timing of the peak effect with ABPM in patients using lisinopril and the time-to-peak varied considerably in this population. In contrast, Cirillo *et al*,[32] using hourly office BP measurements up till 8 h after drug intake of 2.5–80 mg lisinopril, reported a dose-independent time-to-peak of 4–5 h. By not using 24-h ABPM, the real peak effect may have been missed. For enalapril, others report a peak effect within 8 h.[9,27] Thus, in most of our patients office BP was taken before the maximum BP-lowering effect was reached, after which the dose was adjusted. As stated earlier, when given within the therapeutic dose range, ACE inhibitors dose-dependently influence BP at trough and only slightly at peak. Therefore, we did not expect that titration of office BP in this study would cause hypotensive events. In view of the great variation in timing of peak effects, for T:P ratio calculation, defining the peak as maximum BP fall during any time period within 24 h may be better because the use of a fixed time window may introduce bias.[15,20,27]

In line with our previous observations, we found a correlation between (absolute) changes in MAP and T:P ratio,[20] which was more significant for BP changes during night-time than daytime. One may hypothesise that patients with high T:P ratios have responded to the drug, whereas patients with low ratios did not respond or received inadequate doses of the drug. However, in the latter group office BP was such that no dose adjustment was needed, suggesting that these patients too, were responding to the drug. The T:P ratio in these patients, however, shows that the drug is no longer active at trough and that either a dose adjustment should be made or the drug should be given more frequently. Some authors advocate the determination of T:P ratio only in responders. However, there are no exact definitions of responders available. In addition, exclusion of non-responders from data analysis, on what criteria ever, may result in a reduction of 30–40% of the original population and therefore, a loss of randomisation.[18,22]

We are aware of the limitations of this study with a small number of patients. Although office BP monitoring were performed by an independent physician, the study was not blinded. In addition, no placebo was used. The value of placebo in antihypertensive drug trials using ABPM has been discussed extensively. A placebo or acclimatisation effect during the first few hours of ABPM has been observed by some authors,[33,34] while others found no effect of placebo.[35,36] Omboni *et al*[18] found that placebo correction may worsen the scatter in the T:P ratio. Others argue that when placebo effects are not subtracted, T:P ratio values may become too high.[6] However, placebo correction reduces the peak effect and consequently, increases T:P ratio value.[18] If placebo should influence BP during the first hours of ABPM, then, in the present study, the effect of both ACE inhibitors will be affected similarly and, due

to the late timing of the peak effect, T:P ratio will remain unchanged.

We found a trend towards better tolerability of lisinopril, while others found no difference between the two drugs.[2–4] For both ACE inhibitors, the addition of thiazide did not affect the occurrence of adverse effects, which was also reported by others.[37] As side effects were not primary end-points of this not blinded study, conclusive statements regarding side effects cannot be made.

In summary, our data demonstrate that, based on 24-h ABPM and T:P ratio values, lisinopril with or without addition of HCTZ, has a stronger antihypertensive effect and a longer duration of action than equivalent doses of enalapril in patients with essential hypertension. For both drugs, T:P ratio values correlated with changes in both daytime and nighttime MAP. For both ACE inhibitors, in the dose-range used, neither the BP-lowering effect nor T:P ratio values were dose-dependent. However, these findings may be biased due to the small number of patients. For any type of antihypertensive drug, whenever T:P ratios are calculated to give information regarding 24-h BP control, they should be assessed in individual patients from 24-h BP data obtained after adequate curve smoothing. In addition, for T:P ratio values to become meaningful, they should never be evaluated without taking into account the magnitude of the antihypertensive drug effect and the circadian BP profile.

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