Management of antihypertensive treatment with Lisinopril: a chronotherapeutic approach

C. MACCHIARULO, R. PIERI, D. CHIEPPA MITOLO*, A. PIRRELLI

Department of Clinical Methodology and Medico-Surgical Technologies – Division of Hypertension, Medical School, University of Bari (Italy)
Department of Pharmacology and Human Physiology, Pharmacology Section - Bari (Italy)

Abstract. – Risk for cardiovascular events seems to be higher in the early morning, also as consequence of a rise in blood pressure (BP) values due to the characteristic circadian pattern of BP variability. Therefore, a suitable therapeutic BP control should be tightest during the early morning. On the basis of the ambulatory blood pressure monitoring (ABPM) studies, it has been previously demonstrated that the antihypertensive effect of once daily drug, generally administrated in the morning, decreases at the end of the dosing period. A chronotherapeutic approach to the management of hypertension (this field has been pourly investigated so far) would allow the assessment of the optimum timing of drug dosing, according to the circadian BP rhythm and to the chronorisk maps, in hypertensive patients affected by associated vascular pathologies. This would increase the therapeutic effects. The aim of this study was to assess BP changes due to ACE-inhibitor (Lisinopril 20 mg/die) once daily administration at three different times (8.00 AM, 4.00 PM, 10.00 PM), in order to optimise the dosing time. 40 subjects (mean age± SD: 45±10) affected by primary mild to moderate hypertension were submitted to ABPM for 24 hours, by means of Spacelabs 90207, before and after pharmacological treatment. Patients were randomised to take the drug at 8.00 AM, 4.00 PM or 10.00 PM, and they repeated ABPM every two months, by changing the dosing time. The chronobiological analysis showed: 1) a sensible decrease both in Systolic (S)BP and Diastolic (D)BP without affecting the circadian rhythm, in all evaluations; 2) a greater reduction of SBP and DBP from 6.00 AM to 11.00 AM, period in which cardiovascular risk is higher, after 10.00 PM dosing; 3) no other sensible reduction in SBP and DBP occurred after night administration as compared to that caused by other dosing times. Lisinopril administration at 10.00 PM. has been shown to be much more useful since, although BP circadian rhythm was unmodified, it protects hypertensive patients from both vascular chronorisk and Cruickshank effect (J-curve). Therefore, a chronobiologic approach is expected to be useful in the assessment of antihypertensive treatment in order to increase the therapeutic effect already obtained with the traditional statistic methods.

Key Words:

Chronopharmacology, Antihypertensive therapy, Ambulatory blood pressure, Chronobiologic rhythm, Blood pressure variability, Drugs administration timing.

Introduction

Blood Pressure (BP), just as other biological functions, is characterised by a circadian rhythm, both in hypertensive and in normotensive subjects; this pattern is associated with lower BP values during sleeping time and periods of minimal activity and higher BP levels during wakefulness and mental and physical activity. At 3.00 o'clock in the night BP values begin to rise slowly until arousal (7:00 o'clock in the morning) when BP rapidly rises to its peak occurring at 10.00 AM; while a natural fall in pressure occurs in the afternoon in untreated hypertensive patients[1-5]. It therefore is desirable that BP control should be tightest during the early morning.

The development of antihypertensive drugs with particular pharmacokinetics impose a careful research about evaluation of therapeutic effect and possible changes on the circadian pattern of BP due to it. Indeed many of this currently available drugs have sophisticated release mechanisms or have long half-lives that permit once-daily administration, this increasing patient compliance and decreasing side effects, moreover they are typically taken in the morning after

wakefulness.

Through ambulatory blood pressure monitoring (ABPM) research , it has been evaluated the distinct circadian pattern of BP and its changes due to pharmacological therapy, as well as the period of greatest activity of the antihypertensive drugs. Indeed studies using 24-hours ABPM have shown that pharmacodynamic activity of several drugs taken once-daily in the morning (e.g. Beta blockers, Ace inhibitors, Ca antagonists) is attenuated at the end of the dosing period[6-11].

This may coincide with the early-morning rapid increase in the BP when patients undergo the greatest risk of developing of cardiovascular events[12-14].

In fact, epidemiological studies have shown the chronobiological recurrence of many cardiovascular diseases especially peak incidences of myocardial infarction, angina pectoris and stroke in the early morning between 6.00 and 11.00 AM[15,16], period in which chronobiological risk increases, due to haemodinamic and hemocoagulative factors of platelet aggregation and neurohormonal factors, and to the BP rapid increase at awakening[1,17-20,21].

It is therefore necessary a suitable therapeutic BP check during that period, above all in hypertensive patients, showing associated vascular disease ,by choosing the most appropriate antihypertensive therapy administration timing[21].

Aim of the study

Timing of drug dosing to much the circadian BP rhythm is a fairly new concept in antihypertensive therapeutics. At beginning of our study in this field we have evaluated Lisinopril for its pharmacokinetic features; it neither is metabolised at hepatic level nor it significantly blinds to plasma proteins. It reach a bioavailability of 25%.

This study evaluate the possible changes in BP profile, all over 24 hours, induced by the ACE inhibitor drug, Lisinopril (20 mg/die) once daily administration at three different hours, in order to optimise the administration timing.

Patients and Methods

We studied a group of forty patients (22 females, 18 males) aged 45 ± 10 (mean ± SD) years affected by mild-moderate primitive hypertension. They all shared homogenous life style, similar living habits and daily rhythms of life. Patient were selected after occasional sphygmomanometric measurement and none had ever taken antihypertensive therapy. Everyone had been informed about the study aim and had given his consent.

To evaluate BP chronobiologic rhythm we have used a Spacelabs 90207 computerised ambulatory blood monitor (Spacelabs, Inc., Redmond, Washington). This monitor was programmed to measure systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) by oscillometric method. Recordings were performed during 24 hours every 15 minutes from 7 AM to 11 PM and every 20 minutes during the night (11 PM to 7 AM).

Patients began pharmacological treatment whit Lisinopril, 20 mg/die monodose, and they have been were randomised in three groups to take the drug at 8.00 AM, or at 4.00 PM or at 10 PM. Every group of patients repeated ABPM every two months, by changing, after wash-out week, the dosing hour. At the end of study all the patients had taken the drug at three scheduled hours.

Statistical analysis

Clinic Blood Pressure values have been evaluated as the average of three consecutive measurements and the difference between these average values, obtained at baseline and during treatment and in three different administration times (8.00 AM, 4.00 PM, 10.00 PM), was assessed by Anova test and by Bonferroni test for repeated assessments.

The ambulatory blood pressure values analysis included the calculation, before and after treatment, of the 24h, day-time (period between 7.00 AM and 11.00 PM) and night-time (period between 11.00 PM and 7.00 AM) average values (± SD) and the average values for each hour of recording period.

Analysis was performed by traditional statistic methods (hourly averages, SD of the averages, Anova test).

Besides we have considered by statistical analysis BP averages values (± SD) of the period between 6.00 AM and 11.00 AM in which chronorisk increases, and BP averages

Table I. Blood pressure and heart rate sphygmomanometric values found at three different administration times.

	Before treatment	After Lisinopril 8 AM	After Lisinopril 4 PM	After Lisinopril 10 PM
SBP mmHg	160.11 ± 5.23	132.62 ± 7.02[*]	134.63 ± 8.05[*]	133.12 ± 7.52[*]
DBP mmHg	100.71 ± 7.01	85.24 ± 5.02[*]	87.22 ± 7.25	85.52 ± 7.05[*]
HR bpm	85.88 ± 10.31	87.62 ± 11.43	82.74 ± 12.51	83.20 ± 10.18

Data are mean ± DS: SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HR = Heart rate.
[*] $p < 0.05$ versus before treatment.

values (± SD) of the period between 11.00 PM to 6.00 AM, in which BP falls naturally. We have calculated this BP values before and after treatment in the three different administration times (8.00 AM, 4.00 PM, 10.00 PM).

To evaluate, with a statistical significance whether a BP rhythm variability occurred and whether the therapeutic treatment affected it, SBP and DBP daily profiles were analysed by inferential analysis (statistical study of mathematical functions, deriving from original data series extrapolation).

We analysed ABPM original data by means of the four harmonics Fourier's model. This model emphasized once more that the studies of the biological rhythms cannot be done by traditional methods because those methods are based on the inspective trend of the curve representing hourly averages of pressure data.

Results

All patients after 2-months Lisinopril treatment, at each one of the administration timing, showed a major clinical SBP and DBP decrease ($p < 0.05$), on the contrary no HR variation has been assessed (Table I). SBP and DBP mean values over 24 hours and particularly during daily (7.00 AM-11.00 PM) and nightly hours (11.00 PM-7.00 AM) recorded by ABPM after treating at the different timing of administration (8.00 AM or 4.00 PM, or 10.00 PM) have been proved to be significantly lower, if compared with the values before treatment.

No significant change has been observed as for HR and mean pressure values over 24 hours and at the hours periods taken into account, notwithstanding the timing of administration, namely: 8.00 AM, 16.00 PM or 10.00 PM (Table II).

The 24-hour pressure pattern, drowned from hourly averages of ABPM recordings before and after the treatment, clearly shows a major decrease in both SBP (Figure 1) and DBP (Figure 2) after Lisinopril over 24 hours in each one of the administration timing, compared to the values before the treatment.

It can easily be noted how severe the pressure decrease is in the 6.00 AM to 11.00 AM interval, when the drug is administered at 10.00 PM compared to the one observed at the other administration timings.

10 PM administration timing pressure decrease overnight (11.00 PM – 6.00 PM) is not

Table II. Blood pressure (mmHg) and heart rate (bpm) values in estabilished time ABPM detected.

	Before treatment	After Lisinopril 8 AM	After Lisinopril 4 PM	After Lisinopril 10 PM
SBP 24 hours	137.97 ± 15.94	126.16 ± 14.37[*]	128.01 ± 16.40[*]	122.78 ± 14.03[*]
SBP hours (7-23)	142.89 ± 14.27	130.64 ± 13.11[*]	133.34 ± 14.30[*]	130.82 ± 11.69[*]
SBP hours (23-7)	126.63 ± 13.64	115.85 ± 11.60[*]	116.33 ± 14.57[*]	114.85 ± 12.36[*]
DBP 24 hours	91.22 ± 15.47	80.76 ± 14.26[*]	83.85 ± 15.32[*]	81.39 ± 13.76[*]
DBP hours (7-23)	96.42 ± 13.56	85.58 ± 12.71[*]	89.03 ± 13.00[*]	86.63 ± 11.36[*]
DBP hours (23-7)	79.18 ± 12.66	69.69 ± 11.11[*]	70.88 ± 12.38[*]	70.06 ± 11.52[*]
HR 24 hours	78.78 ± 14.85	77.35 ± 15.90	78.74 ± 11.72	75.26 ± 13.63
HR hours (7-23)	82.90 ± 14.27	81.49 ± 16.03	83.10 ± 14.73	79.09 ± 13.13
LHR hours (23-7)	69.39 ± 11.51	67.98 ± 10.81	69.22 ± 13.48	67.06 ± 10.80

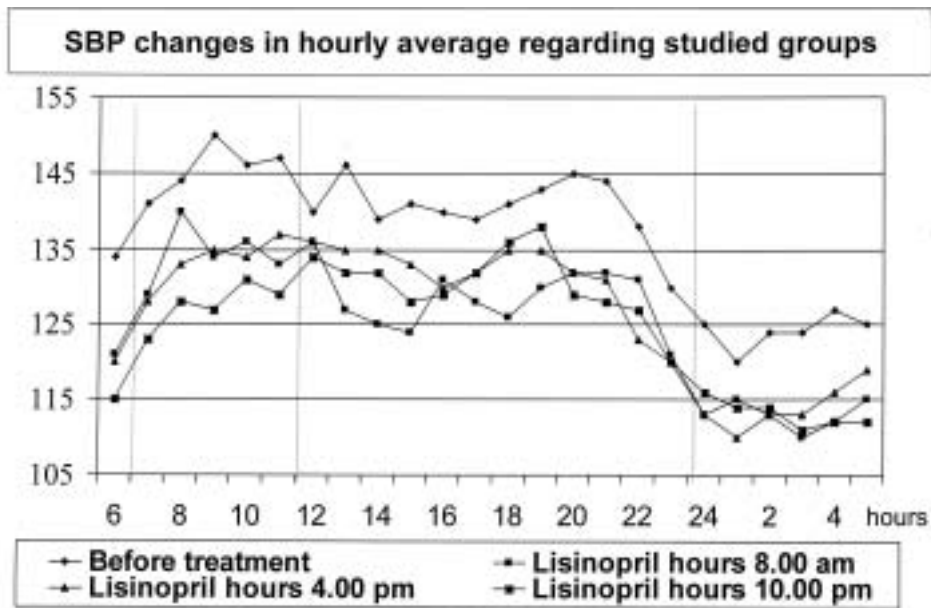[*] $p < 0.05$ versus before treatment.

Figure 1.

higher than the one found with the drug administration at 8.00 AM or 4.00 PM for both SBP (Figure 1) and DBP (Figure 2).

Chronobiologic analysis showed that the previous circadian rhythm remains after Lisinopril for all the three administration timings for both SBP (Figure 3) and DBP (Figure 4).

During the 6 AM to 11 AM interval, the curve relating to the 10 PM administration

timing shows a higher BP decrease, but it doesn't allow any further nocturnal reduction compared to the one induced by the other administration timings.

The statistical analysis of SBP and DBP value averages in the 6 AM to 11 AM time interval demonstrated how important the pressure decrease was caused by the drug, in each one of the administration timing, com-
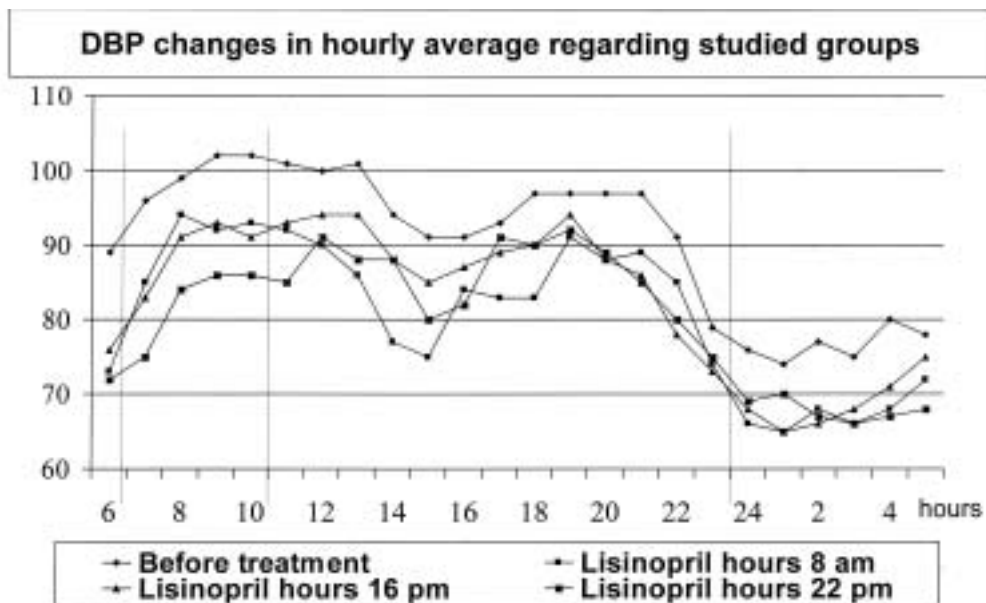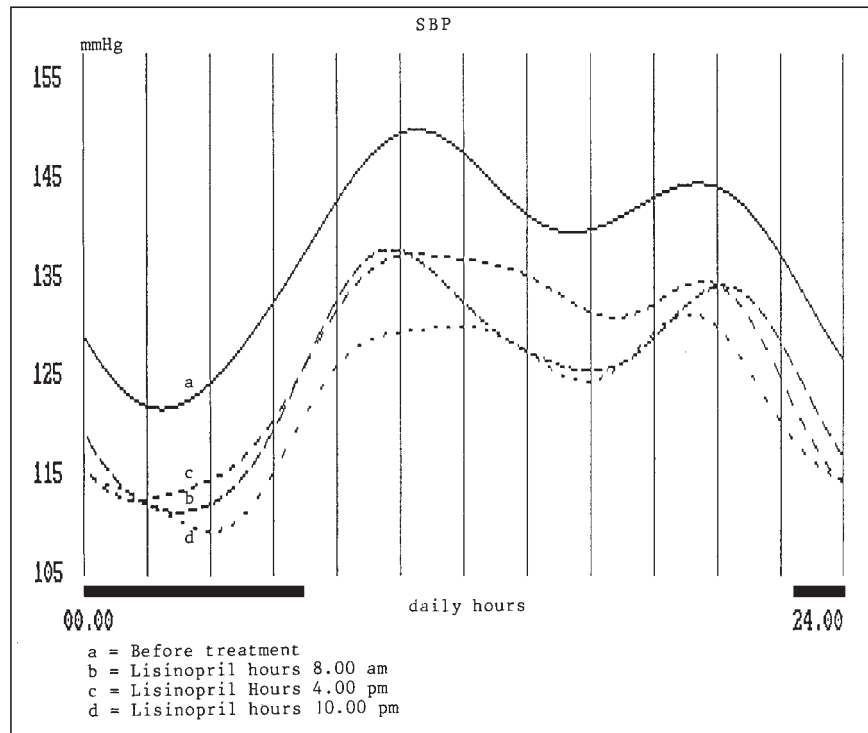

Figure 2.

Figure 3.

a = Before treatment
b = Lisinopril hours 8.00 am
c = Lisinopril Hours 4.00 pm
d = Lisinopril hours 10.00 pm

pared to the same values prior to treatment.

Moreover, Lisinopril administrated at 10 PM induced a more significantly BP decrease compared with Lisinopril administered at 8.00 AM or 4.00 PM (Table III).

In 11.00 PM – 6.00 AM interval both SBP and DBP severely decreased in all the three timings of administration compared to base-

a = before treatment
b = Lisinopril hours 8.00 am
c = Lisinopril hours 4.00 pm
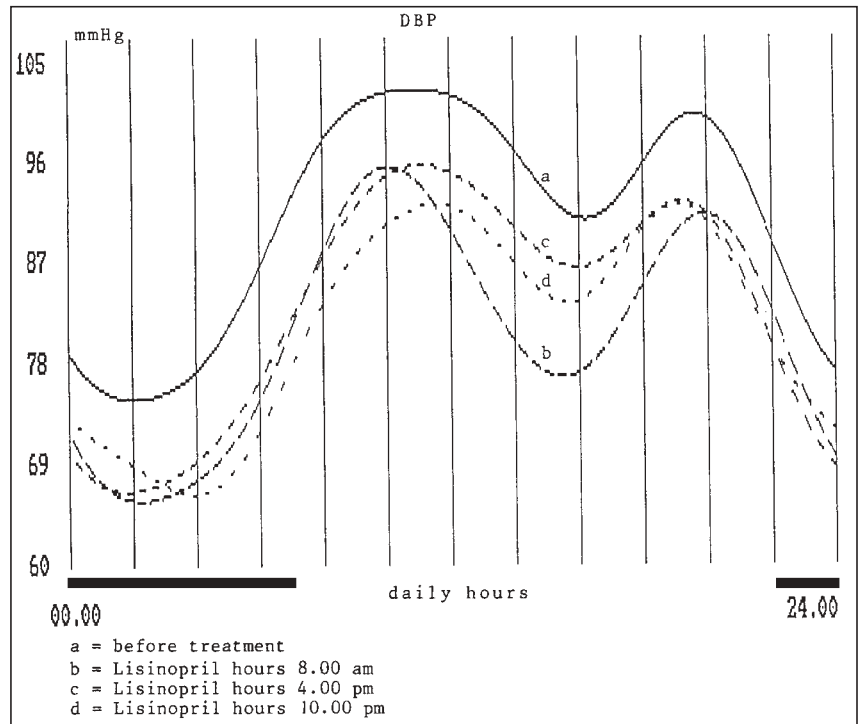d = Lisinopril hours 10.00 pm

Figure 4.

Table III. Blood pressure reduction following three different times of lisinopril administration.

6 AM to 11 AM	Before treatment	After Lisinopril 8 AM	After Lisinopril 4 PM	After Lisinopril 10 PM
SBP mmHg	144.00 ± 4.86	135.1 ± 6.72[•]	133.2 ± 4.32[•]	122.1 ± 4.8[•*]
DBP mmHg	99.45 ± 3.85	90.10 ± 7.91[•]	91.10 ± 5.83[•]	80.10 ± 4.24[•*]
11 PM to 6 PM	Before treatment	After Lisinopril 8 AM	After Lisinopril 4 PM	After Lisinopril 10 PM
SBP mmHg	125.4 ± 3.60	115.67 ± 3.58[•]	116.97 ± 3.66[•]	114.93 ± 3.73[•]
DBP mmHg	78.10 ± 2.49	69.70 ± 3.50[•]	71.34 ± 3.26[•]	71.74 ± 3.08[•]

Data are mean ± DS: SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.
• = $p < 0.05$ versus before treatment
* = $p < 0.05$ versus Lisinopril 8 AM and Lisinopril 4 PM administration.

line values. Such values quite overlap for the three timings of administrations (Table III), thus showing that no further SBP and DBP decrease occur overnight, period in which BP is Known to be physiologically lower, due to the evening administration, compared to the values related to the other timings of administration.

In conclusion chronopharmacology arises from the intersection of Chronobyology, the study of rhythmical fluctuations of biological systems, and Pharmacology. It aims at optimising the drug administration timing to enhance its therapeutic effect, to reduce its posology and the decrease the undesired side-effects, by taking seriously into account the chronotoxicologic activity of the drug itself[11,22].

Drugs, following their metabolic pathway, deal with biological periodicity , at different levels, which influence their effects and disappearance[23].

Actually, according to timing, they vary both the biosystem's bioavailability and sensivity, this conditioning its desired and undesired effects[24].

Lisinopril, a drug inhibiting the angiotensin converting enzyme, has already been widely tested for its antihypertensive efficacy[25-26].

The drug efficacy was confirmed from this study results, in terms of a decrease in both BP 24-hour values and BP daily and nocturnal values for each one of the administration timing.

Data demonstrate that when the drug is administered in the evening it reduces more greatly BP in the early morning, it keeps its activity at the end of the administration interval and it does not induce excessive hypotension, during sleep, when BP is physiologically lower even in essentially hypertensive patients.

Let us therefore assume that Lisinopril administration at 10 PM is more favourable, because by respecting the BP circadian rhythm, it protects better hypertensive patients from both vascular chronobiological risk, in the morning hours, when pressure rises, and from the Cruickshank's effect (J curve) in night hours[22,27-29].

A chronobiologic approach of the antihypertensive therapy can therefore be envisaged, thus allowing the detection of the most effective drug taking "right time", respecting the endogenous biologic rhythms, above all in those patients affected by associated vascular events for whom the optimal administration timing choice could increase therapeutic results.

References

1) MILLAR-CRAIG MW, BISHOP GN, RAFTERY EB. Circadian variation of blood pressure. Lancet 1978; 1: 795-797.

2) RAFTERY EB. Clinical significance of Blood Pressure Variability. 9th Symposium Blood Pressure Variability 1983: 51-63.

3) PICKERING TG, JAMES GD. Determinants and conseguences of the diurnal rhythm of blood pressure. Am J Hypertens 1993; 6 (Suppl 1): 166s-169s.

4) WALSH SJ, WHITE WB. The rise and fall of ambulatory blood pressure (abstr). Am J Hypertens 1994; 7: 106A.

5) STAESSEN J, BULPITT CJ, O'BRIEN E et al. The diurnal blood pressure profile: a population study. Am J Hypertens 1992; 5: 386-392.

6) NEUTEL JM, SCHNAPER H, CHEUNG D, GRAETTINGER WF, WEBER MA. Anthypertensive effects of b-blockers

administered once-daily: 24-hour measurements. Am Heart J 1990; 120: 166-171.

7) Neutel JM, Smith DHG, Ram CVS et al. Application of ambulatory blood pressure monitoring in differetiating between antihypertensive agents. Am J Med 1993; 94: 181-187.

8) Graettinger Wf, Lipson JL, Klein RC, Cheung DG, Weber MA. Comparison of antihypertensive therapies by non invasive techniques. Chest 1989; 96: 74-79.

9) Bainbridge AD, MacFadyen RJ, Stark S, Lees KR, Reid JL. The antihypertensive efficacy and tolerability of a low dose conbination of ramipril and felodipine ER in mild to moderate essential hypertension. Br J Clin Pharmacol 1993; 36: 323-330.

10) Palatini P, Racioppa A, Raule G, Zaninotto M, Penzo M, Pessina AC. Effect of timing of administration on the plasma ACE inhibitory activity and the antihypertensive effect of quinapril. Clin Pharmacol Ther 1992; 52: 378-383.

11) Deedwania PC, Nelson JR. Pathophysiology of silent myocardial ischemia during daily life. Circulation 1990; 82: 1296-304.

12) Mulcahy D, Cunningham D, Crean P et al. Circadian variation of total ischaemic burden and its alteration with anti-anginal agents. Lancet 1988; 2 (8614): 755-759.

13) Muller JE, Ludmer PL, Willich SN et al. Circadian variation in the frequency of sudden cardiac death. Circulation 1987; 75: 131-138.

14) Marler JR, Price TR, Clark GL et al. Morning increase in onset of ischemic stroke. Stroke 1989; 20: 473-476.

15) Muller JE, Stone PH, Turi ZG et al. Circardian variationin the frequency of onset of acute myocardial infarction. N Engl J Med 1985; 313: 1315-1322.

16) Reingerg A, Ghata J, Halberg F et al. Rytmes circadiens du pouls, de la pression artériel, des excrétions urinaire en 17-hydroxycorticosteroides, catecholamines et potassium chez l'homme adulte sain, actif et au repos. Ann Endocr (Paris) 1970; 31: 277-287.

17) Quyyumi AA. Circadian rhythms in cardiovascular disease. Am Heart J 1990; 120: 726-733.

18) Willich SN, Levy D, Rocco MB, Tofler GH, Stone PH, Muller JE. Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. Am J Cardiol 1987; 60: 801-806.

19) Waters DD, Miller DD, Bouchard A, Bosch X, Theroux P. Circadian variation in variant angina. Am J Cardiol 1984; 54: 61-64.

20) Withe WB. Assessment of patients whit office hypertensionby 24-hour non invasive ambulatory blood pressure monitoring. Arch Intern Med 1986; 146: 2196-2199.

21) Bolzano K, Arriaga J, Bernald H et al. The antihypertensive effect of Lisinopril compared to atenol in patients with mild to moderate hypertension. J Cardiovasc Pharmacol 1987; 9 (Suppl 3): S43-S47.

22) Zachariah PK, Bonnet G, Chrysant S et al. Evaluation of antihypertensive efficacy of lisinopril compared to metoprolol in moderate to severe hypertension. J Cardiovasc Pharmacol 1987; (Suppl 3): S53-S52.

23) Cruickshank JM. Coronary flow reserve and the j curve relation between diastolic blood pressure and myocardial infarction. BMJ 1988; 297: 1227-1230.

24) Berglund G, Samuelsson O. Lowered blood pressure and J-shaped curve. Lancet 1987; 1: 1154-1155.

25) Floras JS. Antihypertensive treatment, myocardial infarction, and nocturnal myocardial ischaemia. Lancet 1988; 2: 94-96.