Comparing Different Treatment Schedules of Zomen (Zofenopril)

H. BĂLAN¹,², ELENA POPESCU², GABRIELA ANGELESCU²
¹“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania, Clinic of Internal Medicine
²Clinical Emergency County Ilfov Hospital, Bucharest, Romania

Background. Chronotherapy of hypertension became, during the last years, a main target in optimal BP values control, during 24 hours. Many clinical studies have demonstrated a different effect on blood pressure of the majority of angiotensin-converting enzyme inhibitors (ACEIs), studied as function of the moment of their administration. Until now, the majority of clinical proofs sustain the greater benefit offered by bedtime administration of ACEIs, concerning especially a significantly greater efficacy in reducing BP during the asleep period, thus increasing the prevalence of “dippers”, the circadian profile considered to offer the best cardio-vascular prognosis, compared to at awakening administration.

Materials and methods. This study investigated time-dependent effects of zofenopril (Zomen, 30 mg, Berlin-Chemie, Menarini Group, Romania) administration on ambulatory blood pressure values. We studied 33 consecutive untreated hypertensive patients (19 men, 14 women), 56 ± 12.7 years old, with grade 1 or 2 uncomplicated essential hypertension (according to the European Society of Hypertension-European Society of Cardiology guidelines) (diagnostic formulated by casual determination and confirmed by an ABPM session at baseline), using zofenopril as monotherapy. The drug was initially administered in a single dose, at bedtime, during one month; after that period, we performed for all of them a new ABPM session, and, after that, for another month we administered the same drug, in single dose, at awakening. Blood pressure was measured for 48 hours before and after one month of treatment.

Results. The blood pressure reduction during diurnal activity was similar for both treatment schedules. Bedtime administration of zofenopril, however, was significantly more efficient than at awakening administration in reducing asleep blood pressure. The awake:asleep blood pressure ratio was decreased after zofenopril on awakening but significantly increased towards a more dipping pattern, (from 60.60% to 90.90%) after at bedtime administration.

The proportion of patients with controlled ambulatory BP increased from 51.51% to 84.84% (p < 0.001) by bedtime administration.

Conclusions. Nocturnal blood pressure regulation is significantly better achieved at bedtime as compared with at awakening administration of zofenopril, without any loss in efficacy during diurnal active hours; this might be clinically important, because nighttime blood pressure has been shown to be a more relevant marker of cardiovascular risks than diurnal mean values. The change in the dose-response curve, the increased proportion of controlled patients, and improved efficacy on nighttime BP values by bedtime administration of zofenopril should be taken into account when prescribing this ACEI for treatment of essential hypertension.

Key words: Zofenopril, essential hypertension, ambulatory blood pressure monitoring, chronotherapy, angiotensin-converting enzyme inhibitors.

Many parameters of the cardiovascular system, for an example: blood pressure (BP), heart rate (HR), stroke volume, cardiac output, total peripheral resistance, vascular tone, plasma volume, renal flow, renal resistance, and of vasculo-active substances: norepinephrine and epinephrine, angiotensin and aldosterone, dopamine, serotonin, prorenin and renin, endothelin, natriuretic peptide system, prostagladins (prostacycline) show a temporal, predominant circadian, variability [1][2].

So, one can assume, now, that a temporal organization is present in the clinical manifestations of most cardiovascular diseases. The sensitivity of the cardiovascular system to both pathological mechanisms and therapeutic interventions should be, and it really is, time-dependent.

The circadian variation in BP represents the effect of the circadian variability of internal factors as: autonomic nervous system tone, vasoactive hormones, hemotologic and renal variables [1][2]. BP is also influenced by a variety of external factors, including ambient temperature/humidity, physical activity, emotional status, alcohol, meal or caffeine consumption, and especially the sleep/wake routine.
Because the main steps in the mechanisms regulating BP are circadian-stage dependent, (1–5) it is not surprising that antihypertensive medications might display a circadian time dependency in their pharmacokinetics and effects [1][2]. Despite the great number of published evaluations of antihypertensive drug efficacy, rarely has the time schedule of drug administration been investigated [5].

Previous studies have demonstrated, for instance, a different effect of the ACEIs: benazepril [6], enalapril [7], quinapril [8], ramipril [9] and perindopril [10] when administered at awakening or at bedtime, proving a better efficacy and more benefic influences on BP values, awake/asleep ratio and circadian profile for bedtime administration. The HOPE (Heart Outcomes Prevention Evaluation) study can be considered the largest trial of chronotherapy in hypertension, ramipril being administered in the evening. A HOPE substudy on ambulatory BP monitoring (ABPM) [11] revealed that in subjects treated with ramipril at bedtime was obtained a marked BP reduction, particularly during nighttime sleep, a fact that was associated with a reduction in the prevalence of nondippers (patients with < 10% decline in the nocturnal relative to the diurnal BP mean).

Accordingly, this prospective, head-to-head trial was designed to compare, using BP data collected by 48-hour ABPM, the antihypertensive efficacy of the ACEI zofenopril when ingested as a monotherapy either at bedtime or at awakening for one month duration in previously untreated patients with essential hypertension.

METHODS

Subjects
We studied 33 consecutive untreated hypertensive patients (19 men, 14 women) with grade 1 or 2 uncomplicated essential hypertension (according to the European Society of Hypertension-European Society of Cardiology guidelines) (diagnostic formulated by casual determinations and confirmed by an ABPM session at baseline), all caucasians, all the subjects being diurnally active, 56 ± 12.7 years old. The 48 hours ABPM sessions (using an ABPM-04, Meditech, Canada device) (with measurements at 15 minutes from 06.00–22.00 and at 30 minutes during the night, for 48 hours) were performed at baseline, before initiating the drug treatment, and after one month of at bedtime administration of zofenopril – 30 mg, as monotherapy, respectively after another one month of at awakening administration of the same drug, as mono therapy.

Inclusion and exclusion criteria
Inclusion criteria were age ≥ 18 years and a diagnosis of previously untreated grade 1 or 2 essential hypertension according to the ESH/ESC guidelines, as determined by repeated (6 assessments) (within the 3 months before recruitment) conventional/casual clinic BP measurements (systolic BP [SBP]: 140 to 179 mm Hg and/or diastolic BP [DBP]: 90 to 109 mm Hg) and confirmed by an 48-hour ABPM session at the time of recruitment (baseline). The diagnosis of hypertension based on 48-hour ABPM required an awake BP mean of ≥ 135/85 mm Hg or an asleep BP mean of ≥ 120/70 mm Hg (12). Pregnant women, shift workers, heavy drinkers (alcohol intake >80 g/d), heavy smokers (> 20 cigarettes per day), and heavy exercisers were excluded, as were subjects with sleep apnea obstructive syndrome (based on declaration of heavy snoring or frequently interrupted sleep by apnea episodes – made by husband/wife), with severe arterial hypertension (grade 3, BP ≥ 180/110 mm Hg), with diabetes mellitus, or with secondary arterial hypertension and cardiovascular disorders, including concomitant unstable angina pectoris, heart failure, stroke, life threatening arrhythmia, nephropathy, retinopathy, or previous (within the last year) myocardial infarction or coronary revascularization.

All the subjects included are receiving their routine medical care in the Medical Clinic of the Clinical Emergency Ilfov County Hospital.

Demographic characteristics and analytic parameters
The demographic characteristics are presented in Table I.

Blood samples were obtained in the clinic from antecubital vein, after nocturnal fasting, around 8.00 a.m., on the day before the first ABPM session, before initiating the treatment.

Study design
This was a prospective, head-to-head, unicenter clinical study. All the 33 subjects that met the including criteria completed the study and provided all the required information for the trial.
**Table 1**

Demographic Characteristics and Analytic Parameters of the subjects

<table>
<thead>
<tr>
<th>Demographic characteristic/analytic parameter</th>
<th>Value ± SD</th>
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<tbody>
<tr>
<td>Total number of subjects</td>
<td>33</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Masculin:</td>
<td>19</td>
</tr>
<tr>
<td>Feminin:</td>
<td>14</td>
</tr>
<tr>
<td>Age (years ± SD)</td>
<td>56 ± 4,4</td>
</tr>
<tr>
<td>Height (cm ± SD)</td>
<td>162,1 ± 9,4</td>
</tr>
<tr>
<td>Weight (kg ± SD)</td>
<td>70,6 ± 11,5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26,7 ± 4,7</td>
</tr>
<tr>
<td>Waist (cm ± SD)</td>
<td>90,0 ± 9,3</td>
</tr>
<tr>
<td>Hip (cm ± SD)</td>
<td>102,3 ± 82</td>
</tr>
<tr>
<td>SBP (mm ± SD)*</td>
<td>157,3 ± 18,3</td>
</tr>
<tr>
<td>DBP (mm ± SD)*</td>
<td>92,1 ± 9,1</td>
</tr>
<tr>
<td>Non-dippers</td>
<td>10 (30,30%)</td>
</tr>
<tr>
<td>Dippers</td>
<td>22 (66,66%)</td>
</tr>
<tr>
<td>Extreme dipper</td>
<td>1 (3,03%)</td>
</tr>
<tr>
<td>Glucose (mg/dl ± SD)</td>
<td>93,3 ± 11,2</td>
</tr>
<tr>
<td>Chreatinine (mg/dl ± SD)</td>
<td>0,88 ± 0,16</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl ± SD)</td>
<td>182 ± 22,1</td>
</tr>
<tr>
<td>Triglycerides (mg/dl ± SD)</td>
<td>112 ± 43,2</td>
</tr>
<tr>
<td>Uric acid (mg/dl ± SD)</td>
<td>5,0 ± 1,6</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl ± SD)</td>
<td>286 ± 62,4</td>
</tr>
</tbody>
</table>

* The values correspond to the average of 6 conventional BP measurements obtained for each subject at baseline (before initiating the treatment).

During the inclusion period, at each of the 2 visits to their general practitioner were obtained 6 clinic/casual BP measurements, in the classical conditions recommended by WHO, with validated devices, using the appropriate cuff size. All the 33 subjects were active during daytime (from 06.00 a.m. to 10.00 p.m.), with a nocturnal resting period (from 10.00 p.m. to 06.00 a.m.). All the 33 subjects received, for an initial one month period, as monotherapy, at bedtime administration, zofenopril (Zomen, Berlin-Chemie, Menarini Group), 30 mg/d).

After one month of treatment with this timed schedule all of them had a new 48 hours ABPM session. After that new ABPM session all the subjects were moved to morning administration of the same drug, in the same dose. The dose of 30 mg is the one recommended by the pharmaceutical society.

**ABPM assessment**

The SBP, DBP, and HR of each participant were automatically measured every 15 minutes from 6.00 a.m. to 10.00 p.m. and every 30 minutes during the night, for 48 consecutive hours, before and after timed therapy, with a properly calibrated ABPM-04 device (Meditech, Canada), with AAMI and BHS validations. Participants were instructed to continue their usual activities with minimal restrictions and to follow a similar schedule during the 2 days of the ABPM session and to avoid daytime napping.

The main physical restriction is represented by the necessity to stop the movements of the arm where the cuff is fixed.

BP series were not considered valid for analysis if > 20% of the measurements were missing (no matter the reason), if data were missing for an interval of b > 2 hours, if data were obtained while patients had an irregular rest-activity schedule during the 2 days of monitoring, if the nighttime sleep period was < 6 hours or > 12 hours during ABPM, or if the quality of the sleep was quoted < 7 on a scale from 1 to 10 (subjects were specially asked to do that, because we had not the possibility to use actigraphy). Protocol-correct data series were collected at baseline and after one month of treatment for both timed-scheduled regimens, from all the 33 patients and, therefore, were included in this efficacy, prospective, head-to-head-study.

To correct for measurement errors and outliers, BP and HR were edited according to conventional criteria [13] (and that are automatically rejected by the software of the device used). Thus, readings of
SBP > 250 or < 70 mm Hg, DBP > 150 or < 40 mm Hg, and pulse pressure (difference between SBP and DBP) > 150 or < 20 mm Hg were automatically discarded.

As we had not the possibility to use actigraphs we asked every subject to keep very thoroughly diary with the type and exact time of the activities they had during the 48 hours of ABPM sessions.

The drug studied

Zofenopril (Zomen, Berlin-Chemie, Menarini Group) is one of the many representatives of ACEI, the class of antihypertensive drugs most widely used today.

Its special qualities [14–24], that made us choose it for this chronotherapeutic study, are represented by:

– the presence of the sulfhydryl group (a fact that generates a higher lipophilicity, that means a higher capacity to penetrate all tissues and a greater effect persistence (that means a longer acting period) [25], especially in the myocardium and in the aortic wall (where its concentrations are higher than the plasmatic ones);
– a particular affinity for ECA, the capacity to inhibit ECA activity at all levels and cellular sites [26][27];
– benefic effects for the endothelium [19][20] [26–30] – the “corner stone” of the action of all antihypertensive drugs;
– the capacity to act as a “scavenger” for iNOs, increasing the NO liberation [29][30];
– the capacity to significantly and benefically influence those with metabolic syndrome (MS) or diabetes mellitus (DM), by reducing the insulin resistance [30][31].

In conclusion, besides inhibiting the RAAS it offers the possibility to attenuate/reverse the target organ damage, the cardio-protective effects being in close connection with its high lipophilicity; it has a significant efficacy, proved by ABPM, especially for doses ranging from 30 to 60 mg [19][31]; it has the capacity to reduce the incidence of any kind of cardiovascular event, including death, a fact explained not only by NO-mediated effects, but also by the attenuation of the matricial metalloproteinase, that acts in cardiovascular remodeling and in atherosclerotic processes; a proven efficacy of over 24 hours, a powerful argument in favor of an increased adherence/compliance; very rare and of reduced intensity side effects.

Statistical methods

The number of patients needed in a parallel group study to achieve a 90% chance of detecting a 5 mm Hg treatment effect using ABPM can be calculated after the following formula:

\[
N = 10 \times \frac{SDD^2}{\text{difference}^2}
\]

the answer being 16, so the number of 33 subjects is sufficient.

So, the study can have 90% power to show as significant at the 95% level differences in efficacy of 5 mm Hg in daytime or nighttime BP means between treatment groups.

Hourly BP means obtained before and after treatment were compared by paired \( t \) test corrected for multiple testing. In so doing, the level of significance was established at \( p \leq 0.002 \), after dividing the usual level of 0.05 by the number of tests (24, 1 for each hourly mean) done on the same variable. Both the absolute and the relative changes from baseline in awake, asleep, and 24-hour BP means, as well as in the awake:asleep BP ratio (an index of BP dipping, defined as the percentage of decrease in BP during the hours of nocturnal rest relative to the mean BP obtained during the hours of daytime activity) and in the so-called morning BP (average BP during the first 2 hours after wake-up time) were compared by repeated-measures ANOVA. Within-group comparisons of ABPM characteristics before and after treatment were performed using a paired \( t \) test.

BP measurements, including pulse pressure, were significantly reduced after treatment (\( p < 0.001 \)) and to a comparable extent in both timed-scheduled treatment regimens. HR remained unchanged after treatment.

Zofenopril (ZOMEN) at bedtime

Table II offers the SBP values and Table III offers the DBP obtained after at bedtime administration of zofenopril, determined by 48-hour ABPM session; because the results did not vary between the 2 consecutive days of sampling, it was possible to pool the BP data of both days of the session. Treatment with zofenopril administered at bedtime resulted in a statistically significant reduction of the 24-hour BP mean from baseline (decrease of 13.56/12.72 mm Hg in SBP/DBP; \( p < 0.001 \)).
Table II
SBP after at bedtime administration of zofenopril

<table>
<thead>
<tr>
<th>HOURS AFTER AWAKENING</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE SBP (mm Hg ± SD)</td>
<td>130.5 ± 2.20</td>
<td>136.2 ± 2.15</td>
<td>139.2 ± 2.20</td>
<td>144.5 ± 2.18</td>
<td>143.9 ± 2.17</td>
<td>145.2 ± 2.20</td>
<td>141.2 ± 2.18</td>
<td>138.3 ± 2.18</td>
<td>136.2 ± 2.20</td>
<td>135.3 ± 2.17</td>
<td>134.6 ± 2.18</td>
<td>134.5 ± 2.16</td>
</tr>
<tr>
<td>AT BEDTIME ADMINISTRATION SBP (mm Hg ± SD)</td>
<td>117.5 ± 2.20</td>
<td>121.3 ± 2.12</td>
<td>127.0 ± 2.14</td>
<td>122.3 ± 2.11</td>
<td>121.2 ± 2.11</td>
<td>121.2 ± 2.11</td>
<td>121.9 ± 2.11</td>
<td>120.7 ± 2.10</td>
<td>119.5 ± 2.12</td>
<td>122.4 ± 2.12</td>
<td>123.9 ± 2.13</td>
<td>125.2 ± 2.14</td>
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</table>

Table III
DBP after at bedtime administration of zofenopril

<table>
<thead>
<tr>
<th>HOURS AFTER AWAKENING</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE DBP (mm Hg ± SD)</td>
<td>85.2 ± 1.20</td>
<td>87.3 ± 1.20</td>
<td>89.2 ± 1.21</td>
<td>91.39 ± 1.22</td>
<td>90.8 ± 1.22</td>
<td>90.5 ± 1.23</td>
<td>92.8 ± 1.20</td>
<td>88.6 ± 1.20</td>
<td>89.5 ± 1.20</td>
<td>90.2 ± 1.22</td>
<td>91.3 ± 1.21</td>
<td>91.3 ± 1.21</td>
</tr>
<tr>
<td>AT BEDTIME ADMINISTRATION DBP (mm Hg ± SD)</td>
<td>74 ± 1.20</td>
<td>77.7 ± 1.20</td>
<td>81 ± 1.21</td>
<td>83.5 ± 1.22</td>
<td>81.2 ± 1.22</td>
<td>79.8 ± 1.22</td>
<td>79.1 ± 1.20</td>
<td>78.5 ± 1.20</td>
<td>78.1 ± 1.22</td>
<td>80.6 ± 1.20</td>
<td>82.1 ± 1.21</td>
<td>83.2 ± 1.21</td>
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</tbody>
</table>

Bedtime administration offered a good control of BP values (by ABPM), for the subjects, i.e. values below the diagnostic thresholds mentioned above. The effects of treatment were greater on the asleep BP mean, compared to those obtained after at awakening administration.

This effect changed the circadian profile of the subjects: at baseline 22 of them (66.66%) were “dippers”, 10 (30.30%) were “non-dippers” and 1 (3.03%) was “extreme dipper”; after bedtime administration we obtained the following distribution of their circadian profiles: 30 (90.90%) “dippers”, only 3 (10.10%) remaining “non-dippers”.

Bedtime administration of zofenopril exerted no effect on the 24-hour HR mean (increase of 0.3 bpm; P = 0.610).

Zofenopril at Awakening

Table IV offers the SBP values and table V offers the DBP values obtained after at awakening administration of zofenopril, determined by 48-hour ABPM session; because the results did not vary between the 2 consecutive days of sampling, it was possible to pool the BP data of both days of the session. This timed treatment resulted in significant reduction in the 24-hour mean of SBP/DBP from baseline, by 11.06/10.02 mm Hg (P < 0.001).

Despite the significant effect on BP, HR remained unchanged after at awakening administration (decrease of 1.2 bpm in the 24-hour HR mean; P = 0.295). BP reduction with at awakening administration was statistically significant (P < 0.001 after correcting for multiple testing) over all of the 24 hourly intervals, but the effects of treatment were lesser on the asleep than on the awake BP mean.

Comparison Between Treatment Groups

All the subjects were confirmed by a 48-h ABPM session as being hypertensives. After 1 month of treatment, the efficacy of zofenopril on the awake BP mean was almost similar for both groups, both in absolute as well as in the percentage of relative changes from baseline. Results, however, reveal a greater efficacy with bedtime dosing in regulating asleep BP (p < 0.001 between the two timed-schedules).
There was a significant (p < 0.001) increase in this time relative BP decline or awake:asleep ratio when zofenopril was administered at bedtime, thus showing a significant decrease when zofenopril was ingested on awakening. BP reduction is significantly greater during the first 6 hours after treatment, that means during the sleep hours. Moreover, efficacy is gradually lost more rapidly when zofenopril is ingested on awakening. Thus, the BP reduction is significantly greater during the last 12 hours of the dosing interval with bedtime administration of zofenopril. These differences in dose-response curve also reflect a markedly different efficacy or at bedtime vs. at awakening zofenopril ingestion in controlling morning BP. Finally, with regard to the safety profile, there was only slight dizziness in two patients, at the beginning of each schedule of the timed-treatment.

This efficacy, prospective, head-to-head trial, however, does not provide the required sample size to properly evaluate potential differences in adverse effects depending on the time of zofenopril administration.

### DISCUSSION

Results of this prospective, head-to-head trial indicate that 30 mg/d of ramipril significantly reduces BP for the entire 24 hours. Zofenopril dosing on awakening and at bedtime showed similar efficacy in reducing the awake BP mean; however, the BP-lowering effect was significantly

<table>
<thead>
<tr>
<th>Table IV</th>
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<tbody>
<tr>
<td><strong>SBP after at awakening administration of zofenopril</strong></td>
</tr>
<tr>
<td><strong>HOURS AFTER AWAKENING</strong></td>
</tr>
<tr>
<td><strong>BASELINE SBP</strong> (mm Hg ± SD)</td>
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<tr>
<td><strong>AT AWAKENING</strong></td>
</tr>
<tr>
<td><strong>SBP (mm Hg ± SD)</strong></td>
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<tr>
<td><strong>HOURS AFTER AWAKENING</strong></td>
</tr>
<tr>
<td><strong>BASELINE SBP</strong> (mm Hg ± SD)</td>
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<tr>
<td><strong>AT AWAKENING</strong></td>
</tr>
<tr>
<td><strong>SBP (mm Hg ± SD)</strong></td>
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</table>

<table>
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<th>Table V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DBP after at awakening administration of zofenopril</strong></td>
</tr>
<tr>
<td><strong>HOURS AFTER AWAKENING</strong></td>
</tr>
<tr>
<td><strong>BASELINE DBP</strong> (mm Hg ± SD)</td>
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<tr>
<td><strong>AT AWAKENING</strong></td>
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<tr>
<td><strong>ADMINISTRATION</strong></td>
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<tr>
<td><strong>SBP (mm Hg ± SD)</strong></td>
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<tr>
<td><strong>HOURS AFTER AWAKENING</strong></td>
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<tr>
<td><strong>BASELINE DBP</strong> (mm Hg ± SD)</td>
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<tr>
<td><strong>AT AWAKENING</strong></td>
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<td><strong>ADMINISTRATION</strong></td>
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lower on the asleep BP mean after morning as compared with bedtime administration of zofenopril. Accordingly, there was a significant decrease in the proportion of “nondipper” patients only after treatment in the bedtime-dosing group. This might be clinically relevant, because nondipping has been related to an increase in end-organ injury and cardiovascular events [32–34].

Moreover, independent prospective studies have also concluded that nighttime BP is a better predictor of cardiovascular mortality than the awake or the 24-hour BP means [32][35][36]. A number of previous publications reviewed elsewhere [35] [36] have documented morning-evening administration-time differences in the pharmacokinetics and/or pharmacodynamics of several different classes of BP-lowering medications. Clinical studies also demonstrated different effects of the ACE inhibitors benazepril, enalapril, quinapril, ramipril and perindopril when dosed in the morning versus the evening [6–10]. In all of the cases, evening administration of these medications resulted in a higher effect on nighttime BP and a significant modification of the circadian BP profile toward more of a “dipper” pattern [35][36]. In the present study, zofenopril also efficiently reduced morning BP and nighttime BP to a greater extent when ingested at bedtime. Results, however, should not be generalized. Our trial was restricted to a small number of caucasian, previously untreated patients with grade 1 or 2 essential hypertension, who received a 30mg/d dose of zofenopril. With respect to contributing factors to the circadian BP pattern, a prominent circadian variation has been demonstrated for plasma renin activity, ACE, angiotensin II, aldosterone, atrial natriuretic peptide, and catecholamines [37], all reflecting the marked circadian structure of the renin-angiotensin-aldosterone system. Plasma renin activity has its peak during nighttime sleep and a trough in the early afternoon [38]. Plasma aldosterone presents a circadian pattern with high values at the beginning of daily activity and lower values at the beginning of nocturnal rest. Thus, we hypothesize that the administration time-dependent effects of the ACE inhibitor zofenopril on BP demonstrated here might be related to the circadian variation in the renin-angiotensin-aldosterone system, with its activation occurring during the nocturnal sleep span and not just a consequence of terminal half-life. Similar conclusions have been proposed earlier regarding the time-dependent administration effects on ambulatory BP of valsartan, telmisartan, and olmesartan, angiotensin receptor blockers characterized by a markedly different terminal half-life but all showing greater efficacy and ability to remodel the circadian BP pattern when administered at bedtime [35]. On the other hand, appreciable ingestion time differences in the pharmacokinetics of BP lowering are well known. They result from circadian rhythms in gastric pH and emptying, in gastrointestinal motility, biliary function and circulation, in liver enzyme activity and blood flow to the digestive system, kidney, and other organs, among other factors [39]. Particularly relevant is the circadian pattern in the glomerular filtration rate, with a maximum in the daytime and a minimum at night [40]. Thus, zofenopril might be expected to be cleared more slowly overnight, thus potentially prolonging its duration of action.

The potential reduction in cardiovascular risk associated with the normalization of the circadian BP pattern (converting a “nondipper” to “dipper” pattern, possible through bedtime administration of an angiotensin receptor blocker or an ACE inhibitor is still a matter of debate [41]. So far only 1 study has been specifically designed to investigate whether normalizing the circadian BP profile toward more of a dipper pattern by the use of timed therapy reduces cardiovascular risk [42].

The final findings from this trial (orally presented in ISC meetings in 2009 – Akko, Israel, and in 2010, Vigo, Spain), where ABPM was repeated periodically during follow-up, indicate that the probability of cardiovascular and cerebrovascular event-free survival is strongly correlated with the awake:asleep BP ratio. Most important, results suggest that increasing this ratio toward more of a dipper pattern decreases cardiovascular risk, whereas decreasing the awake:asleep BP ratio is associated with an increased morbidity and mortality.

The same kind of conclusions were presented by a substudy of the Heart Outcomes Prevention Evaluation Study [43] patients in the active treatment group received ramipril at bedtime. Results from a small substudy, in which hypertensive patients were evaluated with 24-hour ABPM, showed a marked BP reduction, particularly during nighttime sleep, thereby reducing the prevalence of nondippers. The authors concluded that the beneficial effects on cardiovascular morbidity and mortality seen with ramipril in the Heart Outcomes Prevention Evaluation Study might relate to the 8% increase in the awake:asleep BP ratio seen after ramipril was administered at bedtime (11). In light of these findings, evaluation of the potential decrease in
cardiovascular risk from the proper modeling of the circadian BP profile by chronotherapy (i.e. by bedtime administration of drugs blocking the renin-angiotensin-aldosterone system), beyond reduction of BP levels, deserves further prospective investigation [44][45].

Perspectives

The results of this study on subjects with grade 1 or 2 uncomplicated essential hypertension, comparing the effects obtained at bedtime at or awakening administration of zofenopril demonstrate a normalization of the circadian BP profile toward more of a dipper pattern only when zofenopril is administered at bedtime. The change in the dose-response curve, extended duration of therapeutic action, increased proportion of controlled patients, and improved efficacy on nighttime BP with administration of zofenopril at bedtime should be taken into account when prescribing this ACE inhibitor for treatment of essential hypertension.

Cronoterapia hipertensiunii arteriale a devenit, în ultimii ani, o țintă principală pentru controlul optimal al valorilor tensionale, pe durata celor 24 de ore. Multe trialuri au demonstrat existența unui efect diferit asupra valorilor tensionale a majorității inhibitorilor enzimei de conversie a angiotensinei (IECA), în funcție de ora administrării. Până acum, majoritatea dovezelor clinice susțin beneficiul superior obținut prin administrarea vesperală a IECA, adică o eficacitate semnificativ superioră în reducerea valorilor tensionale pe timpul noptii, crescând astfel prevalența profilului ”dipper”, profil considerat a oferi cel mai bun prognoză cardio-vasculară, în comparație cu administrarea matinală.

Prezentul studiu a investigat efectele administrării dependente de timp a zofenoprilului (Zomen, 30 mg, Berlin-Chemie, Menarini Group) asupra valorilor tensionale obținute prin monitorizare ambulatorie automată a valorilor tensionale (MAATA).

Am studiat 33 de pacienți hipertensiivi consecutivi netratați (19 bărbați, 14 femei), cu vârsta de 56 ± 12.7 ani, cu HTAE necomplicată stadiul I sau II (conform ghiderelor Societății Europene de Hipertensiune și a Societății Europene de Cardiologie), diagnostic stabilit prin determinări obișnuite și confirmat printr-o sesiune de MAATA la introducerea în studiu, utilizând monoterapia cu zofenopril.

Medicamentul a fost inițial administrat în doză unică, la culcare, timp de o lună; după această perioadă s-a realizat pentru toți subiecții o nouă sesiune MAATA. Ulterior, tot pentru o lună, același medicament a fost administrat, în aceeași doză, dimineața.

Sesiunile MAATA au avut, toate, durata de 48 de ore.

Rezultate. Reducerea tensionii arteriale în timpul activității diurne a fost similară pentru ambele scheme de tratament. Administrarea la culcare a zofenoprilului a fost, totuși, semnificativ mai eficientă decât administrarea matinală din punctul de vedere al reducerii valorilor TA în timpul noptii.

Raportul perioadă de veghe/perioadă de somn al valorilor tensionale a avut o creștere semnificativă spre o evoluție de tip ”dipping” după administrarea la culcare (de la 60.60% la 90.90%).

Prin administrare la culcare proporția pacienților cu valori tensionale controlate optimal a crescut de la 51.51% la 84.84% (p < 0.001).

Concluzii. Reglarea valorilor nocturne ale TA este semnificativ mai bine realizată prin administrarea la culcare în comparație cu administrarea matinală, fără vreo diminuare a eficacității terapeutice pe valorile din timpul zilei.

Concluzia este importantă și din punct de vedere clinic deoarece s-a demonstrat că evoluția nocturnă a valorilor TA este un marker mai relevant al riscului cardio-vascular decât valorile medii din timpul zilei. Modificarea curbei doză-răspuns, proporția crescută de pacienți cu valori controlate ale TA și
ameliorearea eficacității asupra valorilor nocturne ale TA obținute prin administrarea la culcare a zofenoprilului trebuie avute în vedere când acest IECA este utilizat în tratamentul HTAE.

**Corresponding author:** Assoc. Prof. Horia Balan, MD, PhD, Clinic of Internal Medicine, Clinical Emergency County Ilfov Hospital, 49–51, Bd. Basarabia, Bucharest, Romania E-mail: drhoriabalan@yahoo.com

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