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Chronobiologically Explored Effects of Telmisartan[#]

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Abstract

Effects of Micardis (Telmisartan), alone or with low-dose aspirin, on blood pressure and other cardiovascular endpoints are examined in 20 patients with MESOR-hypertension in a crossover, double-blind, randomized study consisting of three Stages, each lasting 7 days: I-placebo, II-Micardis, and III-Micardis with low-dose aspirin. Treatment was administered each day at a different circadian stage, upon awakening, and 3, 6, 9, 12, 15 and 18 hr after awakening. During each stage, the following variables were measured at 3-hr intervals during waking: systolic and diastolic blood pressure, heart rate, ejection fraction, intrarenal resistive index, acceleration time, and serum creatinine. Each data series was analyzed by single cosinor. Results were summarized by population-mean least squares spectra. At matched treatment times, the MESOR and circadian amplitude of each variable were compared among the three treatments by paired t-tests. A prominent circadian rhythm characterizes all variables. Micardis was associated not only with a lowering of blood pressure, but also with a reduction of the circadian blood pressure amplitude. The ejection fraction was increased, and the resistive index and acceleration time were decreased, the effect being more pronounced when low-dose aspirin was added to Micardis. Any circadian-stage dependent effect of Micardis, with or without low-dose aspirin, will require monitoring over spans longer than a single day for a given treatment administration time.

Keywords

blood pressure; chronodiagnosis; chronotherapy; circadian hyper-amplitude-tension (CHAT); ejection fraction; heart rate; low-dose aspirin; Micardis (Telmisartan)

Introduction

Chronobiological trials have demonstrated the merits of considering abnormalities in the circadian blood pressure (BP) pattern as part of the diagnosis (and prognosis) (chronodiagnosis) of BP disorders. Benefits from timing the administration of treatment (chronotherapy), even

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for 24-hr formulations, also were shown. Circadian hyper-amplitude-tension (CHAT), a condition characterized by an excessive circadian amplitude of BP, has been associated with a very large increase in cardiovascular disease risk, larger than the risk of an elevated BP itself, an increase in cerebral ischemic events, and nephropathy particularly (1–3).

A treatment that lowers the circadian BP amplitude was related to a larger protection against cardiovascular morbidity and mortality than a comparable treatment that left the circadian amplitude of BP unaffected (4). Regarding chronotherapy, of interest to the drug industry is the circadian variation affecting pharmacokinetic parameters such as drug absorption and distribution, drug metabolism, and renal elimination. But even more important are the pharmacodynamics, which can show large differences in outcome as a function of the drug administration pattern, even in the absence of notable changes in pharmacokinetics (5).

Against this background, the present study examines the effect on BP and other cardiovascular variables of Micardis (Telmisartan), alone or in combination with low-dose aspirin in patients with midline estimate statistic of rhythm (MESOR)-hypertension. Telmisartan, an orally active, long-acting angiotensin II receptor antagonist, is effective in the treatment of hypertension (6), with a long half-life of 20 to 30 hr (7). The drug selectively inhibits the angiotensin II AT₁ receptor subtype without affecting other receptor systems involved in cardiovascular coordination (7). The maximal effect is reportedly obtained by 80 mg per day, with side effects comparable to those of placebo. As compared with placebo, 40 and 80 mg of Micardis decreased systolic BP (SBP) and diastolic BP (DBP) with statistical significance in patients with mild to moderate hypertension (6), more than Losartan (Cozaar), another antihypertensive agent with the same mechanism of action.

Subjects and Methods

The study, approved by the local Institutional Review Board, was conducted at the Gerontology Institute of Mostite, Czech Republic. Twenty patients (10 men and 10 women), 35 to 63 years of age, participated in the study, after providing informed consent. Each patient had a clinical examination, including X-ray, ultrasound, echocardiography, and chemical tests. They had been diagnosed with essential hypertension II ($N = 14$) or III ($N = 6$) according to the WHO classification. Three patients also were diagnosed with hyperlipoproteinemia, two other patients had noninsulin dependent diabetes mellitus (NIDDM), and another patient had Raeven's syndrome. In addition to Micardis, 3 patients were taking statins and the 3 NIDDM patients were taking oral antidiabetic drugs. The patients' characteristics are listed in Table 1.

The study was designed as a crossover, double-blind, randomized trial, comprising three stages, implemented during 3 consecutive weeks. Placebo, Micardis (80 mg daily), or Micardis and low-dose (100 mg) aspirin were taken for 7 days, each day at a different circadian stage (upon awakening, i.e., 06:00, and 3, 6, 9, 12, 15, and 18 hr after awakening). The study started in September 2001. During each study stage, venous blood samples were collected at 3-hr intervals for the determination of serum creatinine. At each sampling time, SBP and DBP were obtained with a mercury sphygmomanometer, heart rate (HR) was measured by ECG, and ejection fraction (8) was assessed by echocardiography. Doppler measurements (9,10) of intrarenal resistive index (RI), estimated as the ratio of renal artery to abdominal aorta (at a locality of a distal renal artery), and of the acceleration time (AT), also were obtained concomitantly.

For each variable and each subject, during each stage of the study, the data were analyzed by cosinor (11,12), which involved the least squares fit of a 24-hr cosine curve, yielding point and 95% confidence interval estimates for the MESOR, a rhythm-adjusted mean value, and for the circadian amplitude and acrophase, measures of the extent and timing of predictable change

within a day. The analyses were carried out on the 7-day profiles first, and to each separate day next. In the former case, least squares spectra also were computed in the frequency range of one cycle per week to one cycle in 7 hr. For each variable, the MESORs during the three study spans were compared by paired *t*-tests to ascertain any effect of Micardis and the further addition of low-dose aspirin to this treatment.

Results from the day-to-day analyses were summarized by population-mean cosinor (11,12). At matched treatment times, the MESOR and circadian amplitude of each variable were compared among the three study stages by paired *t*-test. Any circadian stage dependent treatment effect was further assessed by the least squares fit of a 24-hr cosine curve to the individual daily estimates of MESOR and circadian amplitude, assigned to the time of treatment administration on that day.

Results

In the least squares spectra, the circadian component was invariably the most prominent, together with harmonics with periods of 12 and 8 hr, as illustrated for SBP, DBP, and ejection fraction in Figure 1. In addition, an about-weekly (circaseptan) component was found to be statistically significant for HR during the placebo span, and for SBP and DBP during the Micardis span. A circasemiseptan component, with a period of 3.5 days, also was detected during the Micardis span for SBP, DBP, RI, and serum creatinine, and for SBP during treatment with Micardis and low-dose aspirin.

As compared with placebo, Micardis was associated with a 2.5 ± 0.4 beats/min decrease in HR ($t = 6.404$; $p < .001$), a 11.7 ± 0.7 mmHg (S) and 10.5 ± 0.6 mmHg (D) decrease in BP ($t = 15.629$; $p < .001$ and $t = 18.041$; $p < .001$, respectively), a $3.98 \pm 0.39\%$ increase in ejection fraction ($t = 10.217$; $p < .001$), and a 0.006 ± 0.001 sec decrease in AT ($t = 6.165$; $p < .001$). Only a small decrease of 0.115 ± 0.043 ($t = 2.671$; $p = .008$) was found in RI. No change was detected for serum creatinine. The addition of low-dose aspirin to Micardis was associated with a slight further increase in ejection fraction of $1.01 \pm 0.54\%$ ($t = 1.878$; $p = .062$), and a further decrease in RI of 0.44 ± 0.06 ($t = 7.240$; $p < .001$) and in AT of 0.006 ± 0.001 sec ($t = 5.368$; $p < .001$).

As seen in Figure 1, Micardis also affected the circadian BP amplitude, being associated with a decrease of 2.1 ± 0.3 mmHg ($t = 7.138$; $p < .001$) in the case of SBP and of 1.3 ± 0.3 mmHg ($t = 4.224$; $p < .001$) in the case of DBP. Micardis also was associated with an increase in the circadian amplitude of EF by $0.57 \pm 0.16\%$ ($t = 3.593$; $p < .001$), of RI by 0.036 ± 0.016 ($t = 2.247$; $p = .026$), and of AT by 0.0021 ± 0.0005 sec ($t = 4.416$; $p = .002$). The addition of low-dose aspirin to Micardis was associated with a decrease in the circadian amplitude of HR by 1.6 ± 0.4 beats/min ($t = 4.600$; $p < .001$), a further decrease in the circadian amplitude by 0.8 ± 0.3 mmHg of both SBP ($t = 2.872$; $p = .005$) and DBP ($t = 2.585$; $p = .011$), and an increase in the circadian amplitude of RI by 0.06 ± 0.02 ($t = 3.245$; $p = .001$) and of AT by 0.0022 ± 0.0022 sec ($t = 3.873$; $p < .001$).

The circadian stage dependent effect on BP of Micardis, with or without low-dose aspirin, is shown in Figure 2. One-way analyses of variance (ANOVA) indicate a circadian stage dependence of Micardis treatment as compared with placebo in terms of the circadian amplitude of SBP ($F = 3.076$; $p = .007$), as well as a circadian stage dependence of low-dose aspirin when used in combination with Micardis, affecting both the MESOR ($F = 4.128$; $p = .001$) and the circadian amplitude ($F = 3.245$; $p = .005$). Aspirin taken upon awakening brought about more of a decrease in both the MESOR and the circadian amplitude of SBP than at any other time. As seen in Figure 2, particularly for DBP, Micardis is most effective in decreasing BP when taken 6 to 9 hr after awakening. At these two timepoints, the decrease in DBP is

statistically significant, whereas it is not at any other time, when comparisons are made for each timepoint separately. The circadian stage dependent effect of Micardis versus placebo on the MESOR of DBP is statistically significant by one-way ANOVA ($F = 2.434$; $p = .029$).

Discussion

Chronobiological trials have considered several approaches to optimize the circadian timing of antihypertensive drugs. One such study was conducted at the National Institutes of Health (13). Another compared the usual three-times-a-day administration schedule with the timing of propranolol, Clonidine, and α -methyl-dopa in a single dose given about 2 hr before the daily peak in SBP and/or DBP (14). Results from the latter study showed that the single dosing schedule was associated with an enhanced hypotensive effect, obtained with a lesser dose, and was accompanied by fewer side effects. Six test times, equally distributed along the 24-hr scale or during the waking span, also were successfully used to determine in a double-blind, placebo-controlled N-of-1 study the best time of administration of the diuretic Hydrochlorothiazide, further showing that the patient did not need the medication (15). Six test times also served for investigating the optimization of the ant clotting (16) and antihypertensive (17,18) effects of low-dose aspirin.

The effect on BP of Cozaar (Losartan), alone or in combination with a diuretic, had been investigated on 13 patients with MESOR-hypertension by around-the-clock automatic ambulatory monitoring (19). Losartan potassium, a first available oral angiotensin II receptor (type AT₁) antagonist for the treatment of hypertension (20), and its active metabolite inhibit the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor found in many tissues, such as vascular smooth muscle. Reportedly, the full anti-hypertensive efficacy of Losartan may take up to 12 weeks (21). Tolerance is apparently good (22). Beyond a reduction in BP, Losartan treatment has been associated with a reduction in left ventricular mass index in patients with left ventricular hypertrophy (23–26), a strong independent indicator of the risk of cardiovascular morbidity and death. This result was corroborated by two recent reports from the LIFE (Losartan Intervention For Endpoint reduction in hypertension study) steering committee (27,28). For a similar BP lowering, Losartan was more effective than Atenolol in reducing cardiovascular morbidity and mortality as well as mortality from all causes in patients with hypertension, diabetes, and left ventricular hypertrophy, thus conferring benefits beyond the reduction in BP per se (27,28). An antiplatelet effect of Losartan in therapeutic doses (29) apparently was independent of changes in BP, plasma markers of fibrinolytic activity, and endothelial perturbation. AT₁ receptor antagonism may selectively modulate L-selectin expression on leukocytes, the endogenous stimulation of AT₁ receptors by the renin-angiotensin system possibly contributing to the activation of leukocytes and the decreased expression of L-selectin in coronary artery disease (30).

In patients with end-stage renal disease, Losartan administration was reportedly accompanied by a decline in plasma aldosterone as well as by an increase in plasma renin activity, resulting in a decline in plasma uric acid concentration despite the fact that the patients had no residual renal function (31). In patients with mild to moderate essential hypertension as well, Losartan treatment was associated with a lowering of uric acid concentrations (32,33). Lozano et al. (34) further report a reduction in microalbuminuria by Losartan in hypertensive patients with non-insulin-dependent diabetes mellitus (NIDDM), whereas Brenner et al. (35), who studied NIDDM patients with nephropathy for an average of 3.4 years, conclude that “Losartan conferred significant renal benefits,” primary outcome measures used in this study being the doubling of reference serum creatinine concentration, end-stage renal disease, or death.

In the 13 MESOR-hypertensive patients studied earlier (19), treatment with Losartan was associated with a small average decrease of 4 mm Hg in DBP ($p = .049$ by paired t -test). Large interindividual differences in the response to treatment were observed, varying from a 14 mm Hg decrease to a 6 mm Hg increase. The addition of a diuretic to the treatment plan invariably was associated with a decrease in both SBP and DBP, as well as with a decrease in the circadian amplitude of BP. The decreases were substantial, extending up to 42 and 31 mm Hg for SBP and DBP, respectively, and could be validated statistically on an individualized basis both by parameter tests (36) and by self-starting Cumulative Sum (CUSUM) (37), as reported earlier (19).

The major result of the present study is the demonstration of a substantial decrease in the circadian amplitude of BP associated with Micardis treatment and its further reduction by the addition of low-dose aspirin. The decrease in circadian amplitude of BP may be of particular importance for patients diagnosed with CHAT. Such a drug effect on an endpoint of BP variability is usually not considered and may underlie the large benefits conferred by angiotensin II receptor antagonists in reducing cardiovascular morbidity and mortality, beyond their ability to decrease BP.

Of all the variables investigated in this study, the largest circadian stage dependent effect was found for BP, being statistically significant for DBP by one-way ANOVA. In this case, the cosinor approach could not ascertain a 24-hr variation in the response to treatment, but for both SBP and DBP, a circadian component was demonstrated for the daily MESORs (assigned to the time of treatment) on Micardis, but not on placebo or on Micardis combined with low-dose aspirin. There may have been large interindividual differences in the response to treatment, notably since the subjects were hypertensive patients, some with other complicating conditions, who also took additional medications. Low-dose aspirin taken upon awakening is found to further decrease both the MESOR and the circadian amplitude of SBP and DBP. This effect is seen only at this particular timepoint and not at any other time.

Low-dose aspirin had been shown previously to have optimal anticlotting effects also upon awakening (1). The latter results need to be qualified by the fast rotating treatment times used in the present study design. The effect of Micardis after the placebo stage was likely incomplete on the first day of treatment, which was assigned to treatment upon awakening. This incomplete decreasing response of BP to Micardis may account for the larger BP decrease seen when low-dose aspirin is added to the treatment plan, as assessed 1 week later (when the effect of Micardis can be anticipated to be more complete).

Future designs need to maintain the same treatment at the same time for spans longer than a single day, even if the variables are measured for only 24 hr on the last day of each study stage. Of further interest are the effects observed from the addition of low-dose aspirin to Micardis, notably in terms of a slight increase in ejection fraction and of a large decrease in RI and AT, quite apart from the further reduction in the circadian amplitude of BP.

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Figure 1.

Least squares spectra of blood pressure and ejection fraction reveal peaks at frequencies of 7, 14, and 21 cycles per week, corresponding to periods of 24, 12, and 8 hr. Results reflect the prominence of the circadian component. The presence of harmonic terms (with periods of 12 and 8 hr) indicates that the circadian waveform differs from sinusoidality. Note that the circadian rhythm of blood pressure has a reduced circadian amplitude on treatment with Micardis, alone or with low-dose aspirin, as compared with placebo.

Figure 2.

Circadian stage dependent effect of Micardis, alone or with low-dose aspirin (by comparison with placebo), on SBP and DBP. Treatment was administered at a different circadian stage during each day of a 1-week monitoring span, first upon awakening, then successively 3, 6, 9, 12, 15, and 18 hr after awakening. The fact that the response of blood pressure to treatment is not immediate is apparent from the lesser response on day 1 (at the time of awakening) as compared with subsequent days, particularly noticeable for the circadian amplitude of SBP, but also for the MESOR of both SBP and DBP. Note the large decrease in the MESOR of both SBP and DBP on treatment versus placebo. Note also large decrease in circadian amplitude of blood pressure.

Table 1

Patients investigated

Patient number	Gender	Age(years)	Height (cm)	Weight (kg)	Fat (%)	Diagnosis	Treatment
1	M	50	162	72	30	EH II	MI
2	F	44	160	78	33	EH II	MI
3	M	52	172	68	25	EH II	MI
4	F	40	165	60	30	EH II	MI
5	F	60	160	65	28	EH II	MI
6	F	54	170	74	30	EH III	MI
7	M	57	180	85	24	EH III	MI
8	M	42	182	88	26	EH II	MI
9	M	40	178	80	28	EH II	MI
10	M	42	180	82	22	EH II, HLP	MI, ST
11	F	39	172	70	27	EH II, HLP	MI, ST
12	M	52	182	84	30	EH III	MI
13	F	44	162	68	28	EH III, HLP	MI, ST
14	M	60	175	65	30	EH II	MI
15	F	63	163	70	33	EH II	MI
16	F	38	170	70	25	EH II, DM II	MI, OAD
17	F	35	165	62	22	EH II, DM II	MI, OAD
18	M	42	180	82	24	EH III	MI
19	F	36	160	57	22	EH II	MI
20	M	44	175	92	24	EH III, X syndrome	MI, OAD, ST

F = female; M = male; EH II, III = essential hypertension; HLP = hyperlipoproteinemia; DM II = diabetes mellitus; X syndrome = Raeven's syndrome (obesity, hyperinsulinemia, hyper-liproteinemia, glucose intolerance).

MI = Micardis; ST = statins; OAD = oral antidiabetic drugs.