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INDIVIDUALISED COMBINATION CHRONOTHERAPY OF COEXISTING CHAT AND MESOR-HYPERTENSION INCLUDING DILTIAZEM HCL

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A b s t r a c t

In order to adjust the anti-hypertensive treatment of a 72-year-old man with MESOR-hypertension complicated by circadian hyper-amplitude-tension (CHAT), different strategies are evaluated to optimize the timing of treatment administration. Parameter tests and a self-starting cumulative sum (CUSUM) control chart are used to verify the effectiveness of various treatment modifications.

K e y w o r d s

circadian rhythm in blood pressure, antihypertensive chronotherapy, essential hypertension

INTRODUCTION

An elevated mean value of blood pressure (BP) is associated with an increased risk of vascular complications (*1*). Irrespective of whether the mean value of BP is elevated or not, too large a circadian amplitude of BP carries a large vascular disease risk *(2, 3*), larger than any of the other risk factors assessed concomitantly (*4, 5*). Whereas the relation to risk is linear for the BP MESOR, it is nonlinear for the case of the circadian BP amplitude (*6, 7*).

Because BP varies greatly, the conventional diagnosis of „hypertension“ vs. „normotension“ can be associated with a large error (*8*). For this reason, MESOR-hypertension has been defined as an elevation of the chronome (time structure)-adjusted mean values of BP above the upper 95% prediction limit of clinically healthy subjects of the same gender and ethnicity in the same age group (*9, 10*). Similarly, CHAT has been defined as a circadian amplitude exceeding the upper 95% prediction limit for clinically healthy peers matched by gender, age and ethnicity *(4, 5*).

Since a deviant BP warrants treatment, the question arises concerning the optimization of anti-hypertensive treatment. Timing according to the circadian BP

variation is one strategy (*11, 12*). The optimal time of administration of antihypertensive agents can result in an enhanced hypotensive effect, achieved with smaller doses, and resulting in fewer and less severe side effects (*13, 14*). A control chart approach was also used to examine the possibility of optimizing treatment (*15)* and treatment timing (*16, 17*). The optimization of treatment of a patient with MESOR-hypertension complicated by CHAT is the topic herein.

SUBJECT AND METHODS

A 72-year-old man conventionally diagnosed as hypertensive since the age of 34 years and currently treated with nifedipine (10 mg around 08:00 and 21:00) automatically measured his BP and heart rate (HR) around the clock at 30-min intervals with an ambulatory monitor (ABPM-630 from Colin Medical Instruments, Komaki, Japan), starting one day after his arrival in Minnesota from Russia on March 31, 1998. With a time-specified exception between the vertical event lines II and III in Figure 1, most of the time, his rest/activity schedule is regular, awakening around 07:00 and retiring for sleep around 21:30. The data were analyzed by chronobiologic serial section and other rhythmometric techniques (*18-20*). A sphygmochron led to the diagnosis of CHAT, which prompted the addition of diltiazem HCl (Blocalcin 90 retard, Lachema) to his treatment. A self-starting cumulative sum (*15, 21*) served to optimize the timing of administration of this drug while the peaks in the BP acceleration curve (*18*) were used to adjust the times of administration of nifedipine.

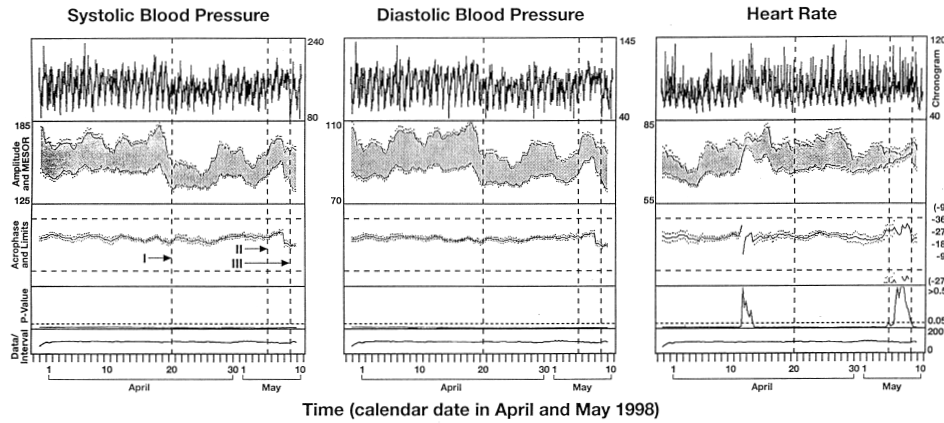
In order to further assess the response to treatment modifications, 1-week spans before and after each change were compared by parameter tests (*22*). In particular, three treatment modifications are considered herein: 1. the addition of Blocalcin to the treatment plan on April 21; 2. the change in timing of Blocalcin medication from evening to morning administration on May 26; and 3. the change in timing of nifedipine administration, scheduled according to the BP acceleration profile, on June 16.

RESULTS

Figs. 1 and 2 illustrate the changes in systolic (S) and diastolic (D) BP over several months. Results stem from chronobiologic serial sections, wherein data in an interval of 2 days are analyzed by single cosinor at a trial period of 24 hours. This interval is progressively displaced by an increment of 4 hours throughout the data series and estimates of the circadian characteristics of SBP and DBP are displayed as a function of time. Vertical dashed lines indicate events, which consist primarily of treatment modifications, as listed in *Figs. 1 and 2*.

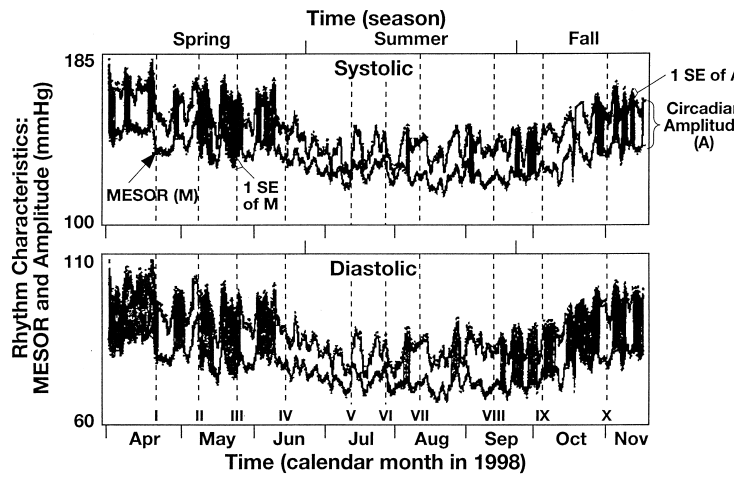
Table 1 summarizes BP and HR changes detected by self-starting CUSUM. The MESOR and the circadian amplitude of SBP and DBP are decreased after the addition of Blocalcin (in the morning around 06:00) on April 21, 1998. By CUSUM, the change was found to coincide with the time of treatment modification. The changes are further illustrated in *Fig. 3* in moving periodograms plotted as contour maps. The reduction in circadian amplitude is readily apparent by the lighter shading at periods around 24 hours after adding Blocalcin to the treatment plan.

When Blocalcin was administered in the evening instead of in the morning, the circadian amplitude increased, although the difference could not be validated with statistical significance. When the timing of Blocalcin resumed in the morning



* Treated with nifedipine (N), 10 mg at awakening and again at bedtime before event I; after I, 10 mg of N ~14:30 and diltiazem hydrochloride (D) 90 mg on awakening are added. Diltiazem is omitted between II and III, with long work spans, restricting sleep to <4 hrs/day.

Fig. 1.
Circadian hyper-amplitude-tension (CHAT) of 72-year-old man*.



* Vertical dashed lines indicate changes in dose and/or timing of treatment with nifedipine (2-4 x 10 mg/day) and diltiazem hydrochloride (1 x 90 mg/day). Lower line: MESOR, M; distance between 2 lines: circadian amplitude, A; distances from curves to dots below M line and above upper line are standard errors of M and A, respectively. CHAT (when A exceeds parameterdesm, shaded), rare in summer, apparently prevailing in spring and fall, seems to be more consistent in diastolic than in systolic blood pressure.

Fig. 2.
Circannual variation as yet unassessed but probably contributing to intermittent circadian systolic (TOP) and diastolic (bottom) hyper-amplitude-tension (CHAT) (in a man 72 years of age, treated for mesor-hypertension)*.

Table 1:
Individualised assessment of treatment effects on blood pressure (BP) and heart rate (HR) by self-starting cumulative sum (CUSUM) (GSKat; M, 72 y)*

Rx Change		Effect		
Date (1998)	Change	When detected	Estimated date of onset	Effect
April 21	Addition of Blocalcin retard (Diltiazem HCl, 240 mg/day) taken in the morning (~6 AM)	April 23	April 21	Decrease in SBP-MESOR
		April 26	April 21	Decrease in circadian A of SBP
		April 25	April 21	Decrease in DBP MESOR
		May 8	April 23	Decrease in circadian A of DBP
		April 13	April 7	Increase in HR-MESOR (cause unknown; occurred about 1 week after arrival in MN)
May 6	Withdrawal of Blocalcin			
May 9	Resuming addition of Blocalcin			No statistically significant changes taken in the evening (~8 PM) detected
May 26	Timing of Blocalcin changed from PM to AM			No change in BP-MESOR detected with statistical significance; slight decrease in the circadian A of both SBP and DBP not detected with statistical significance, but tracking to May 27, just 1 day following the change in Rx timing
June 16	Other anti-hypertensive drugs timed by BP accel-eration (and change of residence)	June 18	June 13	Decrease in SBP-MESOR
		June 25	June 11	Decrease in circadian A of SBP
		June 24	June 13	Decrease in DBP-MESOR
		June 23	June 12	Decrease in circadian A of DBP
		June 19	June 2	Increase in HR-MESOR

*SBP = systolic blood pressure; DBP=diastolic blood pressure
MESOR (midline-estimating statistic of rhythm): rhythm-adjusted mean
A: amplitude (2A is a measure of the extent of predictable change within a cycle)

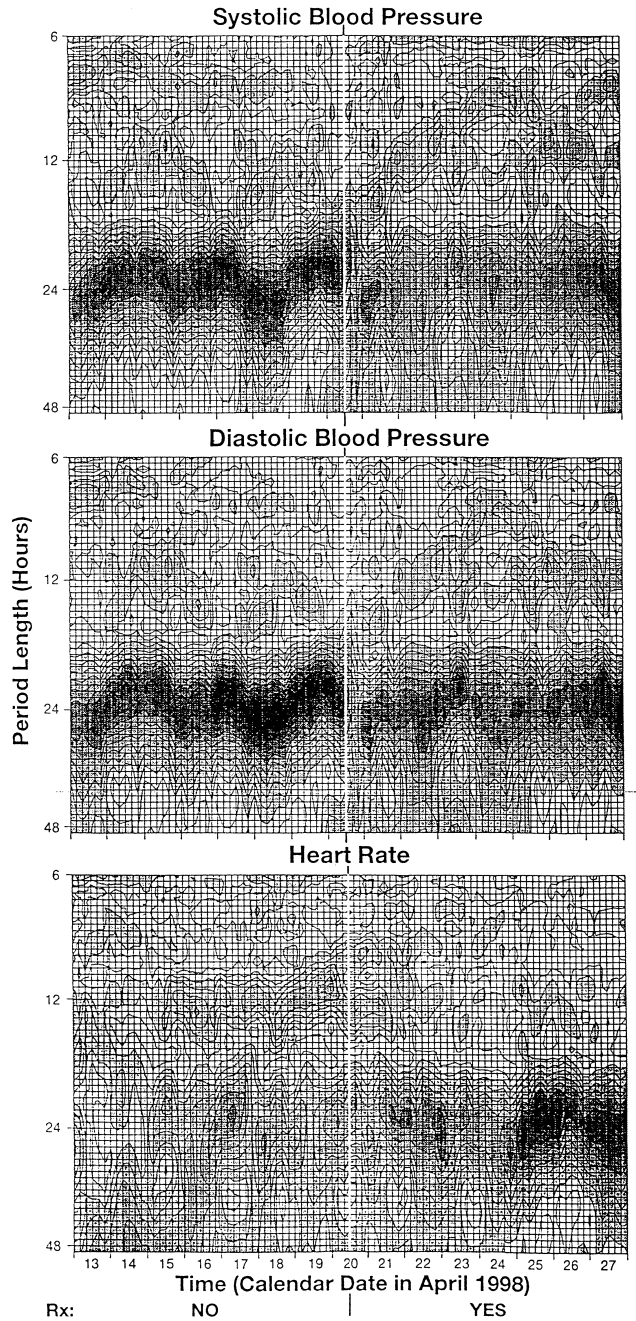


Fig. 3.
CHAT treated by diltiazem hydrochloride (Rx).

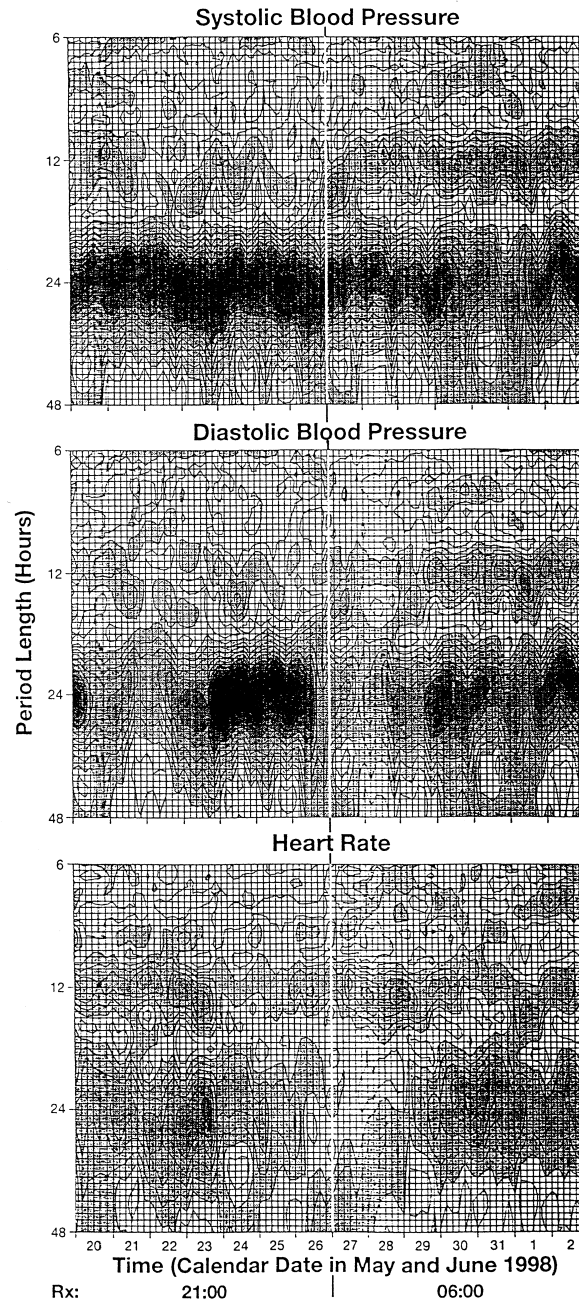
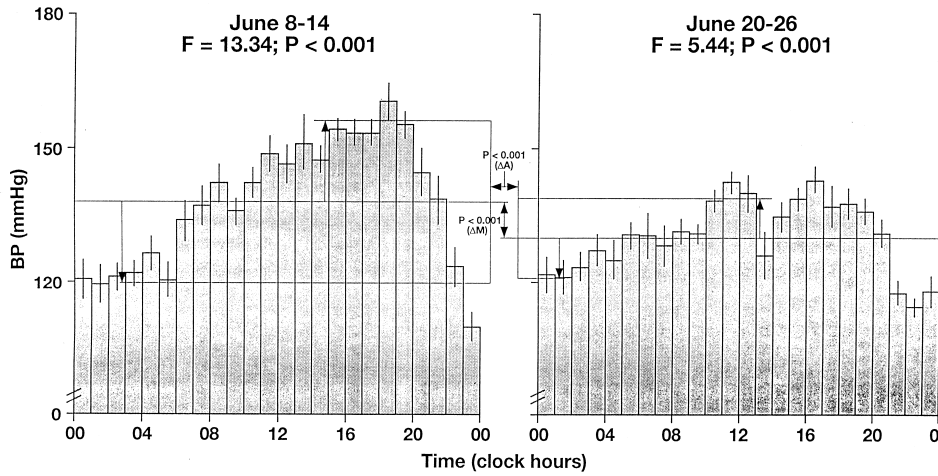


Fig. 4.
CHAT treated by diltiazem hydrochloride (Rx) at different circadian time (awakening versus bedtime)

Table 2
Assessment of effects of treatment modifications by parameter tests*

Variable	Before change			After change			P-values from comparison of			
	M	A	ϕ	M	A	ϕ	M	A	ϕ	(A,ϕ)
				1. Addition of Blocalcin (AM) in treatment plan						
		April 13-19			April 24-30					
SBP	148.8	23.4	-221°	139.7	15.6	-211°	<0.001	<0.001	0.060	<0.001
DBP	87.7	17.1	-218°	80.6	12.7	-218°	<0.001	<0.001	0.955	<0.001
HR	71.6	5.8	-231°	68.1	9.5	-241°	<0.001	0.001	0.296	0.003
				2. Blocalcin timed AM vs. PM						
		May 18-24			May 29-June 4					
SBP	137.2	26.8	-200°	138.4	16.5	-216°	0.351	<0.001	0.003	<0.001
DBP	78.1	17.6	-201°	79.2	11.7	-216°	0.201	<0.001	0.004	<0.001
HR	65.5	7.0	-231°	67.5	6.6	-245°	0.008	0.733	0.127	0.288
				3. Timing of nifedipine changed according to BP acceleration						
		June 8-14			June 20-26					
SBP	137.4	18.4	-221°	130.1	9.1	-197°	<0.001	<0.001	0.003	<0.001
DBP	79.0	12.7	-218°	75.4	7.5	-194°	<0.001	<0.001	<0.001	<0.001
HR	69.1	3.7	-245°	69.4	7.2	-219°	0.672	0.008	0.104	0.006

*M = MESOR (midline-estimating statistic of rhythm), a rhythm-adjusted mean
A = circadian amplitude, a measure of predictable change within a day
ϕ = circadian acrophase, a measure of timing of overall high values recurring each day; ϕ expressed in (negative) degrees, with 360° 24 h and 0° = 00:00
SBP = systolic blood pressure
DBP = diastolic blood pressure
HR = heart rate
SBP and DBP expressed in mm Hg; HR in beats/min



* Starting on June 16, 1998, one of four daily 10 mg of nifedipine tablets, taken at 3- to 4-h intervals during waking, was shifted to the middle of the sleep span (at 03:00), 2 hours before the peak in acceleration, while 90 mg of diltiazem hydrochloride treatment continued on awakening; ΔM = difference in MESOR; ΔA = difference in circadian amplitude.

Fig. 5.
Timing nifedipine (Rx) according to the acceleration of systolicblood pressure (BP)*.

hours, the decrease in circadian amplitude could not be validated by CUSUM, but parameter tests comparing 1-week spans after vs. before the change found the difference to be significant (P<0.001), *Table 2*. This is further illustrated in *Fig. 4* by a tendency toward lighter shadings in the circadian band for SBP and DBP, indicative of a smaller circadian amplitude in the contour maps of the moving periodogram results.

A further statistically significant decrease in both the MESOR and the circadian amplitude of BP is found when the timing of nifedipine was adjusted to precede by 1.5 to 2 hours the major peaks of the acceleration curve of BP (P<0.001), *Table 2*. *Fig. 5* illustrates this result by comparing the circadian pattern of SBP during the week of June 20-26 vs. the week of June 8-14, 1998 (after vs. before the change in timing of nifedipine administration).

DISCUSSION

Several chronobiological methods are available to optimize the scheduling of antihypertensive treatment adjusted for the given patient. Not only can the BP be lowered, but an excessive circadian amplitude can also be normalized and decrease the risk of cardiovascular damage (*23*). Further study is needed to find out whether treatment used to reduce an excessive circadian BP amplitude will be as beneficial in reducing the incidence of adverse vascular events as it is by lowering the BP MESOR. Results in *Fig. 2* suggest the additional need for taking

into consideration any circannual variation in BP characteristics, since CHAT (marked by blackened areas) tends to occur more frequently during the winter than during the summer.

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INDIVIDUALIZOVANÁ KOMBINOVANÁ CHRONOTERAPIE SOUČASNĚ SE VYSKYTUJÍCÍ „AMPLITUDOVÉ„ A „MESOROVÉ„ HYPERTENZE, VČETNĚ DILTIAZEMU

S o u h r n

Cílem studie je posouzení různých způsobů optimalizace časového podávání léku při terapii hypertenze typu cirkadiánní hyperamplitudy krevního tlaku u 72-letého muže. Pro ověření účinnosti různých modifikací léčby jsou použity parametrické testy a kontrolní diagram CUSUM .

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