

IATROGENIC EXCESSIVE BLOOD PRESSURE VARIABILITY (CHAT): IMPLICATIONS FOR CHRONOTHERAPY

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Abstract

The aim of the study was to describe circadian hyper-amplitude-tension (CHAT) in an 82-year-old man treated with sotalol hydrochloride (Betapace), a beta-adrenoceptor blocker with class III anti-arrhythmic properties. Our results showed an increase in diastolic blood pressure, assessed as rhythm-adjusted mean value (MESOR), after treatment withdrawal and a decrease in both systolic and diastolic blood pressure (MESOR) after resuming treatment. This was accompanied by a considerable decrease in the double amplitude of both systolic and diastolic blood pressure.

Key words

Essential hypertension, Chronotherapy, Circadian variability

INTRODUCTION

The meta-analyses of randomised controlled trials have found that some drugs, such as calcium antagonists, compare less favourably with other first-line anti-hypertensive therapies, despite a seemingly similar blood pressure (BP)-lowering effect (1). Chronobiologic trials, however, have shown that different anti-hypertensive agents can have drastically different effects on the circadian BP amplitude but similar BP-MESOR lowering effects (2). Our results have also demonstrated a possibility to achieve different effects with the same dose of the same drug by solely changing its administration schedule (3).

In this study, a case of an 82-year-old man diagnosed with circadian hyper-amplitude-tension (CHAT) is described. The patient was treated with sotalol hydrochloride (Betapace), a beta-adrenoceptor blocker with class III anti-arrhythmic properties, twice daily. We investigated whether this condition associated with a large increase in vascular disease risk even in normotensive patients can be related to treatment in terms of dosage and timing.

CASE REPORT AND METHODS

An 82-year-old man with a history of coronary artery disease and triple and quadruple coronary artery bypass grafting was treated with Betapace (80 mg) twice a day (upon awakening and at bedtime), to avoid fibrillation and to reduce a slightly elevated BP MESOR. Blood pressure was measured longitudinally around-the-clock at 30-minute intervals (with few interruptions) throughout the investigation (June 1 to July 5, 2001). An ambulatory monitor (TM-2421, A&D, Tokyo, Japan) was used. The originally prescribed treatment was first withdrawn (June 11–21) and then changed to a single morning tablet (June 21–26). The data were evaluated by sphygmochron analysis. This combined parametric and non-parametric approach is used to assess circadian variation in BP and any deviation from time-specified reference limits derived from data provided by clinically healthy peers of the same gender and similar age (2–5). The effects documented by parameter tests (6) were validated by resuming the initial treatment schedule (June 28–30), withdrawing it again (July 1–4) and going back to a single morning tablet (starting July 5).

RESULTS

Changes in the MESOR and circadian double amplitude (2A) and acrophase (time of overall high values recurring each day) of systolic (SBP) and diastolic (DBP) blood pressure associated with treatment withdrawal and going back to a single morning tablet are summarised in *Table 1*.

The results show an increase in the MESOR of DBP ($P=0.005$) after treatment withdrawal, a decrease in MESOR of both SBP ($P=0.002$) and DBP ($P<0.001$) after resuming treatment with a single morning tablet, accompanied by a considerable decrease in 2A of both SBP ($P=0.022$) and DBP ($P=0.038$).

As compared to treatment twice daily, a single daily tablet in the morning was associated with a highly significant decrease in the circadian double amplitude of SBP ($P<0.001$) and DBP ($P=0.003$). When treatment twice daily was resumed and subsequently withdrawn, the circadian double amplitude of both SBP ($P=0.017$) and DBP ($P=0.037$) increased; in the absence of treatment, the MESOR of both SBP ($P=0.004$) and DBP ($P<0.001$) was increased.

Table 1
Blood pressure monitoring during treatment with sotalol

Treatment Schedule	SBP			DBP		
	MESOR	2A	Acrophase	MESOR	2A	Acrophase
Twice daily	127.7±15	42.9±4.2	16:48±0:	67.4±11	25.2±30	16:56±0:28
No treatment	130.4±15	34.0±4.1	16:00±0:8	71.9±11	21.2±3	15:36±0:32
Once daily (a.m.)	123.5±15	20.0±4.2	14:16±0:8	66.1±09	12.8±24	14:24±0:44
Comparison						
F	5.534	7.634	3.971	9.235	4.981	4.144
(P)	(0.006)	(0.001)	(0.024)	(<0.001)	(0.010)	(0.020)

SBP, systolic blood pressure; DBP, diastolic blood pressure; MESOR, rhythm-adjusted mean value; 2A, double amplitude; acrophase, time of overall high values recurring each day; F, statistical significance (F-value); (P), statistical significance (P-value).

Changes in heart rate variability, gauged by the 24-hour standard deviation (SD) of heart rate (HR), were also observed, namely, a significant increase from 7.4 to 11.7 beats/min after withdrawal of twice daily treatment (Student's *t*-test = 2.858; *P*=0.012). With a single morning tablet, the SD of HR was 8.9 beats/min and this was not statistically different from the SD of the HR value when two tablets daily or no tables were administered.

The increase in heart rate variability in the absence of treatment was detected by a cumulative sum control chart (7) one week after treatment withdrawal. It was estimated that the increase in heart rate variability in the absence of treatment took place only 3 to 4 days after the treatment had been removed.

DISCUSSION

This case is presented to call attention to the desirability of checking long-term effects of Betapace. Since occasional BP profiles cannot detect long-term treatment effects, monitoring for a minimum of 7 days around the clock is recommended (8). Whether a single 80 mg dose upon awakening also provides an adequate anti-arrhythmic activity can be investigated by concomitant, 7-day, around-the-clock electrocardiographic and BP monitoring. Possible implications of undesirable alterations of the circadian BP pattern due to treatment have recently been suggested by a trial of benidipine (once a day) vs. nifedipine (twice a day). This treatment, associated with a reduction in circadian BP amplitude (benidipine), has generally been accompanied by a lower incidence of strokes and cardiovascular events (9). The chronobiological investigation reported herein was not blinded and treatment was withdrawn rather than replaced by a placebo. The measurements, however, were taken automatically, during sleep as well as during waking hours, often without the awareness of the subject. These results are corroborated by findings from group trials (9, 10). They also warrant further investigation into long-term treatment and its withdrawal in terms of chronobiology.

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IATROGENNÍ EXCESIVNÍ VARIABILITA KREVNÍHO TLAKU (CHAT) DŮSLEDKY PRO
CHRONOTERAPII

S o u h r n

Cílem studie bylo popsat cirkadiánní hyperamplitudu (CHAT) u pacienta stáří 82 let, který byl léčen sotalolem (beta blokátor třetí třídy s antiarytmickými vlastnostmi). Naše výsledky ukazují vzestup diastolického krevního tlaku (měřeného jako MESOR) po vysazení léčby a pokles systolického a diastolického krevního tlaku (MESOR) po jejím opětovném nasazení, což bylo rovněž vyjádřeno jako pokles dvojité amplitudy jak systolického tak diastolického krevního tlaku.

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