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Why continued surveillance? Intermittent blood pressure and heart rate abnormality under treatment

G. S. Katinas^a, G. Cornélissen^a, K. Otsuka^b, E. Haus^a, E. E. Bakken^c, and F. Halberg^{a,*}

¹Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA

²Tokyo Women's Medical University, Medical Center East, Tokyo, Japan

³North Hawaii Community Hospital Inc., Kamuela, HI, USA

Abstract

Several opinion leaders have monitored their blood pressure systematically a sufficient number of times a day for chronomic (time structural) analyses, from the time of encountering chronobiology until their death; they set an example for others who also may not wish to base treatment on single spotchecks in a health care office. Such self-measurements, while extremely helpful, were not readily feasible without a noteworthy interruption of activities during waking as well as of sleep. New, relatively unobtrusive instrumentation now makes monitoring possible and cost-effective and will save lives. Illustrative results and problems encountered in an as-one-goes self-survey by GSK, a physician-scientist, are presented herein. Both MESOR-hypertension and CHAT (circadian hyper-amplitude-tension) can be intermittent conditions even under treatment, and treatment is best adjusted based on monitoring, rather than “flying blind”.

Keywords

Surveillance; Blood pressure; Heart rate

Dedicated to the memory of Howard Levine. MD (1916–1981), professor of medicine at the University of Connecticut and director of medical education at New Britain (CT) General Hospital. who knew and benefited from the value of systematic self-measurements.

1. Background

Howard Levine [1–23], the late professor of medicine at the University of Connecticut and director of medical education at New Britain General Hospital, continued self-measurements several times each day for the surveillance during treatment of his blood pressure deviation until the day of his death from amyotrophic lateral sclerosis, the associated weakness notwithstanding. Frederic C. Bartter (of Bartter syndrome fame) likewise advocated self-monitoring [24–26]; like Levine. he also had his data analyzed, and wrote, regarding a patient whose blood pressure was diagnosed differently by two physicians who saw him at different times of day [24]:

« By conventional standards, this patient is clearly normotensive every morning. But the blood pressure determined each day at 6 in the afternoon provides especially convincing evidence that this patient is a hypertensive. [...] »

« My plea today is that information contained in [data curves compiled under differing circumstances, such as 24 h a day/7 days a week] become a *routine minimal amount* of information accepted for the description of a patient's blood pressure. *The analysis of this information by cosinor should become a routine.* It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, to wit. an estimate of M [the time structure or chronome-adjusted mean, or MESOR] ... an estimate of [the amplitude] A itself, and finally an estimate of acrophase, ϕ [a measure of timing]. In this way, a patient can be compared with himself at another time, or under another treatment, and the patient can be compared with a normal or with another patient [24] (cf. [8,25]).»

Dr. Marianne Haus (like her chronobiologist son EH, the latter with a 30-year record) self-measured her blood pressure, which under treatment happened to reach up to 200 mmHg systolic values at the start of monitoring [26]. After a number of years, she learned that her treatment was no longer necessary; after discontinuance of unnecessary treatment, realized in view of the as-one-goes examination by self-measurements, her systolic blood pressure fell to values below 100 mmHg (without treatment!) [26–28]. Earlier, by self-measurements, we noted the disappearance of MESOR-hypertension with age [22].

Another co-author, F.H., has, with interruptions, a record of about two decades of automatic monitoring, complemented by preceding self-measurements and has detected and repeatedly eliminated at least intermittently, both CHAT and/or MESOR-hypertension, sometimes only by changes in treatment timing [27–29]. Dr. Yoshihiko Watanabe is a champion of systematic, rather than interrupted, automatic measurements: he has reported on his half-hourly values now covering 18 years [30–43], demonstrating, as did FH by superposed epochs [44], an association of his blood pressure with magnetic storms by cross-spectral coherences [32]. The overall champion of blood pressure measurements is undoubtedly Dr. Robert B. Sothorn, whose data, about five times per day for 38 years, are also available in the literature, demonstrating the time course of blood pressure in clinical health [45–47].

Analyses of chronobiologic trials in health with a 28-year follow-up on a clinically healthy group [48,49] and a group of patients [50] (cf. [51,52]) have revealed several risks. In addition to that of high blood pressure or separately, there can also be blood pressure overswinging or CHAT; even in the absence of a MESOR-deviation such as an elevation, CHAT carries a risk of hard events greater than that associated with MESOR-hypertension [50] (cf. [27]). Other risks, such as an odd timing of the circadian blood pressure rhythm (circadian ecphasia), a high pulse pressure and a low heart rate variability are beyond our scope herein, but not less important [29,51,52]. Here we report a case of intermittent MESOR-hypertension, an increase in the chronome (time structure)-adjusted average, or MESOR, complicated by intermittent CHAT, both persisting under continually adjusted and only transiently successful treatment, perhaps since as yet treatment could not be adjusted with a lag of only minutes rather than days and/or because of some extent of refractoriness to the particular treatment used.

2. Subject and methods

GSK, who has been treated for high blood pressure since the age of 34 years in 1959, started automatic monitoring of blood pressure and heart rate at half-hourly intervals in 1998, at 72 years of age, on the day after his arrival as a visiting professor at the University of Minnesota. He has continued monitoring ever since while undergoing and adjusting his antihypertensive and other treatment; his contributions to his own health care and to science include a demonstration of transyears, “years” longer than a calendar year that were reported earlier [53,54] (cf. [28]). His record yielded individualized reference values for his blood pressure and heart rate. He used a device from Nippon Colin (Komaki, Japan) first and an A&D (Tokyo) device thereafter. Table 1 gives an indication of the medications he used and manipulated,

based on an about-weekly study of his record analyzed time-microscopically by sphygmochron [29,51,52]. To test for changes in timing his medication, he used a descriptive model of the physiological blood pressure behavior based on folding (stacking) data according to the length of the cycle's period (in a plexogram) and determining the speed (V) and acceleration (V_v) of his blood pressure dynamics computed as the first and second finite differences:

$$V = \Delta y_k / \Delta t_k = (y_k - y_{k-1}) / (t_k - t_{k-1}),$$

$$V_v = \Delta V / \Delta t_k = (V_k - V_{k-1}) / (t_k - t_{k-1})$$

3. Results

All figures of this publication reveal, for this case, more completely than was done earlier in others [55–58], that MESOR-hypertension under closely surveyed conditions can be a greatly changing phenomenon, as is CHAT [59]. Fig. 2 suggests that CHAT has been successfully treated for a number of days but also reveals the return of CHAT thereafter. Fig. 2A shows a total of several weeks without CHAT following frequent changes in treatment; Fig. 2B suggests again that changes in treatment can eliminate CHAT for a while but its return cannot be predicted, Fig. 2C–E. All figures reveal that albeit intermittent CHAT is present most of the time, 24-h spotchecks can show either the presence or the absence of CHAT on different days of half-hourly monitoring. Once CHAT is diagnosed, even a week of monitoring does not suffice. Fig. 3 shows the time course of both the MESOR (top) and the amplitude (bottom), each characterized by very great variability, the many changes in treatment (itemized in Table 1) notwithstanding.

The treatment dosage and timing affect 24- and 12-h components differently, Fig. 4. The reduction of an excessive 24-h amplitude shown in black in the chart below is accompanied by an increase in the 12-h amplitude. Accordingly, we see changes in the ratio of the circasemidian-over-circadian amplitude which is normally smaller than unity, but can change to above unity as seen in Fig. 5. It was noted earlier that closing the loop, preferably automatically, between monitoring blood pressure and treatment will be desirable [29].

The temporal variation after a change in treatment, shown in Fig. 4, had been seen earlier in Fig. 6 [53]. During the first half of April 1998, CHAT prevailed notwithstanding nifedipine treatment. In an attempt to lower the circadian amplitude of blood pressure, this drug was replaced by diltiazem. An effect seemed to occur immediately, but it lasted only for about 1 week, as seen in the moving spectrum. Had one stopped monitoring after 7 days, the reappearance of CHAT would have been missed. There is no substitute for continuous surveillance unless one takes a chance on "flying blind" [60] and missing the return of a silent high-risk condition.

Moving spectral windows are particularly useful when they are combined with global spectra, as in Fig. 7. They allow us to examine the dynamics of many components in the particular spectral element of a chronome contemporaneously and allow the detection of the particular time spans when any special changes in a wide spectral range occur, so that these can be scrutinized in the light of diaries.

4. Conclusion

Supermarkets, garages and small rodents' blood pressure in pharmaceutical industry laboratories are being monitored to prevent theft or rape or to produce drugs, respectively. Only the absence of demand prevents doing to humans what is state of the art for mice, so that the drugs produced with monitoring are not used without this technology, which GSK's data suggest may be useful. An editorial accompanying a chronobiologic paper [60] advised that

the current practice of spotchecks corresponds to “flying blind” into a mountain range. Some of these risky mountains can be compared with CHAT, a very high-risk of stroke and other severe diseases [27,29,50–52]. Monitoring to prevent or reduce the extent and thus the impact of these conditions is cost-effective, when, through the BIO-COS project (corne001@umn.edu), automatic monitors can be obtained with an 80% price reduction along with chronomic (time-structural) analyses, shown here. The prevention of crippling disease, now feasible, should be a top priority so that prehabilitation eventually dispenses with the need for rehabilitation.

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THE VARIABILITY OF TREATED (Rx) SYSTOLIC MESOR-HYPERTENSION COMPLICATED BY CIRCADIAN HYPER-AMPLITUDE TENSION, BRIEFLY CHAT*

* Half-hourly records (with gaps) of the blood pressure of a 72 year-old man at the start of observations. Original data (N = 90326) of G.S.K. on different Rx. Rx at start: Diltiazem 90 mg at ~ 06:00 + Nifedipine 10 mg at ~ 10:00, 15:00 and 20:00; many adjustments Rx during 7 years.

Fig. 1.

Chronogram of GSK's automatic systolic blood pressure measurements, made by wearable recorders (the last model used was a TM-2421, produced by A&D ENGINEERING INC); records were begun on the day after arrival in Minneapolis (MN, USA) after crossing 9 time zones (from East to West) from St-Petersburg (Russia) on March 30 1998. GSK suffers from hypertension since 1959. His treatment in Russia was repeatedly adjusted but only after occasional spotchecks. After the beginning of automatic half-hourly around the clock monitoring, Rx changes were instituted many times, mainly not in the kind of drugs or their dose, but in changing the timing of medication. This general view of the chronogram shows many spikes, consisting of several consecutive gradually increasing and then decreasing values

that because of this pattern are not likely measurement artifacts and which could not be detected without systematic monitoring. © Halberg.

Fig. 2.

A–E Daily swings (the double circadian amplitude, 2A) of the circadian component of the chronome (time structure) during the span from 1998 to 2002 show intermittent CHAT; various regimens of treatment were aimed at correcting it but were only partially and transiently successful. Different events other than treatment might impact the double amplitude, such as transmeridian flights and short lasting illnesses but are not here identified. One can only speculate about the time course of blood pressure if treatment had not been adjusted! © Halberg.

**CONSECUTIVE DAILY AVERAGES (above) and CIRCADIAN SWINGS (below)
of SYSTOLIC BLOOD PRESSURE (SBP) DURING ~ 6 YEARS
ALTERNATE BETWEEN ACCEPTABILITY (gray) and UNACCEPTABILITY (black)***

* Values from non-overlapping with 1-day intervals serial sections on half-hourly around the clock data; GK (M, 72-78 y) on varying treatments.

Fig. 3.

Daily values of MESOR (above) and double amplitude (below) during 6 consecutive years show that MESOR-hypertension does not always coincide with CHAT (see 1999, 2001–2002) but may occur particularly at the transitions from MESOR-normotension to MESOR-hypertension or at a change in the opposite direction. © Halberg.

TREATMENT'S DOSAGE AND TIMING HAS DIFFERENT EFFECT UPON 24- AND 12-HOUR COMPONENTS IN SPECTRAL ELEMENT OF THE SYSTOLIC BLOOD PRESSURE* CHRONOME

* GSK, treated MESOR-hypertensive 73-year old man, monitored every ~30 minutes. Amplitude values in the gliding spectrum, corresponding to CHAT, are shown in 3 darkest shading grades (see key). NOTE: Increasing dosage of diltiazem from 270 mg to 360 mg at ~7 a.m. decreased not only MESOR, but also 24-hour amplitude. Continued dosage of 360 mg, but divided into two parts (270 mg at ~7 a.m. and 90 mg at ~4 p.m.) eventually led to intermittent CHAT. 12-hour amplitude was not immediately affected by change in dosage, but increased thereafter, occasionally matching value of 24-hour amplitude.

Fig. 4.

Effect of too high a dose of Blocalcin(Diltiazem): it suppresses the circadian component without apparent impact on the circasemidian one. During the span when GSK took a dose of 270 mg at 07:00 h. the MESOR was higher than the limit for a healthy peer group; thereafter the dose was increased to 360 mg in order to try to lower the MESOR. A depression of the circadian amplitude was seen immediately. After 9 days, this dose was divided into 2 portions, in an attempt to restore the circadian rhythm: 270 mg at 07:00 h and 90 mg at 16:00 h. A restoration of the circadian rhythm took about 2 weeks to occur and remained seemingly more intermittent than usual for about 5–6 weeks. Occasionally, CHAT reappeared as seen by the black areas. © Halberg.

INTRA-INDIVIDUAL VARIABILITY IN WAVEFORM OF SYSTOLIC BLOOD PRESSURE (SBP)*

* GSK, treated MESOR-hypertensive 73-year old man, monitored every ~ 30 minutes.

Treatment in 1999: diltiazem; A (May 12 – 14) – 270 mg at 7 a.m., B (May 27 – 29) – 360 mg at 7 a.m., C (July 23 – 25) – 270 mg at 7 a.m. and 90 mg at 4 p.m.

** Data from 3 consecutive days were first stacked for 24-hour span and 7.2-hour intervals of the stacked data were then fitted with a third-order moving polynomial, displaced in ~0.5-hour increments. *** Circasemidian / circadian amplitude ratio.

Fig. 5.

It is not possible to classify people according to daily profiles of their systolic blood pressure based on only occasional 1–3 day-long monitoring profiles, notably in the presence of treatment and repeated changes in the scheduling of its administration. Different patterns (A–C) were obtained during different time spans with intervals of several weeks between those records. These features are resolved as rather different spectral components on the right: in A the circadian component is maximal; it is practically not detected in B (note the bigeminal form of the plexogram's curve). A circasemidian component changed less than the circadian in the spectra on the right. © Halberg.

A **NEED FOR LONG-TERM SURVEILLANCE:
TREATMENT CHANGES SYSTOLIC (S) CHAT*
INTO TRANSIENT S-CHAT**
WHICH LATTER APPEARS AFTER A WEEK**

* CHAT: Circadian Hyper-Amplitude Tension.

** In GK, 72- year old man, whose blood pressure was measured at mostly 30-minute intervals, and analyzed as a moving spectrum in separate 48-hour intervals, displaced in 8-hour increments through the data set.

***Rx-1: Nifedipine 2 x 10 mg at 8 a.m. and 8 p.m.; Rx-2: Diltiazem 3 x 90 mg at 10 a.m, 3 p.m and 8 p.m.

Fig. 6.

Fig. 6A Gliding (moving) spectrum; the density of shading corresponds to the values of the amplitude; eliminating CHAT might be achieved by changing treatment. This effect, however, might not be consistent; CHAT reappeared again in about 1 week. Without continued monitoring the reappearance of CHAT will be missed. © Halberg.

Fig. 6B The same gliding spectrum as in Fig. 6A is shown as a 3D chart. The height of "mountains" corresponds to the amplitude. Darkened tops show CHAT.

Gliding amplitude (A) spectral window (I, II) shows relative prominence of spectral components, mostly intermittent CHAT* with occasional ultradian prominence.

Fig. 7.

Gliding spectra for the analysis of blood pressure reveal the dynamics in time of all of the spectral components. While in the total (global) spectrum (III, right) only peaks are revealed, the gliding window permits to distinguish contemporaneously all peaks characterizing the dynamics of the time course underlying the global spectrum and show also components with a relatively small amplitude. An excessive circasemidian amplitude comparable to CHAT was also detected in this amplitudogram around April 10. Any risk associated with this condition and/or of a broader circadian-to-ultradian or circadian-to-extracircadian variance transposition remains to be assessed.© Halberg.

Table 1

MAIN EVENTS in Rx

00 – 1998 03 30 2100 – –09, 21	Arrival to Minnesota from St.-Petersburg after crossing 9 time zones to the West and 28 h sleep deprivation
Medications used :	
B = Diltiazem (trade name Blocalcin)	
F = Nifedipine (trade name Fenigidin)	
LASIX	
Triampur = 125 mg of Hydrochlorothiazide (H) + 125 mg of Triamtren	
Propanolol	
Lisinopril	
Hydrocortisol+Lipase	
Crestor	
N = Nifedipine 10 mg in capsule (trade name Nifedipine)	
01 – 1998 04 20 – B: 90 mg at 06 F: 10 mg at 15, 20	
02 – 1998 05 06 – Rx not regular	Sleep restriction
03 – 1998 05 09 – Rx not regular	Normal sleep
04 – 1998.05 11 – F: 10 mg at 10, 15, 19; B: 90 mg at 21	B moved to the evening
05 – 1998 05 27 – F: 10 mg at 10, 14, 18, 21; B: 90 mg at 21	F added
06 – 1998 06 16 – B: 90 mg at 06; F 10 mg at 03, 10, 15, 21	Timing F chosen and then adjusted by acceleration (2 h before its peaks)
07 – 1998 07 14 – B: 90 mg at 04; F 10 mg at 21	F dosage decreased, Timing adjusted by acceleration
08 – 1998 07 29 – B: 90 mg at 04; F 10 mg at 07, 21	F added. Timing adjusted by acceleration
09 – 1998 08 13 – B: 90 mg at 03; F – same	Timing adjusted by acceleration
11 – 1998 09 14 – B: 90 mg at 04:30; F – same	Timing of B changed, to see whether delaying B by 1.5 h can change the blood pressure and heart rate
12 – 1998 10 05 – B: 90 mg at 00; F 10 mg at 03, 21	Timing changed (adjusted to the peaks of acceleration (coinciding with peaks)
13 – 1998 11 02 – B and F: both moving schedule (the same dosage)	Adjusted by acceleration every 3 – 4 days
14 – 1999 01 28 – B: 45 mg $\times$ 4 per day, moving schedule	Only B (no N) – Adjusted by acceleration
15 – 1999 02 17 –	Melatonin instead of B (no B, no N)
16 – 1999 03 09 – B: 270 mg at 07	Increase B, no N. no Melatonin
19 – 1999 04 18 – same	Acyclovir 800 mg $\times$ 7 daily added because of Herpes zoster
20 – 1999 04 27 – same	End of Acyclovir intake
21 – 1999 05 12 – B 180 mg at 07, 90 mg at 19	B same daily dosage, but 1 tablet moved to evening
22 – 1999 05 25 – B 360 mg at 07	B increased dosage, taken once a day in the morning.
23 – 1999 06 05 – B 270 mg at 07, 90 mg at 16	adjusted by acceleration, 4 h before the evening peak
26 – 1999 08 19 – B 270 mg at 07, F 10 mg at 16–17	Evening dosage of B replaced by F
27 – 1999 09 29 – B 90 mg at 07; F 10 mg at 07, 16	Dosage changed

00 – 1998 03 30 2100 – –09, 21

**Arrival to Minnesota from St.-Petersburg
after crossing 9 time zones to the West and
28 h sleep deprivation**

34 – 2000 02 26 – F 10 mg at 03, 18, 21	Only F
35 – 2000 03 17 – F 10 mg, 10 mg, 5 mg, 5 mg	Adjusted by acceleration
38 – 2000 08 29 – F 10mg, 10mg, 10mg, 5mg	Adjusted by acceleration
40 – 2001 03 03 – F same,	LASIX because of ankle oedema
41 – 2001 03 06 – F same	
43 – 2001 04 13 – F 10 mg × 4 times/day	Adjusted by acceleration
46 – 2001 08 09 – F 10, 10, 10 5 mg	Adjusted by acceleration
Triampur 10 mg at ~ 21	
47 – 2001 09 11 – F same	no Triampur
50 – 2001 11 15 – F 30 mg at 07,	Without paying attention to acceleration
Propanolol 10 mg at 07, 13, 16	Adjusted to the physician's prescription
51–2001 11 26 – F 30 mg at 07	Suddenly felt weak,
No Propanolol at 16	SPP = 160. DBP = 105, HR = 48
52 – 2001 11 27 – F 30 mg at 07, Propanolol 10 mg at 07, 21	
53 – 2002 01 03 – Immunization Hepatitis–A and Polyo.	Next 2 days felt like cold with much serous discharge from nose
54 – 2002 01 06 – Immunization Pneumococcus and Influenza	Next days felt well
55 – 2002 01 09 – F 30 mg at 07, Propanolol 10 mg at 07	Because of decrease in HR
56 – 2002 01 14 – F 10 mg at 09, 15 21 Propanolol 10 mg at 07	
56 – 2002 01 21 – F 10 mg at 09, 15 21,	no Propanolol
58 – 2002 01 28 – F 10 mg at 07, 12, 16, 21	F added
61 –200205 20 – F 10 mg at 07, 12, 16	F dosage decreased
68 – 2002 11 08 – Flu-shot	
69 – 2002 11 09 – F 10 mg at 07, 12, 16 H 0.125 mg at 09	
73 – 2002 11 25 – F 10 mg at 07, 12, 16	No H
76 – 2003 02 26 – F same Lisinopril 20 mg at 09	added by physician's
77 – 2003 02 28 – Injection of Hydrocortisol+Lipase in the left palm	because of pains (Dupuitrairie contracture)
80– 2003 03 28 –Lisinopril 10 mg at 14	
83 – 2003 04 22 – Lisinopril 10 mg at 08–09 F 10 mg at 06, 09, 14	Adjusted by acceleration
84 – 2003 05 07 – F 10 mg × 3 / day No more Lisinopril.	Adjusted by acceleration
88 – 2003 07 10 – F total 30 mg / day. mostly 10 mg at 01–03, 10 mg at 07, 5 mg at 12, 14–16	Adjusted by acceleration,
91 – 2003 09 26 – F total 35 mg / day 10 mg at 01–02, 05–06, 5 mg at 09, 12, 15 ~ 5-6-7a.m.- 10 ~ 9a.m.-5 ~ 12 - 5 ~ 3p.m.-5	Not taking acceleration into account

00 – 1998 03 30 2100 – –09, 21

Arrival to Minnesota from St.-Petersburg
after crossing 9 time zones to the West and
28 h sleep deprivation

93 – 2003 10 12 – F 10 mg $\times 3$ or $\times 4$	at no regular time during the day Triampur at 09.
96 – 2003 11 24 – F 10 mg at 02, 06, 11, 15 Triampur at 09	If ankle oedema only, not recorded every time
122 – 2004 08 16 – F same Cosopt 1 drop at 07 and 21 to the left eye Timolol 1 drop at 07 right eye.	Visit to the oculist, later daily
124 – 2004 08 26 – F same Physical therapy procedures (including U-sound to the fight sacro-iliac joint)	
125 – 2004 09 01 – Same	
127 – 2004 09 10 – Same	
128 – 2004 09 16 – Same	
130 – 2004 09 30 – Same	end of procedures
132 – 2004 10 24 – F same Crestor 0.05 mg at 21	Because of high lipid concentration in blood
138 – 2004 11 03 – Flu shot	
141 – 2004 11 06 – F 5 mg at 01, 03, 05, 07, 09, 11, 13, 15	
143 – 2004 12 13 – F 5mg at 03, 05, 07, 09, 11, 13, 15, 17.	
149 – 2005 03 22 – F at 03, 06, 09, 11, 13, 15, 17	Dosage decreased because Sphygmochron and chronograms shown low BP and absence of Circadian Rhythm,
150 – 2005 03 28 – No F B 90 mg at 03 and 11	at 12:30 weakness, bradycardia to 40/min, lasting to the evening
151 – 2005 03 29 – B 45 mg at 08:30	
152 – 2005 03 30 – B 45 mg at 05:30 and 11:30	
153 – 2005 03 31 – B 45 mg at 04:30	
154 – 2005 04 01 – 05 B 45 mg at 03 – 04	
156 – 2005 04 07 – B 45 mg at 07:45	
158 – 2005 04 08 – No B:	at 6:45 still in bed strong bradycardia.
159 – 2005 04 12 – N $\times 3$ / day	After 4 days having NO Rx, Adjusted to waveform.

From beginning blood pressure recording - to 2004 08 15:

Glaucoma treatment: after awakening:

Timolol maleat 0.5% solution
1 drop in both eyes
before going to bed:
Timolol maleat 0.5% solution
1 drop in the right eye,
Xalatan latanoprost 0.005% solution
1 drop in the left eye.

From 2004 08 15:

Glaucoma treatment: after awakening:

Timolol maleat 0.5% solution
1 drop in the right eye,
Cosopt dorsolamide hydrochloride-timolol
maleat

00 – 1998 03 30 2100 – –09, 21

**Arrival to Minnesota from St.-Petersburg
after crossing 9 time zones to the West and
28 h sleep deprivation**

1 drop in the left eye,

before going to bed:

Cosopt

1 drop in the left eye,

Xalatan 0.005 % solution 1 drop in the left eye.

1 drop in the left eye.