



Influence of Altiazem PP-180 on Hemodynamic Parameters in Arterial Hypertension Patients under Outpatient Conditions

GR Zhakiyeva^{1*}, LM Tulegenova², NZ Ibragimova³, SM Kelimberdiyev²
and KK Tokbayeva³

¹ Associate Professor and HOD, General Practice of Internship and Postgraduate Training, West Kazakhstan Marat Ospanov State Medical University, Aktobe, Kazakhstan

² Professor, Department of General Practice of Internship and Postgraduate Training, West Kazakhstan Marat Ospanov State Medical University, Aktobe, Kazakhstan

³ Assistant Professor, Department of General Practice of Internship and Postgraduate Training, West Kazakhstan Marat Ospanov State Medical University, Aktobe, Kazakhstan

*Corresponding e-mail: gulzhahan.zhakieva@list.ru

ABSTRACT

The aim of this research work is to study the effect of altiazem PP-180 on hemodynamic parameters in 78 II-degree arterial hypertension patients under outpatient conditions. Hemodynamic effect of altiazem PP-180 hypotensive action was successfully observed at 07.00 a.m., 10.00 a.m. and 10.00 p.m. intake time, with normal patients' routine. Altiazem PP-180 causes a distinct hypotensive effect in II-degree arterial hypertension patients when used under outpatient conditions at different times of a day both fixed or random. The most productive hemodynamic effect of altiazem PP-180 hypotensive action can be observed when taken at 07.00 a.m., 10.00 a.m. and 10.00 p.m. provided that a normal work/rest routine is kept. When administered at 07.00 a.m., 10.00 a.m. and 10.00 p.m., altiazem PP-180 causes substantial decrease of peripheral vascular resistance, end-diastolic and end-systolic volumes. Hypotensive effect of altiazem PP-180, when administered at 01.00, 04.00 and 07.00 p.m. as well as at non-fixed times of day shows a less favourable hemodynamic effect: reduced cardiac output associated with total and peripheral vascular resistance index.

Keywords: Arterial hypertension, Altiazem, Time-dependent effects, Chrono efficacy

INTRODUCTION

The problem of optimization of a long-term supportive therapy of uncomplicated arterial hypertension (AH) is one of the most urgent issues in modern cardiology. Despite successful treatment of this disease a lot of problems related to the condition of elevated arterial blood pressure (ABP) remain unsolved, and the results of dispensary observations tend to be unsatisfactory. Due to the lack of clear scientifically grounded recommendations on medication-assisted treatment of various types of AH, doctors in practical healthcare are forced to administer treatment intuitively, based on their personal experience. Patients do not take medicine on regular basis, therefore their ABP can hardly be controlled and remains elevated [1-4].

Therefore, the search for an optimal individualized approach to the treatment of AH patients with hypotensive drugs is considered to be an urgent issue. Selection of the time of day when the hypotensive action of a drug tends to be the most effective and leads to favourable hemodynamic changes in a patient seems quite promising. It would allow patients to decrease hypotensive drug dosage frequency and reduce drug load, which would result in a decrease of side effects of antihypertensive agents. Given a wide variety of hypotensive drugs practicing physicians are not always aware of the optimal time of drug intake and dosage during the day under outpatient conditions [5-8].

At present, a great selection of hypotensive drugs is available with the drugs of calcium channel blocker class being of particular interest [4,9,10]. A number of research works demonstrate the ability of some drugs of this class to prevent the development of cardio-vascular complications [1,3,11,12]. At the present time, extended-release diltiazem is widely used and highly researched from the perspective of evidence-based medicine [12].

Diltiazem refers to non-dihydropyridine calcium channel blockers and produces an effect both on arteries and myocardium [13-17].

Large-scale random research works targeted at the evaluation of clinical efficacy of such drugs have mainly covered clinical laboratory evaluation of diltiazem pharmacological effect. Diltiazem, presented in new 24-hour extended-release dosage forms, is regarded as the most effective. It takes an interposition between dihydropyridine drugs and verapamil derivatives. Unlike verapamil, it does not cause acute cardio depression and does not lead to a sudden excessive activation of the sympathetic nervous system resulting in tachycardia, as dihydropyridine drugs do. Besides, there are a lot of AH patients with co-morbidity who are not recommended to take drugs of a different class; in particular, these are tachycardia-prone patients, patients with pulmonary pathology, peripheral vasospasm-prone patients; in this instance, it would be preferable to use diltiazem [8,14,17,18].

The study of both hypotensive and other effects of diltiazem would create an opportunity to comprehensively evaluate its efficacy in terms of arterial pressure control, its effect on endothelial dysfunction, and an opportunity to prevent cardiovascular complications.

At the present time, when administering hypotensive therapy, the preference is given to the drugs which are able not only to effectively control ABP but to influence primary pathological links while forming systematic AH due to their organ-protective action, as well. Ultimately, such an approach should improve the prognosis for AH patients, under the condition of drug chronic administration. In this regard, an integral part is taken by drugs, such as diltiazem, which are targeted at the correction of endothelium malfunction, i.e. correction of its dysfunction based on a 24-hour extended-release action [19,20].

The results of large-scale research work testify to substantial advantages of the group of drugs represented by diltiazem [15,16,20,21].

Various publications contain a large amount of information concerning the efficacy and safety of such drugs, including Altiazem-180 [2,7,22].

Nevertheless, the problem of the study of time-dependent effects of A-180, its Chrono efficacy under outpatient conditions based on a normal work/rest routine remains unsolved.

The objective of the research was to study of time-dependent hemodynamic effects of altiazem PP-180 and the parameters of blood circulation in II-degree arterial hypertension patients under outpatient conditions.

MATERIALS AND METHODS

The 78 II-degree arterial hypertension patients aged 42 to 73 were enrolled in the research (average age= 57.65 ± 0.6). About 28 research subjects were men and 50 were women. Duration of the disease made up 4 to 23 years (9.2 ± 0.12 on average).

The average duration of the patients' dispensary observation amounted to 7.4 ± 0.11 years. All the research groups were divided into 2 parts: an experiment group and a control group. The control group consisted of 30 patients who were administered A-180 once a day at random hours, whereas the experimental group included 48 patients who were randomly assigned to take A-180 once a day at a set time.

The I group contained 8 patients who took 180 mg of altiazem once a day at waking hours (7.00 a.m.). The II group included 8 patients who took 180 mg of altiazem three hours after waking up (10.00 a.m.). The III group had 8 patients who took the prescribed drug 6 hours after waking up (at 01.00 p.m.). The group IV - 9 AH patients who took A-180 nine hours (9 hours) after waking up (04.00 p.m.). The V group contained 7 patients who took the drug 12 hours after waking up (at 07.00 p.m.), and the VI group included 8 patients who took A-180 fifteen hours after waking up (at 10.00 p.m.).

During 3 days prior to treatment and during 10 days of the treatment course by altiazem PP-180 the patients had their ABP taken by means of Korotkoff sound technique and had their pulse measured 6 times a day every 3 hour by medical personnel or applying self-measurement.

All the patients in the research group underwent EKG and echocardiography procedures prior to and during the 10 day-course of treatment by altiazem PP-180 by means of Aloka ultrasound equipment (Japan). The patients' systolic

discharge (SD), end-diastolic dimension (EDD), end-systolic dimension (ESD), dimensions of aorta diameter and left atrium were measured. Cardiac minute output (CMO), stroke volume and cardiac indices (SVI and CI), total peripheral resistance, peripheral vascular resistance index (TPR and PVRI) and double product (DP) were determined according to generally accepted formulas. End-diastolic and end-systolic volumes (EDV and ESV) were determined according to Teicholz formula (1972).

Left ventricular mass (LVM) was determined in accordance with the formula suggested by American Heart Association and by American Society of Echocardiography. Interventricular septum thickness (IST) and left ventricular posterior wall thickness (LVPWT), end-diastolic dimension (EDD) measurement data were used.

$$LVM = 0.80 \times [1.04 \times (EDD + IST + LVPWT) - (EDD)].$$

During one week prior to drug administration, the patients did not take any other medicine that could influence their hemodynamics. The received data on chrono-drug-responsiveness to altiazem PP in hypertensive disease (HD) patients, the measurements results of hemodynamics indices prior and during treatment were analysed by means of variation statistics method, including a differential method based on electronic data processing machine PC/AT.

The difference was considered accurate if the differential was $p < 0.05$. In order to determine the circadian rhythm of hemodynamics parameters the method of Cosinor-analysis by Halberg [23] and the linked samples method were applied.

The essence of Cosinor-analysis is in cosine wave modelling of parameters, amplitude and acrophase deviation by means of the least square method [24]. Average daily rhythm level MESOR (MESOR - Midline Estimating Statistic of Rhythm), equals the arithmetical mean amplitude value.

Rhythm acrophase, the time of the indices' highest value, shows how much the cosine wave peak, approximating the given biorhythm, lags behind the cosine wave peak of the reference rhythm. While studying daily rhythms the rhythm of the Earth's rotation around its axis is considered as reference rhythm with the assumed reference time of acrophase at midnight. The acrophase measurement units are time units (second, minute, hour) or tangent units (degrees) [25-28].

The average amplitude of a daily rhythm presents the amount of difference between the index of maximum deviation and MESOR of approximating cosine wave. The amplitude measurement units may be expressed in the percentage of parameter deviation relative to MESOR or original physiological units.

Approximating curve or the researched rhythm "U" can be formularized as follows:

$$U = Co + C \times \cos (W \times T \times J),$$

Where Co - average level around which deviation occurs; C - deviation amplitude; W - angular frequency (i.e., reciprocal of period duration); t - time; J - acrophase.

Cosinor-analysis should be applied in two stages. At the first stage mathematical processing of data received during visual research has to be handled. It is called individual Cosinor-analysis. During the first stage, basic parameters of every rhythm must be determined individually. Then average group Cosinor-analysis must be done. The essence of this method is based on finding an average cosine wave for the group as a whole based on cosine waves peculiar to every individual separately [29,30].

Vector averaging of individual values must be performed and confidence intervals of amplitudes level and acrophase of daily deviation of the researched indices should be determined. It should be kept in mind that the parameters of individual group representatives may change.

Rhythm amplitude and acrophase are graphically represented in a circle in the form of a vector originating from the middle of the circle. Confidence limits of acrophase are depicted by lines tangent to an ellipse which shows the accuracy of the rhythm period. If the ellipse does not cover the centre of the circle, the 24-hour rhythm period is 95% accurate, and if it covers the centre of the circle, it is not accurate [31-33].

Average amplitude deviation, acrophase which is the time period of maximum indices, and MESOR were determined within the bounds of the research.

While analysing Chrono responsiveness to altiazem PP the following criteria had to be considered:

- Set-in time for the stable clinical and hypotensive effect in days;
- SABP, DABP, average ABP, DP within 24 hours prior to, during and after treatment;
- SD, CI, CMO, SVI, TPR, PVRI, LVM dynamics prior to and after treatment;
- Mechanism of altiazem PP-180 hypotensive effect;
- Changes in daily ABP, HR, DP profile prior to, during and at the end of the course of treatment;
- Characteristics of the 24-hour rhythm of all researched parameters, including MESOR, amplitude, and acrophase;
- Determination of circadian rhythm of SABP, DABP, average BP, HR and DP prior to, during and at the end of the course of treatment by altiazem PP-180.

The research was conducted with consideration of international ethical guidelines, including European Convention on Human Rights and Biomedicine developed by the Council of Europe and any amendments thereto, as well as bioethical national legislative regulations.

RESULTS AND DISCUSSION

The conducted research testified to an evident hypotensive effect of A-180 at all drug intake times: both at a set time and at a random time.

Nevertheless, it must be noted that the most evident hypotensive effect was observed when the drug was administered at 07.00 a.m., 10.00 a.m. and 10.00 p.m. Thus, the following showings were observed: a significant decrease in a daily average SABP from 193.75 to 145.5 mmHg (28% decrease), DABP decreased from 105.625 to 81.25 mmHg (23% decrease) and average ABP - from 134.625 to 1203.125 mmHg (25% decrease).

The evident hypotensive effect was achieved due to a decrease of TPR from 2134.675 to 1602.375 (24% decrease), PVRI from 1134.338 to 849.338 (25% decrease). The decrease of HR from 90.0 to 71.75 beats per minute was observed (22% decrease). Favourable hemodynamic effect of the drug was followed by a significant increase in cardiac output - SD increased from 60.625 to 71.6 ml (18%), ESV decreased from 59.3 to 39.2 ml (33%), EDV - from 128.5 to 100.7 ml (21%).

Ejection fraction increased from 45.3% to 52.6%. The decrease of left ventricular mass from 400.4 to 296.8 g. (25%) should be noted, as well. Hypotensive effect of the drug was achieved on the third day of treatment (Table 1).

Table 1 Effects of altiazem PP-180 on hemodynamics parameters when administered at 07.00 a.m. (waking hours)

Parameters	Before treatment	After treatment	P value
	M ± m	M ± m	
SABP, mmHg	193.75 ± 5.846	147.5 ± 2.339	<0.0003
DABP, mmHg	105.625 ± 2.214	81.25 ± 0.765	<0.0002
Average ABP, mmHg	134.625 ± 2.915	103.125 ± 1.152	<0.0001
HR, beats per 1 min.	90.0 ± 2.062	71.75 ± 1.598	<0.0002
SD, ml	60.625 ± 2.304	71.625 ± 3.307	<0.0029
CMO, l/min	5.32 ± 0.304	5.239 ± 0.209	≈ 1.00
CU, ml/m ²	32.2 ± 1.544	38.125 ± 2.319	<0.0037
CI, l/min/m ²	2.775 ± 0.171	2.75 ± 0.156	1.00
TPR, dyn.s.cm ⁻⁵	2134.675 ± 166.896	1602.375 ± 86.307	<0.01
PVRI, dyn.s. cm ⁻⁵ /m ²	1134.338 ± 88.398	849.338 ± 38.124	<0.01
LVM, gr.	400.4 ± 39.202	296.85 ± 19.77	<0.018
ESV, ml	59.375 ± 0	39.25 ± 0.06	<0.005
EDV, ml	128.5 ± 0	100.75 ± 8.93	0.05
EF, %	45.375	52.625	-
DP, relative value units	174.5 ± 7.671	108.5 ± 4.88	<0.004
Side effects; The day when the effect of drug administration can be observed 3.25 ± 0.153			

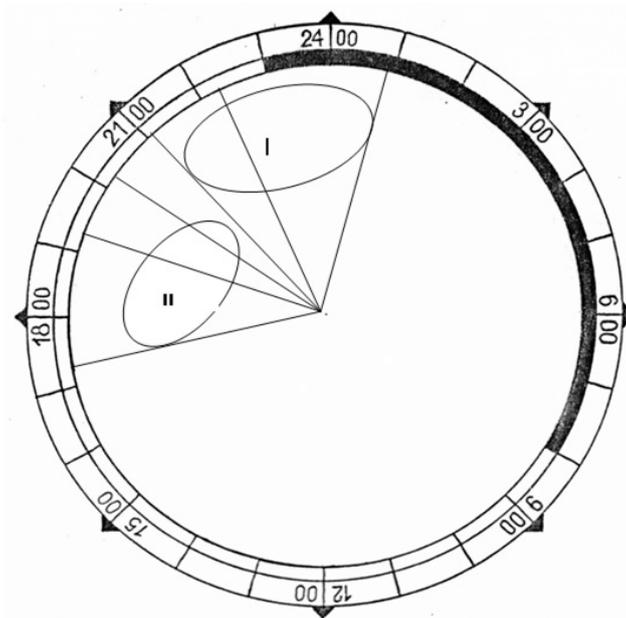


Figure 1 Cosinor of Circadian rhythm SABP prior to (I) and after (II) treatment at 07.00 a.m. by altiazem PP-180

Amplitude prior to treatment - 16.99 ± 2.52 (12.64-21.34);

After - 10.52 ± 1.66 (17.17-20.45)

Acrophase prior to treatment - 22.03 (20.07-24.59);

After - 19.23 (17.17-20.45)

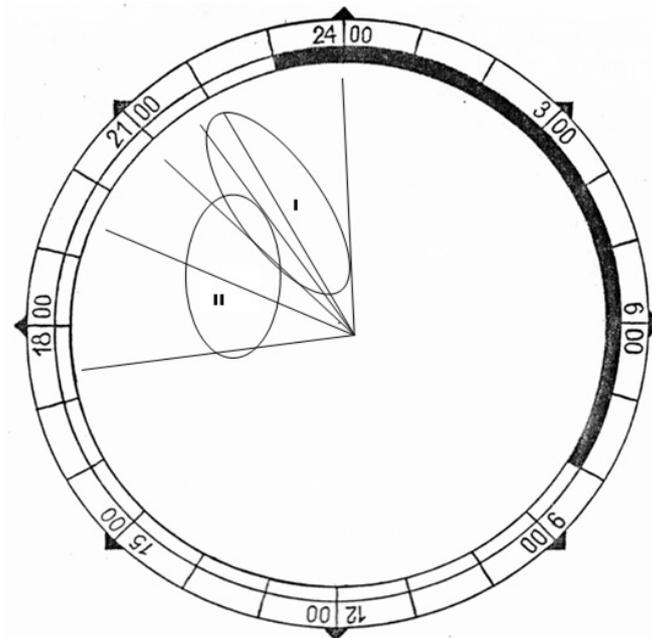


Figure 2 Cosinor of circadian rhythm DABT prior to (I) and after (II) treatment at 07.00 a.m. by altiazem PP-180

Amplitude prior to treatment - 7.45 ± 2.16 (3.72-11.18);

After - 5.19 ± 1.60 (2.42-7.96)

Acrophase prior to treatment - 22.01 (21.00-23.57);

After treatment - 19.50 (17.38-21.48)

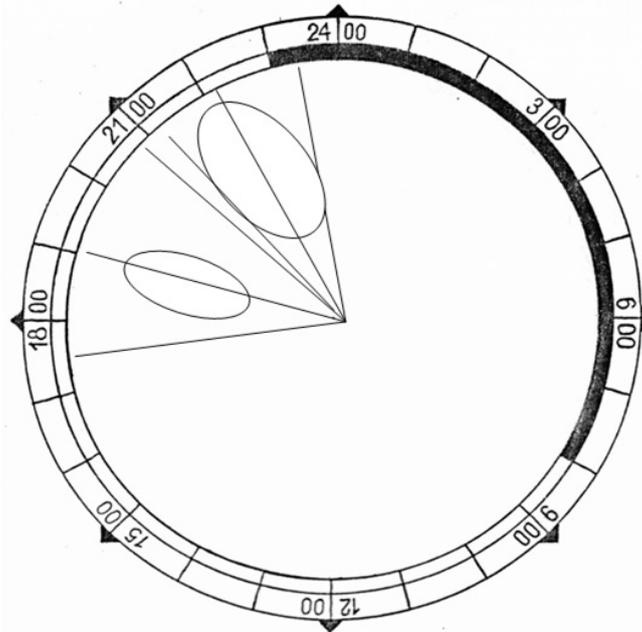


Figure 3 Cosinor of the circadian rhythm of average ABP prior to (I) and after treatment (II) by altiazem PP-180 at 07.00 a.m.

Amplitude prior to treatment - 10.63 ± 2.01 (7.16-14.10);

After treatment - 6.93 ± 1.42 (4.48-9.39)

Acrophase prior to treatment 22.02 – (21.15-23.15);

After treatment - 19.01 (17.37-20.53)

The study of Chrono structure dynamics of circadian rhythms of some hemodynamics parameters affected by Altiazem when administered at 07.00 a.m. (at waking hours) testifies to the decrease of MESOR SABP, DABP, HR, Average ABP, and DP. A slight decrease of rhythm amplitude was observed, especially SABP, Average ABP и DP and a shift of SABP, DABP, HR, Average ABP и DP rhythms acrophase from late evening hours (≈ 10.00 p.m.) to earlier evening hours (07.00 p.m.) (Table 1 and Figures 1-3).

The data presented in this work testify to a normalizing effect of A-PP-180 when administered at waking hours (at 07.00 a.m.) on circadian hemodynamics organization.

When administered at 10.00 a.m. the drug showed a significant decrease of SABP: from 80.8 to 136.2 mmHg (24%), DABP decreased - from 101.0 to 80.0 mmHg (20%). A clear hypotensive effect was caused by the decrease of TPR: at 10.00 a.m. - from 2004.8 to 1563.0 dyn.sec.cm (22%) as well as by the decrease of PVRI from 1192.8 to 869.1 dyn. sec.cm/m (27%), which points to a vasodilatory effect of the drug.

A significant increase in cardiac output was also noted. Therefore, SD increased from 58.2 to 74.1 ml (27%) and ejection fraction from 42% to 51.6%. At the same time a decrease of ESV from 92.5 to 74.1 ml. (19%) and EDV - from 153.8 to 120.5 ml (21%). Myocardium energy consumption decreased, which became evident due to the decrease of DP from 148.9 to 88.8 relative value units (40%).

LVM decreased considerably (by 31%) (Table 2). Clinical and hemodynamic effects were achieved on the 5th day provided A-180 was administered at 10.00 a.m.

Table 2 Effect of altiazem PP-180 on hemodynamics parameters at 10.00 a.m. intake time (3 hours after waking up)

Parameters	Before treatment	After treatment cp	p value
	M ± m	M ± m	
SABP, mmHg	180.875 ± 5.029	136.250 ± 3.03	<0.0004
DABP, mmHg	101.0 ± 0.935	80 ± 0	<0.0001
Average ABP, mmHg	123.75 ± 2.344	98.750 ± 1.042	<0.0002
HR,beats per 1 min.	85.75 ± 1.433	68.375 ± 1.620	<0.0007
SD, ml	58.25 ± 3.454	74.125 ± 1.980	<0.0039
CMO, l/min	5.293 ± 0.343	4.864 ± 0.349	≈ 1.00
SVI, ml./m ²	35.65 ± 2.348	39.238 ± 2.652	≈ 1.00
CI, l/min/m ²	2.738 ± 0.259	2.913 ± 0.165	≈ 1.00
TPR, dyn.s.cm ⁻⁵	2004.875 ± 178.95	1563.413 ± 70.762	<0.02
PVRI, dyn.s.cm ⁻⁵ /m ²	1192.863 ± 107.523	869.138 ± 38.360	<0.013
LVM, gr.	377.463 ± 40.367	260.175 ± 23.42	<0.013
ESV, ml	92.51 ± 0.01	74.125 ± 0.01	<0.05
EDV, ml	153.875 ± 00	120.5 ± 3.68	0.05
EF,%	42	51.625	≈ 0.05
DP, relative value units	148.95 ± 5.653	88.8 ± 2.896	<0.0002

Side effects 1; The day when the effect of drug administration can be observed 5.25 ± 0.293

Similar results were achieved when A-180 was administered at 10.00 p.m. Thus, the most evident hemodynamic effect of altiazem PP-180 hypotensive action was observed when administered at 07.00 a.m., 10.00 a.m., 10.00 p.m.

On the contrary, taking altiazem PP-180 at 01.00 p.m.; 04.00 p.m. and 07.00 p.m. as well as at random intake times of the day did not show an obvious hemodynamic effect of A-180.

The study of hemodynamic parameters when taking A-180 at 01.00 p.m. showed a decrease of cardiac output which led to a decrease of SD by 16% and ejection fraction 8.2%. At the same time, a significant 40% increase of TPR and a 42% increase of PVRI was observed, which demonstrated a vasoconstrictive effect of altiazem. Besides, a slight 11% decrease of ESV and a 9% decrease of EDV was noted. Clinical hypotensive effect of Altiazem became obvious on the 4th-5th day of treatment (Table 3).

Similar changes were observed when the drug was administered at 04.00 p.m.; 07.00 p.m. and at random times of the day.

Hypotensive effect of Altiazem within these time periods was conditioned by the decrease in cardiac output. An increase of TPR and PVRI should also be noted. In these series of research work, the dynamics of ESV and EDV was not favourable [34-36].

Table 3 Effect of Altiazem PP-180 on hemodynamics parameters at 01.00 p.m. intake time (6 hours after waking up)

Parameters	Prior to treatment	After treatment	p value
	M ± m	M ± m	
SABP, mmHg	190.0 ± 3.536	142.5 ± 2.339	<0.0001
DABP, mmHg	100.625 ± 0.585	80.625 ± 0.585	<0.0001
Average ABP, mmHg	130.125 ± 1.096	101.0 ± 0.984	<0.0001
HR beats per 1 minute.	92.00 ± 1.658	72.5 ± 1.723	<0.0002
SD, ml	71.75 ± 1.998	60.25 ± 2.409	<0.0012
CMO, l/min	6.284 ± 0.329	3.876 ± 0.352	<0.004
SVI, ml./m ²	37.925 ± 1.140	31.713 ± 1.353	<0,001
CI, l/min/m ²	3,293 ± 0.191	2.084 ± 0.211	<0.005
TPR, dyn.s.cm ⁻⁵	1728.188 ± 97.847	2429.013 ± 314.757	<0.10
PVRI, dyn.s. cm ⁻⁵ /m ²	901.350 ± 48.128	1287.363 ± 156.75	<0.08
LVM, gr.	303.225 ± 21.763	248.050 ± 20.122	<0.01
ESV, ml	118.375 ± 00	91.5 ± 00	<0.1
EDV, ml	181.0 ± 0.312	149.0 ± 0.75	≈ 0.05
EF,%	51.875	43.625	-
DP, relative value units	175.00 ± 5.839	106.80 ± 2.901	<0.0001

Side effects 1; The day when the effect of drug administration can be observed 4.875

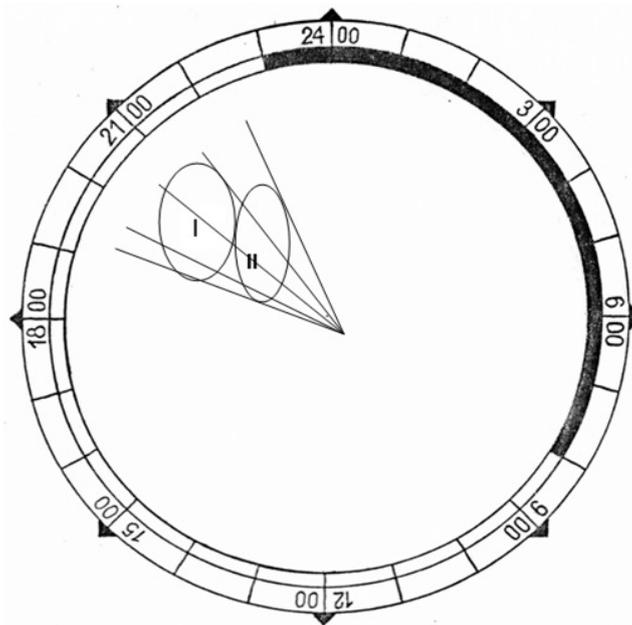


Figure 4 Cosinor of the circadian rhythm of SABP prior to (I) and after (II) treatment at 01.00 p.m. by altiazem PP-180

Amplitude prior to treatment – 13.56 ± 1.67 (10.67-16.46);

After - 13.49 ± 2.14 (9.79-17.18)

Acrophase prior to treatment - 21.20 (19.52-22.16);

After - 20.41 (19.39-21.34)

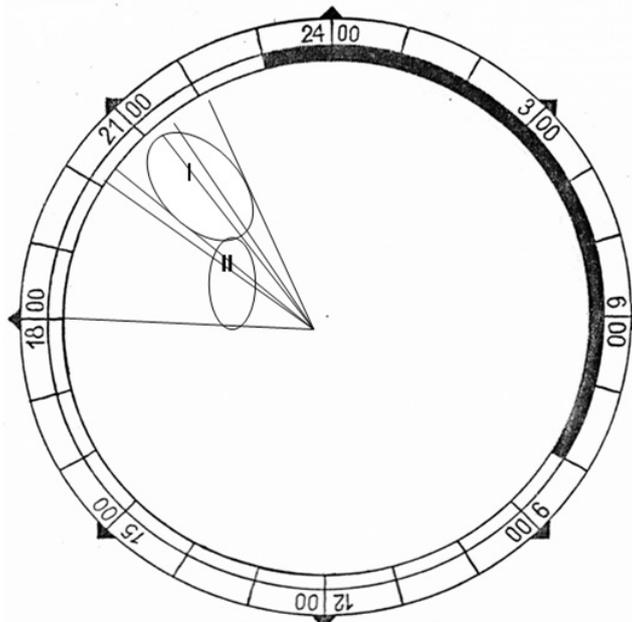


Figure 5 Cosinor of the circadian rhythm of average ABP prior to (I) and after (II) treatment at 01.00 p.m. by Altiazem PP-180

Amplitude prior to treatment - 10.45 ± 1.13 (8.50-12.40);

After - 6.40 ± 1.53 (3.76-9.04)

Acrophase prior to treatment - 21.30 (20.28-22.06);

After - 20.25 (18.21-21.40)

The analysis of the Chrono structure of circadian rhythms of hemodynamics parameters prior to and after Altiazem PP-180 has been administered at 01.00 p.m. testified to the damage of DABP rhythms Chrono structure (Table 3). Along with the decrease of MESOR DABP disappearance of circadian rhythm DABP was noted at the end of treatment. The decrease of MESOR SABP was not significant – from 160.52 ± 3.63 to 150.64 ± 2.41 mmHg, the rhythm amplitude remained unchanged and equalled 13.56 ± 1.67 mmHg. The shift of rhythm SABP acrophase was insignificant (from 21.20 to 20.41). MESOR HR decreased from 84.88 ± 1.74 to 74.56 ± 1.22 beats per 1 minute. The HR amplitude changed insignificantly from 5.48 ± 0.94 to 3.90 ± 0.69 beats per minute. Similar to SABP acrophase HR rhythms acrophase also underwent an insignificant shift from 21.24 to 20.29. MESOR of average ABP and DP decreased, the amplitude of these rhythms also showed a noticeable reduction, the acrophase of these rhythms underwent a slight change similar to SABP and HR rhythms acrophase (Figures 4 and 5) [37-39].

ESV decreased insignificantly, on the contrary, EDV increased by 5% when altiazem was administered at 04.00 p.m. An insignificant decrease of LVM came under notice, as well. All hemodynamic effects were achieved for a little over than 5 days. Side effects were observed in one patient.

Considering the obtained results, it has been concluded that it is reasonable to administer altiazem PP-180 to patients at 07.00 a.m., 10.00 a.m., and 10.00 p.m. when the drug shows the most evident hypotensive effect.

CONCLUSION AND FUTURE PERSPECTIVES

- Altiazem PP-180 causes a clear hypotensive effect in II-degree AH patients when administered at different intake times both fixed and random under outpatient conditions.
- The most evident hemodynamic effect of the hypotensive action of altiazem PP-180 can be observed when administered at 07.00 a.m.; 10.00 a.m. and 10.00 p.m. with a normal work-rest routine.
- When administered at 07.00 a.m., 10.00 a.m., and 10.00 p.m. Altiazem PP-180 causes a significant decrease in peripheral vascular resistance, end-systolic and end-diastolic volumes and an increase in cardiac output.
- Hypotensive action of altiazem PP-180 when administered at 01.00 p.m.; 04.00 p.m., and 07.00 p.m. as well as at random hours of the day showed a less effective hemodynamic effect: a decrease in cardiac output accompanied by an increase in total peripheral resistance and peripheral vascular resistance index.

Perspectives of further research

It is considered worthwhile to continue the research of time-dependent effects of altiazem PP-180 and blood circulation parameters in II-degree arterial hypertension and concomitant coronary heart disease patients.

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