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INFLUENCE OF MIANSERIN ON THE ACTIVITY OF SOME HYPOTENSIVE DRUGS IN SPONTANEOUSLY HYPERTENSIVE RATS

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Mianserin might be an alternative drug in patients with depression accompanied by hypertension because of its effectiveness and lack of side effects in the circulatory system. However, a few studies reported in literature show influence of the drug on blood pressure. We investigate interactions between mianserin and commonly used hypotensive drugs (propranolol, enalapril and prazosin) in spontaneously hypertensive rats (SHR). The experiments were performed in two experimental designs: a single administration of both mianserin and a hypotensive drug, and repeated administration of mianserin with a single administration of a hypotensive drug. Arterial blood pressure was measured by bloodless method with manometer made by LETICA. A single administration of mianserin caused a statistically significant decrease in systolic, diastolic and mean blood pressure in the 60th minute of observation and intensified hypotensive effect of prazosin. However, long-term administration of mianserin in SHR rats had no significant influence on arterial blood pressure. Chronic and single administration of mianserin with propranolol or enalapril did not influence the circulatory system. A long-term administration of mianserin intensified the hypotensive effect of prazosin.This interaction might suggest possibility of dangerous complications in the treatment of humans with this drug combination.

Key words: *mianserin, prazosin, interaction, spontaneously hypertensive rats, hypertensive drugs, blood pressure*

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INTRODUCTION

In spite of all new theories [11, 16, 19, 21–24], the basic theory by Schildkraut, which underlines significance of the decreased activity of monoaminergic neurons, is still valid. Most of antidepressants specifically increase noradrenergic and serotonergic transmission in the central nervous system. This group of drugs includes mianserin, which is an antagonist of α_2- and α_1-adrenergic receptors, and through these receptors exerts influence on monoaminergic transmission. Blockade of α_2-adrenergic receptors leads to the increased noradrenaline release into the synaptic cleft, as well as to the increased 5-HT transmission *via* heteroreceptors which are located on the endings of serotonergic neurons. These receptors become desensitized when the drug is administered for a long time. However, long-term administration of mianserin does not result in down-regulation of β-adrenergic receptors though a decrease in brain adenyl cyclase activity was observed [13]. Except for the influence on α_2-adrenergic receptors, mianserin is an antagonist of other receptors, such as serotonin 5-HT_{1C}, 5-HT_2 [18] and 5-HT_3 [27], as well as H_1- and H_2-histamine receptors. Anticholinergic side effects are weak [17].

Mianserin is thought to demonstrate very slight effect on the cardiovascular system (no cardiotoxicity). It is also safer than other tricyclic antidepressants. However, mianserin influence on the circulatory system has not been definitely determined. Various experiments brought varying results as to the influence of the drug on blood pressure. According to the studies of Ostapowicz et al., temporary increase in blood pressure after mianserin administration does not depend on the drug dose [17]. However, the studies performed by Jakitowicz et al. [9] demonstrated slight, but statistically significant changes: a decrease in systolic blood pressure (orthostatic, after standing up), decrease in diastolic blood pressure (in standing patients), as well as a decrease in total vascular resistance. Bucknall et al. [1] found no cardiovascular response in their study comparing the activity of mianserin to trodazon in patients with cardiovascular diseases. Elliot et al. [5] reported that first dose of mianserin (30 mg) did not cause any decrease in blood pressure, either when administered immediately or after a long-term (2 weeks) treatment of patients with hypertension. Only sedation and transient orthostatic hypotonia was observed after the first dose in healthy volunteers. In a randomized study that compared the influence of amitriptyline and mianserin (after 6 days of administration) on circulatory system parameters, it was demonstrated by ECG and echocardiography that mianserin showed no influence on the contractility and chronotropism of the heart but increased average arterial blood pressure [25].

There is not much data in the literature concerning interactions between mianserin and hypotensive drugs. Available data reveal only that mianserin does not influence the activity of sympatholytic drugs. Contrary to tricyclic antidepressants, mianserin does not eliminate hypotensive activity of clonidine, methyldopa, betanidyne and guanetidine [5].

It seems that mianserin, due to its effectiveness and lack of side effects in the circulatory system, might be an alternative drug for patients with depression accompanied by hypertension. However, earlier studies performed on normotensive rats have demonstrated a disadvantagenous interaction between mianserin and prazosin [7]. Thus, interactions between mianserin and 3 commonly used hypotensive drugs were investigated. Propranolol, enalapril and prazosin were selected for the study, because of their frequent administration in the therapy of hypertension and various mechanisms of activity.

Propranolol is one of the best known, nonselective β-adrenolytic drugs, which apart form peripheral activity, probably shows central activity as well. According to some data, propranolol is an antagonist of 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2B} receptors [12]. Mianserin also blocks some serotonin receptors, so it is possible that these drugs interact affecting arterial blood pressure.

Enalapril is a basic drug in the therapy of hypertension. It belongs to a group of angiotensin convertase inhibitors. Enalapril blocks the vasoconstriction activity of angiotensin II through the inhibition of angiotensin I conversion to active angiotensin II. Mianserin affects peripheral α_1-adrenergic receptors, thus, an interaction between the drugs seems possible. The results of previous studies in normotensive rats demonstrated that repeated administrations of mianserin did not change the hypotensive effect of enalapril.

Prazosin is an α_1-adrenolytic, so we can expect the interaction with mianserin which, among others,

also acts *via* these receptors. In normotensive rats, a single dose of mianserin significantly increased the hypotensive effect of prazosin [7].

MATERIALS and METHODS

The study was conducted on spontaneously hypertensive male rats with initial body weight between 240–280 g, which had free access to standard feed and water. Their body weight was monitored during the experiments. The animals were housed in standard plastic cages, 10 animals per cage, in a constant temperature of 22°C and a 12 h light-dark cycle. All experiments were conducted between 8 a.m. – 2 p.m.

All experiments were performed with the permission of the Local Ethics Committee for the Experiments on Animals (no. Ł/BD/102).

The following pharmaceutical preparations were used in the experiments: mianserin (Jelfa, Jelenia Góra, Poland), propranolol (Polfa, Warszawa, Poland), enalapril (Polpharma, Starogard Gdański, Poland), prazosin (Polpharma, Starogard Gdański, Poland), methylcellulose (Sigma). Mianserin, enalapril and prazosin were administered *ip* in a volume of 0.1 ml per 100 g of the animal's body weight and 0.4 ml per 100 g in case of propranolol. Mianserin tablets were suspended in 1 % solution of methylcellulose. The doses of pharmaceutical preparations were as follows: 10 mg kg^{-1} for mianserin, 5 mg kg^{-1} for enalapril, 4 mg kg^{-1} for propranolol and 1 mg kg^{-1} for prazosin.

The experiments were performed in two experimental designs: a single administration of mianserin and a hypotensive drug (6–8 animals), and repeated administrations of mianserin with a single administration of a hypotensive drug (8 animals).

In case of single drug administration, measurements of arterial blood pressure (systolic, diastolic and average pressure) were carried out at three time points: 15th, 30th and 60th minute and before the drug administration. At least three measurements were carried out at each time point. To estimate the drugs interaction, mianserin was administered 15 min before the hypotensive drug.

In long-term studies, mianserin was administered to the animals at a dose of 10 mg kg^{-1} for 14 days. The control group received 1% solution of methylcellulose (0.1 ml kg^{-1}) for 2 weeks. Control arterial blood pressure measurement was carried out after the first week of drug administration. Twenty four hours after the last administration of mianserin (or solution of methylcellulose), the rats received a single dose of one of three hypotensive drugs. Then, at the 15th, 30th and 60th minute after drug injection, measurements of arterial blood pressure were carried out (at least three measurements for each time point).

Arterial blood pressure was measured by a manometer manufactered by LETICA, consisting of blood pressure recording device (LE 5002) and a unit transmitting the data to the recorder (LE 5650/6). Before the measurements, the animals were placed inside a warming chamber (about 34°C) for 30 min. The aim of the procedure was to calm the animals and dilate the tail blood vessels. Arterial blood pressure measurements were carried out with the use of a special manometer sleeve containing pulse detector on the tail.

Statistical analysis

The results obtained in the experimental part were analyzed with the use of STATISTICA 5.0 program. Normality of distribution was checked with the use of Kolmogorow-Smirnoff test with Lillieforse corrections. To estimate the variation of differences in the obtained results, a test with separate estimation of variance (Fisher's test) or U Mann-Whitney test (non parametric test). The initial values of arterial blood pressure were assumed as 100%.

RESULTS

Spontaneously hypertensive rats (SHR) selected for the experiments had medium arterial blood pressure values as follows: systolic pressure 224.02 mmHg, diastolic pressure 159.82 mmHg, mean: 180.75 mmHg.

A single administration of mianserin at 10 mg kg^{-1} caused a statistically significant decrease in systolic, diastolic and mean blood pressure at the 60th minute of observation when compared to the group which received 0.9 % NaCl. Prazosin given at a single dose of 1 mg kg^{-1} significantly decreased the systolic blood pressure at 15th minute and diastolic and average blood pressure at all time points. The hypotensive effect of prazosin was intensified after mianserin administration (all parameters) but only at the 60th minute of observation (Tab. 1).

Table 1. The influence of a single administration *ip* of mianserin (M) and prazosin (PZ) on arterial blood pressure in SHR

Time after drug administration (min)	Mean changes in arterial blood pressure (% of initial values)											
	systolic				diastolic				mean			
	NaCl	M	PZ	M+PZ	NaCl	M	PZ	M+PZ	NaCl	M	PZ	M+PZ
0	100	100	100	100	100	100	100	100	100	100	100	100
15	96.18 ± 10.80	93.98 ± 12.01	77.33[a] ± 11.78	75.71[ab] ± 13.13	100.89 ± 12.10	92.20 ± 32.86	80.33[a] ± 13.80	73.45[a] ± 22.65	99.18 ± 9.62	92.77 ± 23.30	79.72[a] ± 11.63	73.32[a] ± 16.99
30	98.18 ± 5.96	90.56 ± 14.38	89.83 ± 10.12	81.21[a] ± 17.72	102.27 ± 9.06	88.21 ± 22.56	80.25[a] ± 14.07	76.83[a] ± 21.23	100.73 ± 7.33	88.61 ± 16.44	82.54[a] ± 14.61	78.36[a] ± 17.53
60	99.78 ± 10.58	83.67[a] ± 8.80	89.58 ± 10.49	65.64[ac] ± 10.22	101.72 ± 9.54	71.91[a] ± 27.82	88.05[a] ± 7.67	48.31[ac] ± 15.73	100.99 ± 7.02	76.77[a] ± 19.49	88.90[a] ± 6.53	55.24[ac] ± 11.22

Each parameter is presented as the mean and standard deviation (SD); [a] $p < 0.05$ in comparison with NaCl, [b] $p < 0.05$ in comparison with mianserin (M), [c] $p < 0.05$ in comparison with prazosin (PZ)

Table 2. The influence of a single administration *ip* of mianserin (M) and propranolol (P) on arterial blood pressure in SHR

Time after drug administration (min)	Mean changes in arterial blood pressure (% of initial values)											
	systolic				diastolic				mean			
	NaCl	M	P	M+P	NaCl	M	P	M+P	NaCl	M	P	M+P
0	100	100	100	100	100	100	100	100	100	100	100	100
15	96.18 ± 10.80	93.98 ± 12.01	82.96[a] ± 12.65	91.84 ± 9.22	100.89 ± 12.10	92.20 ± 32.86	76.38 ± 29.88	81.33[a] ± 20.73	99.18 ± 9.62	92.77 ± 23.30	78.81[a] ± 22.05	92.29 ± 12.82
30	98.18 ± 5.96	90.56 ± 14.38	99.13 ± 12.15	87.83[b] ± 12.70	102.27 ± 9.06	88.21 ± 22.56	90.35 ± 23.72	83.49 ± 24.67	100.73 ± 7.33	88.61 ± 16.44	93.59 ± 18.20	84.94 ± 18.44
60	99.78 ± 10.58	83.67[a] ± 8.80	95.33 ± 15.13	85.90[a] ± 13.77	101.72 ± 9.54	71.91[a] ± 27.82	83.58 ± 28.69	80.76[a] ± 25.74	100.99 ± 7.02	76.77[a] ± 19.49	88.45 ± 22.18	82.50[a] ± 20.58

Each parameter is presented as the mean and standard deviation (SD); [a] $p < 0.05$ in comparison with NaCl, [b] $p < 0.05$ in comparison with propranolol (P)

Table 3. The influence of a single administration *ip* of mianserin (M) and enalapril (E) on arterial blood pressure in SHR

Time after drug administration (min)	Mean changes in arterial blood pressure (% of initial values)											
	systolic				diastolic				mean			
	NaCl	M	E	M+E	NaCl	M	E	M+E	NaCl	M	E	M+E
0	100	100	100	100	100	100	100	100	100	100	100	100
15	96.18 ± 10.80	93.98 ± 12.01	87.82 ± 6.07	89.25 ± 9.19	100.89 ± 12.10	92.20 ± 32.86	93.12 ± 24.72	78.64[a] ± 16.89	99.18 ± 9.62	92.77 ± 23.30	90.33 ± 15.84	82.46[a] ± 10.40
30	98.18 ± 5.96	90.56 ± 14.38	90.89 ± 11.54	84.63[a] ± 9.61	102.27 ± 9.06	88.21 ± 22.56	82.88[a] ± 13.60	71.95[a] ± 21.08	100.73 ± 7.33	88.61 ± 16.44	85.71[a] ± 10.95	78.09[a] ± 17.14
60	99.78 ± 10.58	83.67[a] ± 8.80	96.21 ± 8.46	87.68[a] ± 7.79	101.72 ± 9.54	71.91[a] ± 27.82	97.14 ± 25.61	68.95[ab] ± 8.99	100.99 ± 7.02	76.77[a] ± 19.49	96.09 ± 17.03	76.76[ab] ± 8.39

Each parameter is presented as the mean and standard deviation (SD); [a] $p < 0.05$ in comparison with NaCl, [b] $p < 0.05$ in comparison with enalapril (E)

A single administration of propranolol (4 mg kg^{-1}) caused a statistically significant decrease systolic and mean blood pressure only in the 15th minute of examination, with no significant influence on diastolic pressure. No statistically significant differences were observed (except for the systolic blood pressure at the 30th minute) after combined administration of mianserin and propranolol when compared to the group of animals receiving only propranolol (Tab. 2).

Enalapril at the dose of 5 mg kg^{-1} caused a significant decrease in diastolic and medium blood pressure at the 30th minute of observation. No influence of this drug on systolic blood pressure was observed. Enalapril, when administered after mianserin and compared to the group receiving only enalapril, caused a statistically significant decrease in diastolic and medium blood pressure at the 60th minute of the experiment (Tab. 3).

Mianserin administered for 14 days did not cause statistically significant changes in the values of systolic, diastolic and medium blood pressure.

In rats receiving mianserin for 14 days, a single administration of prazosin caused a statistically significant decrease in systolic, diastolic and medium blood pressure when measured 15, 30 and 60 min after the administration, compared to the group receiving prazosin at a single dose (NaCl + prazosin) (Tab. 4).

No significant influence on blood pressure was demonstrated after combined administration of mianserin and propranolol when compared to the group receiving a hypotensive drug (Tab. 5).

Table 4. The influence of repeated administrations *ip* of mianserin (M) and prazosin (PZ) on arterial blood pressure in SHR

Time after drug administration (min)	Mean changes in arterial blood pressure (% of initial values)								
	systolic			diastolic			mean		
	M+D	D+PZ	M+PZ	M+D	D+PZ	M+PZ	M+D	D+PZ	M+PZ
0	100	100	100	100	100	100	100	100	100
15	95.62 ± 7.49	78.45 ± 6.23	66.70[ab] ± 10.32	106.67 ± 19.75	82.21 ± 11.28	61.95[ab] ± 20.41	100.84 ± 8.32	73.98 ± 12.54	64.23[ab] ± 14.72
30	97.06 ± 8.07	87.20 ± 10.15	66.16[ab] ± 9.48	112.46 ± 19.48	78.29 ± 9.23	64.89[ab] ± 11.35	104.86 ± 11.47	85.62 ± 12.22	67.80[ab] ± 10.16
60	94.92 ± 8.18	82.66 ± 8.96	67.98[ab] ± 9.75	104.01 ± 10.81	90.02 ± 5.26	67.62[ab] ± 11.90	98.37 ± 5.20	91.21 ± 8.45	67.92[ab] ± 7.63

Each parameter is presented as the mean and standard deviation (SD); [a] $p < 0.05$ in comparison with mianserin and 1% solution of methylcellulose (M+D), [b] $p < 0.05$ in comparison with 1% solution of methylcellulose and prazosin (D+PZ)

Table 5. The influence of repeated administrations *ip* of mianserin (M) and propranolol (P) on arterial blood pressure in SHR

Time after drug administration (min)	Mean changes in arterial blood pressure (% of initial values)								
	systolic			diastolic			mean		
	M+Dl	D+P	M+P	M+D	D+P	M+P	M+D	D+P	M+P
0	100	100	100	100	100	100	100	100	100
15	95.62 ± 7.49	84.52 ± 9.85	90.06 ± 16.72	106.67 ± 19.75	80.52 ± 16.21	93.13 ± 14.89	100.84 ± 8.32	81.28 ± 6.26	89.60 ± 12.66
30	97.06 ± 8.07	98.68 ± 13.22	88.98 ± 12.80	112.46 ± 19.48	87.76 ± 13.59	87.87[a] ± 17.20	104.86 ± 11.47	95.42 ± 12.25	86.08[a] ± 11.94
60	94.92 ± 8.18	92.12 ± 12.82	95.67 ± 11.63	104.01 ± 10.81	81.23 ± 11.45	94.36 ± 17.11	98.37 ± 5.20	86.56 ± 12.14	93.13 ± 13.69

Each parameter is presented as the mean and standard deviation (SD); [a] $p < 0.05$ in comparison with mianserin and 1% solution of methylcellulose (M+D)

Table 6. The influence of repeated administrations *ip* of mianserin (M) and enalapril (E) on arterial blood pressure in SHR

Time after drug administration (min)	Mean changes in arterial blood pressure (% of initial values)								
	systolic			diastolic			mean		
	M+D	D+E	M+E	M+D	D+E	M+E	M+D	D+E	M+E
0	100	100	100	100	100	100	100	100	100
15	95.62 ± 7.49	89.62 ± 8.05	90.20 ± 11.26	106.67 ± 19.75	90.21 ± 16.11	74.46[a] ± 20.46	100.84 ± 8.32	88.32 ± 14.56	79.74[a] ± 17.21
30	97.06 ± 8.07	92.56 ± 12.85	87.37 ± 12.33	112.46 ± 19.48	85.26 ± 11.24	74.73[a] ± 13.29	104.86 ± 11.47	81.67 ± 13.25	78.45[a] ± 12.17
60	94.92 ± 8.18	94.92 ± 9.55	90.05 ± 12.41	104.01 ± 10.81	95.96 ± 17.02	74.94[a] ± 19.36	98.37 ± 5.20	95.21 ± 14.64	79.58[a] ± 16.93

Each parameter is presented as the mean and standard deviation (SD); [a] $p < 0.05$ in comparison with mianserin and 1% solution of methylcellulose (M+D)

A single administration of enalapril in rats receiving repeated mianserin caused a statistically significant decrease in systolic, diastolic and medium blood pressure, when measured at the 15th, 30th and 60th minute of observation compared to the control group (mianserin + diluent). No statistically significant changes were observed in blood pressure after the administration of enalapril. The results are shown in Table 6.

DISCUSSION

Tricyclic antidepressants remain the primary group of drugs used in the pharmacotherapy of affective diseases. They are distinguished by high (70%) therapeutic effectiveness even in severe depression. The disadvantage of these drugs is a large number of side effects, including adverse reactions in the circulatory system. This group of drugs evokes orthostatic hypotonia as a result of α_1-adrenergic receptor blockade as well as tachyarrhythmia as a parasympatholytic effect. Mianserin does not seem to exert any important influence on the circulatory system. However, these data need to be confirmed by further observations. Bucknall et al. [1] observed no changes in the cardiovascular system after a 3-week period of mianserin administration in patients with depression and concomitant cardiovascular diseases. Elliot et al. [5] observed a decrease in blood pressure in healthy volunteers after a single administration of mianserin. Jakitowicz et al. [9], after a 2-week mianserin therapy, observed a decrease in arterial systolic pressure in supine position and after standing up. However, diastolic blood pressure was significantly decreased only in standing position. Moller et al. [14] concluded that in older persons receiving mianserin at a daily dose of 60 mg for 5 weeks, the frequency of orthostatic blood pressure drops was significantly higher with no influence on resting blood pressure and heart rate. ECG record analysis revealed lower contractility of the left ventricle. However, Ostapowicz at al. [17] observed a temporary increase in blood pressure in depressed patients within the first 2 weeks of mianserin treatment. After the 4th week of therapy, this effect was not observed.

In our own experiments performed on SHR, we observed that mianserin at a single dose of 10 mg kg^{-1} caused statistically significant decrease in arterial blood pressure (systolic, diastolic and medium) at the 60th minute of observation when compared to the control group. Similar experiments on normotensive rats revealed a decrease in all blood pressure parameters 15 min after mianserin *ip* administration [7]. In this case, there was a difference in the time of manifestation of mianserin hypotensive effect.

However, long-term administration of mianserin (14 days, 10 mg kg^{-1}) in SHR rats had no significant influence on systolic, diastolic and medium blood pressure. In normotensive rats, after similar time of mianserin use, we observed an increase in blood pressure but the changes regressed in the 3rd week of mianserin administration [7].

This effect of mianserin probably results from the differences in the sensitivity of α_1-adrenergic

receptors in healthy and hypertensive animals. It seems that the effect of mianserin on the circulatory system is not linked to its central, but peripheral activity. Inhibition of noradrenaline and phenylephrine hypertensive activity was observed in rats with damaged spinal cord [6]. Some reports indicate that mianserin is a weak antagonist of peripheral α_1-adrenergic receptors [4] which, in case of, for example, interactions with other drugs, can lead to vascular effects.

Interaction with prazosin seems to confirm the hypotensive activity of mianserin. Statistically significant decrease in blood pressure in SHR rats was observed at the 15th, 30th and 60th minute after combined administration of the drugs when compared to the control group. When compared to the influence of prazosin alone on blood pressure, a significant decrease in all hemodynamic parameters was observed at the 60th minute of observation. It shows that mianserin enhances the hypotensive activity of prazosin. In normotensive rats acute administration of mianserin and prazosin led to statistically significant decrease in blood pressure at all time points of observation [7]. These results indicate higher sensitivity of normotensive rats to peripheral activity of mianserin.

Interactions between mianserin and enalapril were also studied. Statistically significant decrease in systolic and mean blood pressure was observed at the 60th minute of experiment for the group treated with mianserin with enalapril when compared to the SHR group receiving enalapril alone. Similar comparison in case of normotensive rats revealed no significant differences in blood pressure values only at the 30th minute of examination (a significant decrease in diastolic pressure). Enalapril inhibits the synthesis of angiotensin II and, thus, affects a series of processes connected with its activity, among others, the contractions of blood vessels. Mianserin blocks the α_1-adrenergic receptors and can also act as a vasodilator. In SHR rats, the interaction between these drugs results in strengthened hypotensive effect but is not sufficient in case of healthy animals.

The observed results concerning interactions between mianserin and prazosin, suggest that caution is required during combined administration of these drugs to patients.

A combined administration of mianserin with propranolol seems to have no influence on the circulatory system. A significant decrease in systolic blood pressure, but only at the 30th minute after administration, was observed in the SHR group of rats receiving mianserin and propranolol compared with the group, which received propranolol alone. In normotensive rats, no statistically significant changes were observed except for mean blood pressure at the 30th minute of examination [7]. It seems that the interactions during a single administration of mianserin and propranolol do not significantly affect the blood pressure parameters.

Mianserin, contrary to most of antidepressive drugs, shows no cholinolytic activity [10]. It exerts no influence on arterial blood pressure induced by acetylcholine in rats anesthetized with pentobarbital [3]. It does not evoke heart rhythm disturbances related to the blockade of the vagus nerve. Rare supraventricular rhythm disturbances, which are present, are linked to the blockade of the K^+ channels in the atria. No pulse fluctuations in the studied animals were observed during experiment [2]. Also Rajewska et al. [20], using mianserin in elderly patients, observed no significant changes in pulse frequency and ECG records. However, there were cases of tachycardia and ECG disturbances in hyperexcitable children receiving mianserin at a dose of 40 mg a day [26].

The influence of repeated administration of mianserin on hypotensive effect of drugs depended on a drug which was administered. Single dose of prazosin administered to animals receiving mianserin for 14 days caused a statistically significant decrease in all blood pressure parameters at all time points when compared to the prazosin-treated group (NaCl+ prazosin). It is noteworthy that there was a very high decrease in arterial blood pressure, so it may suggest an increased sensitivity of peripheral α_1-adrenergic receptors after long-term administration of mianserin. Some data suggest that in spontaneous blood hypertension, initial receptor sensitivity is increased. Their additional blockade by mianserin may lead to even stronger up-regulation of α_1-adrenergic receptors. That explains significant blood pressure decrease after the administration of prazosin. In normotensive rats, repeated administration of mianserin and prazosin led to such a decrease in blood pressure that it was difficult to measure properly. The pulse reached 500 beats *per minute*, while the initial values were about 300 *per minute* [7].

A single administration of propranolol or enalapril in SHR rats receiving mianserin for 14 days did

not cause blood pressure decrease when compared to the group receiving diluent for a long time and a suitable hypotensive drug when necessary. Similar results were obtained in normotensive animals.

Clinical studies showed that there were no circulatory system side effects after mianserin treatment when compared with standard antidepressants. No significant changes in blood pressure, heart rate and orthostatic hypotonia were observed [20]. Also in animals with experimental heart infarction, no influence of mianserin on hemodynamic parameters and ECG record was observed [15]. In our studies on SHR rats, we demonstrated that the influence of mianserin on the circulatory system was of little importance. The influence was noticeable only at the 60th minute of observation while a long-term mianserin treatment had no influence on blood pressure. However, side effects of mianserin were stronger in the presence of prazosin. Mianserin, when administered on a long-term basis, intensified the hypotensive effect of prazosin at all time points of the experiment. It suggests a negative interaction and possibility of dangerous complications in the treatment of humans. Combined administration of mianserin and propranolol or enalapril seems to be the safest therapy.

In the course of administration of drugs in 3 rats, we observed some symptoms similar to convulsions, intensifying with sound stimulus. According to the literature, rat inbreeding can cause petit mal epilepsy [8]. The observed attacks were probably linked to petit mal epilepsy and manifested themselves, triggered by mianserin and its combined use with propranolol or with prazosin.

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