Assessment of Therapeutic Drug Efficiency

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The efficiency of drug therapy should be evaluated by not only its directed action on specific organ or target parameter, but also its effects on general regulatory and adaptive status.

Key Words: *cardiorespiratory synchrony; adaptation; doxasozin; corinfar retard*

Evaluation of the efficiency and safety of therapeutic drugs is routinely based on evaluation of some specific physiological parameters such as arrhythmia indices or blood pressure. Disadvantages of such assessment were revealed in multicenter randomized placebo-controlled studies of drug preparations, which demonstrated increased incidence of cardiovascular complications despite attaining principal aim of the therapeutic treatment [3]. For example, class 1 antiarrhythmic drugs established as "golden standard" in elimination of ventricular rhythm disturbances increased mortality almost 3-fold, although they exerted significant and reliable positive antiarrhythmic effect on the target organ (heart) [2]. Most therapeutic drugs are xenobiotics and cause additional strain of the regulatory and adaptive processes. Manifestations of side effects and their influence on the quality and duration of life depend on the degree of general adaptation (disadaptation) to administration of the drug. The study of the dynamics of adaptation potential under the action of therapeutic drugs requires the search for novel safe methods with established interrelation between the changes in the key parameters and severity of the disease course. The optimal approach to integrative study of the regulatory and adaptive potencies of the organism exposed to the action of therapeutic drugs is based on the use of non-invasive probe of cardiorespiratory synchronicity (CRS) characterized with objective numerical indices and extensive base of medical cases thereby providing reliable assessment of disadaptation during various clinical states [4-6,8,11].

Our aim was to compare the efficiency of drug action on the target organ (parameter) and general regulatory and adaptive status of the organism.

MATERIALS AND METHODS

For testing novel principles of assessment of therapeutic drug efficiency, we chose hypotensive drugs with clear indices that assess their effect according to the target level of blood pressure [9]. Group 1 patients (n=88) were treated with α_1-adrenoceptor blocker doxasozin, while group 2 patients (n=96) were treated with calcium antagonist corinfar retard.

In all patients, we measured the following parameters: blood pressure, HR, Kerdo index, functional alteration index (FAI), Hildebrandt index, heart rate variability (HRV), and CRS index assessed according to [7,10]. They were recorded initially, at the peak of drug action (acute probe), after 6 weeks and after 6 months in the subgroup of patients, in whom the target level of blood pressure was attained (69.6%). After recording the initial ECG and pneumogram, the patients were instructed to breathe synchronously to photostimulator flashes at a frequency controlled by the researcher. The aim of each probe was synchronization between the preset respiration rate and HR. The following parameters were analyzed: minimum and maximum boundaries of the synchronization range; the

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synchrony range equal to the difference between the synchronized heart and respiratory rates at the maximum and minimum CRS boundaries; the difference between the minimum CRS boundary and initial HR; the duration of CRS development at the minimum and maximum boundaries of the range.

RESULTS

To exclude the negative effect of elevated blood pressure on the resulting adaptation indices used for comparative assessment of the dynamics of adaptation potential of the organism, we selected patients, whose blood pressure was normalized by drug therapy. Acute probe with doxasozin decreased CRS by 59.8% (Table 1). By the end of 6-month treatment, CRS was still decreased by 30%. Similar trend was observed for HRV with a decrease in variation of *RR* intervals in acute probe and after 6 weeks of treatment. Kerdo index increased without attaining the level of autonomic balance. Single intake of corinfar retard increased the synchronization range by 12.1%. This increase was more pronounced (>33%) after 6 months of treatment (Table 2). Acute probe revealed an increase in HRV, which was also observed after 6 weeks of treatment, but returned to initial value after 6 months. In both groups, the Hildebrandt index and FAI did not change significantly during the entire course of treatment.

The drug treatment results in the changes in the regulatory systems and functional reserves of the organism. First, these changes involve the respiratory and cardiovascular systems responsible for providing oxygen and nutrients to organs and tissues. Therefore, the adaptive changes in the regulatory mechanisms are most pronounced in the regulation of cardiorespiratory system [1]. Probably, this is the reason why CRS parameters reflecting interaction of the respiratory and cardiovascular systems are the most sensitive indicators of the dynamics of regulatory-adaptive potencies of the organism under therapeutic treatment.

While both drugs (doxasozin and corinfar retard) normalized blood pressure, they produced opposite effects on the key CRS parameters. Starting from the acute probe, corinfar retard (calcium antagonist) widened the CRS range and decreased the time needed for synchronization at the lower and upper boundaries of this range. Although pharmacodynamics of both drugs are similar and based on the decrease in total peripheral hydraulic resistance, doxasozin induced overstress in regulatory systems of the organism resulted probably from the direct

TABLE 1. Effect of Doxasozin on Hemodynamics and Adaptation in Hypertensive Patients (*M*±*m*)

Parameter	Initial	Acute probe	6 week administration	6 month administration
HR, bpm	76.2±2.6	84.8±2.9	80.1±2.7	78.7±3.1
Blood pressure				
systolic	162.4±2.1	138.6±2.4***	132.0±2.2***	134.6±2.5***
diastolic	96.1±2.1	93.5±1.9**	92.2±2.2**	88.7±2.6***
Synchronization range				
lower boundary	80.2±2.4	92.4±3.1**	86.5±3.6**	86.3±2.8**
upper boundary	88.4±1.1	95.7±0.9*	90.1±3.4	91.9±3.2
width	8.2±1.2	3.3±0.9***	3.6±1.4**	5.6±1.3**
Duration of synchrony development				
at lower boundary	23.3±0.8	32.0±1.1**	30.0±1.7***	28.0±1.8**
at upper boundary	27.9±1.6	32.5±2.4***	34.0±2.3*	26.0±1.9
Difference between minimum border and HR	3.8±0.9	7.7±1.1*	5.6±1.4*	4.0±1.6
HRV SDNN	40.2±3.3	31.3±2.4**	36.4±2.9**	42.2±3.6
pNN50	8.6±1.9	3.4±0.9**	6.8±2.1**	9.2±2.4
Kerdo index	-26.12	-10.66	-15.11	-12.71
FAI	3.646	3.394	3.232	3.225
Hildebrandt index	4.763	4.711	5.006	5.621

Note. Here and in Table 2: SDNN — standard deviation in duration of the intervals between sinus contractions; pNN50 — repetition rate of *RR* interval that differed greater than by 50 msec. *$p<0.05$, **$p<0.01$, ***$p<0.001$ in comparison with initial (before treatment).

TABLE 2. Effect of Corinfar Retard on Hemodynamics and Adaptation in Hypertensive Patients (*M*±*m*)

Parameter	Initial	Acute probe	6 week administration	6 month administration
HR, bpm	77.2±2.3	82.8±3.9	80.1±2.6	81.7±3.7
Blood pressure				
systolic	168.4±2.7	146.6±2.4***	138.0±2.2***	134.6±2.1**
diastolic	94.1±2.1	92.5±1.9**	90.2±2.2**	86.7±2.6**
Synchronization range				
lower boundary	79.4±2.9	84.3±2.7	79.1±2.4	80.7±3.1
upper boundary	86.8±1.0	92.9±1.7	88.1±2.6	86.8±2.0
width	7.4±0.9	8.9±1.1**	9.0±2.5**	10.1±2.2**
Duration of synchrony development				
at lower boundary	26±2.3	19.4±1.9	21.1±2.9	18.1±2.2
at upper boundary	22.4±2.1	17.5±2.4	20.4±2.8	17.4±1.9
Difference between minimum border and HR	2.1±0.9	1.5±0.5	3.0±1.6	2.0±1.7
HRV				
SDNN	47.4±3.3	69.3±2.4**	64.4±2.1**	43.2±3.6
pNN50	9.9±1.2	16.4±1.9**	14.8±2.1**	8.8±1.7
Kerdo index	-21.89	-11.71	-18.53	-10.17
FAI	3.78	3.496	3.311	3.255
Hildebrandt index	5.514	5.175	4.756	4.919

blockade of adrenoreceptors. The impairment of CRS parameters agrees with the data of multicenter placebo-controlled study demonstrating poorer prognosis in doxasozin-treated patients [2]. Despite the lack of negative inotropic action, doxasozin increased mortality and/or led to progressive cardiac insufficiency, although its hypotensive action was adequate. It cannot be excluded that doxasozin-induced decrease in adaptive potential is a risk factor leading to unfavorable prognosis.

The CRS parameters are most informative during long-term monitoring of the adaptive potential in comparison with other indices of regulatory-adaptive potencies of the organism (FAI, Kerdo index, HRV, and the Hildebrandt index), because only CRS parameters significantly differed from the initial values after 6-month treatment. Thus, we demonstrated rationality to assess efficiency of the drug action on general regulatory-adaptive status of the organism, which opens new vistas to individualize treatment and to improve prognosis for the patients.

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