Studies of Nuclex effect under cardiovascular disorders, influenza and acute upper respiratory tract infection

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Abstract: The obtained results have confirmed the efficacy of Nuclex in terms of normalisation of parameters of coronary reserve, and in terms of elimination of the main signs and symptoms of influenza and acute upper respiratory tract infection (URTI), in particular, normalisation of body temperature, disappearance of headache, catarrhal phenomena, and general fatigue. The decrease in intensity of these signs and symptoms in the study group appeared one to three days earlier than in the control group, and this difference remained significant until the end of treatment. On the 14th day of Nuclex intake influenza A virus H1N1 could not be found by means of PCR in 58.33% of the study group patients, meanwhile in the control group patients the virus was still detectable. The results have clearly demonstrated the significant difference in the treatment efficacy between the control and study groups thus favouring the latter. Nuclex has been proven effective to completely remove the influenza virus from the body.

Keywords: influenza; upper respiratory tract infection; URTI; virus AH1N1 cardiovascular diseases; treatment; Nuclex.
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Mykola I. Shved studied internal diseases and cardiology in Ternopil State Medical Institute. He graduated from clinical studies and postgraduate studies in internal disease and cardiology. He defended his PhD thesis in 1980 and PhD doctoral thesis in 1989. He worked as an Assistant, Assistant Professor and Professor of Internal Medicine of Ternopil State Medical University. From 1989 to 2012, he is the Head of the Department of Internal Medicine Ternopil State Medical University. Currently, he heads the Department of Emergency States in Internal Medicine. He is the author of over 500 published works, including six monographs, three textbooks, eight textbooks, 14 guidelines, 22 newsletters, and eight patents. The monographs are devoted to treatment of patients with diagnosis and treatment of cardiogenic shock, pharmacotherapy in rheumatology and endocrinology, rehabilitation of cardiac patients.

Olena A. Prokopovych studied internal diseases and cardiology in Ternopil State Medical University of I.Ya. Gorbachevsky. From 2009 to 2011, she worked as an Assistant of the Department of Internal Medicine. She is currently an Assistant of the Department of Emergency States in Internal Medicine Ternopil State Medical University of I.Ya. Gorbachevsky. She defended her PhD thesis in 2012. Her scientific papers in recent years were devoted to the development of rational approaches to treatment of patients with acute myocardial infarction with liver dysfunction and the problem of influenza in patients with cardiovascular disease.

Pavlo M. Babych holds a higher technical education. His qualifications include system engineering and CAD-system. In 1991, he is in Kiev Polytechnical Institute, Faculty of Electronic Technics. Since 2006, he is the Adviser of the State Pharmacological Centre at Ministry of Health of Ukraine (now The State Expert Center MoH Ukraine). He took part as a biostatistician in carrying out of many clinical trials. He has published about 60 scientific works devoted to application of statistical methods.

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1 Introduction

Epidemics of influenza and upper respiratory tract infection (URTIs) are accompanied by heavy mortality and life-threatening complications among certain individuals. The population most at risk includes subjects with chronic conditions, such as cardiovascular disease (Davis et al., 2006). Yet, the interrelationship between URTI, influenza and acute myocardial infarction remained unclear for a long period of time. Numerous studies reported the seasonality of cardiovascular mortality patterns similar to the seasonal patterns of URTI and influenza circulation (Housworth and Langmuir, 1974; Eickhoff et al., 1961; Ailing et al., 1981).

Clinical findings in patients with influenza were consistent with typical systemic effects, such as high temperature, muscle pain and fatigue, and also indicated frequent episodes of myocardial ischemia (Greaves et al., 2003; Ison et al., 2005; Paul, 1963; Verel et al., 1976). These results led to the hypothesis that influenza may play a role in triggering cardiovascular events. Systemic inflammation and activation of inflammatory cells also act as key components of development, progression and destabilisation of atherosclerotic plaques. Hence, the markers of systemic inflammation are used for prediction of risk of cardiovascular events.

It is well known that the influenza infection is associated with strong prothrombotic and proinflammatory effects (Madjid et al., 2004) which are thought to play a role in the progression and destabilisation of atherosclerotic plaques resulting in plaque rupture, occlusion of the coronary arteries and development of myocardial infarction (White and Chew, 2008). Moreover, influenza can act as an acute inflammatory stimulus of the rapid-onset endothelial dysfunction (Harskamp and van Ginkel, 2008; Madjid et al., 2005). Cardiac complications of influenza infection, such as myocarditis and pericarditis are well recognised, but the role of influenza as a trigger of acute myocardial infarction is less clear. In the current literature, we have revealed a plethora of facts in support of a significant role of influenza (including influenza-like illness and acute respiratory infection) in the triggering of acute myocardial infarction or cardiovascular death. Many observational studies in different settings with a range of methods reported consistent associations between influenza and acute myocardial infarction. There was weaker evidence of an association with cardiovascular death. Only two small randomised trials assessed the protection provided by influenza vaccine against cardiac events in people with existing cardiovascular disease and found that influenza vaccination provided significant protection against cardiovascular death. A pooled estimate from a random-effects model suggested a protective, though non-significant, effect. The authors believe influenza vaccination should be encouraged wherever indicated, especially in people with existing cardiovascular disease, among whom there is often suboptimum vaccine uptake (Warren-Gash et al., 2009).

In conclusion, there is convincing evidence that URTI and influenza can trigger acute myocardial infarction and increase the risk of cardiovascular death. The use of anti-viral medications can be an effective way to reduce the risk of adverse cardiovascular events in patients who have cardiovascular disease.

Cardioprotective medications such as Nuclex exhibit a specific antiviral activity, which is achieved by the conformational change of neuraminidase and hemagglutinin receptors of influenza and parainfluenza viruses. The non-specific antiviral activity of Nuclex is achieved by an increase of interferon production in vivo and by stimulation of non-specific antiviral defence (Tkachuk et al., 2010). Nuclex has also been shown to
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Possess specific cardioprotective properties. In myocardial infarction, it has been implicated in limitation of zone of myocardial ischemic injury and necrosis, thus providing preservation or increase of the left ventricular ejection fraction (Parhomenko et al., 2009). Humoral regulation is accompanied by the activation of pituitary-adrenal system with an increase in the levels of endogenous glucocorticoids. Nuclex optimises adrenergic and cholinergic regulation of the heart, improves coronary and systemic bloodflow mediated by sympathetic and parasympathetic nervous system. In particular, it counteracts the catecholamine-mediated constriction of the coronary and peripheral vessels and lowers arterial blood pressure (Neshcheret et al., 2009). Nephroprotective properties are demonstrated by an increase of glomerular filtration rate which is the index of global kidney function (Honskyy, 1992).

The aim of the present study was to evaluate the therapeutic efficacy of cardioprotective medication ‘Nuclex’ in patients with cardiovascular diseases (chronic ischemic heart disease, cardiosclerosis, stable angina pectoris, metabolic cardiomyopathy, rhythm disorders), who had influenza or URTI as compared with the basic therapy.

2 Materials and methods

This clinical trial was pursued as open, randomised, comparative, parallel and was conducted under the supervision of the State pharmacological centre of the Ministry of Health of Ukraine. This trial was planned as superiority trial. A total of 170 patients were included in this study with a simple randomisation method were divided into the test (85 patients) and the control (85 patients) groups. Men and women aged 18 to 70 years with the diagnosis of URTI or influenza having concomitant cardiovascular disorders (chronic ischemic heart disease, cardiosclerosis, stable angina pectoris, metabolic cardiomyopathy, and rhythm disorders) participated in the study. The main inclusion criteria were as follows: evidence of viral infection (detected by positive immunofluorescent test); fever $\geq 38^\circ C$ with pain; subjective complaints (weakness, myalgia, headache, sore throat, and cough).

Tamiflu was used as a comparative medication in this study. Moreover, patients were treated according the standard protocol for respective nosologic entity. ‘Nuclex’ was prescribed at initial dosage of 0.5 grams 3 times per day for 5–7 days, afterwards the treatment was continued until the 14th at the dosage of 0.25 grams twice daily. Tamiflu was prescribed according to the instruction included in the packaging.

During the study, the enrolled patients continued to receive treatment for their respective cardiovascular diseases (with ACE-inhibitors, diuretics, cardiac glucosides, statins, anticoagulants, antiaggregants, antiarrhythmic, and metabolic medications). Nitroglycerin and other antianginal medications were prescribed to control angina pectoris symptoms. Patients also continued taking medications in usual doses, which were previously prescribed to treat concomitant conditions.

Analysis of the treatment efficacy in each of the groups was assessed using the following primary variables: headache, asthenia, catarrhal signs (cough), body temperature (less than 37ºC). The followings were taken as secondary variables in this trial: fever, sore throat, joint pain, myalgia, fatigability, nasal discharge, itching and burning in the nasal ducts, catarrhal signs (cough, rhinitis, etc.), intensity of which was
estimated according to verbal analogue scale (0–3 points). ECG and echocardiograms were analysed separately.

The study included: biochemical blood analysis (Honskyy, 1992) and immunological examination, which was performed with monoclonal antibodies using the flow cytometer (Beckmann-Coulter). Immunoglobulin levels were assessed using Mancini method (Grinevich and Kamenets, 1986; Pokrovsky, 1969). Electrocardiogram registration in 12 standard leads was performed using Cardimax FX-326U electrocardiographic machine, echocardiographic examination in M- and B-Doppler-modes were performed with the use of Aloka SSD 2000 equipment (Bobrov et al., 1997). Influenza virus was identified by means of identification of RNA of influenza virus A and RNA of Influenza virus B. In case of positive results for influenza virus A, additional polymerase chain reaction analysis for influenza virus A/H1/N1 was performed on a Rotor-Gene 6000 amplifier (Vozianova and Pechinka, 2002).

2.1 Statistical methods

Statistical analysis of the data was performed with the use of Microsoft Excel and SPSS 13.0 statistical software. Descriptive analysis included the calculation of n, mean, median, standard deviation, minimum, maximum for quantitative variables, while count and percentage were calculated for categorical variables. Graphical methods, confidence interval estimation (estimation of 95% CI for means and medians depending on the normality of distribution of data), and two-factor ANOVA were used. Mann-Whitney test or Student test for independent samples (depending on the normality of data distribution) was used for assessment of significance of difference between the two groups, Wilcoxon’s signed-rank test or student’s t-test for paired data was used to compare data before and after treatment. Normality of data was checked by Shapiro-Wilk’s test. Confidence interval for two medians difference was calculated by Hodges-Lehmann method. For Shapiro-Wilk’s test, the level of significance was predetermined at 0.01 level, for all other tests the level of significance was chosen as 0.05 (Lapach et al., 2002; Maltsev et al., 2006; Chubenko et al., 2003; Chow et al., 2003).

3 Results and discussion

Diagnosis of influenza and URTI was confirmed by means of immunofluorescent express-method (MFA) and serologically (HIR). Influenza virus A was detected in 32.94% of patients, influenza virus B – in 8.24% of patients, parainfluenza virus – in 41.18% of patients, adenoviral infection – in 8.24% of patients, respiratory-syncytial infection – in 9.41% of patients.

3.1 Efficacy analysis in groups for primary variables

The descriptive analysis of the primary variables listed in Table 1, a tendency to lower mean values was seen in the test group as compared to the control one. Since the analysed data had a non-Gaussian distribution, the adequate measure of central tendency of these data was a median, and quartiles were the measure of distribution.
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Since the data were not in agreement with the normal distribution (according to Shapiro-Wilk’s test), the comparison of efficacy between the two groups by the primary variables was done using the Mann-Whitney test. It was concluded, that the efficacy of therapy including Nuclex (the test group), was significantly higher (p < 0.001), than efficacy of therapy, which did not include this medication (the control group).

Table 1  Results of efficacy analysis based on the primary variables using descriptive statistics in groups (test: n = 85; control: n = 85)

<table>
<thead>
<tr>
<th>Time in days</th>
<th>Group</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>For temperature to normalise</td>
<td>Control</td>
<td>4.33</td>
<td>5</td>
<td>0.93</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>2.84</td>
<td>3</td>
<td>0.37</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>For headache to relief</td>
<td>Control</td>
<td>2.68</td>
<td>3</td>
<td>0.47</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>1.34</td>
<td>1</td>
<td>0.48</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>For catarrhal signs to be gone</td>
<td>Control</td>
<td>6.08</td>
<td>6</td>
<td>0.62</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>4.88</td>
<td>5</td>
<td>0.89</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>For general weakness to be gone</td>
<td>Control</td>
<td>3.25</td>
<td>3</td>
<td>0.55</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>2.09</td>
<td>2</td>
<td>0.63</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2  Interval estimation of primary variables (test: n = 85; control: n = 85)

<table>
<thead>
<tr>
<th>Time in days</th>
<th>Group</th>
<th>Median</th>
<th>95% CI limits</th>
<th>Quartiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>For temperature to normalise</td>
<td>Control</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>For headache to relief</td>
<td>Control</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>For catarrhal signs to be gone</td>
<td>Control</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>For general weakness to be gone</td>
<td>Control</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Thus, it was proven that the therapy including Nuclex was superior to the standard therapy for URTI or influenza in patients with cardiovascular diseases in terms of the primary variables.

3.2 Efficacy analysis based on disease symptoms variables

Intensity of disease symptoms variables was measured according to VAS (verbal analogue scale), which included the following rank-ordered categories, which were equivalent to the number of points: 0 points – no signs, 1 point – mild, 2 – moderate, 3 – severe.

Graphically the dynamics of the mean values of subjective complaints and objective symptoms of the disease is shown in Figure 1 to Figure 10.
A decrease in symptom intensity (high body temperature, fever, headache, sore throat, joint pain, myalgia, itch and burn in the nose, tiredness, general weakness and catarrhal signs) in the main group as compared with the initial conditions (day 0) was statistically significant starting from day 4.
Figure 3  Dynamic of means for ‘catarrhal signs’ variable (see online version for colours)

Figure 4  Dynamic of means for ‘general weakness’ variable (see online version for colours)

On Figure 1 to 4, the dynamics of the main signs and symptoms of the disease is presented graphically: high body temperature, headache, catarrhal signs and general weakness. The mentioned graphs demonstrate that the curves are similar and differences between the groups according to differences (day 1–day 0) in all the variables are statistically significant starting from the day 4. This indicates that the decrease in the symptoms intensity in the main group is much more marked already on the 4th day as compared with the control group. Such decrease remains to be significant for such variables as ‘high body temperature’ till the day 14 (Figure 1), ‘headache’ till the day 10
(Figure 2), catarrhal signs till the day 6 (Figure 3), and also day 21, and in the ‘general weakness’ variable this decrease remains significant till the day 6. Such result implies that the decrease in main symptoms intensity in the main group appears much earlier (on the 4th day) as compared with the control group, and this difference between the two variables remains significant till day 14 and day 21 inclusive.

Figure 5 Dynamic of means for ‘joint pain’ variable (see online version for colours)

Figure 6 Dynamica of means for ‘mialgia’ variable (see online version for colours)
The obtained results show that the decrease in symptoms intensity in the main group are much more prominent and occur earlier as compared with the control group, and this decrease mainly for 2–3 days remains considerable till the end of the treatment.

**Figure 7** Dynamic of means for pruritus and burn in the nasal ducts’ variable (see online version for colours)

![Graph showing dynamic of means for pruritus and burn in the nasal ducts' variable](image)

**Figure 8** Dynamic of means for ‘fatiguability’ variable (see online version for colours)

![Graph showing dynamic of means for fatiguability](image)
Basing on the data, shown in Figures 1 to 10 it could be stated that there was seen a tendency to a faster decrease in symptoms intensity in the main group than in the control group.

In order to evaluate the intensity of symptoms in each group, statistical evaluation was done according to a mixed model: dependent variable – criteria of the analysed symptom, ‘time’ factor – fixed (levels: day 0, day 2, day 4, day 6, day 8, day 10, day 14 and day 21), ‘patients’ factor – random. For those dependent variables, which were not in agreement with ANOVA (residuals distribution normality), ANOVA ranking was used (Greaves et al., 2003).

According to ANOVA results, effect of the ‘time’ factor was significant, indicating a positive influence of treatment on the decrease in symptoms intensity.

**Figure 9** Dynamic of means ‘fever’ variable (see online version for colours)

**Figure 10** Dynamic of means ‘sore throat’ variable (see online version for colours)
3.3 Analysis of treatment efficacy in subgroups infected with different viruses

A comparative analysis was additionally conducted between the test and the control groups in patients subgroups, infected with different viruses, according to the following primary variables:

- time to temperature normalisation
- time to disappearance of headache
- time to resolution of general fatigue.

A Mann-Whitney test was used to compare the subgroups of the study and the control groups. Statistically significant differences between the study and control groups in terms of primary variables were found and a tendency to lower mean values in the main group as compared with the control group was observed.

Thus, it could be concluded that the therapy efficacy in the study group which was taking Nuclex was higher than the efficacy of the conventional therapy only in terms of the mentioned variables (time of temperature normalisation, time of headache relief, and time of the general weakness relief).

Results of our study indicate that independently of the virus (influenza or parainfluenza), which comprises 80% of patients, the medication essentially shortens the time of resolution of the major URTI symptoms.

3.4 Analysis of treatment efficacy in the subgroup of patients with AH1N1 virus

Virological investigation by means of PCR has shown that on the 1st day of treatment in the test group among patients with influenza virus A there were 46.15% (12 patients) infected with AH1N1 strain, while in the control group 26.6% (8 patients) were infected with AH1N1 strain. On the 14th day of treatment with Nuclex 7 of 12 patients infected with AH1N1 virus have shown no signs of virus presence, meanwhile among eight patients treated with Tamiflu, only one was virus free. During the 14 days of treatment in the test group the proportion of the patients with AH1N1 virus decreased significantly to 19.23% (p = 0.016, McNewmar test), while in the control group the proportion of such patients remained unchanged (23.33%; p = 1.000, McNewmar test).

Thus, on the 14th day after treating patients of the study group with Nuclex, PCR method did not detect AH1N1 virus in 58.33% of patients, meanwhile in patients of the control group virus was detected in 87.5% of patients. This shows that there is considerable difference in the treatment efficacy between the control and the test groups in favour the latter and points out to the Nuclex ability to almost completely eliminate the influenza virus from the body. Moreover, we have found that influenza virus AH1N1 is able to stay in the organism for a long period even after the main symptoms are gone. It could be assumed that more prolonged treatment with Nuclex (up to 21st day) can lead to the complete elimination of the virus.

We have also discovered the ability of influenza virus to stay in the organism for a long period of time even after treatment with a specific antiviral medication Tamiflu. This necessitates PCR detection of influenza virus RNA and more prolonged treatment with antiviral medications till the complete elimination of the virus.
Nuclex medication has shown specific antiviral effect in vitro and in vivo models. It was established that the Nuclex’s antinfluenzal effect resides in the inhibition of neuraminidase hemagglutinin activities during the interaction with influenza AH1N1 virion, besides; the medication is a prolonged inducer of α-interferon in vivo experiments (Tkachuk et al., 2010).

Obtained data of clinical trail argue for Nuclex usage in URTI and influenza treatment and confirm data, obtained in experimental models on its high efficacy as compared to the referent medication Tamiflue.

3.5 Analysis of changes in ECG and echocardiogram (EchoCG)

According to the examination protocol of patients on the first (day 0) and on the last (day 21) the following parameters of ECG and EchoCG were analysed: duration of RR interval, ST segment, duration and amplitude of QRS complex, dimensions and volume of the right ventricle (RV), right atrium area (ARA), mean pulmonary artery pressure, ejection fraction (EF), form of T wave and rhythm disorders.

According to results of electrocardiographic examination there was a considerable increase in the cardiac rate, pathological changes in the form of T wave, abnormalities in bundle branch conductivity, arrhythmias (premature complexes). In all patients, undergoing EchoCG, right heart overload was found along with a decrease of EF to 45% to 48%, increased pressure in the pulmonary artery to 35–40 mmHg.

Results of the serial changes analysis of these measurements by means of descriptive statistics are shown in Table 3.

Table 3  Results of ECG and EchoECG parameters analysis in the test and the control groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time (visits)</th>
<th>Test group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>RR interval duration, sec</td>
<td>Day 0</td>
<td>0.56</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Day 21</td>
<td>0.58</td>
<td>0.6</td>
</tr>
<tr>
<td>ST segment displacement, cm</td>
<td>Day 0</td>
<td>2.08</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Day 21</td>
<td>2.17</td>
<td>2</td>
</tr>
<tr>
<td>QRS complex duration, sec</td>
<td>Day 0</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Day 21</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>RV area, cm²</td>
<td>Day 0</td>
<td>3.05</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Day 21</td>
<td>2.66</td>
<td>3</td>
</tr>
<tr>
<td>IVhouna III, cm²</td>
<td>Day 0</td>
<td>15.20</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Day 21</td>
<td>14.87</td>
<td>13</td>
</tr>
<tr>
<td>Mean pressure in the pulmonary artery, mmHg</td>
<td>Day 0</td>
<td>38.17</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Day 21</td>
<td>28.65</td>
<td>29</td>
</tr>
<tr>
<td>EF, %</td>
<td>Day 0</td>
<td>48.48</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Day 21</td>
<td>53.30</td>
<td>53</td>
</tr>
<tr>
<td>Amplitude of T wave, mm</td>
<td>Day 0</td>
<td>5.32</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Day 21</td>
<td>4.34</td>
<td>4.1</td>
</tr>
</tbody>
</table>
Parameter ‘QRS complex’ during the treatment course did not change in any of the patients in both groups. For this reason, further analysis of this parameter was not carried on.

The relative increase (decrease) in ECG and EchoCG measurements on the 21st day as compared with the initial data (in %) and the significance of these changes was estimated with the Wilcoxon signed-rank test (p-value). The results are shown in Table 4.

Table 4  Comparative increase (decrease) in ECG and EchoECG parameters on the 21st day as comparing to the initial state

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test group</th>
<th></th>
<th>Control group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>p</td>
<td>%</td>
<td>p</td>
</tr>
<tr>
<td>RR interval duration, sec</td>
<td>3.42</td>
<td>0.003*</td>
<td>-5.84</td>
<td>0.000*</td>
</tr>
<tr>
<td>St segment displacement, cm</td>
<td>-12.83</td>
<td>0.000*</td>
<td>-7.28</td>
<td>0.000*</td>
</tr>
<tr>
<td>QRS complex duration, sec</td>
<td>-24.95</td>
<td>0.000*</td>
<td>-30.04</td>
<td>0.000*</td>
</tr>
<tr>
<td>RV area, cm²</td>
<td>-18.30</td>
<td>0.000*</td>
<td>-22.85</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

Note: *The changes before and after the treatment are statistically significant (the confidence level is less than 0.05 according to the rank-ordered Wilcoxon test).

According to the results listed in Table 5, it could be stated that changes in such parameters as ‘duration of RR interval’, right ventricular area (RVA), right atrium area (ARA), mean pulmonary artery pressure and changes in the form of T wave on the 21st day were statistically significant as compared with the initial data in both groups.

Table 5  Comparison of changes of ECG and EchoCG parameters (for parameters according to which the groups were initially homogeneous)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mann-Whitney U</th>
<th>Wilcoxon W</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle area, cm² (day 21 – day 0)</td>
<td>2,884.5</td>
<td>6,539.5</td>
<td>-2.563</td>
<td>0.010</td>
</tr>
<tr>
<td>Right auricle area, cm² (day 21 – day 0)</td>
<td>2,881</td>
<td>6,536</td>
<td>-2.442</td>
<td>0.015</td>
</tr>
<tr>
<td>Mean pressure in the mumanary artery, mmHg (day 21 – day 0)</td>
<td>2,313</td>
<td>5,968</td>
<td>-4.123</td>
<td>0.000</td>
</tr>
<tr>
<td>Amplitude of T wave, mm (day 21 – day 0)</td>
<td>3,393</td>
<td>7,048</td>
<td>-0.695</td>
<td>0.487</td>
</tr>
</tbody>
</table>

There were significant changes towards normalisation of ST segment and ejection fraction in the study group, while in the control group ST segment and ejection fraction did not change significantly by the 21st day of treatment.

3.6 Group comparison on the basis of ECG and EchoECG parameters

Group comparison was carried out based on the differences (day 21 – day 0) in ECG and EchoCG parameters. Since the groups were homogenous at the initial level thru the
parameters of volume RV, area RA, pressure in the pulmonary artery and changes in the form of T wave, for their comparison according to these parameters Mann-Whitney test was used (as the distribution of the data was not normal according to Shapiro-Wilk’s test). Results of Mann-Whitney test are shown in Table 5.

As it can be seen from Table 5, it was proven that there are statistically significant differences between groups on the basis of changes in such parameters as: ‘area of the right ventricle’ (p = 0.010), ‘area of right atrium’ (p = 0.015) and ‘the mean pressure in the pulmonary artery’ (P < 0.000).

The ranked ANCOVA was used for comparison of changes of ‘RR interval duration’, ‘ST segment deviation’ and ‘ejection fraction’ between the groups. According to the obtained results, statistically significant differences in changes of ‘RR interval duration’ (p = 0.003), ‘ST segment deviation’ (P < 0.000) and ‘EF’ (P < 0.000) were found in the course of treatment between the study and control groups.

Thus, according to ECG and EchoCG results, there was a clinically and statistically significant improvement in the study group, while in the control group the improvement was less marked.

The obtained results from preclinical studies permit us to conclude that the RNA medication Nuclex has a wide spectrum of cardioprotective actions, including endothelium-protective, antioxidant, anti-inflammatory, and hemopoietic actions. The medication acts as a stabiliser of erythrocytes (antihemolytic action) and stimulates spinal cord stem cell migration (Tkachuk, 2004, 2008; Tkachuk and Yakovenko, 2006; Tkachuk et al., 2006, 2009, 2010). Specific anti-inflammatory properties of Nuclex provide its superior properties when compared to other antiviral medications based on the low molecular purine nucleosides. Studies have shown that single dose RNA administration caused a short-term dose-dependent dilatation of the coronary arteries in the left circumflex artery circulation. RNA administered either as a single dose or as infusion into coronary blood flow resulted in optimisation of adrenergic and cholinergic regulation of cardiac function and of coronary and systemic blood flow (Neshcheret et al., 2009).

It is also known the other pathophysiological mechanism of cytocardi- and angioprotective action of RNA medications, which is being turned on under conditions of coronary blood flow distortion, during translocation and ctitivation of phospholipases, which damage membrane phospholipids in cardiomyocytes, which, in turn leads to formation of biologically active substances with coronaryconstrictive and chemoattractive properties. Namely because of such factors happens activation of pathological processes and damage of ischemic erythrocytes. In experimental models we have shown that yeast RNA inhibits formation of not only free arachidonic acid (AAC) in white blood cells of ischemic rats, but also inhibits an increase in the content of toxic phospholipids lisoforms in cells’ plasma membranes, which leads to a drastic increase in their permeability. Moreover, the medication inhibits activity of lipid generator of free oxygen radiclas contemporary with the formation of constrictive eicosanoids, due to lipoxygenase and cyclooxygenase pathways of free arachidonic acid oxidation.

The obtained results from the clinical studies have confirmed cardioprotective effect of Nuclex medication in the risk group of patients with influenza and URTI. This has been proven by the dynamics of such measurements as ‘duration of RR interval’, ‘right ventricle area (RVA)’, ‘ARA’, ‘mean pressure in the pulmonary artery’ and ‘changes in the form of T wave’. Significant positive changes of ejection fraction in the course of treatment with Nuclex should be particularly mentioned, as there were no statistically significant changes of ejection fraction in the control group throughout the study period.
In conclusion, the results of the present study as well as the previously published results of experimental studies demonstrate significant amount of evidence of the beneficial antiviral effects of Nuclex. Nuclex acts at all stages of influenza and influenza-induced cardiovascular complications. On the molecular level the mechanisms include the blockage of the viral entry into the cell and exit from the cell through the antihemagglutinin and antineuraminidase action, modulation of anti-inflammatory reactions by acting upon phospholipid and arachidonic acid metabolism. On the organism level, Nuclex acts through normalisation of cardiac and systemic blood flow parameters.

The unique combination of specific antiviral, antiinflammatory and cardioprotective properties of Nuclex allows it to be used for influenza and URTI treatment in patients at risk for cardiovascular disease. It can also be used for prevention of influenza in these patients, especially if vaccination is not possible.

References


