received aerius in a dose of 2.5 ml for 10 days, another group of patients (10 children) - The disappearance of clinical manifestations of acute urticaria in 90% of children who was treated with aerius and 70% of children - with cetrine. Thus, in children with acute urticaria the preparation of aerius is more effective.

CONCLUSIONS

1. In the distribution of children by age, sex and place of residence, more often acute urticaria occurs in the age group from 7 to 10 years (28%), in boys (55%) of the rural population (45%).

2. Among the etiological factors of acute urticarial are most common food allergens - 94.6%, on citrus fruits - 37.7% and cow's milk protein - 30.4%.

3. In children with acute urticaria, the aerius preparation is more effective than cetrine.

REFERENCES

1. Ivanova O. N., Kondyurin E. G., Petrov P. G. Immunopatologiya infektsionnykh zabolevanij [Immunopathology of infectious diseases]. Gomeostaz i infekcionnyj process: tez.dokl. konf. s mezhdunar. uchastiem [Homeostasis and infectious process: proc. of Conf. with int. participation]. Moscow, 2006, P. 314.

2. Lysikova I. V. Rasprostranyonnost' allergicheskikh zabolevanij u detej po rezul'tatam mul'titsentrovykh issledovanij v ramkakh mezhdunarodnoj programmy ISAAC [The prevalence of allergic diseases in children according to the results of multicentre studies in the framework of the international program ISAAC]: author. dis. Cand. med.Sciences. Moscow, 1999, 20 p.

3. Petrov R. V. Immunologiya [Immunology]. Moscow, 2007, P.52.

The author:

Ivanova Olga Nikolaevna - doctor of medical sciences, Professor, Department of Pediatrics and pediatric surgery of the Medical Institute NEFU, Yakutsk, Russia, E – mail: olgadoctor@list.ru.

A.V.Mel'nik, N.I.Logvinenko, S.V.Astrakov

EXPERIENCE OF USING THE INDACATEROL FROM THE POSITION OF CARDIOVASCULAR SAFETY

ABSTRACT

Clinical efficacy of inhalation therapy by Onbrez®Breezhaler® and examination of the effect on the leading clinical symptoms, quality of life (COPD Assessment Test), lung function, heart rate, QTc interval and the potassium level in blood in hospital patients with COPD were under study.

Based on the found evidence we can conclude that once daily administration of indacaterol at a dose of 150 mcg is an effective treatment for patients with COPD. It provides significant bronchodilation, reduces clinical manifestations, improves the quality of life of patients and has a favorable cardiovascular safety profile.

Keywords: COPD, treatment, indacaterol, Onbrez®Breezhaler®.

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. According to the results of modern epidemiological studies from 2 to 26% of the adult population suffer COPD in the European countries [6]. Prevalence and unfavorable course of COPD are associated with a high prevalence of tobacco smoking, unfavorable ecological situation, low medical literacy and other factors.

According to the World Health Organization COPD causes the death of more than 3 million people every year [20] and it is in the fourth place on the list of causes of death worldwide [14]. WHO expects that by 2030, chronic obstructive pulmonary disease will be the third leading cause of death [21].

According to numerous studies there is a clear correlation between the decrease in FEV1, cardiovascular morbidity and mortality [15,18,19]. The long-term population-based study indicated that the risk of cardiovascular mortality was more than double among patients with low forced expiratory volume in 1 second than in the group with higher levels of FEV1, at that, it was independent of smoking status [19]. The epidemiology of arrhythmias in the patients with COPD and their connection with a fatal case was examined in the Copenhagen City Heart Study. It is ascertained that COPD is associated with a high incidence of heart rhythm disturbances [16]. It is important to note, the mortality rate of patients with the combination of severe acute COPD and arrhythmia is more than 30%, by comparison with the mortality rate of the same patients but without arrhythmias is 8% [9].

Many researchers demonstrate the high prevalence of different types of arrhythmias in patients with COPD [1-5]. The pathogenesis of arrhythmias in these patients is multifactorial: systemic inflammation, hypercapnia, and oxidative stress lead to the acceleration of atherogenesis and provoke arrhythmias, dysfunction of the left and right ventricles, hypoxia, respiratory acidosis, hypokalemia, hypomagnesemia, and dysfunction of cardiac conduction system. It is necessary to notice the high probability of pharmacological therapy induced arrhythmias with the high doses of bronchodilator drugs [7], the drugs of the 1st line of the majority of patients with COPD.

The using of β2-agonists is accompanied by stimulation of the Na + /K+ and ATPase of skeletal muscle interfacing with β2-adrenoreceptor following elution of muscle fibers Na + and intracellular accumulation of K + increasing, but decrease of concentration of K + in blood [17].

Therefore, an effective and safe treatment of this pathology is one of the priority tasks of modern pulmonology.

The dimension of pharmacological treatment is based on clinical symptoms, post-bronchodilator forced expiratory volume in 1 s (FEV1) and frequency of exacerbations of the disease. It should be noted that patient compliance and adherence to the recommended regimens of medical maintenance are important components of effective treatment. From this point of view, the facilitation of medical treatment regimens and once daily administration are steps towards that.

The big gain of the modern pharmacology is the design of long action b2-agonist (Indacaterol). Virtually all β2-agonists are a mixture of R- and S-enantiomers, the inactive S-enantiomer

is interfaced with adverse proinflammatory reactions in preclinical models. Indacaterol is specifically developed as a single enantiomer to out the adverse proinflammatory reactions. It includes the active R-enantiomer. The inactive isoform (S-enantiomer) is eliminated by chemical synthesis. Onbrez®Breezhaler® is a medicinal product with established a good reputation among the patients with COPD. It has a 24-h bronchodilator effect and is characterized by a fast start of action (within 5 min.) and a good tolerability [8,10-13].

The goal of research consists in clinical efficacy evaluation and examination of the effect of inhalation therapy of Onbrez®Breezhaler® to the leading clinical symptoms, quality of life (COPD Assessment Test), lung function, heart rate, QT interval and the potassium level in blood in hospital patients with COPD.

MATERIALS AND METHODS

The research is based on the follow-up of 53 patients with COPD having hospital treatment at the state-financed health institution of the Novosibirsk Region municipal clinical hospital №25 in the city Novosibirsk. All patients had COPD as a diagnosis. It was verified in accordance with the typical clinical course and lung function (symptoms of obstructive or mixed bronchial airway obstruction and post-bronchodilator forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) less than 70% of predicted values). In accordance with GOLD classification on data set the degree of bronchial airway obstruction, number of exacerbations per year and the severity of clinical symptoms subsequent to the results of mMRC and COPD Assessment Test (CAT) patients were assigned to group B. The duration of the disease varied from a few months to 20 years. The entire group of patients did not have clinical, anamnestic, electrocardiographic, radiographic symptoms of bronchial asthma, unstable angina, postinfarction cardiosclerosis, congestive cardiac failure, congenital heart diseases, various forms of cardiac arrhythmias, myocarditis, pericarditis, cardiomyopathy, renal and hepatic failure. There were 35 men (66%) from 43 to 65 years at the mean age of 57 ± 1,9 years old. And there were 18 women (34%) from 48 to 55 years at the mean age of 51 ± 1,5 years old. They were prescribed the standard treatment focused on the suppression of the inflammatory response and augmentation of the patency of bronchi. The treatment was the broncholytic therapy (150 mg of Indacaterol per day), also mucolytic and antibacterial therapy (third generation cephalosporins). The patients did not take any medications to reduce heart rate. The leading clinical symptoms, quality of life (COPD Assessment Test), lung function, heart rate, QT interval and the potassium level in blood as the risk factors of fatal arrhythmia were measured initially and in 10 days after the treatment.

The statistical analysis was performed using the program Statistica V.6.0.

RESULTS AND DISCUSSION

The heart rate analysis showed the results presented in Figure 1. At primary inspection 29 patients (55%) were recorded with sinus tachycardia, heart rate up to 115,7 ± 10,1 beats per minute ($p < 0.05$) accompanied by hand tremor in 7 patients (13%).

At the 3rd day of treatment the heart rate decreased to 91,6 ± 10,5 beats per minute. There were no complaints of hand tremor. At the 5th day of treatment heart rate was 84,0 ± 3,5 beats per minute. At the 10th day the heart rate was 68,1 ± 8,4 beats per minute.

At the 10th day of the treatment there was no clinically significant increase of QT interval.

Hypokalemia was revealed at the moment of admission in 8 cases (15%). At the 10th day there was no reducing of the concentration of potassium in the blood.

There was a decrease of FEV1 as related to the initial measure at an average of 140 ml at the 5the and 170 ml at the 10th day of attendance.

Figure 2 shows the decrease in the total score of clinical symptoms of COPD (according to COPD Assessment Test) by 40% among men and 47% among women, this corresponded to a moderate impact on the lives of COPD patients (Fig. 1).

CONCLUSION

Based on the evidence found we can conclude once daily administration of Indacaterol at a dose of 150 mcg is an effective treatment for patients with COPD. It provides significant bronchodilation, reduces clinical manifestations, improves the quality of life of patients and has a favorable cardiovascular safety profile.

The positive results can be explained by the structural features of the Indacaterol molecule.

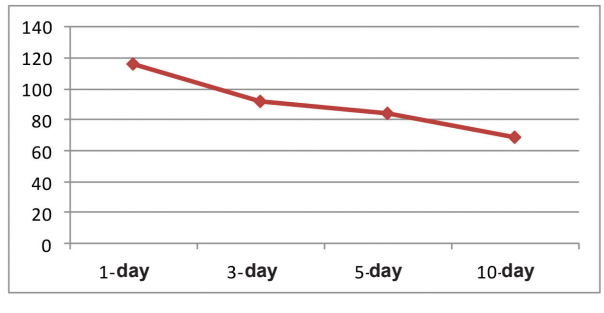

Figure 1. Heart rate dynamics under Indacaterol therapy

REFERENCES

1. Bazdyrev E. D. i dr. Osobennosti vedeniya patsientov s khronicheskoy obstruktivnoy bolezn'yu legkikh v sochetanii s serdechno-sosudistymi zabolevaniyami: metodicheskie rekomendatsii dlya vrachey [Features of patients with chronic obstructive pulmonary disease in combination with cardiovascular disease: methodological recommendations for MD], Kemerovo, 2012, 55 p.

2. E. V. Zaikina, Nizov A. A., Koldynskaya E. I., Zaikina M. V., Rakita D. R. Osobennosti kardial'noy patologii u bol'nykh bronkhial'noy astmoy i KhOBL [Cardiac pathology features in patients with bronchial asthma and COPD] // Sbornik trudov kongressa. XXIII Natsional'nyy kongress po boleznyam organov dykhaniya [Collected works of Congress. XXIII National Congress of Respiratory Diseases], 2013, p.21.

3. Zagiddulin N. Sh., Safina Yu. F., Khalimova G. R., Farkhutdinov U. R. Kharakter aritmiy pri boleznyakh organov dykhaniya [Character of arrhythmias in diseases of the respiratory system] // Sbornik trudov kongressa. XXII Natsional'nyy kongress po boleznyam organov dykhaniya [Collected works of Congress. XXII National Congress of Respiratory Diseases], 2012, p. 240.

4. Shugushev Kh. Kh., Gurizheva M. V., Vasilenko V. M. Nadzheludochkovye aritmii i EKG vysokogo razresheniya u bol'nykh khronicheskoy obstruktivnoy bolezn'yu legkikh na fone bronkholiticheskoy terapii [Supraventricular arrhythmias and high resolution ECG in patients with chronic obstructive pulmonary disease on the background of bronchodilator therapy] // Rossiyskiy kardiologicheskiy zhurnal [Russian Journal of Cardiology], 2010, № 6 (86), p. 40–44.

5. Kh. Kh. Shugushev, Gurizheva M. V., Vasilenko V. M. Vliyanie bronkhodilatatorov na variabel'nost' ritma sertsa u bol'nykh khronicheskoy obstruktivnoy bolezn'yu legkikh [Influence of bronchodilators over the heart rate variability in patients with chronic obstructive pulmonary disease] // Ratsional'naya Farmakoterapiya v Kardiologii [Rational Pharmacotherapy in Cardiology], 2007, № 4, p. 51–54.

6. Atsou K. Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: systematic

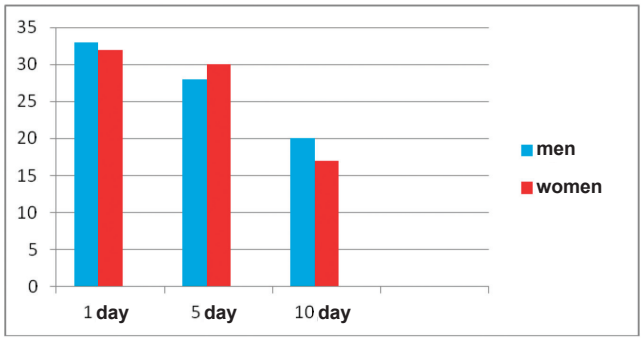

Figure 2. Comparative characteristics of the changes of clinical symptoms (scores according to COPD Assessment Test)

review / K. Atsou, C. Chouaid, G. Hejblum// BMC Medicine. 2011. Vol. 9. P. 7.

7. Bronchodilator use and the risk of arrhythmia in COPD: part 1: Saskatchewan cohort study /M. Wilchesky, P. Ernst, J. M. Brophy , R.W. Platt, S.Suissa// Chest. — 2012. — № 142 (2). — P. 298–304.

8. Efficacy and safety of indacaterol 150 mg once-daily in COPD: a double-blind, randomised, 12-week study/ G. Feldman, T. Siler, N. Prasad et al.// BMC Pulm Med 2010; 10: 11.Gulsvik A. Cardiac arrhythmias in patients with serious pulmonarydiseases /A. Gulsvik, V. Hansteen, E. Sivertssen // Scand J Respir Dis. 1978. Vol. 59. P. 154–159.

10. INABLE 1 study group. Effect of indacaterol on exercise endurance and lung hyperinflation in COPD/ D.E. O'Donnell, R. Casaburi, W. Vincken et al.//Respir Med 2011; 105 (7): 1030–6.

11. INHANCE Study Investigators.Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium/ J.F. Donohue, C. Fogarty, J. Lötvall et al.//Am J Respir Crit Care Med 2010; 182 (2): 155–62.

12. INLIGHT-2 (Indacaterol Efficacy Evaluation Using 150-mg Doses with COPD Patients) study investigators Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison/O. Kornmann, R. Dahl, S. Centanni et al.//Eur. Respir J 2011; 37 (2): 273–9.

13. On behalf of the INVOLVE Study Investigators. Efficacy of a new once-daily, long-acting inhaled b2-agonist indacaterol versus twice-daily formoterol in COPD/R. Dahl, K. F. Chung, R. Buhl et al.// Thorax 2010; 65: 473–9.

14. Pauwels R.A. Burden and clinical features of chronic obstructive pulmonary disease (COPD)/ R.A. Pauwels, K.F. Rabe // Lancet 2004; 364: 613–20.

15. Pulmonary function is a long_term predictor of mortality in the general population: 29-year follow_up of the Buffalo Health Study /H.J. Schunemann, J. Dorn, B.J. Grant et al.// Chest. – 2000. – Vol. 118. – P. 656-664.

16. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study / P. Buch, J. Friberg, H. Scharling, P. Lange, E. Prescott // Eur Resp J. – 2003. – Vol. 21 (6). – P. 1012-1016.

17. Rennard S.I. Bronchodilator sin chronic obstructive pulmonary disease. In: Management of chronic obstructive pulmonary disease. Ed. N.M.Siafakas. Eur. Respir .Monograph 2006; 11: 266-80

18. Respiratory symptoms and long-term cardiovascular mortality/A. Frostad, V. Soyseth, T. Haldorsen et al.// Respir Med 2007: 101: 2289–96.

19. Sin D.D. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature / D.D. Sin, L. Wu, S.F. Man// Chest. 2005. Vol. 127. P. 1952–1959.

20. World Health Organisation Website. Chronic Obstructive Pulmonary Disease http://www.who.int./ respiratory/copd.

21. World Health Organization. COPD predicted to be third leading cause of death in 2030. Available from: http://www.who.int/respiratory/copd/World_Health_Statistics_2008/en/. Accessed May 1, 2014.

The authors:

1. Melnik Aleksey Vladimirovich - the head of the therapeutic department, the doctor pulmonologist of the State Educational Establishment of Higher Professional Education of the NSO «GKB No. 25», Novosibirsk, a.v.melnik@list.ru;

630075, Novosibirsk, ul. Alexander Nevsky, 1a

2. Logvinenko Nadezhda Ivanovna - MD, professor of FPK and PPV of GBOU VPO of the Ministry of Health of the Russian Federation, nadejda-logvinenko@yandex.ru;

Russia, 630091, Siberian Federal District, Novosibirsk Region, Novosibirsk, Red Avenue, 52

3. Astrakov Sergey Viktorovich - MD, Professor, Novosibirsk State University, State Medical University of the National Medical University of the Ministry of Health of the Russian Federation, Chief Physician of the State Educational Establishment of the Federal State Institution of Higher Professional Education «State Security Committee No. 25», Novosibirsk, astr_sv@mail.ru

630091, Novosibirsk, ul. Krasny prospect, 52.