Application of Long-Acting β2-Agonists in the Treatment of Chronic Obstructive Pulmonary Disease in Patients with Concomitant Ischemic Heart Disease

DOI: 10.17691/stm2017.9.1.20
Received October 17, 2015

© **N.Y. Grigor'eva,** MD, DSc, Professor, Department of Faculty and Polyclinic Therapy;
M.V. Mayorova, PhD Student, Department of Faculty and Polyclinic Therapy;
A.N. Kuznetsov, MD, DSc, Professor, Head of the Department of Faculty and Polyclinic Therapy

Nizhny Novgorod State Medical Academy, 10/1 Minin and Pozharsky Square, Nizhny Novgorod, 603005, Russian Federation

The aim of the investigation was to study clinical efficacy and cardio safety of long-acting β2-agonist indacaterol in patients with chronic obstructive pulmonary disease (COPD) I–II grade in the stage of moderate exacerbation with concomitant ischemic heart disease.

Material and Methods. Twenty patients (10 men and 10 women) with COPD and associated ischemic heart disease aged from 46 to 66 years (average age 57.2±7.9 years) have been examined. All patients received 150 μg/day of β2-agonist indacaterol for the treatment COPD during the entire period of observation. Prior to and 3 weeks after the treatment, a complex examination was carried out, including external respiratory function examination 6-minute walk test, and daily ECG monitoring.

Results. By week 3 all patients noted decrease of the main respiratory symptoms. Forced expiratory volume in 1 s before the treatment was 57.64±9.67%, after it reached 64.72±5.45%. Physical load tolerance increased, which is confirmed by 6-minute walk test (initially 345.4±59.2 m, after the treatment 412.8±11.1 m). The results of repeated daily ECG monitoring (at week 3) did not show any new cases of arrhythmia or aggravation of myocardium ischemia.

Conclusion. 150 μg/day of indacaterol in patients with I–II grade COPD in the stage of moderate exacerbation with concomitant cardiovascular pathology does not affect cardio safety.

Key words: ischemic heart disease; chronic obstructive pulmonary disease; indacaterol.

At present, a steady growth of chronic obstructive pulmonary disease (COPD) incidence is noted worldwide. This disease is predicted to occupy the fifth place by 2020 among the most common illnesses in the world, and the third place (the sixth now) among the death causes [1, 2]. According to the data presented by some authors, a leading cause of death of COPD patients with a mild and moderate disease course is not a respiratory insufficiency but ischemic heart disease (IHD) [3]. Large epidemiological studies [4, 5] showed that the risk of cardiovascular mortality in COPD patients is 2–3 times higher and amounts to about 50% of the total number of fatal outcomes.

The frequency of IHD and COPD combination is found to be 18.7–58.3% [6]. In the period of COPD exacerbation, stable angina is observed in 63% of patients, progressive angina in 57% [7]. A high prevalence of comorbid cardiovascular and bronchopulmonary pathology dictates the necessity of conducting investigations on the effect of pharmaceutical agents on the concomitant pathology.

Selection of broncholytic preparations for COPD patients with IHD should be done taking into consideration their negative effect on the cardiovascular system. A recognized leader causing no negative effect on the heart among basic medical means used for treating COPD are M-cholinolytics. For example, application of tiotropium bromide in COPD patients with IHD is not accompanied by arrhythmias, hemodynamic disorders, and the change of the patient vegetative status [6, 8]. However, a slow therapeutic effect in comparison with β2-agonists frequently makes a physician and patient abandon the use of this class of drugs especially in patients with mild forms of COPD. But at the same time, there is a strong evidence that application of methylxanthines and short-acting agonists of adrenergic receptors in order to correct broncho-obstruction and decrease ventilation hypoxia in case of IHD and COPD combination, results in the increase of myocardial oxygen demand, more prominent manifestations of painless myocardial ischemia, cardiac arrhythmias [9, 10]. Other authors do not exclude the possibility of their application in the combination of cardiac and pulmonary pathology given thorough control of hemodynamic and biochemical indices is observed [11]. There are data on the safe long-term application

For contacts: Mariya V. Mayorova, e-mail: kapustinamariya@yandex.ru

of the combined preparation Berodual in treating such patients [12, 13].

At present, it is difficult to think of treating patients with IHD and chronic heart failure without β-adrenoblockers. Certainly, one should take into account the influence of antianginal drugs on the patency and pulmonary hemodynamics when choosing such medicines for patients with COPD. For a long time, calcium antagonists have been considered to be the first-line preparations for patients with IHD having bronchopulmonary pathology. The studies conducted showed that in addition to antianginal, antiischemic, broncholytic effects these agents possess a diversity of positive properties: antioxidant, antiaggregate, broncholytic, reduce blood pressure in the pulmonary artery and improve endothelial function [14]. However, numerous investigations (DAVIT, MDPIT and others) confirm that calcium antagonists in patients with IHD and heart failure, though causing a good antianginal effect, increase cardiovascular lethality and, therefore, worsen the prognosis [15, 16]. No doubt, in this situation β-adrenoblockers are preferable. These preparations (the so-called starting line) cause antianginal, antiischemic, antihypertensive, antiarrhythmic action in acute and chronic IHD forms, reduce the risk and rate of complications and mortality, and improve the longevity and quality of life (recommendations class I, A level of evidence) [14, 17]. In IHD patients with associated COPD, application of β-adrenoblockers was traditionally considered as undesirable due to the probable appearance or aggravation of bronchial obstruction and worsening of pulmonary disease course. The Cooperative Cardiovascular Project (1998) undertaken in the USA showed that the risk of death in patients with COPD and bronchial asthma, having had myocardial infarction, within the period of 2 years without β-adrenoblocker therapy amounts to 27.8 and 19.7%, whereas in case of their application it is 16.8 and 11.9%, respectively. Thus, in this category of patients the use of β-adrenoblockers reduces, in total, the risk of death by 40%. The data of the foreign reviews [18–20] show that selective β-adrenoblockers nebivolol and bisoprolol do not cause statistically significant decrease of the forced expiratory volume in 1 s (FEV1) and worsening of the clinical course of broncho-obstructive diseases [21–23]. Consequently, COPD is not a contraindication to the application of highly selective β-adrenoblockers.

In real clinical practice, a physician faces the task of administering the patient with COPD and IHD a timely treatment with a quick clinical effect and positive influence on the patient life prognosis. In this case, the situations often occur when usage of β2-agonist, on the one hand, and β-adrenoblocker, on the other, is simply necessary. The choice of effective and safe drugs among the representatives of these groups must be grounded.

With the emergence of a long-acting β2-agonist indacaterol (Onbrez Breezhaler; Novartis, Switzerland) in the world market, there appear new opportunities in the treatment of COPD patients with associated cardiovascular pathology. There already exist investigations showing no effect of this drug on hemodynamic indices in patients with COPD and chronic forms of IHD [21–24]. Of practical interest is the study of indacaterol efficacy and safety in destabilization of both diseases in comorbid patients: moderate COPD exacerbation and decompensation of the cardiac activity (unstable hemodynamic indices, growth of chronic heart failure in the presence of various kinds of arrhythmias). Such conditions often lead to hospitalization and demand immediate therapeutic effect. Otherwise, there appears a danger of developing acute coronary syndrome, life-threatening arrhythmias, on the one hand, and aggravation of respiratory failure, on the other.

The aim of the investigation was to study clinical efficacy and cardiac safety of long-acting β2-agonist indacaterol in patients with I–II grade chronic obstructive pulmonary disease in the stage of moderate exacerbation with concomitant ischemic heart disease.

Materials and Methods. Twenty patients (10 men and 10 women) with COPD and associated IHD at the age of 46 to 66 years (mean age 57.2±7.9 years) have been examined. Stable angina, class I (NYHA Functional Classification), was noted in 5, class III in 15 persons, all patients had grade I–II arterial hypertension. Five patients had paroxysms of atrial fibrillation in the history, three had paroxysms of supraventricular tachycardia, two patients had paroxysms of non-sustained ventricular tachycardia.

The diagnosis of COPD was established by the signs presented in the international program “Global strategy for diagnosis, management, and prevention of COPD” (2014) [2]. IHD is classified in compliance with WHO (1979) supplemented by the recommendations of the Russian Society of Cardiology (2007).The diagnosis of stable angina pectoris was made on the basis of the generally accepted criteria [13, 17], heart failure was evaluated by the classification of the New York Heart Association (1964).

Criteria of inclusion in the study were: I–II grade COPD in the stage of moderate exacerbation; concomitant stable angina not higher than class III with unachieved target indices of hemodynamics and different kinds of arrhythmias revealed by daily ECG monitoring; class I–III chronic heart failure. Patients with respiratory failure higher than stage II severity, other pulmonary diseases, unstable angina, myocardial infarction within the last 5 months, diabetes mellitus, heart failure higher than class III were not included into the study.

The study complies with the Declaration of Helsinki (the Declaration was passed in June 1964, Helsinki, Finland, and revised in October 2000, Edinburg, Scotland) and was performed following approval by the Ethic Committee of Nizhny Novgorod State Medical Academy. Written informed consent was obtained from every patient.

Patients were administered antiaggregants, statins,

antiarrhythmics, diuretics, sartans with gradual titration of the dose up to the maintaining one for cardiovascular therapy. A highly selective β-adrenoblocker bisoprolol has been chosen as an antianginal preparation, which can slow down the heart rate (all patients had sinus tachycardia), since the drug has proved its efficacy and safety in IHD patients with COPD in comparison with calcium antagonist verapamil [17].

In all patients, COPD was not higher than medium severity in the stage of moderate exacerbation not requiring administration of antibacterial preparations, but in compliance with the recommendations on managing COPD patients [2] demanding a course (in exacerbation of COPD grade I) or continuous (starting with COPD grade II) intake of broncholytics. All patients received β2-agonist indacaterol at the dose 150 μg/day during the entire period of observation as a COPD therapy.

All patients underwent complete clinical and instrumental examination. The efficacy of treatment was assessed by the patients themselves (subjective assessment of symptom intensity, primarily, cough) and by filling in a specially worked-out protocol of investigation. Cough, one of the clinical symptoms of COPD, was assessed by a numerical score of intensity on the basis of manifestation severity: no cough, 0 points; cough during one brief period, 1 point; cough during more than two periods, 2 points; frequent cough not interfering with every-day activity, 3 points; frequent cough interfering with every-day activity, 4 points; exhausting cough, 5 points. Office measurement of AP and heart rate was done every day. Daily ECG monitoring (Myocard-Holter; NIMP ESN, Russia), external respiratory function examination (Spirosift 3000; Fukuda, Japan) and 6-minute walk test prior to the therapy and at week 3.

Data were statistically processed using Statistica 8.0 program. Results were presented as M±SD, where M is mean, SD is standard deviation. Distribution of variables of the tested parameters was normal or close to it, therefore parametric criteria were applied for statistical analysis. The sample of patients was large enough to have 80% chance of detecting significant difference between the means of all tested parameters at 5% level of significance ($p<0.05$).

Dynamics of daily ECG monitoring indices in patients with COPD and IHD during treatment (M±SD)

Index	Before treatment	3 weeks after treatment
Average HR for 24 h (per min)	78.14±7.44	64.15±6.29*
Average day HR (per min)	81.09±11.97	70.18±10.19*
Average night HR (per min)	61.11±17.31	54.56±11.12*
Episodes of sinus bradycardia	0	in 1 people
Episodes of sinus tachycardia	in 15 people	in 9 people
Episodes of sinus arrhythmia	in 17 people	in 10 people
Paroxysms of atrial fibrillation	in 5 people	0
Paroxysms of supraventricular tachycardia	in 3 people	0
Paroxysms of non-sustained ventricular tachycardia	in 2 people	0
Single SVE	120.41±18.37	78.56±3.42*
Coupled SVE	20.41±0.59	12.23±0.91*
Group SVE	8.32±4.29	5.93±1.91
SVE of the bigeminy type	4.34±0.56	0.71±0.14
SVE of the trigeminy type	2.05±0.52	0.71±0.42
Total number of SVE	154.26±17.22	95.21±14.92*
Single VE	212.23±23.03	72.31±16.21*
Coupled VE	8.25±3.12	3.31±1.13
Group VE	5.06±0.42	0.91±0.11
VE of the bigeminy type	0.38±0.17	0.19±0.07
VE of trigeminy type	0.25±0.13	0.51±0.19
VE of the R–T type	0.13±0.05	0.18±0.02
Total number of VE	225.24±8.06	75.32±5.13*
A number of episodes of ischemic depression of ST segment per 24 h	8.02±0.18	1.11±0.34*

Note. HR: heart rate; SVE: supraventricular extrasystole; VE: ventricular extrasystole; * statistically significant difference of values with the data before the treatment, $p<0.05$.

Results and Discussion. A detailed analysis of one of the main clinical manifestation of COPD, cough, during indacaterol therapy showed the following results. Prior to the therapy, the score of cough intensity was 3.6±0.5. After the first week of treatment a statistically significant reduction of cough intensity to the score of 2.2±0.6 was noted ($p<0.05$). By week 3 this index decreased up to 0.5±0.2 ($p<0.05$ relative to the initial index), 15 patients (75%) noting complete cough cessation.

The main index characterizing the degree of bronchial obstruction during external respiratory function examination, FEV1, increased by 6% of the initial value after 3 weeks of treatment ($p<0.05$).

As mentioned above, application of agonists of adrenergic receptors to correct broncho-obstruction in case of IHD and COPD combination can promote the development of arrhythmias and aggravate myocardial ischemia [9]. Selective long-acting β2-agonist indacaterol induces a marked fast broncholytic effect with concurrent stimulation of mucus secretion and ciliated epithelium activity, the concentration of the preparation in the blood remaining constant after a single intake. However, a simultaneous stimulation of β-adrenoreceptors of the heart can not only result in arrhythmias and increase of the heart rate (HR), but weaken the effect of β-adrenoblockers as well. In this connection, cardiac activity indices, obtained in the course of the daily ECG monitoring, were

evaluated by us initially and after 3 weeks of treatment. It was impossible to suppose the invariance of these indices, since the investigation design provided for active treatment of cardiovascular pathology in the examined patients. Our task was to reveal the side-effects of indacaterol in COPD patients actively treated for IHD, including titration of β-adrenoblocker dose.

After 3 weeks of observation, the data of daily ECG monitoring showed statistically significant dynamics registered as a decrease of HR and various kinds of arrhythmias, which is primarily connected with the effect of the administered β-adrenoblocker bisoprolol (See the Table). None of the patients had aggravation of myocardial ischemia. Of special note is that none of the 5 patients, included in the study, having paroxysms of atrial fibrillations in the history, none of the 3 having paroxysms of supraventricular tachycardia, and none of the 2 with paroxysms of non-sustained ventricular tachycardia in the history had the recurrence of these types of arrhythmias, which was confirmed by the results of the daily ECG monitoring.

By week 3, all patients noted prominent clinical improvement, and regression concerned symptoms of both COPD and IHD. The results of 6-minute walk test, a reliable way of assessing the tolerance of patients to loads, demonstrated the increase of physical load tolerance (initially 345.4±59.2 m, after the treatment 412.8±11.1 m) ($p<0.05$). It is difficult to define exactly whether it was cardiac or pulmonary component that helped to cope with the loads better. In both cases breathlessness is the main clinical symptom, and it has a mixed character in comorbid patients as it may be a manifestation of the respiratory insufficiency, chronic heart failure or even the equivalent of angina. Patients, included in the study, were sure to improve the cardiac activity indices, which was confirmed by the findings of the daily ECG monitoring, and reduction of COPD symptoms. A combined treatment of cardiovascular and bronchopulmonary pathology resulted in significant positive results.

Conclusion. 150 μg/day of indacaterol in patients with I–II grade COPD in the stage of moderate exacerbation with concomitant cardiovascular pathology does not influence cardiac safety.

Study Funding and Conflicts of Interest. The work was not supported by any source. There are no conflicts of interest related to this study.

References

1. Adeloye D., Chua S., Lee C., Basquill C., Papana A., Theodoratou E., Nair H., Gasevic D., Sridhar D., Campbell H., Chan K.Y., Sheikh A., Rudan I.; Global Health Epidemiology Reference Group (GHERG). Global and regional estimates of COPD prevalence: systematic review and meta-analysis. *J Glob Health* 2015; 5(2), https://doi.org/10.7189/jogh.05.020415.

2. Global Initiative for Chronic Obstructive Lung Diseases. *Global strategy for diagnosis, management, and prevention of chronic obstructive pulmonary disease (Updated 2014)*.

3. Celli B.R. Predictors of mortality in COPD. *Respir Med* 2010; 104(6): 773–779, https://doi.org/10.1016/j.rmed.2009.12.017.

4. Avdeev S.N., Baymakanova G.E. Strategy of managing cardiologic patient with COPD. Cardio-pulmonological interrelations. *Serdtse* 2007; 6(6): 305–309.

5. Cavaillès A., Brinchault-Rabin G., Dixmier A., Goupil F., Gut-Gobert C., Marchand-Adam S., Meurice J.C., Morel H., Person-Tacnet C., Leroyer C., Diot P. Comorbidities of COPD. *Eur Respir Rev* 2013; 22(130): 454–475, https://doi.org/10.1183/09059180.00008612.

6. Krasnova Yu.N., Petukhova E.A., Dzizinskiy A.A. Safety of tiotropium bromide in COPD patients with associated ischemic heart disease. *Pul'monologiya* 2006; 1: 94–96.

7. Bova A.A., Lapitskiy D.V. Current approaches to diagnosis and treatment of ischemic heart disease in patients with chronic obstructive pulmonary disease. *Meditsinskie novosti* 2007; 9: 7–14.

8. Wise R.A., Anzueto A., Cotton D., Dahl R., Devins T., Disse B., Dusser D., Joseph E., Kattenbeck S., Koenen-Bergmann M., Pledger G., Calverley P.; TIOSPIR Investigators. Tiotropium respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013; 369(16): 1491–1501, https://doi.org/10.1056/nejmoa1303342.

9. Pavlenko V.I., Naryshkina S.V. Manifestations of painless myocardial ischemia in patients with chronic obstructive pulmonary disease. *Kardiologiya* 2012; 52(2): 36–40.

10. Kutsenko M.A., Chuchalin A.G. Comobidity paradigm: COPD and IHD syntropy. *Russkiy meditsinskiy zhurnal* 2014; 5: 389–392.

11. Yavelov I.S. About safety of long-acting β2-agonists. A cardiologist's point of view. *Pul'monologiya* 2007; 1: 112–116.

12. Dvoretskiy L.I., Sergeeva E.V. Elderly patient with chronic obstructive pulmonary disease, and associated cardiovascular pathology. *Spravochnik poliklinicheskogo vracha* 2006; 9: 27–35.

13. Zykov K.A., Agapova O.Yu. Combined broncholytic therapy in patients with chronic obstructive pulmonary disease and concomitant cardiovascular pathology. *Prakticheskaya pul'monologiya* 2012; 4: 24–30.

14. Russian Society of Cardiology. National recommendations about diagnostics and treatment of stable stenocardia. *Kardiovaskulyarnaya terapiya i profilaktika* 2008; 7(S4): 1–37.

15. Effect of verapamil on mortality and major events after acute myocardial infarction (The Danish Verapamil Infarction Trial II — DAVIT II). *Am J Cardiol* 1990; 66(10): 779–785, https://doi.org/10.1016/0002-9149(90)90351-z.

16. The effect of diltiazem on mortality and reinfarction after myocardial infarction. The Multicenter Diltiazem Postinfarction Trial Research Group. *N Engl J Med* 1988; 319(7): 385–392, https://doi.org/10.1056/nejm198808183190701.

17. Grigor'eva N.Yu., Kuznetsov A.N., Nekrasov A.A., Koroleva T.V. Comparative assessment of clinical efficacy and safety of β-adrenoblocker bisoprolol and calcium antagonist verapamil in patients with stable angina in combination with chronic obstructive pulmonary disease (results of 2-year observation). *Sistemnye gipertenzii* 2011; 1: 31–34.

18. Jabbour A., Macdonald P.S., Keogh A.M., Kotlyar E., Mellemkjaer S., Coleman C.F., Elsik M., Krum H., Hayward C.S. Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary

disease. *J Am Coll Cardiol* 2010; 55(17): 1780–1787, https://doi.org/10.1016/j.jacc.2010.01.024.

19. Etminan M., Jafari S., Carleton B., FitzGerald J.M. Beta-blocker use and COPD mortality: a systematic review and meta-analysis. *BMC Pulm Med* 2012; 12(1): 48, https://doi.org/10.1186/1471-2466-12-48.

20. Dal Negro R. Pulmonary effects of nebivolol. *Ther Adv Cardiovasc Dis* 2009; 3(4): 329–334, https://doi.org/10.1177/1753944709339968.

21. Avdeev S.N. Onbrez Breezhaler: actual issues. *Consilium Medicum* 2012; 14(3): 79–86.

22. Task Force Members, Montalescot G., Sechtem U., Achenbach S., Andreotti F., Arden C., Budaj A., Bugiardini R., Crea F., Cuisset T., Di Mario C., Ferreira J.R., Gersh B.J., Gitt A.K., Hulot J.S., Marx N., Opie L.H., Pfisterer M., Prescott E., Ruschitzka F., Sabaté M., Senior R., Taggart D.P., van der Wall E.E., Vrints C.J.; ESC Committee for Practice Guidelines, Zamorano J.L., Achenbach S., Baumgartner H., Bax J.J., Bueno H., Dean V., Deaton C., Erol C., Fagard R., Ferrari R., Hasdai D., Hoes A.W., Kirchhof P., Knuuti J., Kolh P., Lancellotti P., Linhart A., Nihoyannopoulos P., Piepoli M.F., Ponikowski P., Sirnes P.A., Tamargo J.L., Tendera M., Torbicki A., Wijns W., Windecker S.; Document Reviewers, Knuuti J., Valgimigli M., Bueno H., Claeys M.J., Donner-Banzhoff N., Erol C., Frank H., Funck-Brentano C., Gaemperli O., Gonzalez-Juanatey J.R., Hamilos M., Hasdai D., Husted S., James S.K., Kervinen K., Kolh P., Kristensen S.D., Lancellotti P., Maggioni A.P., Piepoli M.F., Pries A.R., Romeo F., Rydén L., Simoons M.L., Sirnes P.A., Steg P.G., Timmis A., Wijns W., Windecker S., Yildirir A., Zamorano J.L. 2013 ESC guidelines on the management of stable coronary artery disease. *Eur Heart J* 2013; 34(38): 2949–3003, https://doi.org/10.1093/eurheartj/eht296.

23. Worth H., Chung K.F., Felser J.M., Hu H., Rueegg P. Cardio- and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD. *Respir Med* 2011; 105(4): 571–579, https://doi.org/10.1016/j.rmed.2010.11.027.

24. Yorgancioglu A. Indacaterol in chronic obstructive pulmonary disease: an update for clinicians. *Ther Adv Chronic Dis* 2011; 3(1): 25–36, https://doi.org/10.1177/2040622311426204.