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BETA-BLOCKER USE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract: The most appropriate choice of pharmacological treatment of heart rhythm disorders occurring in patients with chronic obstructive pulmonary disease (COPD) and cardiovascular comorbidity is often a topic of debate between pulmonologists and cardiologists in clinical practice, although numerous studies and clinical trials have demonstrated evidence to support the use of selective beta-blockers (BBs) in these patients.

Keywords: Chronic Obstructive Pulmonary Diseases, Safety, Treatment, Beta blockers.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVDs) frequently coexist, and the therapeutic modality of certain pathology is directly dependent on pathology of another (1). CVDs are the most important comorbidities in patients diagnosed with COPD (1). COPD shares risk factors (age, smoking, genetic base, systemic inflammation) with a number of disease processes related to cardiovascular system and they are also associated with cardiac arrhythmias, coronary heart disease, hypertension, right and/or left ventricular failure, hypokalemia and hypomagnesaemia (2, 3, 4). Pharmacological approach to patients with COPD is reflected in prisms of cardiovascular status, taking into account the effects of angiotensin-convertin-enzyme inhibitors, blockers of angiotensin receptors, beta blockers (BB), calcium channel blockers and diuretics, and their effect on the respiratory system as well as their interactions with drugs that are used primary in COPD treatment. On the other hand, the influence of bronchodilator on the cardiovascular system is often unfavorable. Theophylline has numerous well-defined cardiac effects, including a dose-dependent increase in heart rate, enhancement of atrial automaticity, and acceleration of intracardiac conduction (2). Theophylline is associated with following rhythm disorders (sinus tachycardia, premature atrial beats, supraventricular tachycardia, atrial fibrillation, unifocal and multifocal atrial tachycardia, and ventricular arrhythmias) (3). BBs may have negative effect on lung function in patients with COPD, but if not used they may contribute to increased cardiovascular events, especially in high-risk patients (2). Even though there is a clear evidence of BBs efficiency, there is a general hesitation of their use in patients with COPD, because of contraindications and fear of inducing adverse reactions and bronchospasm (4). BBs are basically divided into selective and non-selective in relation to the mechanism of action and site of action. Also they are divided into three generations, the first one as non-selective, (the β1 and β2 receptor blockers), the second one as cardio selective beta-blockers that block the β1 receptors, but also β2 receptors in higher doses, and third generation which has an effect on vasodilatation. BBs may have β2-intrinsic sympathomimetic activity, as well as alpha-adrenergic blockade. Treatment of heart rhythm disturbances and correction of hypertensive status in patients diagnosed with COPD are corrected by calcium channel blockers

(verapamil) with addition of inotrope (digoxin) at low or high doses depending on cardiac status of the patient (presence of heart failure (HF)). Given that beta blockers have great benefit on the heart rate, heart function, electric stability as well as on survival and mortality associated with cardiovascular status, taking into account increased pulmonary arterial pressure, and tricuspid valve status, therapeutic modality in patients diagnosed with COPD and associated CVD is of great significance, and is often dubious in relation to a pulmonologist and cardiologist (or specialist of internal medicine). Due to the high cardiovascular comorbidity in COPD, BBs have been proposed as a therapeutic option (because of cardio protective effects in addition to reducing heart rate and improving systolic and diastolic dysfunction) (5, 6). It has been shown that the use of selective blockers in standard doses is effective and safe for use in patients diagnosed with COPD, thus at high doses should be used with caution (depending on which BB is used), while non-selective BBs should be avoided (6-10).

AIM

To examine the difference in the number of exacerbations in patients treated with a combination of verapamil and digoxin or a beta-blocker alone in different COPD patient stages and to emphasize focus on the safety of BB use in patients diagnosed with COPD.

PATIENTS AND METHODS

The study included 68 patients (n = 68) diagnosed with COPD who were followed-up during a 12-month period, and the numbers of exacerbations were analyzed. Patients were examined in the Clinical Hospital of Bukhara State Medical University. The patients were divided according to the stage of COPD into two groups: a) GOLD II (moderate), and b) GOLD III (severe), with a subdivision created in each group in relation to the use of either a combination of verapamil and digoxin or the use of beta-blockers alone in their pharmacological treatment. The inclusion criteria were the following ones: a) A diagnosis of COPD, b) the ejection fraction (EF) of a left ventricle (LV) >35%, and c) GOLD II (FEV1 / FVC <0.7, FEV1 predicted 50-80%), or GOLD III (FEV1 / FVC <0.7, FEV1 predicted) stage of the COPD. The exclusion criteria were EFLV <35% and a lethal outcome during a follow- up period (2 patients). Exacerbation was defined as functional deterioration of the COPD symptoms verified by spirometric functional testing, frequency of hospitalizations according to GOLD stage assignment or verified clinical symptoms deterioration.

RESULTS

In the GOLD II group, 24 patients who were on verapamil and digoxin therapy and 15 patients were on selective beta-blocker therapy (8 patients were on metoprolol, 6 patients were on bisoprolol and 1 patient was on nebivolol) were monitored. In the GOLD III group, 20 patients who were on verapamil and digoxin therapy and 9 patients who were on selective beta-blocker therapy (3 patients were on metoprolol, 6 patients were on bisoprolol) were monitored. Regardless of the pharmacological treatment, there is a statistically significant increase in the number of exacerbations in patients diagnosed with the COPD, during a 12-month period

follow-up, in the GOLD III group (severe) compared to the GOLD II group (moderate) (1. for the patients taking verapamil and digoxin, a two-tailed t-test was used to analyze the results between the GOLD II and GOLD III groups, p = 0.01, and 2. for the patients taking beta-blockers, a two tailed t-test was also used to analyze the results between the GOLD II and GOLD III groups, p = 0.003. (Table 1).

Pharmacological therapy	Number of exacerbations during 12 months		Two-tailed T test
	GOLD II (AVE ± STDEV)	GOLD III (AVE ± STDEV)	
Group I: verapamil and digoxin (AVE ± STDEV)	1.333 ± 0.963 (N=24)	2.100 ± 0.912 (N=20)	0.010*
Group II: beta-blockers (AVE ± STDEV)	0.600 ± 0.632 (N=15)	1.889 ± 0.928 (N=9)	0.003*

Table 1. COPD exacerbations are increased the GOLD III stage. (The number of exacerbations are increased in the GOLD III stage for COPD patients receiving either verapamil and digoxin or beta-blocker therapy. "AVE": average or mean number of exacerbations; "STDEV":standard deviation; *p<0.05.)

Within the GOLD II group of patients diagnosed with COPD, there appears to be no statistically significant difference in the number of exacerbations between the patients taking verapamil and digoxin (n = 24) and the patients taking beta-blockers alone (n = 15), although, in patients taking beta-blockers, there appears to be a trend towards a decrease in the exacerbations when compared to the exacerbations in patients taking verapamil and digoxin (p = 0.007). Within the GOLD III group of patients diagnosed with COPD, there is no difference in the number of exacerbations between the patients taking verapamil and digoxin (n = 20), and the patients taking beta-blockers (n = 9), as analyzed by a two-tailed t-test, p = 0.577 (Table 2).

Pharmacological therapy	Number of exacerbations during 12 months		Two-tailed T test
	verapamil and digoxin (AVE ± STDEV)	beta-blockers (AVE ± STDEV)	
GOLD II	1.333 ± 0.963 (N=24)	0.600 ± 0.632 (N=15)	0.007*
GOLD III	2.100 ± 0.912 (N=20)	1.889 ± 0.928 (N=9)	0.577

Table 2. COPD exacerbations are decreased during a 12-month treatment with beta-blockers. (The number of exacerbations are decreased in the GOLD II category for the COPD patients receiving beta-blockers. "AVE": average or mean number of exacerbations; "STDEV": standard deviation; *p<0.05.)

CONCLUSION

The use of selective beta-blockers in the treatment of cardiovascular comorbidity in patients with COPD represents far better choice of pharmacological therapeutic approach in treatment of patients within the GOLD II (moderate) stage of COPD.

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