COMPARATIVE PHARMACODYNAMIC CHARACTERISTICS OF IVABRADINE IN PATIENTS WITH CORONARY ARTERY DISEASE: STABLE ANGINA PECTORIS

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ABSTRACT

The development of recommendations based on the results of clinical trials with a unified approach to treatment, modern drugs for the treatment of coronary artery disease, undoubtedly, led to a significant improvement in the quality of life of patients and prognosis, at the same time, the disease is still prognostically unfavorable. improving the quality of life and prognosis, slowing down the progression of the disease became possible due to the creation of a new drug, an inhibitor of If-channels, ivabradine. The effective effect of ivabradine on the incidence of outcomes (death or hospitalization for coronary artery disease) was manifested in patients of different sex and age in the early stages of treatment and was maintained throughout the observation period.

Key words: coronary heart disease, lipid spectrum, sympathoadrenal system, ivabradine

INTRODUCTION

According to WHO estimates, the annual death rate from all CVDs is 17 million people, the main cause of which is coronary heart disease (CHD). In 2008, the total mortality from coronary heart disease in the world amounted to 7.25 million people, which in the general structure of mortality amounted to 12.8%. In Russia, IHD is one of the most frequent reasons for the population seeking outpatient and inpatient care for all CVDs and accounts for 28%. Among the risk factors for coronary artery disease, a significant role is assigned to the heart rate (HR). An increase in heart rate leads to the development of myocardial ischemia and is the main indicator of the risk of developing CVD, at least in men. In the general population, the risk of death from CVD significantly increases when the heart rate is> 84 beats / min and decreases when the heart rate is <60 beats / min.

For patients with coronary artery disease, B-blockers are the first-line anti-ischemic drugs. By decreasing heart rate, lengthening diastole and improving myocardial perfusion during a longer diastole, B-blockers help to reduce myocardial oxygen consumption and lead to a decrease in myocardial ischemia. Patients included in our study, at the time of inclusion in the study, most often received bisoprolol (56.09% ± 0.49) and metoprolol tartrate as antianginal therapy. It should be noted that all B-blockers have a number of side effects that sharply limit their use in a number of concomitant pathologies: deterioration of airway patency in bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD); deterioration of peripheral blood flow; with arterial hypotension and disorders of the cardiac conduction system. Therefore, the emergence of a new class of drugs designed to regulate the ionic sodium flux in the 1r-channels of sinus node cells holds great promise in the treatment of cardiovascular diseases such as stable angina pectoris and heart failure. The first representative of this class of drugs is ivabradine. If the inhibitor is ivabradine, it lowers the heart rate without harming myocardial contractility, hemodynamics or electrophysiological characteristics of the heart [1]. The rationale for the appointment of beta-blockers was evidence of chronic hyperactivation of the sympathoadrenal system in patients with progressive and severe (FC II-IV) coronary artery disease, as well as the successful use of drugs of the beta-blocker group, which reduce the risk of sudden death, death from the progression of chronic heart failure and reduce the number of hospitalizations. The study of the action of beta-blockers showed that a significant effect on the symptoms and prognosis in chronic heart failure is exerted by the decrease in heart rate

(HR) caused by them as a risk factor for death and complications of cardiovascular diseases [5]. At the same time, in the conditions of real medical practice, a decrease in heart rate to target values is often not achieved.

MAIN PART

New approaches to the drug therapy of coronary artery disease with the aim of improving the quality of life and prognosis, slowing the progression of the disease became possible thanks to the creation of a new drug, an inhibitor of If-channels, ivabradine. In 2005, ivabradine, the first If channel inhibitor, was approved by the European Medicines Evaluation Agency (EMEA) for clinical use as a symptomatic antianginal and anti-ischemic drug in chronic stable angina pectoris [6]. The drug specifically binds to f-channels when the channels are open and selectively inhibits If-flow. Its action, therefore, is aimed at reducing the rate of diastolic depolarization and lowering the heart rate, while the more activated the channels, the stronger the binding of the drug to the channel and the manifestation of inhibitory properties. This leads to a decrease in myocardial oxygen demand and an increase in oxygen delivery to the myocardium (due to diastole lengthening), and also allows vasodilation of the coronary arteries to be maintained even at the peak of the load, providing a direct antianginal effect of ivabradine. Due to its selective effect on I - flow, the drug does not affect other ionic flows in the cells of the sinus node, does not slow down atrioventricular conduction, and preserves myocardial contractility and its electrophysiological properties. The use of the drug is not accompanied by a "rebound" or "withdrawal" syndrome, it provides an optimal ratio of effectiveness / tolerance [6, 7].

For inclusion in the study, 34 patients were selected, including 16 - in the ivabradine group, the rest - in the placebo group. The average duration of treatment was 3 months. During the study, several people from both groups were excluded, the results were analyzed in a patient in the ivabradine group and the placebo group. The clinical characteristics of patients in both groups are presented in table. 1

Table 1
Clinical characteristics of patients included in the study SHIFT

Parameter	**Group**	
	ivabradine	**placebo**
Average age	60,7 ±1 1,2	60,1 ± 11,5
Body mass index, kg / m2	28,0 ± 5,1	28,0 ± 5,0
Ischemic etiology,%	68	67
FC II NYHA, %	49	49
FC III NYHA,%	50	50
FC IV NYHA,%	2	2
Duration of the course of ischemic heart disease, years	3,5 ± 4,2	3,5 ± 4,2
Previous myocardial infarction,%	56	56
Diabet, %	30	31
Arterial Hipertension, %	67	66
Average heart rate, beats / min	79,7 ± 9,5	80,1 ± 9,8
Average left ventricular ejection fraction,%	29 ± 5,1	29 ± 5,2
Mean systolic blood pressure, mm Hg Art.	122 ± 16,1	121,4 ± 15,9

Average diastolic blood pressure, mm Hg Art.	75,7 ± 9,6	75,6 ± 9,4

Ivabradine or placebo was added to the standard therapy for chronic heart failure, which included ACE inhibitors or angiotensin II receptor blockers, beta-blockers, diuretics, aldosterone antagonists, digoxin and other drugs (isosorbidadinitrate, etc.) in the same ratio in both groups of patients. Background therapy for coronary artery disease reflected the true picture of clinical practice.

After randomization, beta-blockers received 89% of patients in the ivabradine group and the same number in the placebo group. In each of the study groups in the treatment of coronary artery disease, the target dose of beta-blockers reached 26% of patients, while at least 50% of the target dose of b-blocker was received by 56% of patients.

A month after the start of treatment, the heart rate was: in the ivabradine group with an average dose of 6.4 ± 1.6 mg 2 times a day - 64 beats / min, in the placebo group - up to 75 beats / min. After 32 months. treatment average heart rate was 67 and 75 beats / min, respectively.

Primary endpoint events (mortality from complications of cardiovascular disease or hospitalization for exacerbation of coronary artery disease) were observed with ivabradine (24%) and (29%) in the placebo group (hazard ratio 0.82; 95% CI 0.75–0, 90; p <0.0001). The events were mainly due to hospitalization of patients due to worsening of the course of heart failure: 16% in the ivabradine group, 21% in the placebo group (p <0.0001); and deaths from heart failure: 3% versus 5%, respectively (p = 0.014).

Thus, in the ivabradine group there was a lower incidence of death from heart failure (–26%; p = 0.014) and hospitalizations due to worsening heart failure (–26%; p <0.0001) (Fig. 3). Calculations have shown that in order to prevent one death from complications of cardiovascular diseases or one hospitalization for worsening coronary heart disease, 26 patients should take ivabradine for one year.

It is important to note that the positive effect of ivabradine was observed in patients with chronic heart failure of ischemic and non-ischemic genesis. The effect in the ivabradine group on cardiovascular mortality did not differ significantly compared with the placebo group, at the same time mortality from coronary artery disease decreased statistically significantly (hazard ratio 0.74, 95% CI from 0.58 to 0.94; p = 0.014) ...

It should be noted that in the ivabradine group, a decrease in the risk of death and hospitalization due to heart failure was observed in the early stages - after 3 months. from the start of treatment. Despite the complexity and combination of drug treatment of moderate and severe chronic heart failure, patients noted good drug tolerance.

Table 2
Results of ivabradine treatment for other endpoints

End point	Relative risk	95% DI	Credibility
Primary composite endpoint	0,82	[0,75; 0,90	p < 0,0001
Total mortality	0,90	[0,80; 1,02]	p = 0,092
Mortality due to coronary heart disease	0,74	[0,58; 0,94]	p = 0,014
Hospitalization for any reason	0,89	[0,82; 0,96]	p = 0,003
Hospitalization for cardiovascular disease	0,85	[0,78; 0,92]	p = 0,0002
Cardiovascular mortality / hospitalization for coronary artery disease or non-fatal myocardial infarction	0,82	[0,74; 0,89]	p < 0,0001

Changes (decrease) in IHD FC were observed 6 weeks after the initiation of ivabradine treatment, while significant improvement was noted by patients in the case of severe heart failure: 1 out of 7% of the FC IV

subgroup remained; FC III - 53% of 93%; FC II - 44% of those previously referred to FC III. Among all patients in the ivabradine group and the placebo group during treatment, improvement was noted by 28 and 24%, respectively, stability of the state - 68 and 70%, respectively, worsening of the state - 5 and 6%, respectively.

Side and undesirable effects in the ivabradine group developed less frequently than in the placebo group ($p = 0.02$).

The use of ivabradine led to an 18% ($p < 0.0001$) decrease in the risk of mortality from complications of cardiovascular diseases and hospitalizations for coronary artery disease. The effective effect of ivabradine on the incidence of outcomes (death or hospitalization for coronary artery disease) was manifested in patients of different sex and age in the early (after 3 months) terms of treatment and was maintained throughout the observation period.

CONCLUSION

Thus, improvement of the clinical condition in patients with chronic coronary artery disease can be achieved with the use of the If-channel inhibitor ivabradine. Based on the data obtained in the SHIFT study, ivabradine is included in the National Recommendations for the Diagnosis and Treatment of Chronic IHD. The treatment with ivabradine significantly increases the quality of life of patients with coronary artery disease: exertional angina.

LITERATURE

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