TREATMENT OF STABLE CORONARY HEART DISEASE: FOCUS ON B-ADRENOBLOCKERS

Nadirova Yu.I., Jabbarov O.O., Alyavi A.L., Kenjayev M.L., Xodjanova Sh.I., Jumanazarov S.B., Bobosharipov F.G.
Tashkent medical academy

Annotatsion: The article considers the possibility of treatment of stable angina pectoris with a long-acting B-adrenoblockers- metoprolol succinate. The drug is effective, metabolically neutral, has good tolerability and can be prescribed for concomitant pathology.

Stable angina treatment with a prolonged-action beta-adrenoblocker, metoprolol succinate, is discussed. The medication is effective, metabolically neutral, well tolerated and could also be used in patients with comorbidities.

Key words: Coronary heart disease, stable angina, beta-adrenoblockers.

Among different diseases of cardiovascular system, coronary heart disease (CHD) occupies the first "honorably sad" place. The relevance of IHD is due to the fact that this disease is very widespread and is the main cause of mortality, as well as chronic heart failure (CHF). IHD is a multifactorial disease, and the complexity of its diagnosis in the early stages of its development is well known. One of the most common manifestations of CHD is stable angina pectoris (SS). Its most typical symptom is considered to be chest pain of compressive nature, occurring at physical load (FN), emotional stress, going out into the cold, walking against the wind, at rest after a big meal. This type of angina pectoris is called "stable angina pectoris.

The prevalence of angina pectoris depends significantly on age and gender. At the age of 45-54 years old angina occurs in 2-5% of men and 0.5-1% of women, at the age of 65-74 years - in 11-20% of men and 10-14% of women. In 20% of patients angina attacks preceded the development of myocardial infarction (MI), postinfarct angina is observed in 50% of patients. In Russia ~ 10 million of working-age population suffer from CHD, more than one third of them have CC. Death rate from CHD in persons aged <65 years over the last 20 years decreased by 50%, which should be associated with more active tactics of acute MI (AMI) treatment: the use of thrombolysis, early revascularization, but the overall mortality from CHD remained unchanged. This can be explained by the aging population, when the mortality rate naturally increases, despite the use of modern medications. Mortality from IHD in men aged < 65 years is 3 times higher than in women; at an older age the mortality rate in both sexes levels off, and after 80 years of age it becomes 2 times higher in women

than in men. Importantly, only 40-50% of angina patients in the population are aware of their disease and do not take the treatment indicated [1].

The main cause of CHD is coronary artery atherosclerosis (CA), angina pectoris attacks occur much less frequently in unchanged CA. The factors contributing to the disease development are functional overload of the heart, histotoxic effect of catecholamines, changes in blood coagulation and anti-coagulation systems, insufficient development of collateral circulation. The development of an angina attack is usually accompanied by increased heart rate (HR), which is observed during PH, psycho-emotional stress, alcohol intake. Tachycardia nowadays is considered to be significant because it increases myocardial oxygen consumption and decreases coronary blood flow, shortening the diastole period of the heart. The works, performed in the last 15-20 years, have shown the independent importance of heart rate increase as a risk factor (FR) of cardiovascular diseases (CVD) [2]. This fact dictates a wide use of drugs that slow heart rate. Such drugs are p-adreno-blockers (p-ABs) as a basic therapy of CHD and, in particular, stress coronary artery disease.

CC in its "pure" form is much rarer than in combination with other cardiovascular pathology. Such combination is observed rather frequently - 82% [6]. Particularly, SS is combined with arterial hypertension (AH) in 70% [7], with CHF [8] - in 46% of women and 22% of men, with heart rhythm disturbances - in 63% [9], 43% of SS patients have history of MI [10]. CC can be observed in patients with diabetes mellitus type 2 (DM-2), with peripheral arterial disease (PAD) of atherosclerotic origin, chronic obstructive pulmonary disease (COPD). All this may influence the choice and tactics of treatment, including the choice of one or another p-Ab.

It is known that p-Abs are a very heterogeneous group of drugs by their pharmacological and pharmacokinetic effects, so the properties of any one of them, for example, atenolol, which is widespread in the world and the country, should by no means be transferred to all other drugs. Unfortunately, a similar tendency can be seen in many domestic and foreign publications. The only common property of this entire group of drugs is competitive antagonism with respect to P1-adrenergic receptors. Along with inhibition of P^-adrenergic receptors, p2- and p3-adrenoreceptors may or may not be blocked. The ability of various p-ARBs to affect P3-adrenoceptors has not been adequately studied.

In November 2006, new European Society of Cardiology Guidelines for the Treatment of CC were published. The previous guidelines were published in 1997. It is quite natural, that during this period some approaches to treatment have changed, new directions of drug therapy appeared, however, the significance of p-ARBs was not questioned, and it concerned both the patients with previous AMI and those suffering from stable forms of CHD. This large group of drugs refers to antianginal agents of hemodynamic action. Their improvement was going in several directions:

- obtaining highly cardioselective drugs that act mainly on p1-receptors, but not on p2-receptors;
- getting prolonged-acting medications (1st generation medications had to be taken 3 times a day).

Currently, for the treatment of CHD, as well as for AH and CHF, cardioselective drugs are used, the main property of which is the predominant blockade of B-adrenoreceptors. Hydrophilic drug of the 2nd generation atenolol, for unclear reasons considered as a reference p-AB and widely used in such large studies as INVEST (International Vferapamil SR/Trandolapril study), LIFE (Losartan Intervention For Endpoint reduction in hypertension), ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm), etc., has a whole range of adverse effects and contraindications for use: bronchospasm, peripheral vasoconstriction, increased plasma atherogenicity, hyperuricemia, hyperkalemia, erectile dysfunction. In this regard, it is necessary to remind once again: it is necessary to prescribe cardioselective, lipophilic drugs of the 2nd generation, blocking mainly Pi-adrenoreceptors, having much less side effects than the 1st generation drugs and the water-soluble drug of the 2nd generation - atenolol.

Among numerous drugs of the 2nd generation the most interesting is lipophilic metoprolol, which appeared on the pharmaceutical market in the 1970s and is currently available in three forms: metoprolol tartrate of short and long action, and metoprolol succinate, which affects almost all stages of the cardiovascular continuum, while sufficient therapeutic concentration of the drug in blood remains little changed even with a single daily intake. The metoprolol succinate tablet is developed on the basis of high pharmaceutical technology: it contains several hundred granules of metoprolol succinate. After entering the gastrointestinal tract under the influence of hydrochloric acid and enzymes, each granule disintegrates in the mode set for it for further penetration through the gastric mucosa and further functions as an independent delivery system of the drug into the bloodstream. The process of absorption is 20 h. This form of release allows maintaining a nearly constant drug concentration in the blood, unlike the "normal" (short-acting) metoprolol tartrate. Metoprolol succinate Betaloc ZOC®, (AstraZeneca, UK) is available in 25 mg, 50 mg and 100 mg tablets.

The emergence of p-ABs on the pharmaceutical market has made it possible to treat CHD, particularly CC, more effectively than was possible with the prescription of short-acting nitrates and pro-

The main reason for this is that the patient's prognosis was not affected by the longterm treatment. According to the current recommendations, in the absence of contraindications, ABs should be administered to all patients who have previously undergone MI or acute coronary syndrome, since many randomized trials have demonstrated the ability of p-ABs to increase the survival rate of such patients. In the

studies, this was noted in an average of 25% [11-13]. The BHAT (Beta-blocker Heart Attack Trial) study demonstrated that propranololol administration on day 5-12 after a previous MI reduced overall mortality by 26%, sudden death (SM) by 28%, recurrent fatal and nonfatal MI by 23% [14-16]. In TIMI II-B study (Thrombolysis in Myorardial Infarction, Phase II-B) it was shown that metoprolol administration immediately after thrombolysis in AMI patients was associated with decreased ischemia and recurrent MI [17]. The results of the international Beta-Blocker Pooling Project study [1S] indicate a possible positive effect of p-ABs on the prognosis of CHD patients without a history of MI. Combined use of p-Ab with other antianginal drugs - prolonged nitrates, calcium antagonists (CA), had heterogeneous results. In a double-blind, randomized IMAGE (International Multicenter Angina Exercise study), the administration of a combination of metoprolol succinate at a dose of 200 mg/day with prolonged nifedipine (40 mg/day) showed that the effect of such a combination was more due to the action of the second added drug [19]. In a repeated analysis of the Gothenburg study results, the benefit of early metoprolol administration on the prognosis of STEMI patients was convincingly proved [19].

Metoprolol succinate has advantages in the treatment of CHD in combination with AH: the number of AH patients responding to therapy with delayed-release metoprolol succinate (50 mg/day) compared to 100 mg/day of conventional metoprolol was estimated. After 12 weeks in the group of patients treated with metoprolol succinate, S9% had a positive antihypertensive effect, whereas, among patients treated with metoprolol tartrate, only 69% responded to therapy [12].

The antianginal efficacy of metoprolol succinate compared with its conventional form (metoprolol tartrate) has been convincingly proven. Metoprolol succinate reduced the number of angina attacks and the need for sublingual nitroglycerin administration, the number of ischemic episodes during Holter monitoring [13].

Metabolic neutrality is extremely important in the treatment of CVDs

The same is true for metoprolol, of course. In 1990, metoprolol succinate was shown to significantly reduce elevated glucose levels after administration of P-agonists in healthy volunteers, unlike metoprolol tartrate administered in similar doses [7]. In another publication, metoprolol succinate (100 mg) was shown to lower HR by 11.3 bpm in hypoglycemia-induced healthy volunteers, atenolol (100 mg) did not change it, and propranolol long-acting (160 mg) lowered HR by 8.7 bpm, masking the hypoglycemic state [24]. In AH patients with and without DM-2 a neutral effect of metoprolol on glucose tolerance parameters was observed, while propranolol reduced them [24].

In the literature, there is an opinion about the unfavorable effect of B-ABs on atherogenesis processes in contrast to the favorable effect of ACs. However, in a 3-year, prospective, randomized, double-blind, placebo-controlled study ELVA (Effect

of Long-term treatment of metoprolol CR/XL on surrogate Variables for Atherosclerotic disease) with 92 patients aged 20-70 years with primary hypercholesterolemia and signs of early common carotid atherosclerosis was shown, that against the background of lipid-lowering and antihypertensive therapy (statins, cholestyramine, gemfibrozil) additional administration of metoprolol succinate at a dose of 100 mg/day was associated with less progression of atherosclerotic lesions compared to the placebo group [8]. The positive antiatherosclerotic effect of metoprolol succinate can be explained by the following points:

- endothelium protection occurs due to blocking of direct damaging action of catecholamines;
- reduction of the negative effect of hemodynamic factors - increased HR and AH - on the endothelium;
- increased synthesis of prostacyclin.

At the same time, the dynamics of lipid levels were similar in the placebo group and in the metoprolol group. Such a conclusion seems to be very significant, because it "removes the accusations" from B-ABs of an atherogenic effect (at least, from metoprolol succinate).

Traditionally, the anti-ischemic effect of B-ABs is considered solely as a consequence of heart rate reduction; meanwhile, it is not taken into account that P-ABs also inhibit the damaging effect of catecholamines on the vascular endothelium.

In the BCAPS (Beta-blocker, Cholesterol-lowering Asymptomatic Plaque Study), also of 3 years duration with a similar ELVA study design, involved 793 patients aged 49-70 with atherosclerotic plaque in the right carotid artery [24]. The dynamics of intima-media thickness was assessed by ultrasound examination. All patients received lipid-lowering therapy (fluvastatin 40 mg/day), one group of patients received slow-release metoprolol succinate at a dose of 25 mg/day, the other - placebo. The progression of atherosclerotic changes slowed down against the background of metoprolol administration compared to the placebo group. Probably, this fact contributed to the reduction of general and cardiovascular mortality among the patients treated with metoprolol. High antianginal efficacy of metoprolol succinate is also due to the fact that elimination of tachycardia in CC patients reduces the risk of atherosclerotic plaque damage due to the reduction of the negative effect of accelerated blood wave [25].

Metoprolol succinate is better tolerated than metoprolol tartrate, possibly due to smaller fluctuations in metoprolol succinate blood concentrations [22].

Another aspect of the "accusation" of p-ABs is the development of erectile dysfunction. It is known that erectile dysfunction is diagnosed 4 times more often in CHD patients compared to healthy individuals. However, according to the data of a prospective study of 65 CHD patients, receiving 100 mg of metoprolol succinate had no significant effect

on erectile function [20]. Similar results were obtained in the subanalysis of the large study MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Heart Failure), dedicated to the role of p-Abs in the treatment of CHF [18].

Speaking about the significance of p-Ab use in patients with CHD with concomitant pathology, it is impossible not to mention the possibility of prescribing metoprolol succinate to patients with CHD in combination with COPD. It has been shown in the works, that administration of metoprolol succinate (on the average 69,08±34,45 mg/day) to patients with CC and/or AH in combination with COPD and/or bronchial asthma of any severity has not worsened bronchial patency (naturally, these patients received adequate bronchodilator therapy). Treatment with metoprolol succinate reduced the frequency and severity of angina attacks and the need for nitrosorbide, and also caused normalization of BP and lower HR [15].

When treating p-Abs (particularly metoprolol succinate) in SS, the HR should be reduced to < 60 bpm if the patient tolerates it well. However, unfortunately, the following happens in real clinical practice: HR in SS patients is reduced to 70 bpm maximum, believing that HR below this value is a manifestation of adverse side effects of the drug. However, the therapeutic effect in this situation is not

The results of this study do not fully achieve: indeed, angina pains become fewer and the patient is less likely to take short-acting nitrates (both the patient and the physician are satisfied), but such "suboptimal" therapy does not solve the main task - reducing the probability of MI and improving the quality of life. Meanwhile, in TIBBS study (Total Ischemic Burden Bisoprolol Study) it was convincingly shown that complete elimination of anginal attacks is combined with increased survival of CHD patients [11]. Sadly, this aspect is little or no considered in real clinical practice.

Another frequently encountered situation in real clinical practice is that the starting dose of metoprolol succinate usually does not exceed 25-50 mg/day, and as a rule, the target dose is not reached (probably, psychologically, the physician is more comfortable to prescribe a low dose than to follow clinically sound recommendations). Meanwhile, in SS and MI patients, the target dose is 100-200 mg/day at a single dose, and the starting dose is 100 mg/day. Why does this happen? Probably the reason is ignorance of the pharmacokinetics of metoprolol succinate, although it is known that with a single dose of 100 mg/day the concentration curve remains flat, and with 200 mg once/day the plasma concentration of the drug is slightly higher than that with 50 mg metoprolol tartrate, and then decreases very smoothly during the day. Therefore, metoprolol succinate in any dose should be administered once, which is very convenient for the patient.

Another aspect of the use of metoprolol succinate is the treatment of CC patients in combination with AH. The drug perfectly reduces BP when administered once, while possessing metabolic neutrality and inhibiting the progression of atherosclerosis -

ELVA study, which is very relevant in antihypertensive therapy. Thus, the spectrum of metoprolol succinate use is very wide:

- CC patients and MI patients (even if they do not have angina attacks);
- patients with CHF;
- AH patients;
- patients with cardiac rhythm disorders;
- patients with so-called "functional" heart disease accompanied by tachycardia (the classic example is neurocirculatory dystonia).

Metoprolol succinate is convenient to take: a 100 mg tablet can be divided in half.

Thus, metoprolol succinate has a wide spectrum of action and has proven itself in numerous, multicenter studies.

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