



## CLINICAL PHARMACOLOGICAL APPROACH TO THE USE OF ANTIANGINAL DRUGS IN THE TREATMENT OF MYOCARDIAL INFARCTION

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### ABSTRACT

*A brief description of modern antianginal drugs presented in the latest revision of the European Society of Cardiology recommendations is given. Angina pectoris is the most common form of chronic coronary insufficiency, the treatment of which consists in reducing the number, duration and severity of attacks of anginal pain, as well as improving the prognosis: preventing the development of such cardiovascular complications as acute myocardial infarction, life-threatening rhythm disturbances and chronic heart failure.*

### INTRODUCTION

Impressive successes in the treatment of coronary heart disease in recent years, caused primarily by the widespread introduction of surgical and endovascular methods of restoring blood supply to the heart in clinical practice, have relegated the use of pharmacological antianginal therapy to the background. Nevertheless, the clinic continues to experience a need for drugs with anti-ischemic properties. This mainly applies to the group of patients with angina pectoris, for whom myocardial revascularization cannot be performed for various reasons, including technical ones. In this regard, it should be noted that the number of patients with diabetes mellitus is constantly increasing [1], whose angina, in addition to atherosclerotic lesions of the epicardial arteries, may be caused by the presence of diabetic myocardial microangiopathy. It should also be emphasized that more than 25% of patients after successful coronary artery angioplasty experience recurrent attacks of anginal chest pain within 5 years [2]. In addition, today we are still unable to fully satisfy all the needs for myocardial revascularization. Thus, clinical interest in antianginal drug therapy remains. To a certain extent, this is confirmed by the attention paid to this section in the latest recommendations of the European Society of Cardiology for the diagnosis and treatment of chronic coronary syndrome [3].

### MATERIALS AND METHODS

Changes in the understanding of the pathogenetic features of some diseases, the use of methods for objective evaluation of drug effectiveness, and the introduction of evidence-based medicine principles into clinical practice have had a significant impact on treatment tactics in cardiology, including pharmacotherapy of chronic coronary syndrome. Treatment of angina involves reducing the number, duration, and severity of attacks of angina chest pain and improving the prognosis - preventing cardiovascular complications. Without dwelling on



the issues of secondary prevention of coronary heart disease, in this review we focus on drug therapy for transient myocardial ischemia aimed at alleviating the condition of patients. In this regard, of particular interest is the analysis of the formation of our ideas about the mechanisms of action of drugs that cause an anti-ischemic effect in patients with angina, which will allow us to establish the main trends in the development of the pharmacology of cardiovascular pathology.

## RESULTS AND DISCUSSION

The search for new antianginal drugs was directed towards developing preparations that enhance coronary blood flow. Following this trend, in the 1970s, preparations with vasodilatory properties were proposed and widely used for the treatment of coronary insufficiency. Carbocromen (intensain, intensordin) gained great popularity among clinicians; in addition to its ability to enhance coronary blood flow, according to researchers, it had a stimulating effect on collateral circulation and prevented platelet aggregation [4, 5]. Dipyridamole (curantil, persantin, antistenocardin) was no less widespread. In addition to its vasodilatory effect, it was also found to have antithrombotic properties [2]. However, as clinical experience accumulated, conflicting data began to appear. Thus, the occurrence of angina attacks was noted with its rapid intravenous administration, which was interpreted as the development of the syndrome of "stealing" the ischemic zone of the myocardium. This circumstance excluded the use of dipyridamole as an antianginal agent. However, it became possible to use it for diagnostic purposes - in the so-called "curantyl test" to detect myocardial ischemia. Difril (corontin, falicor) can be attributed to the number of very popular drugs of the second half of the last century. However, clinical studies by L.A. Myasnikov et al. questioned its effectiveness in patients with angina [3]. The same pharmacological group included such drugs as lidoflazine, ditrimin, a phenothiazine derivative - chloracizine, and diethiphen, which is close to sinestrol [3]. Of the vasodilators, purine derivatives were used - euphyllin, theophylline. It should be noted, however, that the use of euphyllin was associated with a number of serious side effects due to its ability to cause tachycardia, increase heart function and increase myocardial oxygen consumption. Cases of death after intravenous administration of the drug in acute myocardial infarction have been described [4]. In the 1970s, isoquinoline derivatives - papaverine, no-shpa - did not lose their significance as antianginal agents; they were used routinely per os to prevent angina attacks and parenterally to relieve angina attacks. Antianginal properties were attributed to amiodarone [4]. Very modest, if not to say dubious, anti-ischemic properties, but the unconditional antiarrhythmic effect served as the basis for transferring amiodarone to the group of antiarrhythmic agents, where it currently resides. During the described period, attempts were made to use beta-adrenergic stimulants to increase coronary blood flow. Such substances included oxyphedrine (ildamen) and nonachlazine, which has better tolerability, the use of which was recommended for the treatment of severe forms of coronary heart disease [5]. In the recommendations for the treatment of coronary heart disease in the 1970s, one can find mention of the anticholinergic platifillin and the ganglionic blocker quaterone [2]. Among the medications that have been attributed antianginal properties, we find monoamine oxidase inhibitors that affect the adrenergic innervation of the heart - ipraside, nialamide, the antidepressant action of which is combined with dilation of the coronary vessels [4]. Since the 1960s, calcium



antagonists have been included in the arsenal of antianginal agents. The first representative of this group was verapamil (isoptin), which has not only a coronary dilator, but also an antiarrhythmic effect.

Analyzing the medications used to treat chronic coronary insufficiency in the second half of the last century, attention is drawn to a large number of preparations of plant origin: salsolin is an alkaloid isolated from Central Asian saltwort, khellin is extracted from the seeds of ammi dentata, pasticin is contained in parsnip seeds, orangelin is obtained from the roots of mountain knotweed, dimidine is isolated from the roots of Siberian inflated fruit, daukarin is a preparation from carrot seeds, anetine is from fragrant dill [3]. All of them, to varying degrees, have an antispasmodic effect and moderately dilate the coronary arteries. However, no objective confirmation of their ability to cause an anti-ischemic effect in patients with coronary heart disease was found. Atherosclerotic narrowing of the coronary arteries limits the potential for coronary blood flow growth. At the same time, it is known that when myocardial ischemia occurs, as a result of a discrepancy between the metabolic demands of the myocardium and its blood supply, powerful self-regulation mechanisms are immediately activated, aimed at increasing blood flow. Under these conditions, the role of pharmaceuticals that have a vasodilatory effect is minimal, at least in cases where vasospasm does not dominate in the pathogenesis of myocardial ischemia. Understanding this led to a revision of the traditional idea that coronary vasodilator drugs should form the basis of therapy for chronic coronary insufficiency and changed the direction of pharmacological action. The attention of researchers focused on the myocardium: changes in its metabolism, cardiodynamics, accompanied by more economical oxygen consumption. Despite some negative aspects of pharmacodynamics (reduced coronary blood flow, decreased inotropic function of the myocardium, limited cardiac output, development of bradycardia, etc.), beta-blockers (propranolol) have become increasingly widespread, without, however, occupying leading positions in the treatment of angina. A wide range of pharmacological action, including the effect on the hemostasis system, antiplatelet, fibrinolytic, antisclerotic and antianginal effects of the antibradykinin agent - anginine, contributed to its popularity in the treatment of angina pectoris, especially in combination with obliterating atherosclerosis of the peripheral arteries [4]. In order to influence the metabolism of the myocardium, the use of anabolic steroids - methandrostenolone, retabolil was recommended. It was believed that anabolic drugs prevent the development of hypercholesterolemia, improve the potassium balance in the body, increase the content of glycogen, ATP, and creatinine [5]. In practical recommendations of that time, one can find references to drugs that, as a result of influencing the metabolic processes of the heart muscle, are capable of optimizing its energy balance and, at least theoretically, reducing the frequency of chest pain attacks in patients with angina. The drug with the indicated effect included the anaerobic glycolysis activator pyridoxinol glyoxylate, better known as glyosys [3].

The above leads to the conclusion that among the characteristic features of conservative therapy of chronic coronary insufficiency of the 2nd half of the last century, one can single out a significant number of drugs used, mostly with antispasmodic, coronary dilator properties, from different pharmacological groups, having different chemical structures and differing in the mechanism of action. In this regard, the statement of A.P. Chekhov involuntarily comes to



mind: "If a lot of remedies are supposed to be used against some disease, then the disease is incurable." With the introduction of methods for objective evaluation of the effectiveness of drugs into clinical practice, a significant number of them, having demonstrated their ineffectiveness, were excluded from clinical use. The methods of objectively assessing the effectiveness of drug treatment for patients with angina include: paired bicycle ergometric tests, repeated Holter ECG monitoring, isotope studies of myocardial perfusion, stress echocardiography.

## CONCLUSION

Thus, the development of antianginal pharmacotherapy has come a long way, characterized by the search for the main factors of effective pharmacodynamics. The following can be attributed to the features of modern antianginal pharmacotherapy:

- ❖ reduction in the number of pharmacological groups due to the exclusion of drugs with unproven or low effect;
- ❖ improvement of the pharmacological properties of known drugs;
- ❖ revision of the antianginal significance and clinical value of the drugs used;
- ❖ significant increase in generic forms;
- ❖ widespread use of combination dosage forms combining several drugs with different mechanisms of action.

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