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The Importance of Nitrates in Coronary Heart Disease

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Annotation: Nitrates have been used in cardiology since the end of the 19th century. Initially, they were used to relieve attacks of angina pectoris. Since the middle of the 20th century, when long-acting drugs appeared, they began to be prescribed for the prevention of angina attacks. Currently, there is a huge number of drugs from the nitrate group, related to various chemical substances and dosage forms, which makes it difficult for the doctor to choose the most optimal drug for a particular patient.

Keywords: Nitrates, use, mechanism of action, pharmacokinetics, pharmacokinetics.

Introduction: According to modern recommendations for the treatment of coronary heart disease [1], nitrates are included in the main groups of antianginal drugs, along with β-blockers and calcium antagonists. It should be remembered that nitrates, unlike β-blockers and calcium antagonists, do not have any effect other than antianginal, therefore the only indication for prescribing nitrates is the presence of angina attacks in a patient; They (for example, β-blockers) are not prescribed to improve the prognosis of cardiovascular diseases, as well as to treat other cardiovascular diseases, in particular hypertension (for example, β-blockers and calcium antagonists). Currently, nitrates are practically not used for the treatment of congestive heart failure;

Nitrates are effective for all types of angina - stable angina, variant angina, unstable angina. Against the background of nitrate therapy, patients' tolerance to physical activity increases significantly, symptoms of myocardial ischemia decrease. This effect of nitrates can be clearly objectified using tests with dosed physical loads.

In terms of the severity of the antianginal effect, nitrates are not inferior to or even superior to β-blockers and calcium antagonists. Thus, in the KIAP (Cooperative Study of Antianginal Drugs) study conducted in the mid-80s in several clinics of the USSR in patients with ischemic heart disease with stable angina of functional class II-III, nitrates were shown to be the most effective antianginal drugs in 27% of patients. Calcium antagonists and β-blockers significantly exceed calcium antagonists and β-blockers in terms of the severity of their antianginal effect. In another 50% of patients, nitrates were as effective as calcium antagonists and β-blockers [2]. This suggests that in some cases nitrates are the drug of choice for the treatment of angina.

The problem of treating angina pectoris seems to be especially relevant in Russia, since the incidence of coronary heart disease is very high (which, unfortunately, can be judged by the increasing mortality rate from this disease), and such methods of treating angina as coronary artery bypass grafting and coronary angioplasty are still not available (according to the 2001 Treatment Pattern study conducted in various regions of Russia, coronary artery bypass grafting is performed in 3.75% of patients with stable angina pectoris, and angioplasty procedures are performed in no more than 1% of patients). Therefore, the need for nitrate administration in our country remains extremely high.

Research methods and materials: Nitrates are classified by chemical structure, dosage form and duration of action. Currently, three drugs belonging to the group of organic nitrates are used: nitroglycerin (more precisely, glyceryl trinitrate), isosorbide dinitrate and isosorbide-5-mononitrate. The latter drug has recently been used as an independent drug, it is a natural metabolite of isosorbide dinitrate, i.e. it is formed from it when it passes through the liver.

Nitrates easily penetrate all mucous membranes, as well as through the skin, so they are available in various dosage forms. These dosage forms can be divided into:

Absorbed through the mucous membrane of the oral cavity. These include nitroglycerin tablets for sublingual administration, also known as buccal (i.e., intended for application to the mucous membrane of the cheek or gums), nitroglycerin and isosorbide dinitrate, and nitroglycerin and isosorbide dinitrate aerosols.

For oral administration. These are various tablets and capsules of isosorbide dinitrate, isosorbide-5-mononitrate, nitroglycerin. Tablets can be regular (then they act for a relatively short time) or made using special technology that provides a gradual release of the drug, which allows you to extend its effect.

For topical use. Nitroglycerin ointments and special nitroglycerin stickers (patches) for application to the skin. These patches are designed to last for 24 hours.

For intravenous administration. Ampoules with nitroglycerin and isosorbide dinitrate solution.

Nitrates are also divided according to the duration of exposure:

Short-acting drugs (up to 1 hour). These include, first of all, nitroglycerin tablets for sublingual administration, various nitroglycerin aerosols, and isosorbide dinitrate.

Drugs with a moderately long duration of action (1 to 6 hours). These include regular isosorbide dinitrate tablets, regular isosorbide-5-mononitrate tablets, and orally-release nitroglycerin tablets. These drugs also include buccal dosage forms of nitrates - designed to be applied to the gums or mucous membranes of the cheeks.

Drugs with a significantly longer effect are special tablets or capsules of isosorbide dinitrate and isosorbide-5-mononitrate (for example, Olicard - capsules containing microspheres with a measured release of the active substance); nitroglycerin patches for application to the skin. The effect of such tablets and capsules can last for 15 hours or more, and patches can last up to 24 hours.

Most contraindications to the use of nitrates are relative. They should be used with caution in patients with arterial hypotension, hypovolemia, and mitral valve prolapse. Nitrates should not be used in patients with obstructive cardiomyopathy, and their use is contraindicated in cases of increased intracranial pressure and cerebral hemorrhage.

Conclusions: Nitrates have few side effects, but sometimes they can cause certain problems. First of all, this is a headache. When taking nitrates for the first time, most patients experience headaches with regular use, which often decrease significantly in intensity, and sometimes disappear altogether; However, in some patients, the intensity of headaches does not decrease with regular use of nitrates (as a rule, such patients have a head injury), in such cases it is necessary to stop

taking nitrates.

Recent data suggest that the frequency of headaches is somewhat dependent on the dosage form in which the nitrate is administered. Regular isosorbide dinitrate tablets have been shown to cause significantly more headaches than extended-release isosorbide-5-mononitrate tablets (Olicard).

Nitrates sometimes have an excessive vasodilating effect (usually at the beginning of treatment). This is manifested by a significant decrease in blood pressure, nausea, and, rarely, a collapse-like state. However, all these phenomena do not require special therapy, they quickly pass when the patient is placed in a horizontal position; These side effects are more common with short-acting dosage forms and less common with extended-acting dosage forms.

With regular administration of nitrates, their effect can weaken, a phenomenon called tolerance. Sometimes (but not always) tolerance to nitrates can lead to a serious clinical problem. This happens when the effect of nitrates disappears completely (the development of complete addiction). But more often we encounter a weakening of the effect of nitrates, but it remains clinically significant (partial addiction).

Addiction does not develop in all patients and is not always related to the route of administration of the drug; the general rule is that the risk of addiction is higher when the drug is in the body for a long time and its concentration changes little over time. Therefore, addiction often develops with regular use of dosage forms with a significantly long-term effect, primarily with the administration of transdermal dosage forms.

Nitrate dependence is a reversible phenomenon. If the drug disappears from the body for a certain period of time, sensitivity to nitrates is restored. The principle of intermittent administration of nitrates is based on this pattern. It involves administering nitrates during the day in the so-called "nitrate-free period". The duration of this period is considered to be 6-8 hours a day, therefore nitrates are prescribed at night (when the effect of nitrates is not needed for most patients with stable angina), when the drug is absent or its concentration in the blood is minimal. The release forms of the drug Olikard fully meet these requirements.

The intermittent method of nitrate administration significantly reduces the risk of developing addiction, but does not completely eliminate it. It has a number of disadvantages: firstly, it does not provide a 24-hour effect of the drug (some patients still need it), and secondly, when using it, sometimes a rebound syndrome or adverse effect syndrome may occur. This manifests itself in the form of a worsening of the patient's condition (sometimes the paradoxical appearance of angina attacks at rest in patients who did not have them before) in response to the rapid disappearance of the drug from the body. This syndrome is actually a special case of withdrawal syndrome. It is characteristic, first of all, for short-acting and moderately long-acting nitrate dosage forms and does not occur with the use of significantly long-acting oral dosage forms, since the concentration of the drug decreases gradually when they are administered. Thus, this syndrome did not occur with the use of prolonged-release isosorbide-5-mononitrate tablets - the drug Olicard, which was prescribed once a day in the morning.

The only way to implement the high therapeutic efficacy of nitrates in practice and at the same time minimize the risk of their side effects and undesirable effects (primarily the development of addiction to them) is to prescribe these drugs differentially, depending on the severity of cardiovascular disease and the characteristics of the occurrence of myocardial ischemia in a particular patient. In all possible cases, nitrates are prescribed intermittently, so that there is a period of freedom from nitrate exposure during the day - this protects the patient from the development of drug dependence.

In mild angina (functional class I or II), when attacks occur predictably, only during physical exertion, nitrates are prescribed occasionally - in the form of dosage forms with a short or medium-long effect before situations that can provoke an attack of angina. For this purpose, fast-acting forms are best suited - NG or ID aerosols, NG dosage forms for application to the gums, and simple

ID tablets.

In severe cases of angina, when attacks occur more often, with less physical exertion, as well as at rest, nitrates are prescribed in the form of long-acting dosage forms and, if possible, they try to be free from the effects of nitrates during the day. For angina pectoris of functional class III, nitrates are prescribed in such a way as to provide a constant effect throughout the day. For this purpose, either simple ID and IMN tablets are prescribed 3-4 times a day, or, if more convenient, ID or IMN tablets with a significantly prolonged effect are prescribed once a day (for example, the long-acting isosorbide-5-mononitrate drug Olikard, manufactured in Russia by Solvay Pharma).

Discussion: In case of angina of functional class IV, nitrates should be prescribed in such a way as to provide a continuous effect for the entire 24 hours, i.e. continuously. For this purpose, the dosage forms of ID or IMN, which have a significantly longer effect, are prescribed 2 or even 3 times a day. It should be remembered that with this method of prescribing nitrates, the risk of developing dependence on them is particularly high.

How a practicing physician can monitor nitrate exposure

Of course, the practitioner, when prescribing nitrate therapy, should strive to assess the effectiveness of the treatment. The patient is advised to keep a diary, recording the number of angina attacks and the level of physical activity during treatment. The effect of treatment can be discussed if the number of angina attacks during treatment has decreased by at least 2 times with the same physical activity.

In general, the most reliable method for objectifying the effect of antianginal therapy, in particular nitrate therapy, is to conduct a test with a dosed physical load on a treadmill or bicycle ergometer under the influence of the drug and compare it with the results of the same test performed before prescribing the drug. However, this method is not very realistic in clinical practice.

Conclusion: There is also an indirect method for assessing the effect of nitrates. Effective doses of nitrates have been shown to reduce resting systolic blood pressure (SBP) by 15–20 mmHg. Art. If SBP is reduced to a lesser extent, the effect is usually insufficient, and if to a greater extent, the risk of side effects increases; The practitioner can easily assess the extent to which SBP has been reduced during therapy by measuring this indicator before and after taking the drug at the time of its maximum effect (usually occurring 1–2 hours after taking the drug).

Thus, nitrates are very effective antianginal drugs, they should certainly be used as the main drugs for the prevention of angina attacks and to increase the patient's tolerance to physical activity. However, treatment with these drugs should not be carried out in a formulaic manner. Only when nitrate therapy is as individualized as possible will it give the desired result.

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