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Advances in Identification and Clinical Management Strategies of Nitrate Resistance

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Abstract: Nitrates are widely used in acute and critical diseases such as angina pectoris, acute heart failure and hypertension. However, there are still many problems caused by the non-standard use of these kinds of drugs and drug resistance, which need to be paid attention to in clinical practice, scientific research, and patient education. This article mainly reviews the identification and clinical treatment strategies for nitrate resistance.

Keywords: Nitrates; Drug resistance; Clinical

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1. Introduction

Nitrate drug-resistant patients generally refer to the continuous administration after 24–72 h, the original dose of nitrate ester drugs against myocardial ischemia and enlargement vascular effect decreased or disappeared, patients exercise tolerance or need to increase the dose or share the other measures to maintain the original effect [1]. Nitrate drug resistant reaction involving the hemodynamic effect, against myocardial ischemia effect, the prognosis of patients with vascular endothelial function, activity, tolerance and aspects can make those of nitrate medications used in the clinical effect of fall, for the treatment of patients with coronary heart disease and other cardiovascular disease cause an adverse effect, this must cause enough attention to clinical and scientific research, and patient education [2].

2. Mechanisms of resistance to nitrates

The mechanisms of resistance may involve nitrate bioconversion, reduced bioactivity of NO, and activation of counterregulatory mechanisms, such as oxidative stress theory, neurohormone activation theory, mitochondrial dysfunction theory, and sulfhydryl depletion theory. The production of oxidative stress may be an important mechanism of nitrate drug resistance. The increase of reactive oxygen species (ROS) will affect the key enzyme of nitroglycerin (GTN) metabolism, acetaldehyde dehydrogenase 2 (ALDH2), thereby interfering with GTN

bioconversion and NO production [3]. In addition, the polymorphism of the *ALDH2* gene can affect the resistance to nitrate. The wild-type (G allele) of the *ALDH2* gene has a normal catalytic activity of GTN, while the mutant (A allele) has a reduced catalytic activity of GTN. Therefore, the *ALDH2* gene mutant population is a potential population of nitrate resistance.

3. Identification methods of nitrate resistance

There are many methods to evaluate nitrate resistance, such as observation of antianginal effect, bicycle exercise test, measurement of peripheral arterial dilatation, forearm plethysmography, measurement of changes in plasma levels of some factors, and direct measurement of coronary artery dilatation. Among them, the observation of the antianginal effect is a widely used evaluation method in clinical work, and a more accurate and intuitive method is to directly measure the degree of coronary artery dilatation before and after drug use under coronary angiography [4].

3.1. Identification of clinical manifestations

The clinical effect of each dose of nitrate in patients decreases or disappears, or is accompanied by a decrease in exercise tolerance, and it is necessary to increase the dose or combine other measures (combined with sulfhydryl donor or temporary withdrawal of the drug) to maintain the original effect [5].

3.2. Identification of true and false drug resistance

Pseudoresistance refers to drug resistance caused by extravascular factors, which may be related to neuroendocrine feedback regulation and circulating blood volume. Pseudoresistance generally occurs in the early stage of nitrate treatment (24–48 hours), and there is no expected hemodynamic effect on high-dose GTN at the beginning. True resistance refers to resistance caused by vascular factors, including changes in vascular structure and function, which is the most common. It means that the effect of any nitrate agent decreases after 48–72 hours of continuous application, and the drug resistance phenomenon occurs rapidly and disappears after a short withdrawal period (24 hours).

3.3. Identification of cross-resistance

This refers to the emergence of resistance between different drugs or routes of administration, which is manifested as the use of a nitrate drug, reducing the efficacy of different routes, other types of nitrate drugs, NO donor vasodilators or endogenous NO.

3.4. Specific resistance phenomenon

It refers to the same individual different vascular bed resistance, and different system resistance in different organs. In general, resistance occurs first in the venous vascular bed, then in the small arteries, and finally in the large arteries [6].

3.5. New identification method: identification of drug-resistant population

The *ALDH2* gene is related to oxidative stress mechanism, hydroxyl depletion theory and other mechanisms. It has gene polymorphism, and the common mutation is glutamic acid in the wild type is replaced by lysine in the mutant type (*Glu487Lys*). Literature reports that the proportion of the wild homozygous type is significantly higher than that of the mutant type in angina pectoris patients in the effective GTN treatment group, and the wild homozygous type has a stronger response to GTN and a faster onset of action. In the Chinese population, according to a study of sublingual only after administering nitrates *ALDH2* genotype of wild crowd reactivity increased cardiac output,

has nothing to do with whether merge coronary heart disease (CHD), which showed that nitrate ester drug curative effect is affected by the *ALDH2* gene significantly [7].

There are significant regional and ethnic differences in *ALDH2* gene polymorphisms: the proportion of *ALDH2* mutations with low catalytic activity in the Asian population is significantly higher than that in other regions, up to 40%, especially in the East Asian population. Literature statistics showed that 30–50% of the *ALDH2* gene mutation in the Chinese population, and the mutation rate of the *ALDH2* gene also has regional differences in China. The mutation rate of the Han population in the southeast of Fujian and east of Guangdong is the highest, and it shows a significant downward trend from southeast to northwest.

ALDH2 is not only closely related to the metabolism of GTN but also a key enzyme in the process of alcohol metabolism in the human body [8]. The key residue *Cys302* in the enzyme active center plays a crucial role in the catalytic reaction as a nucleophile. Blushes after drinking in the East Asian population are related to the diversity of *ALDH2* dehydrogenase genes. The mutant gene *Glu504Lys* leads to the mutation of *Cys302*, which leads to the severe loss of *ALDH2* activity, leading to the abnormal metabolism of acetaldehyde and the accumulation of acetaldehyde leading to telangiectasia. This population also has abnormal metabolic conversion of GTN to NO. Accepts the patient after asking whether facial redness, after drinking can quickly identify patients may *ALDH2* genotypes, can forecast for the first time as those of nitrate medications curative effect, avoid the bad consequences caused by low reactivity or resistance, this make of nitrate in the emergency department accepts angina patients drug resistance quickly identify the more important [9].

4. Clinical management strategies for nitrate resistance

According to the current guidelines for the application of nitrates, there is no consistent and effective treatment for resistance to nitrates at present, and it is important to identify and prevent it early. Timely identification of nitrate resistance, especially in patients with acute cardiac events who do not respond to GTN, has important clinical value. Once the patients with no response or low response are found, integrated traditional Chinese and Western medicine treatment should be paid attention to [10].

4.1. Improvement of drug use

In general, intermittent administration, eccentric administration, gradual increase, and combination therapy can be used to prevent the occurrence of nitrate resistance.

4.1.1. Intermittent administration method

According to the half-life of nitrate drugs, it is necessary to ensure that there is a certain nitrate-free period every day so that endothelial cells and smooth muscle cells can resume the response to nitrate [11]. (Nitroglycerin should be more than 8–12 hours, indomethacin should be more than 12–14 hours).

4.1.2. Eccentric administration method

Oral administration can be taken at 8 am and 2 pm, medication time in the first 8 hours of 24 hours, not after 16 hours [12]. Therefore, the concentration decreases in the last 8 hours, resulting in an 8-hour nitrate-free interval. “If the drug is administered intravenously, it should not be administered continuously for 24 hours, but only for 15 to 16 hours to ensure that the endothelial and smooth muscle cells can resume their response to nitrate.” If the membrane is applied, the membrane is applied for 16 hours, and the membrane needs to be removed after 8 hours, that is, an 8-hour nitrate-free interval is produced. In addition, there is no time limit when the drug is given by mouth or spray, and it can be used normally [13].

4.1.3. Incremental method

For patients with severe unstable angina pectoris, when the drug concentration in the body drops to the lowest level in the late night or early morning when using intermittent or eccentric dosing methods, angina pectoris is prone to occur. This phenomenon is called the "zero point phenomenon" or "rebound phenomenon." To avoid this phenomenon, a gradual incremental method can be used, such as giving 5 mg, 10 mg, and 15 mg of analgesia in the early, middle, and late, respectively, and adding a dose of non-nitrate vasodilator drugs (such as β-blockers or Ca^{2+} channel blockers) before bed, which can avoid both nitrate resistance and the occurrence of the zero-point phenomenon. If angina pectoris occurs during this period, sublingual administration of nitroglycerin can be used to relieve symptoms[14-15].

4.1.4. Combination therapy

(1) Angiotensin II converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB)

According to the neurohormone activation theory, continuous use of nitrates within 48 hours can lead to the activation of RASS due to the baroreceptor effect, and the secretion of angiotensin II (AngII) and angiotensin II receptor 1 (AT1) increases, which makes the blood vessels more sensitive to a variety of vasoconstrictor substances such as AngII and reduces the vasodilator effect of nitroglycerin. Clinical studies have also shown that ACEI and ARB can reduce the incidence of nitrate resistance in patients with coronary heart disease. Therefore, ACEI or ARB can reduce the sensitivity of blood vessels to vasoconstrictors when using nitroglycerin, which is beneficial in preventing nitroglycerin resistance [16].

(2) Sulfhydryl donor

Several animal experiments have confirmed that nitroglycerin metabolism requires sulfhydryl to produce NO. Continuous use of nitroglycerin leads to the gradual consumption of vascular sulfhydryl groups and the reduction of NO secretion. For example, N-acetylcysteine can enhance its effect by directly non-enzymatic binding to GTN, which is beneficial to restore ALDH2 activity and prevent nitrate resistance. Therefore, the addition of sulfhydryl donor drugs such as N-acetylcysteine, methionine and captopril to nitroglycerin can prevent and reverse the resistance to nitroglycerin [17].

(3) Folic acid

Studies have found that the dysfunction of nitric oxide synthase (NOS) is related to the excessive production of superoxide anion, which may be related to the decreased activity of tetrahydrobiopterin, a cofactor of NOS. Tetrahydrobiopterin supplementation has been shown to reverse the dysfunction of NOS in the high oxidation state caused by continuous use of nitroglycerin, etc. Folic acid is beneficial to the recovery of tetrahydrobiopterin activity. Folic acid supplementation can reverse endothelial dysfunction by regulating tetrahydrobiopterin metabolism and restoring nitric oxide synthase metabolism.

(4) Other pharmacologic diuretics

The mechanism of pseudoresistance to nitrate may be related to the counter regulation effect of RASS activation and the increase of vascular volume. Diuretics can alleviate pseudoresistance by reducing water and sodium retention.

(5) Statins

Atorvastatin can enhance the effect of NO by reducing the generation of oxygen ions in vascular tissue. It can also reduce the production of O^{2-} in endothelial cells by reducing the level of serum low-density lipoprotein cholesterol (LDL-C) and preventing the P21rac isoprenylation pathway to inhibit the activation of NADPH membrane oxidase, thereby reducing the resistance to nitrate drugs.

(6) Vasodilators

Hydralazine can reduce the sensitivity of vascular endothelial cells to vasoconstrictor drugs, thereby

reducing the resistance to nitrates.

(7) Antioxidative drugs

Previous studies have shown that vitamin C, E, coenzyme Q10, and probucol can remove superoxide anion and reduce NO inactivation, and their combined application can maintain the sensitivity of blood vessels to nitroglycerin. L-arginine, folic acid and their derivatives can prevent the uncoupling of eNOS and the increase of superoxide anion and can avoid nitrate resistance. Exogenous methionine or zinc chloride, which induces the production of endogenous methionine, can also prevent the development of nitrate resistance. Carvedilol can not only inhibit sympathetic nerve activity, but also has antioxidant and free radical scavenging effects, and has the preventive effect of nitroglycerin resistance [18].

4.1.5. Other stable angina pectoris

They can be used for physical activity before the temporary preventive use of nitrate, or the presence of chest tightness in the premonitory use of sublingual medication, usually do not use nitrate drugs, to avoid drug resistance. For temporary medication caused by emergencies, short-acting and fast-acting drugs should be selected as far as possible, such as nitroglycerin or isosorbide dinitrate. After taking effect, the blood drug concentration can decrease rapidly, and it is not easy to produce drug resistance .

4.2. Traditional Chinese Medicine therapy

(1) Commonly used drugs for acute onset of chest pain: Suxiao Jiuxin pill, Shexiang Baoxin pill, Kuanchest aerosol, Guanxin Suhe pill, etc.

(2) Commonly used drugs in remission period: Suxiao Jiuxin pill, Fufang Salvia, Suhexiang pill, Qili Qiangxin capsule and other preparations [19].

(3) The main clinical manifestations are shock caused by hypovolemia, decreased blood pressure and decreased heart rate. In this clinical situation, nitrates are relatively contraindicated, and Chinese patent medicine such as Shenmai injection, Shenfu injection, etc. [20]

(4) Oral agents such as Qishen Yiqi pills, Tongmai Yangxin pills, Xinbao pills, etc.

5. Summary

Despite the rapid development of medicine in the past century, nitrates are still the most commonly used drugs for the treatment of acute and critical diseases such as angina pectoris, myocardial ischemia, acute heart failure, and hypertension. However, drug resistance to nitrates is also common, and its resistance mechanism has not been fully elucidated. At present, there is no unified treatment plan for drug resistance, and early and rapid identification and prevention are the most important. A comprehensive understanding of the clinical management strategy of nitrate resistance will greatly benefit the reduction of clinical adverse events and the improvement of patient treatment.

Disclosure statement

The authors declare no conflict of interest.

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