

# **THE EFFICIENCY AND SAFETY OF MEDICINE IN ISCHEMIC HEART DISEASE.**

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**Annotation .** We review the clinical use of nitrates in ischemic heart disease (IHD) and underline open questions that arise from the use of nitrates. The organic nitrates are a safe and effective choice for the management of ischemic syndromes related to coronary heart disease. Although the anti-ischemic effects of these compounds have been recognized for more than a century, the mechanisms by which they exert their beneficial effects are still being delineated. In addition to their well-established venodilative activity, nitrates are now known to cause vasorelaxation of coronary arteries, coronary stenoses, and coronary collateral vessels and to prevent episodic coronary constriction. An antiplatelet effect has also been hypothesized.

**Keywords.** coronarolytics, efficiency, anti-ischemic properties, safety.

## **ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ ЛЕКАРСТВ ПРИ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА.**

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**Аннотация.** Мы рассматриваем клиническое применение нитратов при ишемической болезни сердца (ИБС) и подчеркиваем открытые вопросы, возникающие в связи с применением нитратов. Органические нитраты являются безопасным и эффективным средством лечения ишемических синдромов, связанных с ишемической болезнью сердца. Хотя

антиишемические эффекты этих соединений были признаны более века назад, механизмы, с помощью которых они оказывают свое благотворное действие, все еще очерчиваются. В дополнение к хорошо известному венодилатирующему действию нитраты, как теперь известно, вызывают вазорелаксацию коронарных артерий, коронарные стенозы и коронарные коллатеральные сосуды и предотвращают эпизодическую коронарную констрикцию. Также предполагается антитромбоцитарный эффект.

**Ключевые слова:** коронаролитики, эффективность, антиишемические свойства, безопасность.

The rapid- but short-acting nitrate preparations are useful in arresting and preventing acute attacks of angina pectoris, whereas longer-acting oral and transdermal formulations are indicated for the relief of chronic symptomatic and asymptomatic ischemia. The intermittent nitrate dosing regimens introduced in recent years have reduced the likelihood of tolerance, which greatly limited the usefulness of long-acting nitrates in the past. Intravenous infusion of nitroglycerin is particularly appropriate for the management of unstable angina and the early complications of acute myocardial infarction. Preliminary evidence suggests that intravenous nitroglycerin may also be beneficial in preventing postinfarction ventricular remodeling, although it cannot yet be recommended for this purpose.

In acute myocardial ischemia, short-acting nitrates are therapeutically effective by dilating coronary arteries. Nitroglycerin (also called glyceryl-trinitrate) also affects the mitochondrial function and exerts an antiaggregant effect, which might contribute to its beneficial effect in the therapy of acute coronary syndromes [1,2]. Two well-designed studies have proven that the combination of hydralazine and isosorbide dinitrate is effective and reduces mortality in the therapy of congestive heart failure, particularly in Afro-American patients [5,6]. The use of long-acting nitrates in the therapy of stable IHD was established in old studies that do not satisfy modern requirements. It is known that none of the available long-acting

nitrates exerts 24-h antianginal and anti-ischemic therapeutic effects. Some experimental data [1,8] have shown that nitrates treatment was associated with a strong increase in the expression of endothelin-1 and by a subsequent increase in the sensitivity of the vasculature to vasoconstricting agents such as phenylephrine and angiotensin II. These results cannot be used to support the hypothesis that the use of long-acting nitrates may only exert a preconditioning effect in IHD. The final therapeutic effect would rather be a balance between positive and negative effects on the coronary circulation. Even disregarding the open questions about the negative [7] and positive studies [8] important methodological differences among these meta-analysis statistics do not allow comparing results. Finally, recent data open another question about the therapeutic advantages/disadvantage of long-term nitrates. One thousand four hundred and twenty-nine Japanese patients with chronic vasospastic angina were treated with  $Ca^{2+}$  antagonists and long-acting nitrates or nicorandil: when compared with  $Ca^{2+}$  antagonists alone, combined therapy with nitrates did not improve prognosis; on the contrary, the combined therapy increased the risk for cardiac adverse events, especially when transdermal nitroglycerin and nicorandil were used [6]. Vasospastic angina and microcoronary dysfunction are much more frequent in Japan than in other countries [6], and results in Japanese patients should not be directly extrapolated to non-Japanese patients. Nonetheless, the fact remains that in Japanese patients with stable vasospastic IHD the combined use of  $Ca^{2+}$  antagonists and long-acting nitrates increases the risk for cardiac events. This leads to the question whether the 2013 European Guidelines statement that 'long-acting nitrates can be used as a second-line option in combination with  $Ca^{2+}$  antagonists' [3] is generally wise. Nitrates tolerance is not the same phenomenon as endothelial dysfunction and was first mentioned in 1889, in the Brunton's Textbook Pharmacology and Therapeutics. The pathophysiology of tolerance is not yet fully understood but it shares most of the known mechanisms that induce endothelial dysfunction [1,2.]. We hypothesize that long-term use of nitrates may induce microcoronary dysfunction, a pathophysiologic phenomenon

that is frequently found in patients with cardiac syndrome X [5]. This pathophysiologic mechanism may contribute to the occurrence of nitrates tolerance.

We have learned important facts on the pharmacology of available nitrates [1,2]. Short-acting nitrates are beneficial in acute myocardial ischemia and reduce the occurrence of effort or stress-induced angina and ischemia [1,3,4]. None of the available nitrates exerts 24-h antianginal and anti-ischemic effects. Combined use of hydralazine and isosorbide dinitrate seems to be useful in the therapy of congestive heart failure, particularly in Afro-Americans [5,6]. The long-term use of transdermal nitroglycerin and oral isosorbide nitrates in IHD is weakened by the development of endothelial dysfunction and tolerance. Intermittent therapy reduces tolerance but, especially with transdermal nitroglycerin, rebound ischemia in the drug-free phase still remains a problem [4]. Long-acting isosorbide nitrates induce more endothelial dysfunction than transdermal nitroglycerin, and tolerance occurs with a similar frequency [7]. Also, as yet we do not know whether lower doses of transdermal nitroglycerin would be better than those presently used.

We have conflicting data about the benefits/disadvantage derived from the use of long-acting nitrates in IHD. Multivariate analysis data [7] suggested that they increase the incidence of acute coronary syndromes (a negative effect) while data from the GRACE registry [8] indicate a positive effect in acute coronary syndromes. Important methodological differences among the two studies do not allow comparing results and in any case the statistical methods used to assess outcomes in cardiology are far from perfect [6].

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