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CHOICE IN FAVOR OF TRIMETAZIDINE. ANALYSIS OF A CLINICAL CASE

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ABSTRACT

Cardiovascular diseases (CVD) are the leading cause of death and disability among adults in the world. The key position in the structure of causes of death from CVD is occupied by coronary heart disease (CHD), the most common form of which is stable angina. The goals of treatment for patients with chronic angina should be to relieve symptoms and reduce mortality. This will allow patients to feel better and live longer. The traditional hemodynamic approach to the treatment of CAD is based on the belief that increasing oxygen supply and decreasing cardiomyocyte oxygen demand improves symptoms. However, clinical trial data demonstrate that about a third of patients, despite antianginal therapy, continue to experience anginal pain. Traditional tactics for managing patients with stable angina usually involve the use of drugs that affect circulatory parameters (heart rate, blood pressure). The article presents a clinical case demonstrating the effectiveness of trimetazidine monotherapy in stable coronary artery disease, when the use of first-line drugs (beta blockers, calcium antagonists and nitrates) is not possible. Trimetazidine modulates cardiac metabolism without changing hemodynamic functions, so its use in this clinical situation is optimal. Modulators of cardiac metabolism open the way to a deeper understanding of CAD and its general clinical manifestations as an energy disorder, not just an imbalance between the demand and supply of oxygen and metabolites.

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Relevance.

Cardiovascular diseases (CVD), primarily ischemic heart disease (IHD), are the leading causes of mortality and disability among the adult population worldwide. According to updated data from the Global Burden of Disease Study (GBD, 2019), which included information from 204 countries, the number of deaths from CVD has increased over the past 30 years from 12.1 million to 18.6 million [1].

The largest group of patients with IHD consists of those with stable angina, whose annual mortality rate remains at 2–3%, which is twice as high as that of patients without IHD [2]. Meanwhile, despite advances in pharmacological therapy for this condition, nearly one-third of patients taking

antianginal medications continue to experience angina symptoms, significantly reducing their quality of life. The pharmacological treatment of stable IHD has two primary goals: minimizing and alleviating symptoms, and improving prognosis by reducing the risk of death and nonfatal myocardial infarction.

In clinical practice, physicians often face situations requiring an individualized approach to patients with stable angina. Therefore, it is not always feasible to strictly adhere to the traditional algorithm for selecting antianginal therapy. As an example, we present the case of a 63-year-old female patient with functional class II (FC II) exertional angina. In this case, the therapeutic effect was achieved with monotherapy using trimetazidine at a daily dose of 70 mg (TRIDUCTAN MR, Acino Pharma AG, Switzerland).

Clinical Case.

Patient History. Patient D., a 64-year-old retiree, presented with complaints of general weakness and unpleasant (burning) chest pain during moderate physical exertion (such as brisk walking or climbing stairs to the third floor) and significant psycho-emotional stress. The episodes lasted no more than five minutes and subsided with rest.

Medical History. The patient reported being ill for the past three years, initially experiencing heart pain that resolved within minutes at rest, accompanied by reduced exercise tolerance (chest pain during moderate physical exertion). She also noted a pronounced reaction to psycho-emotional stress, with pressure-like chest pain that resolved with rest, usually after breathing exercises. She has been under the supervision of her family doctor, diagnosed with "IHD: functional class II exertional angina." The recommended medications were taken irregularly due to side effects, including dizziness, swelling of the lower legs and feet, and headaches caused by minimal doses of amlodipine and isosorbide dinitrate. The patient had not taken any medications for the last two weeks.

Lifestyle and Past Medical History. The patient had a history of measles and chickenpox in childhood and chronic gastritis (not associated with *Helicobacter pylori*) in adulthood, with no exacerbations in the last five years. She follows a diet and had no abnormalities during a planned fibrogastroduodenoscopy three years ago. Her allergy history is unremarkable. She has smoked half a pack of cigarettes daily for about five years (smoking index: 3.5 pack-years) and denies alcohol abuse. She previously worked as a deputy head of a regional service and reports no occupational hazards. Family medical history is unremarkable.

Objective Findings. The patient's condition was satisfactory. Height: 170 cm, weight: 68 kg, BMI: 23.5 kg/m², waist circumference: 82 cm. Normal body build. Skin and mucous membranes appeared normal in color and moisture, with no rashes or lesions. Lung auscultation revealed harsh breathing, with no rales. Respiratory rate: 18 breaths per minute. Heart auscultation showed muffled, rhythmic sounds. Blood pressure (BP): 120/80 mmHg, pulse: 52 bpm. The abdomen was soft and non-tender upon palpation, with no hepatomegaly. Percussion revealed a vertical liver span of 10 cm along the right midclavicular line. No peripheral edema was observed.

Laboratory and Instrumental Findings.

- Blood and urine tests: Within normal ranges.
- Biochemical tests: Total cholesterol: 8.03 mmol/L, LDL: 4.3 mmol/L, HDL: 0.8 mmol/L.
- Electrocardiogram (ECG): Sinus bradycardia with a heart rate (HR) of 52 bpm.
- Holter monitoring: Sinus bradycardia, with an average HR of 56 bpm, maximum HR of 82 bpm (daytime), and minimum HR of 48 bpm (nighttime). No rhythm or conduction disturbances.
- Echocardiography: Preserved left ventricular (LV) ejection fraction (EF: 69%). LV dimensions, wall thickness, and valve functions were within normal limits. Mild regurgitation on mitral and tricuspid valves.
- Treadmill test: Performed using the BRUCE protocol without antianginal therapy for two weeks. Moderate exercise tolerance (5.5 METs), with horizontal ST-segment depression of up to 1.3 mm in II, III, aVF, and left precordial leads.

Diagnosis.

The clinical diagnosis was established based on symptoms, objective findings, and instrumental results:

- Ischemic heart disease (IHD): Functional class II exertional angina.
- Heart failure: Stage B with preserved LV ejection fraction.
- Dyslipidemia.

Treatment.

Due to poor tolerance of calcium channel blockers and nitrates and the inability to use beta-blockers because of bradycardia, the patient was prescribed metabolic anti-ischemic therapy with trimetazidine (TRIDUCTAN MR, Acino Pharma AG, Switzerland) at a dose of 70 mg/day (35 mg twice daily). To prevent cardiovascular complications, the patient was also prescribed:

- Acetylsalicylic acid with magnesium hydroxide (75 mg once daily in the evening) – Cardiomagnyl (Acino Pharma AG, Switzerland).
- Rosuvastatin (20 mg/day with titration) – Clivas (Acino Pharma AG, Switzerland).

Follow-Up.

At a two-week follow-up visit, the patient reported improved general well-being, absence of angina during physical exertion and stress, and increased exercise tolerance. The single-dose regimen of TRIDUCTAN MR improved adherence to antianginal therapy. Upon examination, BP was 120/80 mmHg, and the pulse was rhythmic at 57 bpm. No significant changes were observed on ECG or echocardiography.

A repeat treadmill test using the BRUCE protocol showed improved exercise tolerance (7.0 METs) with no symptoms during exercise and only minimal nonspecific ST-segment changes at higher HRs.

The treatment resulted in the resolution of angina episodes, improved exercise tolerance, and positive dynamics on instrumental examination. The therapy was well tolerated, and the patient was advised to continue trimetazidine therapy with a follow-up treadmill test in three months.

Discussion.

The presented clinical case demonstrates the effectiveness of trimetazidine monotherapy, which achieved one of the two primary goals of treating stable angina: symptom relief and an improvement in the patient's quality of life. However, during prolonged and severe ischemia, despite the high rate of lactate production, the myocardium continues to derive part of its energy from beta-oxidation of fatty acids [3]. This metabolic shift, due to substrate competition, suppresses glucose oxidation. Under ischemic conditions, when oxygen delivery to cardiomyocytes is inadequate, fatty acid oxidation not only reduces energy molecule synthesis but also leads to the accumulation of partially oxidized metabolic byproducts and reactive oxygen species, which further impair mitochondrial respiratory chain function [4]. These metabolic changes result in contractile dysfunction and electrical instability of the myocardium, thereby exacerbating ischemia and triggering cardiac rhythm disturbances. Pharmacological strategies targeting the modulation of energy substrate metabolism aim either to stimulate glucose oxidation or to inhibit fatty acid oxidation [5]. The latter is achieved by directly inhibiting enzymes involved in beta-oxidation. Trimetazidine is the first drug in the class of metabolic protectors for ischemic myocardium [6]. Its mechanism of action is based on inhibiting the enzyme that catalyzes the terminal reaction of fatty acid beta-oxidation—long-chain 3-ketoacyl-CoA thiolase (3-KAT). This shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation. These metabolic changes have been confirmed in clinical settings: trimetazidine indeed increases levels of high-energy phosphates in the myocardium of patients with heart failure [7]. According to a meta-analysis of 23 randomized trials, trimetazidine improves angina symptoms compared to placebo or other antianginal drugs [8]. The VASCO-angina study evaluated the effectiveness of trimetazidine in improving the functional capacity of 1,962 patients aged 50 years or older with symptoms of stable exertional angina. The study assessed not only the antianginal capacity of trimetazidine but also the safety of standard and high doses with modified release (70 and 140 mg daily) in both asymptomatic and symptomatic individuals receiving background atenolol therapy. As a result, the tolerance to physical exertion among the group of patients taking trimetazidine was statistically significantly higher than in the placebo group ($p = 0.004$). Thus, the VASCO-angina study

confirmed the effectiveness and safety of standard and high doses of trimetazidine in patients with chronic stable angina receiving background beta-blocker therapy [9]. Additionally, a meta-analysis of 218 studies involving 19,028 patients also demonstrated improved exercise tolerance in patients with stable angina (as measured by stress tests): +46 seconds (95% confidence interval (CI) 28–66) for total exercise duration, +55 seconds (95% CI 35–77) for 1-mm ST-segment depression, and +54 seconds (95% CI 24–84) for the time to angina onset in favor of trimetazidine [10]. A meta-analysis of 17 studies conducted by D. Gao et al. [11] showed a significant protective effect of trimetazidine on overall mortality, cardiovascular events, and hospitalizations. Furthermore, trimetazidine protects the ischemic heart from neutrophil-mediated damage [12]. The use of trimetazidine for stable angina is reflected in both Ukrainian and European clinical guidelines. They recommend adding trimetazidine to first-line therapies if the latter are insufficiently effective and considering it as the treatment of choice for reducing the frequency of angina attacks and improving exercise tolerance in patients with contraindications or insufficient symptom control with beta-blockers, calcium channel blockers, and long-acting nitrates. It is also suggested as a preferred option for patients experiencing adverse reactions to these medications that require dose reduction or discontinuation. Trimetazidine is recommended for earlier use in patients with hypotension and/or bradycardia due to its lack of hemodynamic effects [13]. In conclusion, trimetazidine is the only metabolic cytoprotector with proven efficacy in experimental and clinical studies, and its use is endorsed in clinical guidelines. Based on this evidence, the drug should be actively incorporated into treatment regimens for patients with stable IHD.

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