Nitrovasodilators: Pharmacology and Use in the Treatment of Myocardial Ischemia

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PROLOGUE
Cardiovascular pharmacology is taught during the second year of the PharmD curriculum at North Dakota State University. The course draws heavily on material learned in previous coursework, including biochemistry, pathophysiology, and autonomic pharmacology. This paper summarizes the general approach and content used in teaching the pharmacology of nitroglycerin and related drugs used in the treatment of angina. Relevant aspects of cardiovascular physiology and the pathogenesis of myocardial ischemia are reviewed in depth prior to presenting this material.

INTRODUCTION
Ischemic heart disease is the most common cause of death and disability in the United States. The first clinical sign of myocardial ischemia is usually angina pectoris, a term used to describe the strangling chest pain experienced by many patients with ischemic heart disease. Myocardial ischemia, or lack of oxygen, is caused by an imbalance between oxygen supply and oxygen demand in the heart. This imbalance is usually due to an inability to increase coronary blood flow in response to increased myocardial oxygen requirements. The inability to increase coronary blood flow is often related to atherosclerosis of the large coronary arteries, which leads to a progressive narrowing of the blood vessel lumen and a reduction in coronary blood flow. Reduced coronary blood flow may also be caused by either focal or generalized vasospasm (i.e., intense vasoconstriction) of the major coronary arteries. Antianginal drugs may effectively relieve or prevent acute ischemic episodes by increasing myocardial oxygen supply, decreasing myocardial oxygen demand, or both.

ORGANIC NITRATES
Organic nitrates and nitrites have been used in the treatment of angina for well over 100 years. In 1857, inhalation of amyl nitrite, a volatile liquid and known vasodilator, was found to relieve anginal pain; however, the duration of action was brief and the dosage difficult to control. Organic nitrates were soon discovered to share many of the pharmacologic properties of amyl nitrite, and by 1879 the sublingual administration of nitroglycerin was established for relief of acute anginal attacks. Although the vasodpressant effect of these drugs was deemed necessary for their usefulness in treating angina, the molecular mechanism of action remained a mystery for nearly a century. Research during the 1970s and 1980s established that nitrates and nitrites act via the formation of the reactive free radical, nitric oxide (NO)(1). Thus, the term nitrovasodilator was coined to describe those nitrates, nitrites, and other compounds that are denitrated to release nitric oxide. Nitroglycerin is the best studied member of this class of drugs and is considered the prototype.

ENDOGENOUS NITRIC OXIDE
In parallel with work on the mechanism of action of nitroglycerin and related compounds, the obligatory role of the vascular endothelium in the vasodilator response to acetylcholine was first reported(2). The endothelium comprises the innermost layer of cells within the blood vessel wall. As such, it lies in intimate contact with circulating blood and with smooth muscle cells in the medial layer of the vascular wall. Studies in isolated blood vessels demonstrated that acetylcholine acts upon endothelial cells to release a diffusible vasodilating substance whose chemical identity was unknown. The unidentified mediator was initially named "endothelium-derived relaxing factor (EDRF)" because of its inhibitory effect on vascular smooth muscle. Soon thereafter it was recognized that many other neurotransmitters, hormones, and autacoids require the presence of endothelial cells to produce vasodilation. Research by several laboratories noted striking similarities between the pharmacology of the nitrovasodilators and EDRF, thus leading to the proposal that EDRF is identical to NO. The release of NO from endothelial cells was subsequently confirmed and the importance of NO as a signaling molecule in the cardiovascular system, as well as other systems throughout the body, is now well established. In the cardiovascular system, endothelium-derived NO plays a key role in the local control of blood flow, regulation of blood pressure, and prevention of platelet aggregation and adhesion. Moreover, impaired NO signaling (e.g., decreased NO synthesis, release, or bioactivity) is associated with a number of common cardiovascular disorders (e.g., atherosclerosis, hypertension, diabetes, etc.). In 1998, the Nobel Prize was awarded to Furchgott, Ignarro, and Murad for their work on EDRF/NO-signaling in the cardiovascular system and elsewhere.

CELLULAR MECHANISMS OF ACTION
In endothelial cells, NO is formed from L-arginine by the calcium-calmodulin dependent enzyme, nitric oxide synthase, and it rapidly diffuses to the underlying smooth muscle (Figure 1). Vasodilators that require the presence of endothelial cells to generate NO and produce vasodilation (e.g., acetylcholine) are termed endothelium-dependent vasodilators. Exogenous nitrovasodilators, such as nitroglycerin, form NO directly via

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Fig. 1. The interaction of agonists with endothelial cell receptors (R) leads to activation of nitric oxide synthase (NOS), resulting in the formation of nitric oxide (NO) from L-arginine. NO is also formed directly from exogenous nitrovasodilators, such as nitroglycerin (NTG), isosorbide dinitrate (ISDN), and isosorbide mononitrate (ISMN). NO activates the soluble form of guanylyl cyclase (GC), which catalyzes the formation of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). Increased levels of cGMP cause relaxation of vascular smooth muscle. Phosphodiesterase (PDE) hydrolyzes cGMP to GMP.

denitrification by either enzymatic or nonenzymatic mechanisms in a manner that does not require endothelial cells; such substances are termed endothelium-independent vasodilators. Once formed, NO activates guanylyl cyclase, an enzyme that catalyzes the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP) (3). Increased levels of cGMP lead to the activation of cGMP-dependent kinases, phosphorylation of several proteins, and relaxation of vascular smooth muscle. Cyclic GMP is hydrolyzed to its inactive form by phosphodiesterase enzymes. Recent evidence suggests that NO may also activate, either directly or through cGMP-dependent mechanisms, potassium channels on the smooth muscle cell surface (4, 5). The efflux of potassium ions hyperpolarizes the cell membrane, resulting in vascular smooth muscle relaxation.

PHARMACOKINETIC PROPERTIES AND DOSAGE FORMS

Nitroglycerin, isosorbide dinitrate, and isosorbide 5-mononitrate, an active metabolite of isosorbide dinitrate, are the nitrovasodilators most commonly used in the clinical setting (Figure 2). Amyl nitrite, pentaerythritol teta-nitrate, and erythritol teta-nitrate are also available but their use has greatly diminished. All are lipid soluble and readily absorbed via several routes of administration. Most organic nitrates have very low oral bioavailability due to the presence of high-capacity nitrate reductase enzymes in the liver. One exception is isosorbide mononitrate, which does not undergo significant hepatic metabolism and has nearly 100 percent bioavailability following oral administration. Most denitrated metabolites are glucuronidated and excreted via the kidney.

Nitroglycerin may be administered via several routes, including sublingual, buccal, oral, transdermal, and intravenous (6). Because of its rapid onset (1-3 minutes) and avoidance of first-pass hepatic metabolism, the sublingual route is preferred for achieving therapeutic blood levels rapidly. Rapidly dissolving tablets and an aerosol spray are available for sublingual use. Since nitroglycerin is moderately volatile and adsorbs to plastic, the sublingual tablets must be stored in tightly closed glass containers. The duration of action of sublingual nitroglycerin is relatively brief (~30 minutes). The buccal dosage form is inserted under the upper lip and provides a gradual release of nitroglycerin over several hours, with a somewhat longer onset of effect than the sublingual route.

Oral sustained release products and transdermal dosage forms are used to extend the duration of action of nitroglycerin. Orally administered nitroglycerin requires high doses in order to saturate hepatic enzymes. Nitroglycerin is readily absorbed across the skin and may be applied as either an ointment or transdermal patch. Intravenous nitroglycerin is used to rapidly attain therapeutic blood levels. The concentration can be quickly and safely titrated to the desired level, and the hemodynamic effects can be terminated rapidly by stopping the infusion. Isosorbide dinitrate and isosorbide mononitrate are primarily administered via the oral route.

HEMODYNAMIC EFFECTS: MYOCARDIAL OXYGEN DEMAND

In order to reduce myocardial ischemia, and hence relieve anginal pain, the balance between myocardial oxygen supply and demand must be properly restored. Nitroglycerin and related drugs have little direct effect on cardiac muscle, and most evidence strongly supports the concept that their antiischemic effects are the result of vasodilation. Nitroglycerin causes relaxation of vascular smooth muscle in both arteries and veins, although the effect on veins predominates at low doses. By dilating veins, nitroglycerin increases venous capacitance and decreases venous return to the heart. The resulting decrease in ventricular end-diastolic volume and pressure thereby decreases preload (as described by the Laplace relationship). Arterial dilation by nitroglycerin decreases peripheral vascular resistance and leads to a reduction in afterload. Reduced preload and afterload result in decreased left ventricular wall tension, a major determinant of myocardial oxygen demand. Thus, the anti-ischemic effects of the nitrovasodilators are largely due to their ability to decrease myocardial work and oxygen consumption.
HEMODYNAMIC EFFECTS: MYOCARDIAL OXYGEN SUPPLY

The heart is almost exclusively dependent on aerobic metabolism and an adequate supply of oxygen is critical to sustained cardiac activity. Myocardial oxygen supply is a function of both oxygen delivery and oxygen extraction from the blood. Since oxygen extraction from coronary blood is near maximal at rest, there is little reserve to meet increased demand due to increased cardiac activity. Thus, the most important determinant of myocardial oxygen supply is total coronary blood flow. The nitrovasodilators have several effects on the coronary circulation, including dilation of large and intermediate-size coronary arteries, increased collateral flow, and redistribution of flow to ischemic regions of the heart. Accordingly, these beneficial effects are primarily responsible for the ability of nitrovasodilators to improve myocardial oxygen supply.

ADVERSE EFFECTS AND PRECAUTIONS

The most frequently observed adverse effects of the nitrites are a direct result of the vasodilation produced by these drugs(7). Headache, due to dilation of cranial blood vessels, is common and may be severe. Symptoms of postural hypotension (e.g. dizziness) may also be encountered. Paradoxically, nitrates may increase myocardial oxygen demand in some patients by causing reflex tachycardia.

A potentially dangerous drug interaction may occur with sildenafil, a phosphodiesterase inhibitor that increases intracellular cGMP accumulation. Concurrent use of nitrates and sildenafil may cause a sudden and dramatic drop in blood pressure, prompting the FDA to issue a warning about prescribing sildenafil to patients being treated with nitrovasodilators.

Although rarely used today as a therapeutic agent, amyl nitrite has gained popularity as a recreational drug. Inhalation of amyl nitrite, as well as isobutyl nitrite, purportedly enhances sexual pleasure and produces euphoria. Abuse of these products may cause severe cardiovascular toxicity.

NITRATE TOLERANCE

Continuous or repeated exposure to high doses of organic nitrates rapidly leads to a reduction in the hemodynamic and antianginal effects of these drugs(8). This phenomenon, known as nitrate tolerance, may occur within 24-48 hours following exposure and represents a major limitation to the therapeutic use of organic nitrates. Tolerance is not usually observed with the occasional use of sublingual nitroglycerin, but is most often associated with the use of oral nitrates, transdermal patches, and continuous intravenous administration of nitroglycerin. The cause of nitrate tolerance is unclear but it is likely to be multifactorial. Several mechanisms have been proposed including: (i) decreased activation or desensitization of the NO/cGMP signaling pathway (including reduced bioconversion of nitrates to NO); (ii) expansion of plasma volume; (iii) increased release and/or sensitivity to endogenous vasconstrictors, such as endothelin, angiotensin II, and catecholamines; and (iv) increased production of superoxide anions, which destroy NO. The most widely accepted method for preventing nitrate tolerance is to provide a period of low nitrate exposure during each day. For example, a common dosing strategy for transdermal nitroglycerin is to apply the patches for 12 hours and remove them for 12 hours each day. One concern with this approach is that the patient is unprotected during the nitrate-free interval and may require the use of additional antianginal drugs to prevent an acute attack.

Pharmacologic approaches to preventing nitrate tolerance, including the use of antioxidants, angiotensin converting enzyme inhibitors, and diuretics, have been studied but no proven therapy has yet emerged.

CLINICAL USE

Nitrovasodilators are used in the treatment of most forms of angina(9). Patients with chronic, stable angina often have fixed atherosclerotic lesions that obstruct blood flow in the large coronary arteries. While coronary blood flow (i.e. oxygen supply) at rest may be sufficient to meet myocardial oxygen requirements, the obstruction prevents blood flow from increasing during periods of increased oxygen demand. Under these conditions coronary blood flow is already at a maximal level in most patients, thus any increase in myocardial work can initiate an episode of acute angina. Precipitating factors include physical exertion, emotional stress or excitement, and temperature extremes. The beneficial effects of nitrovasodilators in stable angina are due primarily to their ability to decrease myocardial oxygen demand. By decreasing preload and afterload, nitrovasodilators reduce ventricular wall tension and myocardial oxygen consumption.

In patients with variant (Prinzmetal's) angina, the major underlying cause of angina is vasospasm of one or more coronary arteries. Intense vasoconstriction decreases coronary blood flow, thereby reducing myocardial oxygen supply. Coronary vasospasm can occur in arteries with little or no atherosclerotic plaque and is not associated with an increase in myocardial oxygen demand. Indeed, variant angina may strike at any time of the day or night, including during periods of rest or sleep. In contrast to stable angina, variant angina is most often the result of an abrupt decrease in myocardial oxygen supply (i.e. coronary blood flow) rather than an increase in myocardial oxygen demand. By dilating constricted coronary arteries and restoring coronary blood flow, nitrovasodilators increase myocardial oxygen supply and relieve variant angina.

Nitrovasodilators are also used in treating patients with unstable angina. The pathophysiology of this condition is often complex and may involve several underlying factors superimposed on one another, including rupture of atherosclerotic plaques and thrombus formation, constriction of coronary arteries, and increased myocardial oxygen demand. In these patients, the beneficial effects of the nitrovasodilators are likely due to both dilation of the coronary arteries and a reduction in myocardial oxygen consumption.

Nitrovasodilators are used for the immediate treatment of acute angina, as well as for long-term prevention. Because of its rapid onset of effect, sublingual nitroglycerin is the agent most frequently used to terminate an acute attack of angina. Its short duration of action makes sublingual nitroglycerin unsuitable for long-term maintenance therapy; however, it may be used prophylactically when administered immediately prior to activities known to precipitate an anginal attack (e.g. physical exertion). Patients should be instructed to use sublingual nitroglycerin every five minutes until the pain subsides, and to seek medical attention if the pain is not relieved after three doses. Intravenous nitroglycerin is also used to control acute angina. The oral, buccal and transdermal products have a slow onset of action and are not appropriate for terminating an acute attack. Transdermal nitroglycerin and oral formulations of nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate are widely used in long-term maintenance therapy of angina. Although sustained plasma drug levels can usually be attained with these
products, their clinical efficacy may be limited by the development of tolerance.

References