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TREATMENT OF NITRATE DRUG IN ISCHEMIC HEART DISEASE (ANGINA)

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***Abstract**: The organic nitrates are widely used in the management of coronary artery disease. They are given not only to patients with stable angina pectoris, but also to those with unstable angina, acute myocardial infarction, and heart failure. Although they are effective for the treatment of these disorders, their therapeutic value is compromised by the rapid development of tolerance during sustained therapy. Long-acting nitrates can provide protection against the development of angina for up to 12 hours each day if an appropriate dosing regimen or formulation is used. Regimens with proved effectiveness include intermittent transdermal nitroglycerin, standard-formulation isosorbide mononitrate given eccentrically, and sustained-release isosorbide mononitrate given once daily, but there is some concern that nitrate-free periods may have adverse effects in some patients. Although the mechanism of nitrate tolerance has remained elusive, studies in animals suggest that nitrate therapy causes specific biochemical responses in the vasculature that limit the vasodilator effects of nitrates.*

1. INTRODUCTION

Despite the increasing popularity of interventional procedures, non-invasive treatment continues to be the mainstay of anti-ischaemic management. Many cardiologists regard combined administration of conventional anti-anginal medications (including nitrates, ^-blockers and calcium channel blockers) to be a more rational approach to the management of patients with angina than single-agent therapy. The rationale for this therapeutic strategy is based primarily on our knowledge of the pathophysiology of myocardial ischaemia and the mechanism of action of the various anti-ischaemic drugs. Cardiovascular disease (CVD) includes coronary heart disease (CHD) and stroke. CHD involves ST elevation myocardial infarction, acute coronary syndrome (ACS) and stable angina pectoris. This paper deals with gender considerations in CHD. CVD has traditionally been perceived as a male illness, but it ends the lives of as many women as men. Women's health has traditionally been focused on matters related to sexual and reproductive health. However, CVD is the most common cause of female death in most countries except for Africa. It is in many countries more common than cancer, HIV/AIDS, malaria, and tuberculosis combined. However, according to the World Heart Federation, CVD is indisputably the most serious neglected health problem for women in both developing and developed economies. The lack of awareness among both clinicians and women is especially alarming in countries of low or middle income where public health policy has been largely focused on infectious disease in general and maternal and reproductive health for women specifically.

2. PATHOPHYSIOLOGY

The imbalance between myocardial oxygen supply and myocardial oxygen demand is viewed as the pathophysiological basis of myocardial ischaemia[(1)]. Any factor that causes an increase in myocardial oxygen demand or a reduction in myocardial oxygen supply can provoke ischaemia. Myocardial oxygen requirements rise with increases in heart rate, contractility or left ventricular wall stress. Myocardial oxygen supply is determined by coronary blood flow and myocardial oxygen extraction, with the latter normally being near maximal at rest. For some time, residual coronary flow reserve was thought to remain constant in the presence of a fixed atherosclerotic obstruction. However, Maseri proposed that residual coronary flow reserve is not fixed, but rather is subject to variations throughout the day in response to dynamic changes in vasomotor tone[(2)]. Although residual coronary flow reserve still has an upper limit, this value fluctuates in response to changes in resistance at the site of flow-limiting stenoses. Ischaemic episodes continue to occur at high levels of demand (such as with physical exertion) when that demand exceeds the maximal residual coronary flow reserve, but ischaemia may also occur at lower levels of energy consumption due to a transient reduction in flow reserve. Episodes of intense vasoconstriction can impair resting coronary

flow, resulting in ischaemia at res Ischaemia induces haemodynamic changes during both systole and diastole. These changes include an increase in left ventricular end-diastolic pressure, a decrease in cardiac output, an increase in diastolic stiffness and the development of left ventricular wall motion abnormalities. The electrocardiographic effects of myocardial ischaemia include not only the ST-segment and Twave changes typical of subendocardial or transmural ischaemia, but also arrhythmias.

3. CLINICAL SYNDROMES

Most ischaemic states are a mixture of symptomatic episodes, associated with anginal pain, and asymptomatic episodes, characterized by ST-segment depression in the absence of pain. At present, there is no clear explanation for the occurrence of pain during some ischaemic episodes and the absence of pain during others[3]. Clinical data support the concept of mixed angina (or ischaemia), as well as the traditional stable and unstable forms of disease. For example, a survey by Nesto *et* a[4]. documented symptoms of mixed ischaemia in a high percentage of 110 consecutive patients with a diagnosis of stable angina pectoris (Table 1). Angina occurred at rest in 64 (58%) of these patients and at varying levels of exertion in 75 (68%). Thirty-one patients (28%) reported being awakened from sleep by anginal pain and 52 (47%) experienced angina at lesser levels of exertion upon exposure to cold air. These findings suggest individual variations in the degree of vasoconstriction and the responsiveness of the fixed lesion. Cardiologists have focused considerable attention on the factors responsible for the conversion of a chronic stenotic lesion to an active lesion, i.e. the transition from stable to unstable ischaemia. This process is most likely attributable to disruption of the luminal surface of an atherosclerotic plaque. The probable mechanisms of acute myocardial ischaemia include haemorrhage and rupture of the atheromatous plaque, subsequent formation of an intravascular thrombus, dynamic alterations in coronary tone and rapid progression of atherosclerotic lesions[5]. These latter alterations may range from minor vasomotor changes to total spastic occlusion that may be caused, at least in part, by local platelet aggregation with the release of vasoactive substances. Disruption of normal hormonal balance and impaired coagulation homeostasis resulting from damage to the endothelium may lead to thrombosis, spasm or both. As the disease progresses to acute ischaemia, these events may occur independently or in combination.

Table 1: Angina survey in Nagapattinam government Hospitals

Sr. No	Particulars	Response			
		Yes		No	
		n	%	n	%
1	Angina	64	58	46	42
2	Angina varying level of excretion	75	68	35	31
3	Angina with emotional stress	64	58	46	42
4	Angina awakness from sleep	31	28	79	72
5	Angina exposure to cold air absence of physical activity	33	30	77	69
6	Angina exposure to cold air	52	47	58	52
7	Angina occur after meal	36	33	74	67
8	Development of angina with particular activity	23	21	87	78
9	Angina pain with same levels	51	46	59	55

4. TREATMENT OF MYOCARDIAL ISCHAEMIA

Results of these investigations show that both silent and painful ischaemia are major prognostic factors in patients with coronary artery disease (CAD)(6). It is reasonable, therefore, that the treatment of ischaemia should be directed towards both the amelioration of anginal symptoms and the resolution of signs of ischaemia, as documented by the objective tests outlined above. The findings of one small study suggested that such treatment may indeed have a favourable effect on outcome[7]. In this investigation, adverse cardiac events occurred during a 9-month follow-up period in only one (8%) of 12 patients in whom episodes of painless ischaemia were controlled by anti-ischaemic medication. In contrast, such events occurred in 10 (45%) of 22 patients in whom pharmacological treatment failed to eliminate episodes of silent ischaemia. Larger multicentre trials are currently underway to establish the effect of the treatment of ischaemia per se on prognosis. One of them, the Atenolol Silent Ischemia Trial (ASIST)[8], has been completed and has demonstrated a beneficial effect of atenolol compared with placebo in reducing morbidity associated with ischaemia.

4.1 MEDICAL VS SURGICAL THERAPY

Anti-ischaemic medications eliminate or reduce angina by decreasing myocardial oxygen demand, increasing myocardial oxygen supply, or both. They do not correct the underlying cause of ischaemia, although regression f atherosclerosis has been reported with aggressive lipid-lowering regimens in studies such as the Cholesterol Lowering Atherosclerosis Study (CLAS)[9,10], the Monitored Atherosclerosis Regression Study (MARS)[11]and the Familial Atherosclerosis Treatment Study (FATS)[12] Mechanical approaches to the treatment of myocardial ischaemia do not alter myocardial oxygen demand but do improve myocardial oxygen supply by relieving or circumventing the atherosclerotic obstruction responsible for anginal symptoms. Initially successful coronary artery bypass grafting and percutaneous transluminal coronary angioplasty (PTCA), however, may be followed by the recurrence of angina due to graft occlusion, restenosis post angioplasty or the progression of CAD. ecommendations regarding surgical as compared with medical management of angina are based on the results of large, comparative, multicentre trials sponsored by different sources[13-15]. These trials provided no evidence to indicate that surgical treatment is superior to medical treatment in increasing longevity in patients with mild anginal symptoms and those with one or two diseased coronary arteries. For this reason such patients are best treated medically. Surgery has been shown to be more effective than medical therapy in increasing longevity in symptomatic and asymptomatic patients with significant stenosis of the left main coronary artery[16]. Surgical management may also be preferable to medical therapy in patients with triple-vessel disease, regardless of symptoms, especially in those with continuing ischaemia and impaired left ventricular function. Surgery is also recommended for patients with angina that fails to respond to medical therapy. Comparison of coronary angioplasty with bypass surgery has shown no clearcut advantage in terms of morbidity and mortality.

4.2 Anti-ischaemic drugs

Food and Drug Administration for use in the treatment of angina pectoris[18]. The anti-ischaemic effectiveness of each of these three classes in an individual patient will vary depending on the underlying cause or causes of ischaemia. Drugs that reduce myocardial oxygen consumption would be expected to be a particularly rational choice for the management of ischaemic episodes caused exclusively by an increase in myocardial oxygen demand, such as with physical exertion. Agents that act to reduce coronary vasomotor tone are most likely to be beneficial in the management of ischaemia caused by a reduction in myocardial oxygen supply. In patients with mixed angina, anti-ischaemic medications that affect both myocardial demand and supply may be most appropriate. The other pharmacological properties of anti-ischaemic drugs, as well as their associated side effects and interactions, are also important considerations in the selection of an optimal pharmacological approach to the treatment of angina in an individual patient.

4.3 Nitrates

These are the oldest of the available agents. Organic nitrates have been used for the relief of anginal symptoms for more than 100 years and remain the cornerstone of angina therapy today. In addition to their clinical efficacy in the management of symptomatic and asymptomatic angina, nitrates generally are well tolerated. Nitrate-induced side effects typically are seen in the early phase of treatment and tend to resolve as therapy continues. Nitrates are also less expensive than many of the anti-ischaemic medications introduced in more recent years. The diverse pharmacological actions of nitrate compounds result in alterations in both myocardial oxygen supply and demand, making these drugs especially useful in the treatment of myocardial ischaemia related to decreased supply, increased demand, or both. When given in low doses, nitrates produce venodilation and venous pooling with decreased venous return. As a result, left ventricular volume (pre-load) and pressure and diastolic wall tension are reduced and myocardial oxygen demand is lowered[19]. Larger nitrate doses cause some degree of arterial vasodilation, thereby lowering peripheral vascular resistance and left ventricular systolic wall tension and further reducing myocardial demand. In addition, nitrates dilate epicardial coronary arteries, improve coronary collateral flow and reverse coronary artery spasm, effects that result in an improvement in coronary blood flow. More recent data suggest that nitrates may also have anti-platelet and antithrombotic properties[20] which, if confirmed, could have particular relevance for the management of angina related to an acute decrease in coronary blood flow. Both the vasodilatory action of nitrates and the proposed anti-platelet effect of these drugs are believed to involve nitric oxide. Nitric oxide, which is now known to be identical to endothelium-derived relaxing factor[21], is formed in the vascular smooth muscle membrane as a result of the interaction of nitrates with reduced sulfhydryl groups. Nitrates are available in a wide range of formulations and delivery systems. Sublingual tablets containing nitroglycerin or isosorbide dinitrate have a very rapid

onset of effect but a short duration of action that limits their use to the arrest of acute anginal attacks or the prevention of anticipated attacks. Transdermal patches containing nitroglycerin and oral isosorbide dinitrate formulations are more appropriate for the long-term prophylactic treatment of patients with chronic angina. Isosorbide-5-mononitrate, an active metabolite of isosorbide dinitrate, is a newer oral nitrate preparation also indicated for the long-term management of angina. In contrast to isosorbide dinitrate, which is extensively metabolized in the liver, isosorbide-5-mononitrate is not subject to first-pass hepatic extraction. As a result, the bioavailability of isosorbide-5-mononitrate approaches 100% compared with 19-26% for oral isosorbide dinitrate[22]. The lack of hepatic metabolism of isosorbide- 5-mononitrate reduces the marked inter-individual variations in peak plasma nitrate concentrations reported with isosorbide dinitrate. Nitrate tolerance, manifested by diminution ofthe haemodynamic or anti-anginal effects of therapy, is a major problem. Tolerance may occur as early as 24 h after initiation of treatment with continuous transdermal[23] or i.v [24] administration and has been reported within 1-4 weeks of the initiation of treatment with a three- or four times daily oral nitrate regimen[25]. Nitrate tolerance can be prevented by the use of intermittent dosing schedules that allow for a prolonged nitrate-free interval. In the case of transdermal formulations, the optimal regimen appears to be a 12-14-h period of patch application, followed by an 'off' period of 10-12-h, usually during the night. Eccentric, as opposed to concentric, dosing schedules appear to be most effective in preventing tolerance to oral nitrate formulations.

Table 2: NITRATE PREPARATIONS, ROUTES OF ADMINISTRATION, AND DOSING STRATEGIES.

S.No	DRUG AND INDICATION	ROUTE	DOSE	RANGE FREQUENCY
1	Nitroglycerin tablets	Sublingual	0.3–0.6 mg	1–3 times
2	Nitroglycerin	Sublingual	0.4–0.8 mg	1–3 times
3	Nitroglycerin buccal tablets	Buccal	1–3 mg	Once
Prevention of angina attacks				
4	Nitroglycerin tablets	Sublingual	0.3–0.6 mg	2–5 min before activity
5	Nitroglycerin	Sublingual	0.4–0.8 mg	spray 2–5 min before activity
6	Nitroglycerin buccal tablets	Buccal	1–3 mg	2–5 min before activity
7	Nitroglycerin SR	Oral	2.6–10.4 mg	2–3 times/day
8	Nitroglycerin remove	ointment Transdermal	1–10 cm	3–4 times/day,
9	Nitroglycerin patch	Transdermal	0.2–0.8 mg/hr	Once daily
10	Isosorbide dinitrate SF	Sublingual	2.5–10 mg	5–10 min before activity
11	Isosorbide dinitrate SF,	Oral	10–45 mg	3 times/day
12	Isosorbide dinitrate SR	Oral	20–80 mg	1–2 times/day
13	Isosorbide mononitrate SF	Oral	10 – 20 mg	2 times/day,
14	Isosorbide mononitrate SR	Oral	30–240 mg	Once daily

5. PROBLEMS WITH INTERMITTENT NITRATE THERAPY:

An increased frequency of acute myocardial infarction has been described among workers in the munitions industry after withdrawal from occupational exposure to nitrates.[28,29] Although intermittent nitrate therapy has proved superior to continuous therapy, intermittent therapy may be associated with rebound myocardial ischemia during the nitrate-free period. Patients receiving intermittent

nitroglycerin therapy may therefore have an increase in angina at rest or suffer a fatal myocardial infarction.[26,27] Although these reports are a cause of concern, no such effects were reported in a recent large trial of intermittent transdermal nitroglycerin therapy.[26] In the light of these results, no firm conclusions can be drawn concerning the risk of acute ischemic events during intermittent nitrate therapy. Despite this uncertainty, patients and their physicians should be aware of the fact that the nitrate-free period during intermittent dosing regimens may be associated with increased angina. Intermittent transdermal nitroglycerin therapy also has adverse effects on performance on treadmill exercise tests during the period of withdrawal from nitrates. Adverse effects on exercise tolerance have not been reported in studies of other long-acting nitrates given once daily or in eccentric dosing regimens.[31], The mechanism of adverse responses during the nitrate-free interval of intermittent transdermal nitroglycerin therapy is unclear, but they may be due to a heightened sensitivity to vasoconstrictors. Vascular responses to vasoconstrictor substances are increased during nitrate therapy, perhaps due to local production of endothelin. In animals, withdrawal of nitrate therapy was associated with a decrease in the diameter of epicardial coronary arteries, which was prevented by the concurrent administration of high doses of enalapril.[30] Whether these responses are related to clinical events that occur after nitrate withdrawal is unclear. No information is available concerning such adverse effects during eccentric dosing with isosorbide dinitrate. Isosorbide mononitrate has not been reported to cause either rebound ischemia or adverse effects on exercise performance.[31-33]

6. CONCLUSIONS

The organic nitrates are important drugs for the treatment of patients with angina, but important questions remain about their efficacy. Sublingual preparations of nitroglycerin and isosorbide dinitrate are effective in the treatment of acute episodes of angina. Sublingual preparations are also effective when used prophylactically before activity that causes angina. Long-acting nitrate preparations are effective, but the development of tolerance during sustained therapy continues to be an important clinical problem. Long-acting nitrates can provide protection against the development of angina for up to 12 hours each day if an appropriate dosing regimen or formulation is used. Regimens with proved effectiveness include intermittent transdermal nitroglycerin, standard-formulation isosorbide mononitrate given eccentrically, and sustained-release isosorbide mononitrate given once daily, but there is some concern that nitrate-free periods may have adverse effects in some patients. Although the mechanism of nitrate tolerance has remained elusive, studies in animals suggest that nitrate therapy causes specific biochemical responses in the vasculature that limit the vasodilator effects of nitrates.

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