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Rationale for the use of high dose sustained-release isosorbide-5-mononitrate in ischemic heart disease and chronic heart failure

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ABSTRACT: Isosorbide-5-mononitrate is one of the two pharmacologically active metabolites of isosorbide dinitrate. At variance from its parent drug, it has a longer elimination half-life, no metabolic first-pass, and greater bioavailability, allowing once-daily administration as standard or as sustained-release formulations. Several trials have shown that isosorbide-5-mononitrate, in the form of sustained-released capsules administered once daily at doses ranging between 50 and 100 mg, is an effective symptomatic drug for the treatment of stable angina and chronic heart failure (CHF), and is now indicated for these conditions by American and European guidelines. In particular, at 80 mg once-daily sustained-release isosorbide-5-mononitrate has been shown to have trough plasma levels below the minimum therapeutic concentration (100 ng/mL), ensuring a nitrate-free period as sufficient as to avoid nitrate tolerance. This 80 mg dosage is the only high dose sustained-release formulation of isosorbide-5-mononitrate currently marketed in Italy. Isosorbide-5-mononitrate also exerts positive hemodynamic effects (reduction in filling pressure and systemic vascular resistance, with increase in cardiac output) in heart failure in association with standard medical therapy and hydralazine, with a positive impact on patient prognosis. (Heart International 2007; 3: 98-111)

KEY WORDS: Ischemic heart disease, Angina pectoris, Chronic heart failure, Nitrate, High dose isosorbide-5-mononitrate, Sustained-release, Tolerance, Hemodynamics

INTRODUCTION

Isosorbide-5-mononitrate and isosorbide-2-mononitrate, are the two metabolites originating from the denitration of isosorbide dinitrate in the liver (1-5); they differ from isosorbide dinitrate in terms of drug disposition, but they share similar pharmacodynamic effects and are pharmacologically active.

Isosorbide-5-mononitrate was first released in Germany in 1981 and has been widely used since then in clinical practice in Europe, accumulating a considerably high level of clinical experience (6-8). Molecular, cellular and vascular effects of isosorbide-5-mononitrate have been shown to be qualitatively similar to those observed with other organic nitrates including the parent drug and nitroglycerin (1, 9).

The effects of long-acting nitrates and in particular of isosorbide-5-mononitrate, in angina pectoris and acute myocardial infarction have been studied in a large group of patients (10-12). The positive effects of these drugs in these patients are mainly related to the reduction of myocardial oxygen demand and to the increase in blood flow to the ischemic area (Tab. I) (13).

Treatment with isosorbide-5-monitrate or other long-acting nitrates results in a significant fall in left ventricular filling pressure and in the production of heart rate and systolic blood pressure (BP). The cardiac output response to this drug is related to the initial level of the left ventricular filling pressure and to the degree of its reduction. In various studies, in spite of a significant re-

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duction in systemic BP, there was no change in transmyocardial pressure gradient. Although the available data suggest that isorbide-5-monitrate and other long-acting nitrates can reduce the determinant of myocardial oxygen consumption in patients with myocardial infarction while maintaining coronary perfusion pressure, further studies are needed to establish the effectiveness of this therapy more clearly. Long-acting nitrates have also been shown to improve abnormally contracting myocardial segments in patients with previous myocardial infarction, and to successfully treat variant angina. Their effects are also exerted on the coronary arteries by direct vasodilatation.

Long-acting nitrates are useful in heart failure, because by dilating arterioles and/or veins they have the capacity to modify the loading conditions on the heart and thereby to improve cardiac performance profoundly (Tab. II) (14). The main effect of long-acting nitrates in patients with chronic heart failure (CHF) is a significant reduction in left ventricular filling pressure. There is usually no change or a mild increase in cardiac output. Both systemic vascular resistance and systemic BP can decrease, while the heart rate usually remains unchanged. The combined use of long-acting nitrates with hydralazine has been shown to produce a fall in left ventricular filling pressure and a concomitant increase in cardiac output. Long-term studies have demonstrated the persistence of hemodynamic and symptomatic effects of nitrates, alone or in combination with hydralazine, in the treatment of CHF (15-17).

TABLE I - BENEFICIAL EFFECTS OF LONG-ACTING NITRATES IN PATIENTS WITH CORONARY ARTERY DISEASE (13)

Reduction in myocardial oxygen consumption
• Reduction in preload
• Reduction in systolic wall stress
• Reduction in afterload
Increase in aortic compliance and conductance
• Increase in blood flow to ischemic areas
• Increase in collateral blood flow
• Dilation of coronary stenosis
• Increased sub-endocardial perfusion due to lower left ventricular diastolic pressure
• Prevention of coronary artery spasm
• Anti-adhesive and anti-aggregatory effects on platelets

Pharmacokinetic and clinical pharmacology of isosorbide-5-mononitrate

The pharmacokinetic profile of isosorbide-5-mononitrate is characterized by rapid and complete uptake after oral administration (1, 9). Bioavailability approaches 100% and peak concentrations are typically achieved within 30-45 min after administration. Concomitant ingestion of food has no effect on bioavailability, although time to peak concentration can be delayed slightly.

Distribution of isosorbide-5-mononitrate is so rapid relative to its elimination that it can be considered to follow a one-compartment model with first-order elimination characteristics. Elimination half-life is considerably longer than the parent compound and varies between 4.2 and 10.1 hr, depending on the formulation, and it is one of the longest among the various nitrates (Tab. III).

Disposition of isosorbide-5-mononitrate is not affected by advanced age, renal failure, varying degrees of hepatic dysfunction, concurrent therapy with beta-blockers, and it is not removed by either hemodialysis or peritoneal dialysis.

Notably, however, in one study of patients with left ventricular dysfunction following acute myocardial infarction, bioavailability of isosorbide-5-mononitrate was reduced by 28%, absorption was delayed by 42%, and elimination half-life was prolonged by 29% (9). Since this compound is likely to be used more often for

TABLE II - BENEFICIAL EFFECTS OF LONG-ACTING NITRATES IN PATIENTS WITH HEART FAILURE (14)

• Hemodynamic effects (on systemic and pulmonary circulation)
- Reduction of preload (venodilation and reduction of wall stress)
- Reduction of afterload (arteriodilation, increased aortic compliance and reduced systolic wall stress)
• Coronarodilation
• Antiplatelet action

the management of patients with CHF, more data are needed regarding its disposition in these patients.

In a manner similar to other organic nitrates, evidence of hemodynamic or clinical tolerance has been reported for isosorbide-5-mononitrate, though variable findings were reported in different studies, probably because of differences in the experimental design, sample size and evaluation methods (18, 19). When tolerance develops in association with use of isosorbide-5-mononitrate, however, it is typically characterized by a reduction in peak hemodynamic effects, as well as a shortened duration of action and increased frequency of angina. Furthermore, such tolerance has been shown to develop independent of measured concentrations of isosorbide-5-mononitrate.

Although in one study concomitant administration of N-acetylcysteine was found to prevent evolution of tolerance, the clinical importance of these observations awaits further study (20).

It currently appears that the most successful method for preventing the development of tolerance and maintaining clinical efficacy is the use of a single daily high-dose of slow release isosorbide-5-mononitrate instead of two, three or four daily doses. This is supported by several studies in which isosorbide-5-mononitrate taken once daily at 40 or 50 mg in a sustained-release form prevented the development of tolerance with trough levels of 90 ± 12 ng/mL (21-23), ie <100 ng/mL which is considered the minimum therapeutic concentration, inducing tolerance. The once-daily sustained-release administration of isosorbide-5-mononitrate up to 100 mg, did not reveal tolerance development, as shown in Table IV (22, 24-29). Silber et al first described this in 1983 and showed that intermittent therapy with once-daily ingestion of high-dose sustained-release isosorbide dinitrate was successful in preventing the development of tolerance (27). This also applies to once-daily isosorbide-5-mononitrate, the main active metabolite of isosorbide dinitrate. It is now generally accepted that a daily low-nitrate interval is required to prevent the development of tolerance and that a 12-hr nitrate-free interval should prevent tolerance in most patients. The prolonged duration of action of once-daily high-dosage administration of sustained-release formulations, the improved patient compliance with a single daily administration, and the increased likelihood of maximal antiischemic effects are important reasons for recommending high single daily doses of isosorbide dinitrate or isosorbide-5-mononitrate.

The development of a retard preparation of isosorbide-5-mononitrate began in 1982. The drug release profile was thought able to provide sufficient plasma levels over 24 hr for a once-daily dosing. However, because of the experience with nitroglycerin tolerance appearing in the literature at that time, as well as increasing knowledge about the compound itself, initial data indicated that a 24-hr effect would not have been possible: tolerance would have developed if too high plasma levels were maintained over the whole dosing interval. Therefore, research focused on developing a tablet which would have maintained high enough plasma levels over the day, but which would let the level decrease at night so that tolerance would have been avoided. Subsequently, others have realized the wisdom of this approach and currently there are quite a few different preparations on the market, based on different techniques for controlled release, such as matrix, microgranules and erosion matrix, all showing essentially similar drug release profiles.

According to a recent analysis based on data from healthy volunteers and patients with heart failure (Fig. 1,

TABLE III - PHARMACOKINETICS AND RECOMMENDED DOSES OF AVAILABLE NITRATES (1, 9)

Type of nitrate	Usual doses (mg)	Onset of action (min)	Effective duration of action
Sublingual nitroglycerin	0.3-0.8	2-5	20-30 min
Sublingual isosorbide dinitrate	2.5-10.0	5-20	45-120 min
Buccal nitroglycerin	1-3 tablets three times daily	2-5	30-300 min
Oral isosorbide dinitrate	10-60 two or three times daily	15-45	2-6 hr
Oral slow release isosorbide dinitrate	80-120 once daily	60-90	10-14 hr
Oral isosorbide-5-mononitrate	20 twice daily	30-60	3-6 hr
Oral slow release isosorbide-5-mononitrate	80-120 once daily	60-90	10-14 hr
Oral slow release nitroglycerin	6.5-19.5	20-45	2-6 hr
Nitroglycerin patch	0.4-0.8 mg/hr	30-60	8-12 hr

TABLE IV - PREVENTION OF NITRATE TOLERANCE WITH ONCE-DAILY HIGH DOSE SUSTAINED-RELEASE ISOSORBIDE-5-MONONITRATE IN PATIENTS WITH CORONARY ARTERY DISEASE

Author	Number of subjects	Duration of treatment	Reference drug	Result
Svendsen (25)	24	2 weeks	Isosorbide-5-mononitrate 100 mg twice daily or placebo	The 60 mg once daily is effective as adjunctive to beta-blocker treatment, and nitrate tolerance appeared to develop during the twice-daily regimen only.
Wisenberg (26)	18	2 weeks	Isosorbide-5-mononitrate 30 mg four times daily	Better tolerance to exercise after long-term treatment with sustained release formulation
Mitrovic (24)	20	1 week	Placebo	Problems of tolerance or activation of hormonal counter-regulation due to vasodilation were not observed
Nyberg (28)	19	2 weeks	Placebo	Exercise tolerance until the onset of chest pain and until 1 mm ST segment depression increased significantly 3 hr post dose. The same increase was seen both after a single dose and the same dose under steady-state conditions. No increase was seen with placebo.
Kośmicki (29)	38	28 weeks	Isosorbide-5-mononitrate 40, 80 or 120 mg 4,3, or 2 times daily	12 hours nitrate-free interval is sufficient in order to prevent tolerance in long-term treatment of sustained-release isosorbide-5-mononitrate with 40 mg dose, 18 hr with 80 mg and 24 hr with 120 mg doses.
Kenedi (22)	15	1 week	Isosorbide-5-mononitrate 25, 50 mg or placebo once daily	Compared to placebo, the frequency of anginal attacks and the consumption of nitroglycerin decreased highly significantly, especially with the 100 mg dose.

data on file), peak plasma levels of isosorbide-5-mononitare below the 100 ng/mL minimum therapeutic concentration, useful to avoid tolerance, may be achieved with the 80 mg once-daily sustained-release form. This formulation differs from other sustained-release preparations of isosorbide-5-mononitrate, because the active substance is coated with ethylcellulose and stearic acid in micropellets, allowing a controlled and sustained-release of the principle over the 24 hr, with a gradual increase of drug concentration in plasma and a smooth reduction at the end of the dosing interval.

It can be argued that therapeutic effective plasma concentrations of isosorbide-5-mononitrate can also be achieved after the administration of high-dose sustained-release isosorbide dinitrate (Fig. 2) (28), which is metabolized in the liver into isosorbide-5-mononitrate and isosorbide-2-mononitrate. However, isosorbide dinitrate cannot be administered to patients with liver dysfunction and its bioavailability is much less than that of isosorbide-5-mononitrate.

Efficacy of long-acting isosorbide-5-mononitrate in angina pectoris

Several clinical trials have shown that high-dose once-daily isosorbide-5-mononitrate could be useful for the management of ischemic heart disease. The administration of this agent to patients with stable angina pectoris in a number of short-term, double-blind, placebo controlled clinical trials has been associated with improved exercise performance, as well as reduced frequency of angina (Tab. V). The drug has been favorably compared with other antianginal agents such as beta-blockers or calcium channel blockers, showing a preserved antianginal efficacy when employed in conjunction with these drugs over long-term treatment.

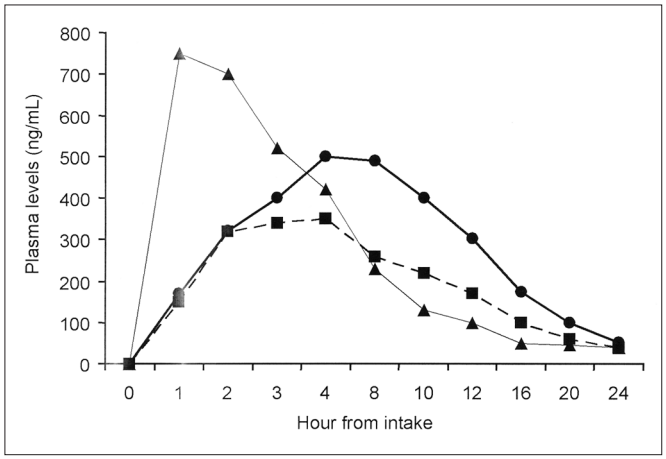

Fig. 1 - *Mean plasma levels of isosorbide-5-mononitrate 40 mg (thin continuous line, closed triangle), sustained-release isosorbide-5-mononitrate 50 mg (dashed line, closed square) and sustained-release isosorbide-5-mononitrate 80 mg (thick continuous line, closed circle) in healthy volunteers or heart failure patients (data on file).*

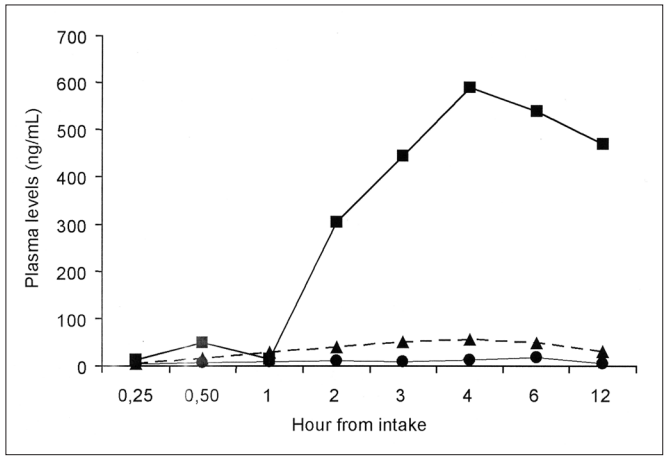

Fig. 2 - *Mean plasma levels of isosorbide dinitrate (thin continuous line, closed circle), isosorbide-2-mononitrate (dashed line, closed triangle) and isosorbide-5-mononitrate (thick continuous line, closed square), after administration of 120 mg of a sustained-release preparation of isosorbide dinitrate to six subjects with angina pectoris (30).*

Effects of long-acting preparations of isosorbide-5-mononitrate are much better documented in angina pectoris and myocardial infarction than are non-retard tablets. The relatively subtle differences in pharmacokinetics between the different brands do not seem to be of sufficient importance to cause relevant differences in efficacy in clinical practice (29, 30).

In chronic angina, improvement in exercise tolerance has been shown to last for 8-10 hr for 50 mg doses. The duration of action for 40 mg formulations is not well documented. The tolerability seems to be equal for all preparations. Whether individual differences occur with respect to different types of controlled or sustained-released formulations, remains to be established. Tolerance does not seem to develop with once-daily dosage and exercise testing performed 24 hr post dose showed that there is no rebound effect, meaning that the effect with the drug is not worse, but equal to that of placebo (31). If the dose is taken in the morning, the benefit will last most of the active day in the majority of cases, which will make these preparations very suitable for the treatment of chronic stable angina pectoris.

Concerning long-acting preparations of isosorbide-5-mononitrate based on doses of ≥80 mg, there is evidence in favor of such a formulation, not only in terms of lack of tolerance but also in efficacy. Silber et al in 1983 first described the good efficacy of such sustained-release formulations, in terms of patient compliance, increased likelihood of maximal anti-ischemic effects and lack of tolerance (27). Chrysant et al (32) studied the efficacy and safety of extended-release isosorbide mononitrate tablets from 30-240 mg once daily, taken in the morning, in 313 patients with stable effort angina. After initial dosing, all groups that received extended-release isosorbide mononitrate had a significant increase in mean total exercise time of approximately 30-50 sec in relation to placebo, 4 and 12 hr after administration. After 42 days of treatment, mean changes from baseline in total exercise time of patients who received 120 or 240 mg of extended-release isosorbide mononitrate significantly exceeded the placebo by approximately 50-60 sec, 4 hr post dosing, and by 30-35 sec, 12 hr post dosing. No significant difference was detected between responses to extended-release isosorbide mononitrate and placebo 24 hr after administration (ie immediately before the next dose). Therefore, there was neither significant activity nor demonstrable rebound of effort-induced angina (zero-hour effect) at the end of the dosing interval. Transient headache was the most prevalent adverse experience.

TABLE V - SUMMARY OF MAIN STUDIES SHOWING THE BENEFIT OF SUSTAINED-RELEASE ISOSORBIDE-5-MONONITRATE IN PATIENTS WITH STABLE EFFORT ANGINA PECTORIS AT HIGH-DOSE 30-240 mg AND SPECIFIC ON 80 mg

Author	Number of subjects	Duration of treatment	Dose of sustained release isosorbide-5-mononitrate (mg od)	Reference drug	Result
Chrysant (32)	313	6 weeks	30, 60, 120 or 240	Placebo	Prolongation of exercise time development of moderate effort-induced angina during long-term treatment by 120 or 240 mg, without induction of nitrate tolerance
Zwinderman (34)	453	24 weeks	100	Sustained-release isosorbide-5-mononitrate 50 mg	Better NYHA angina classification and better improvement of various quality of life indices. Similar incidence of adverse events
Martsevich (36)	30	3 weeks	100	Isosorbide dinitrate 10 or 20 mg tid	All drugs improved exercise tolerance, however effect of mononitrate lasted longer and the incidence of headache and use of nitroglycerine was lower by the end of the study with mononitrate
Lupanov (37)	54	12 weeks	50 and 100	Standard isosorbide-5-mononitrate 40 mg	Sustained-release forms were well tolerated and reduced the frequency of anginal attacks
Cazzola (33)	NA	2 weeks	80	Placebo, isosorbide-5-mononitrate 20 or 40 mg	Reduced number of cardiac ischemic episodes, reduced use of nitroglycerin, reduction in ST segment depression and increase tolerance to exercise
Scardi (35)	NA	NA	80	Placebo	Increased tolerance to exercise
Zito (51)	NA	NA	80	Isosrbide-5-mononitrate 20+20+40 daily	Reduced incidence of headache with sustained-release formulation

NA = Not available

Cazzola et al (33) showed a reduced number of cardiac ischemic episodes, a reduced use of nitroglycerin, a reduction in the degree of ST segment depression and an increased tolerance to exercise under 80 mg isosorbide-5-mononitrate than under placebo or lower doses of the drug (Fig. 3). In a self-controlled, 6-month study, the effects on symptoms and quality of life of 50 and 100 mg sustained-release isosorbide-5-mononitrate, administered once daily, on anginal symptoms and quality of life were assessed in 453 patients with stable angina pectoris (34). Based on their improvements in the New York Heart Association (NYHA) angina classification, patients who received 100 mg daily showed greater improvement than those who received 50 mg daily; the mean difference between treatments was consistent with a significantly greater improvement of mobility and angina indices. The rate of adverse effects differed slightly between the two treatment regimens and was even less problematic with the higher dosage than with the lower dosage. Psychological distress index and life satisfaction scores were also significantly higher with 100 than with 50 mg daily.

According to another study (35) treatment with sustained-release isosorbide-5-mononitrate 80 mg once daily, significantly increased tolerance to exercise as compared to placebo both 5 (+59%) and 10 hr (+44%) post dosing (Fig. 4).

Recently, Martsevich et al (36) assessed in a ran-

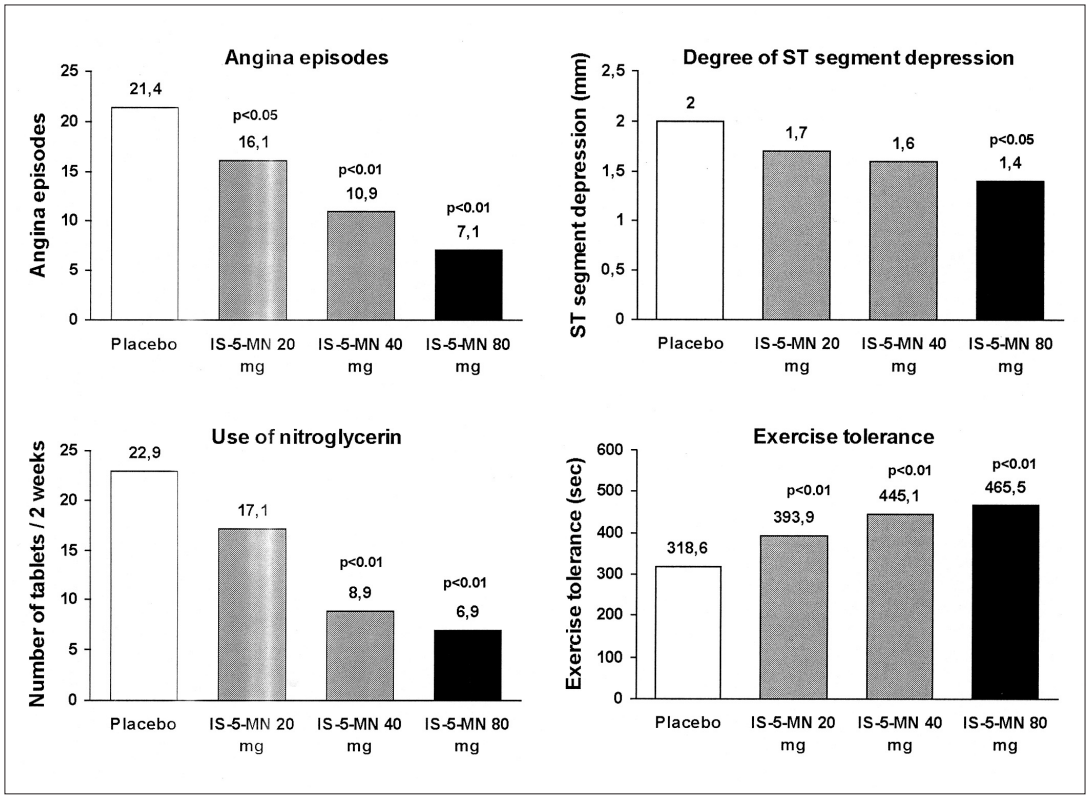

Fig. 3 - *Number of angina episodes, number of tablets of nitroglycerin, degree of ST segment depression and exercise tolerance in angina patients treated with placebo or isosorbide-5-mononitrate (IS-5-MN) at 20, 40 and 80 mg (33).*

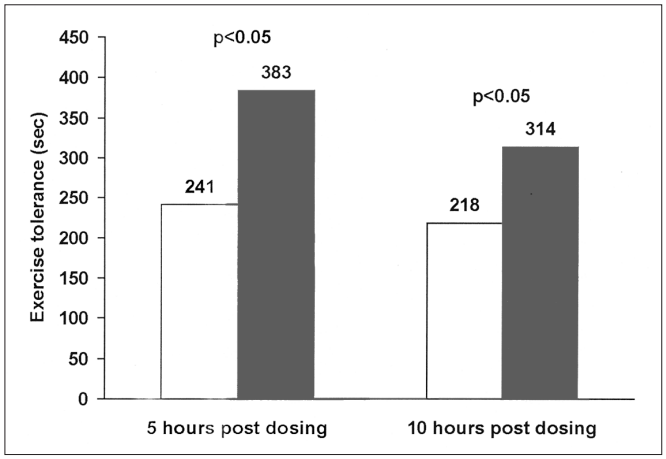

Fig. 4 - *Tolerance to exercise testing in angina patients treated with placebo (open bars) or sustained-release isosorbide-5-mononitrate 80 mg (full bars). Significance (p<0.05) of difference between placebo and active drug treatment is also reported (35).*

domized cross-over study the efficacy and tolerability of 3 weeks of treatment with isosorbide dinitrate 10-20 mg three times daily vs. long-acting isosorbide-5-mono-nitrate 50-100 mg once daily in 30 patients with ischemic heart disease and stable class NYHA II-III heart failure. The use of both isosorbide dinitrate and isosorbide-5-mononitrate was associated with significant improvements in exercise tolerance, though the effect of the mononitrate lasted longer. Nitroglycerin requirement diminished during the first week of use in both drugs and remained on this level by the end of the study with mononitrate, but rose substantially by the end of dinitrate treatment. The number of headache attacks increased during the first week of treatment with both drugs became even higher by the end of dinitrate use and decreased by the end of mononitrate use.

Lupanov et al (37) showed a stable antianginal effect in 85, 80 and 75% of patients with ischemic heart disease and stable angina pectoris treated for 1-3 months with slow release isosorbide-5-mononitrate 100 or 50 mg or non-retard form at 40 mg doses, respectively.

Efficacy of long-acting isosorbide-5-mononitrate in post-myocardial infarction

Concerning the use of isosorbide-5-mononitrate in patients with myocardial infarction, Reifart et al were the first to report such data in 1981 (8, 38). Several

studies have shown that long-acting oral nitrates are useful as a symptomatic treatment of post-myocardial infarction.

However, as shown by a large prospective study, the ISIS-4 trial, the efficacy of nitrates is limited in the long-term mortality of patients with angina following myocardial infarction (39). In this study, 58,050 patients entering hospital up to 24 hr after the onset of suspected acute myocardial infarction were randomized according to a factorial design to treatment with oral captopril (6.25 mg initial dose titrated up to 50 mg twice daily for 1 month) vs. matching placebo, oral controlled-release isosorbide-5-mononitrate (30 mg initial dose titrated up to higher doses once daily for 1 month) vs. matching placebo, or 24 hr of intravenous (i.v.) magnesium sulfate (8 mmol initial bolus followed by 72 mmol) vs. open control. At variance from captopril, isosorbide-5-mononitrate did not show any significant reduction in 5-week mortality, either overall (7.3% mononitrate-allocated deaths vs. 7.5% with placebo) or in any subgroup examined (including those receiving short-term non-study i.v. or oral nitrates at entry). Further follow-up did not indicate any later survival advantage. The only significant side effect of the mononitrate regimen studied was an increase of 15 per 1000 in hypotension. The only positive finding regarding nitrate was that patients allocated to active treatment had fewer deaths on the first 2 days of treatment, which is reassuring concerning the safety of using nitrates early in acute myocardial infarction.

Therefore, concerning the use of long-acting nitrates in ischemic heart disease, these drugs have proved to reduce the frequency and severity of anginal attacks, and to increase exercise tolerance. However, their use is only symptomatic, as studies after myocardial infarction (like the ISIS 4 trial) have failed to show prognostic benefit of such treatment.

Efficacy of long-acting isosorbide-5-mononitrate in chronic heart failure

The first-line goal in the treatment of CHF is to reduce elevated filling pressures and facilitate ventricular emptying. Venodilatation is an important mechanism in improving the hemodynamics in patients with CHF (13). The predominant hemodynamic mechanism of nitrates in these patients is the active relaxation of intestinal and pulmonary capacitance vessels, whereas the decrease in hepatic vascular volume is attributed to the passive expulsion of blood, secondary to reduced distending pressure (40, 41). The rapid favorable reduction in pulmonary capillary pressure and increase in cardiac output, accompanied by a remarkable decrease in systemic vascular resistance, are well known for isosorbide-5-mononitrate, this drug being the ideal adjunct medication for most patients with CHF with and without ischemic heart disease (42, 43).

Clinical evaluation of the usefulness of isosorbide-5-mononitrate for the management of post-ischemic CHF has been favorable. The first data on long-acting nitrates in CHF appeared in 1981. Bödigheimer et al compared isosorbide-5-mononitrate in non-retard tablets with isosorbide dinitrate retard in an open randomized cross-over invasive study in 13 patients with a mean pulmonary artery diastolic pressure of 27 mmHg (44). They found a rapid absorption of isosorbide-5-mononitrate and a 30-35% maximal decrease in pulmonary artery diastolic pressure, right atrial pressure, systolic and diastolic BP at 1 hr, which slowly waned over the next 6 hr. The changes were more pronounced than with isosorbide dinitrate.

Hutton et al (45) found that 15 mg intravenously of isosorbide-5-mononitrate significantly reduced pulmonary capillary wedge pressure within 5 min and caused a subsequent systolic BP fall, indicating that isosorbide-5-mononitrate could well have an important role to counteract the acute vasoconstriction found with loop diuretics; and therefore, be suitable in pulmonary edema. Stephens et al (46) performed an acute dose-response and tolerability study of oral isosorbide-5-mononitrate in 16 patients on stable furosemide treatment (which was withdrawn at least 12 hr before the study) and found that patients tolerated well up to 100 mg. The same authors also investigated the combination of a calcium channel blocker (felodipine) and isosorbide-5-mononitrate (47), finding a further sustained hemodynamic improvement (increased in cardiac index) when isosorbide-5-mononitrate 10 mg 6 hourly was added to 4 weeks of treatment with felodipine. Schneeweiss (42) compared intravenously titrated doses of nitroglycerin (mean 6 mg/hr) and isosorbide-5-mononitrate (mean 6.5 mg/hr) in 10 patients, finding a greater reduction in pulmonary capillary wedge pressure and larger increase in cardiac output with isosor-

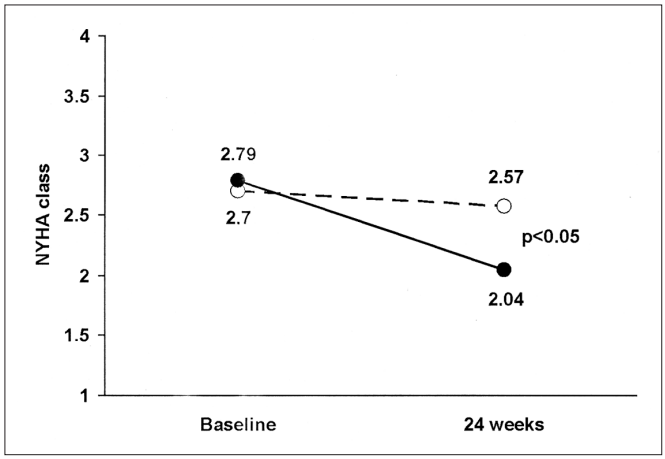

Fig. 5 - *NYHA class before and after 24 weeks of treatment with standard therapy based on ACE-inhibitors, diuretics and digoxin (dashed line, open circle) or with standard therapy + isosorbide-5-mononitrate (continuous line, closed circle) in 47 patients with heart failure. Significance (p<0.05) of the difference between the two study groups at study end is also reported.*

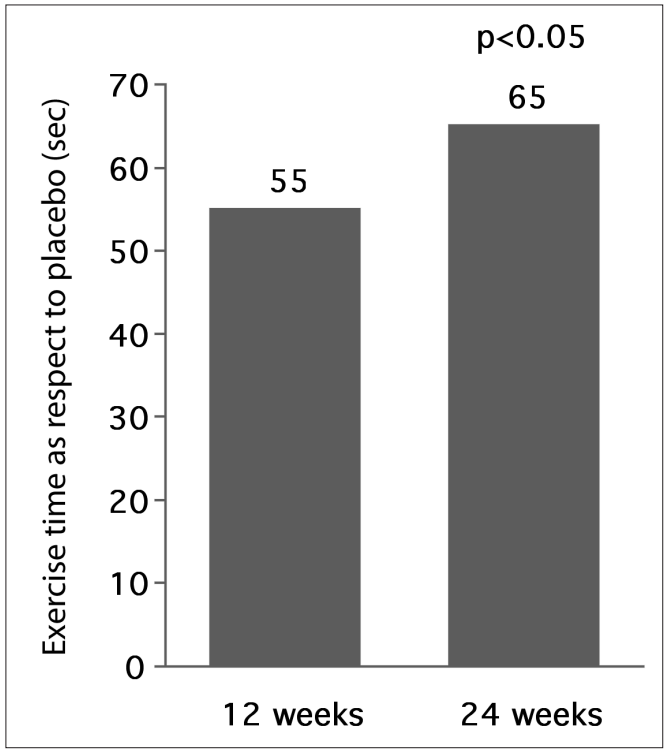

Fig. 6 - *Increase in exercise tolerance in a group of patients with heart failure and an ejection fraction between 31 and 40%, treated with isosorbide-5-mononitrate, added to standard therapy. Results after 12 and 24 weeks of treatment are reported, together with the significance (p<0.05) of the difference vs. placebo (48).*

bide-5-mononitrate.

In 1998, Nikitin et al found that the association of isosorbide-5-mononitrate twice daily with standard therapy (ACE-inhibitors, diuretics and digoxin) for 24 weeks in patients with CHF could improve the NYHA functional class (Fig. 5).

In recent years, few studies have been carried out using high-dose sustained-release isosorbide-5-mononitrate. In the NICE study (48) oral isosorbide-5-mononitrate (50 mg once daily) or placebo was administered to 136 patients (NYHA class II-III) treated for heart failure, all receiving captopril and most also furosemide. After 24 weeks of treatment, the mean change in treadmill exercise duration tended to be greater in patients receiving isosorbide-5-mononitrate than placebo (treatment difference +21 sec). Treatment difference was significantly greater in the prespecified subgroup with ejection fraction 31-40% (+65 sec). No deleterious effects (ie hypotension) were observed with isosorbide-5-mononitrate, although headache was reported in 19% of the active treatment group (Fig. 6).

Tinberg et al (49) studied the efficacy of 11 months of treatment with isosorbide-5-mononitrate at 60 mg doses once daily vs. placebo in 92 patients with evidence of left ventricular dysfunction after acute myocardial infarction previously treated with standard heart failure therapy. Overall changes in echocardiographic measurements were not significantly different between isosorbide-5-mononitrate and the placebo group. However, in a prespecified subgroup with left ventricular ejection fraction ≤40% at baseline, isosorbide-5-mononitrate therapy resulted in a significantly lesser increase of end-diastolic volume index than the placebo. Furthermore, isosorbide-5-mononitrate significantly reduced the serum concentration of atrial natriuretic peptide (mean 20.0 pmol/L), whereas the placebo did not.

Other data on the efficacy of high-dose mononitrate can be inferred from studies based on the use of high-dose dinitrate, which allows the achievement of therapeutic effective plasma concentrations of isosorbide-5-mononitrate compatible with high-dose sustained-released oral preparations. Cohn et al have performed the most important studies in this field. In a large-scale trial that compared the combination of isosorbide dinitrate (up to 160 mg/day) and hydralazine with placebo, the use of the former combination resulted in a reduced mor-

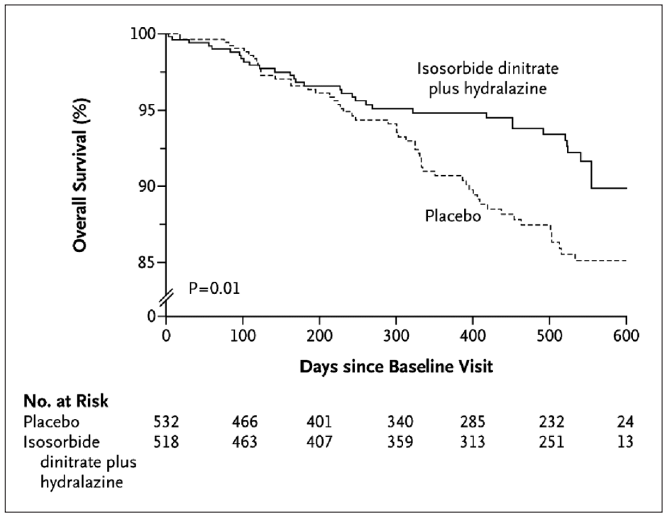

Fig. 7 - *Kaplan-Meyer estimates of overall survival in a study comparing isosorbide dinitrate plus hydralazine vs. placebo in black patients with heart failure (17).*

tality but not in hospitalizations in patients with heart failure treated with digoxin and diuretics (but not an ACE-inhibitor or beta-blocker) (15). However, in another large-scale trial that compared the vasodilator combination with an ACE-inhibitor, the ACE-inhibitor produced more favorable effects on survival (16) a benefit not evident in the subgroup of patients with NYHA class III to IV. Of note, in a trial which was limited to the black population with heart failure, the addition of hydralazine and isosorbide dinitrate (up to 120 mg/day) to standard therapy with an ACE-inhibitor and/or a beta-blocker was shown to be of significant benefit (17) (Fig. 7).

Therefore, isosorbide-5-mononitrate works in CHF as well as in left ventricular dysfunction in conjunction with acute myocardial infarction. A rapid effect is seen with i.v. bolus administration, but oral doses act surprisingly fast as well. Dose requirements seem to vary more than in angina pectoris: some patients can need as much as 100 mg to get an acute effect, whereas patients under treatment with both a diuretic and an ACE-inhibitor already get pronounced effects at oral doses from 5-20 mg. More studies establishing the long-term effects, dose requirements and the tolerance problem in the treatment of CHF are still needed, but it seems well established that in acute exacerbations leading to pulmonary edema or in severe CHF, i.v. and oral long-acting isosorbide-5-mononitrate is a good addition to traditional therapy, based on diuretics, ACE-inhibitors, beta-blockers and inotropic drugs.

Safety of long-acting nitrates

Side effects under treatment with nitrates are common and include headache, flushing and hypotension. Headache can range from a mild throbbing in the head and neck to severe generalized pain. Nitrate-induced headache frequently improve or even disappear with continued drug administration, but about 15-20% of patients treated discontinue therapy because of severe headache associated with nausea and prostration. However, with sustained-release formulations of isosorbide-5-mononitrate the incidence of headache is consistently lower than with short-acting isosorbide-5-mononitrate (Fig. 8).

Indications of guidelines to oral treatment with long-acting nitrates in cardiac disease

Long-acting oral nitrate preparations should be avoided in the early management of acute myocardial infarction and in acute coronary syndrome, and should be used only for chronic management of cardiac ischemic disease. Based on the large evidence of the efficacy and safety of oral nitrates in cardiac ischemic disease American guidelines suggest the use of isosorbide-5-mononitrate slow release up to 240 mg once daily as antinaginal therapy in patients in stabilized unstable angina or non-ST myocardial infarction (class of recommendation I, level of evidence C) (50). Oral nitrates in these patients should be given when they have been free of ischemic discomfort and other manifestations of ischemia for 12-24 hr after prolonged i.v. nitroglycerin infusion, by concomitantly reducing the i.v. nitroglycerin dose and definitively switching to oral nitrates. Oral nitrates should be administered in a non-tolerance producing regimen to avoid the potential reactivation of symptoms, for example, by high-dose regimen ensuring a sufficient nitrate-free interval. In patients with chronic stable angina, oral long-acting nitrates are indicated as initial therapy for the reduction of symptoms when beta-blockers are contraindicated (class I, B) (51). Long-acting nitrates in combination with beta-

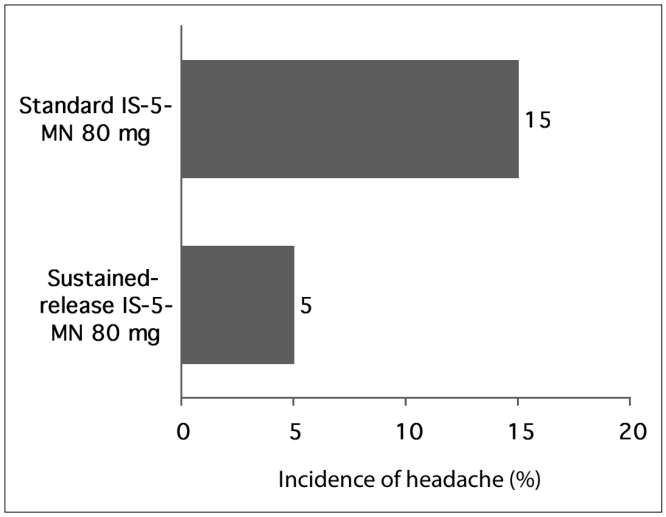

Fig. 8 - *Incidence of headache in patients treated with standard isosorbide-5-mononitrate (IS-5-MN) at a dose of 80 mg daily (20+20+40 mg) or with sustained-release 80 mg isosorbide-5-mononitrate.*

blockers are indicated when initial treatment with beta-blockers is not successful (class I, B) or as substitutes for beta-blockers if initial treatment with beta-blockers leads to unacceptable side effects (class I, C). In line with American guidelines, European guidelines suggest the use of oral nitrates in patients with non-ST segment elevation acute coronary syndrome, only when symptoms are controlled and with an appropriate nitrate-free interval (52). In patients with stable angina pectoris, European guidelines suggest the use of long-acting nitrates such as isosorbide-5-mononitrate to improve symptoms and/or reduce ischemia (53). In the case of beta-blocker intolerance or poor efficacy, long-acting nitrates can be administered (class I, C). If monotherapy with a calcium channel blocker or its combination with a beta-blocker is unsuccessful, the calcium channel blocker can be substituted with a long-acting nitrate (class IIa, C).

Concerning CHF, the only evidence of a prognostic benefit of nitrate use derives from studies based on combination of high-dose isosorbide dinitrate and hydralazine. For this reason, American guidelines (54) indicate (class IIa, A) the addition of a combination of hydralazine and a nitrate to standard therapy with ACE-inhibitors and beta-blockers, in patients with reduced left ventricular ejection fraction and asymptomatic heart failure who have persistent symptoms. Additional strong evidence for the use of such a combination is given for black patients with NYHA functional class III or IV under standard medical regimen for heart failure (class IIa, A). The combination of hydralazine and isosorbide dinitrate should not be used for the treatment of heart failure in patients who have no prior use of an ACE-inhibitor, and should not be substituted for ACE-inhibitors in patients who are tolerating ACE-inhibitors without difficulty. Despite the lack of data with the vasodilator combination in patients who are intolerant of ACE-inhibitors, the combined use of hydralazine and isosorbide dinitrate can be considered as a therapeutic option in such patients (class IIb, C). For patients with more severe symptoms and intolerance to ACE-inhibitors, the combination of hydralazine and nitrates is frequently used, particularly when ACE-inhibitor therapy is limited by hypotension or renal insufficiency. There are, however, no trials addressing the use of isosorbide dinitrate and hydralazine specifically in the population of patients who have persistent symptoms and intolerance to inhibitors of the renin-angiotensin system.

European guidelines also recommend use of the combination hydralazine and nitrates as adjunctive therapy in the management of heart failure, particularly in the case of intolerance of ACE-inhibitors and angiotensin II antagonists (class I, B) (55). Nitrates can be used as adjunctive therapy for angina or relief of dyspnea (class IIa, C).

Table VI shows a summary of guideline indications for the use of long-acting oral nitrates.

CONCLUSIONS

Although large studies in patients with angina pectoris and heart failure addressing the long-term effects of high-dose sustained-release isosorbide-5-mono-nitrate are still needed, the studies performed to date have unequivocally demonstrated that long-acting forms of isosorbide-5-mononitrate taken once daily provide sufficient antianginal effects throughout the day and are better tolerated than short-acting preparations or of isosorbide dinitrate preparations with moderately prolonged activity. The prolonged duration of action of once-daily high-dosage administration of sustained-release formulations, the improved

TABLE VI - SUMMARY OF CURRENT INDICATIONS TO USE OF LONG-ACTING ORAL NITRATES IN CARDIAC DISEASE ACCORDING TO AMERICAN AND EUROPEAN GUIDELINES (53-58)

Type of disease	Indications of American guidelines (AHA/ACC)	Class of recommendation and level of evidence	Indications of European guidelines (ESC)	Class of recommendation and level of evidence
Unstable angina or non-ST elevated myocardial infarction	Antinaginal therapy when symptoms are controlled	I - C	Antinaginal therapy when symptoms are controlled	-
Stable angina	Improvement of symptoms and/or reduction of ischemia:		Improvement of symptoms and/or reduction of ischemia:	
	• If beta-blockers contraindicated	I – B	• If beta-blockers poorly effective or not tolerated	I-C
	• If beta-blockers not tolerated	I – C	• If calcium-antagonists ineffective, also in combination with beta-blockers	IIa-C
	• In combination with beta-blockers if initial treatment with beta-blockers ineffective	I – B	• In vasospastic angina	I-B
	• In syndrome X	I - B	• In syndrome X	I-B
Chronic heart failure	In combination with hydralazine:			
	• In presence of symptoms, added to standard therapy with ACE-inhibitor and beta-blocker	IIa - A	Adjunctive therapy for angina and relief of dyspnea	IIa-C
	• Black patients under standard medical treatment and NYHA class III-IV	IIa – A	In combination with hydralazine, if ACE-inhibitors or angiotensin II antagonsits not tolerated	I - B
	• If ACE-inhibitor not tolerated	IIb - C		

patient compliance with a single daily administration, and the increased likelihood of maximal anti-ischemic effects are important reasons for recommending high single daily doses of isosorbide-5-mononitrate. According to pharmacological and clinical studies, high-dose isosorbide-5-mononitrate given once daily in the form of sustained-release capsules represents the most appropriate dose for treatment of cardiac disease. In particular, the pharmacokinetic and clinical features of 80 mg sustained-release isosorbide-5-mononitrate makes it one of the most indicated choices for the treatment of patients with stable angina or as symptomatic treatment post-myocardial infarction patients. This 80 mg dosage is the only high dose sustained-release formulation of isosorbide-5-mononitrate currently marketed in Italy.

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