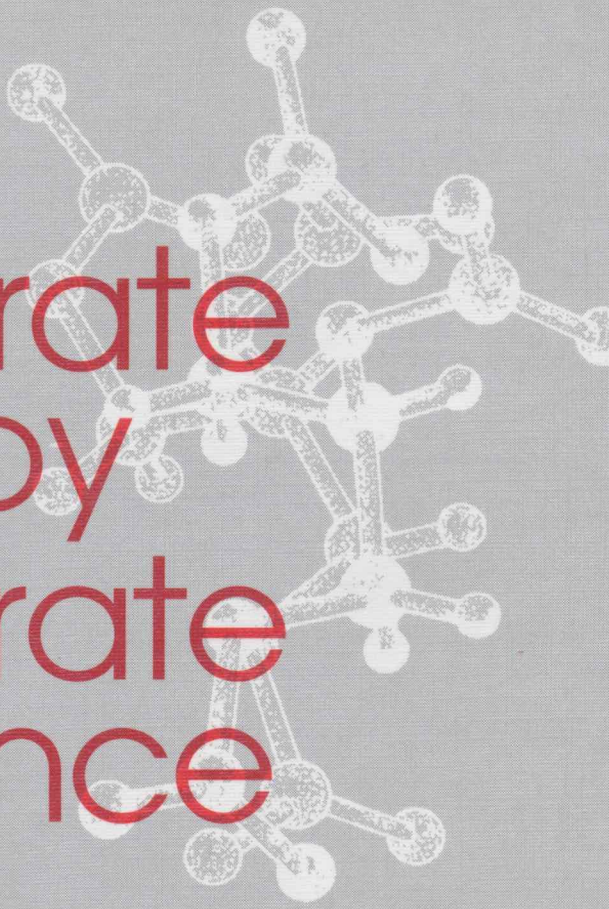

Nitrate Therapy & Nitrate Tolerance

Current Concepts and Controversies

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Rational Therapy with Nitrates

Commitment to a High-Dosage Once-Daily Regimen

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'Few things are more distressing to a physician than to stand beside a suffering patient who is anxiously looking to him for that relief from pain which he feels himself utterly unable to afford.' With this sentence, Sir Lauder Brunton [43] began his publication, when he first introduced the 'use of nitrite of amyl in angina pectoris' in 1867, while 'brandy, ether, chloroform, ammonia and other stimulants have hitherto been chiefly relied upon for the relief'. Twelve years later, William Murrell [228] described the pros and cons of 'nitroglycerin as a remedy for angina pectoris'. Ever since, angina pectoris is treated with sublingual nitroglycerin (NTG). Isosorbide dinitrate (ISDN), first synthesized in 1938, represents the most important oral nitrate.

Although nitrates have been successfully applied for over 30 years as oral [47], buccal [257] and transdermal [72] preparations to prevent anginal pain, two controversies transiently darkened the horizon over nitrates: the questioned bioavailability of ISDN and the tolerance issue.

Since the early seventies it has been known that ISDN is extensively metabolized, i.e. denitrated in the liver [49, 115, 232]. According to theoretic considerations and insufficient laboratory methods, this first-pass metabolism erroneously was thought to preclude the antianginal efficacy of orally administered ISDN. In 1975, fortunately, Stauch et al. [329] discovered that the two denitrated metabolites, the isosorbide-2-mononitrate (IS-2-MN) and the isosorbide-5-mononitrate (IS-5-MN), were vasoactive compounds as well. Therefore, the first-pass effect in the liver had to be regarded as a positive, useful metabolism. In 1976, Michel [217] compared the anti-ischemic effects of intravenous ISDN to those of IS-2-MN and IS-5-MN, revealing equipotent effects for dosages of 1:2:7. After ingestion of ISDN, IS-5-MN is the metabolite with the highest

plasma levels [204, 280]. In pure form, IS-5-MN was first approved in Europe [38, 89, 154] and is now also available in the USA.

Towards the early eighties, the second controversy came up. Although 'remarkable tolerance of nitroglycerin' to its antihypertensive effect was first described in 1888 [333], most clinicians felt the antianginal benefits to remain unattenuated during long-term treatment. There was, however, increasing evidence of a clinically relevant loss of the antianginal (anti-ischemic) properties during chronic application [1, 3, 48, 167, 193, 250, 286, 306, 316]. Unfortunately, this debate about nitrate tolerance resulted either in the prescription of lower dosages or in abandoning oral nitrates at all.

Several authors offered different solutions to the problem of nitrate tolerance. In 1982, Thadani et al. [340] suggested that 'during sustained therapy, isosorbide dinitrate should be prescribed every 2 to 3 h rather than every 6 h for continued beneficial effects'. In 1983, Rudolph et al. [286] recommended the use of low-dose ISDN in non-sustained-release form, i.e. 20 mg given at 8 a.m. and 1 p.m. At the same time, we, in contrast, chose a different approach. In 1983 we introduced the high-dose, sustained-release, once-daily regimen to avoid nitrate tolerance [319].

The following chapter summarizes how and why the 'good old nitrates' should still be used today.

How Do Nitrates Work?

Nitrates decrease oxygen demand by reducing preload and afterload. Although preload reduction is the more pronounced mechanism, the role of afterload reduction has probably been underestimated [173]. In addition, nitrates may increase oxygen supply by relieving coronary spasm. The relaxation of vascular smooth muscle is mediated by the release of cyclic guanosine monophosphate (cGMP).

Venodilatation

It is well established that nitrates induce venodilatation with subsequent reduction of the left ventricular end-diastolic pressure and end-diastolic volume (LVEDV) [16, 62, 64, 127, 178, 201, 302, 336, 376]. In patients with chronic stable angina and reproducible, exercise-dependent ischemia, preload reduction by venodilatation is the prevailing mechanism of nitrates [112, 118, 373]. Neither beta blockers nor calcium-channel blockers offer venodilatation. Therefore, comparing nitrates to nifedipine, ISDN for example leads to the same increase in stroke volume but at lower right atrial pressures, underlining the im-

portance of preload reduction [160]. Venous dilatation occurs at lower plasma NTG levels with the maximal response after 20 min, whereas the arterial effects are seen more rapidly but at higher doses [141].

During resting conditions, the sublingual application of NTG resulted in a 25% decrease of LVEDV in healthy persons [326]. In patients with coronary artery disease, the LVEDV reduction was between 10 and 40% [17, 260, 282, 289]. The sublingual and oral administration of ISDN at rest also led to a 16–36% reduction of LVEDV [17, 170]. During exercise, a mean LVEDV reduction of 10% was reported in healthy persons after sublingual NTG [326]. The corresponding decrease of LVEDV in patients with coronary artery disease was in the range of 20% [260]. In patients with good (anti-ischemic) nitrate response to ISDN, we have observed an LVEDV reduction of 25% at rest, and during exercise of 19% [323].

In healthy volunteers, these volume changes are reflected by an increase in left ventricular ejection fraction (LVEF) at rest from 58 to 64% following sublingual NTG [371] and in patients with coronary artery disease from 43 to 63% [330]. The changes following IS-5-MN are somewhat less pronounced [208]. During exercise, sublingual NTG increased LVEF for more than 10% EF units [37, 260]. In our studies in patients with coronary artery disease, oral ISDN significantly increased LVEF during exercise from 52 to 64% [323]. Recently, the NTG-induced improvement of cardiac function in the ischemic setting has been documented by continuous, ambulatory monitoring of left-ventricular function [222].

Since only anecdotal information has been obtained regarding the nitrate-induced changes in left ventricular volumes at rest in coronary patients with insufficient nitrate response [170], and no such study reported these changes during exercise, we investigated the ISDN-induced changes of LVEDV at rest and during exercise in relationship to the degree of the anti-ischemic effect [323]. Patients with insufficient anti-ischemic effects were characterized by the absence of LVEDV changes during exercise, supporting the concept that preload reduction plays the major role for the anti-ischemic nitrate effects in patients with exercise-dependent ischemia [112, 118]. Others have claimed a lack of coronary dilatation for the explanation of insufficient nitrate response [170].

Dilatation of Coronary Arteries and Balance of Inhomogeneous Flow Distribution

It is known for more than 30 years that nitrates dilate major epicardial arteries [98, 121, 198]. Intracoronary administration of NTG increases the cross sectional area of normal coronary arteries by 40%, and sublingual NTG by 20% [40]. Sublingual ISDN shows similar effects [12, 263]. Nitrates dilate coro-

nary arteries not only in pre- and poststenotic vessels, but also in eccentric lesions with a dynamic component [128]. In moderately stenotic segments (mean 68%) intracoronary NTG increased the area by 40%, in severely stenosed segments (mean 85%) by 36% [40]. Sublingually administered ISDN also led to remarkable dilatation in stenotic lesions, with even greater efficacy in poststenotic vessels and with its advantage of longer duration of action [12]. In patients with exercise-dependent ischemia, the role of nitrate-induced coronary dilatation is still controversial [40, 75, 112, 118, 170, 210].

The nitrate-induced reduction in oxygen demand may decrease myocardial blood flow by 20% in healthy people and in patients with coronary artery disease during resting conditions [56, 197, 288]. During pacing-induced ischemia, a decrease of myocardial blood flow in the normal and poststenotic areas has been reported [94]. On the other hand, in reversible hypokinesia, nitrates increase regional blood flow [288]. This may also be attributed to the nitrate-induced improvement of collateral blood flow [8, 56]. The fact that nitrates decrease blood flow more in normal than in poststenotic areas ('autoregulation') results in a homogenization of the previously inhomogeneous blood flow distribution [94, 332, 345, 367]. This homogenization may in part be attributed to the nitrate-induced increase in collateral blood flow [52, 105, 113].

Nitrate Tolerance: Induction and Circumvention

Definition of Tolerance

Tolerance is defined as the attenuation or loss of one or more pharmacodynamic effects during chronic administration. A progression of the underlying disease must be strictly ruled out. This may sometimes be difficult in patients taking nitrates for years or in patients with unstable angina. Terminologies such as 'partial' or 'total' tolerance are confusing. Some authors refer to the attenuation of a single test parameter, whereas others describe the number of test parameters affected. Even more ambiguous, the term 'partial tolerance' was used to differentiate a very rapid from a slower developing tolerance [34]. Since tolerance regarding venous compliance may develop within 2 h [127], the term 'tachyphylaxis' should be reconsidered.

To prove tolerance, chronic and acute testing is required to document the attenuation or loss of a given test parameter despite the same or even higher plasma levels. Since some studies did not conduct acute testing and many studies did not include the measurement of plasma levels, tolerance may at the best only be suspected. Even if some statistically significant effects were demon-

strable after repetitive dosing, studies without acute testing do not allow differentiation between tolerance and initially insufficient response.

Induction of Nitrate Tolerance

In 1888, Stewart [333] reported in a patient taking NTG for arterial hypertension 'tolerance being so rapidly established'. Ever since, there was never a doubt that tolerance develops rapidly regarding the antihypertensive effects of NTG [35, 294], ISDN [28, 41, 68, 192, 254, 299, 321, 340] or IS-5-MN [158].

In contrast to this generally accepted 'hemodynamic tolerance' along with the disappearance of nitrate-induced tachycardia and headache, tolerance concerning the antianginal/anti-ischemic effects was a matter of marked controversy.

Tolerance following Oral Administration

Many studies with every 6 to 8 h dosing have proven nitrate tolerance. In 1969, Goldbarg et al. [126] found no difference between placebo and ISDN regarding anginal frequency and exercise capacity after 4 weeks of treatment with 10 mg ISDN in non-sustained-release from every 6 h. Similar results were reported in 1970 and 1973 [10, 200]. In 1980, the total disappearance of the anti-ischemic effects during the administration of 20, 40 and 60 mg ISDN in sustained-release form every 8 h was documented [28]. In 1982, the duration of the antianginal effects was found to be considerably reduced during sustained therapy ingesting 15–120 mg ISDN in non-sustained-release form every 6 h [340]. In 1983, another study created tolerance with 40 mg ISDN in non-sustained-release form every 6 h [286]. Also for IS-5-MN in non-sustained-release form, 50 mg thrice a day (t.i.d.), tolerance has been established [158, 310].

However, other studies with every 6 to 8 h dosing did not reveal tolerance development. Oral NTG (2.6 mg every 8 h [364] and 6.5 mg every 4–8 h [71]) did not reveal tolerance development. Non-sustained-release ISDN at variable dosages and dosage intervals (5 mg every 1–4 h [20], 20 or 50 mg every 6 h [68], 40 mg every 8 h [191] and 40 mg every 4 h [303]) did not attenuate the anti-ischemic effects. Similar results were published for sustained-release ISDN 20 mg t.i.d [157], IS-5-MN 20 mg t.i.d. [65, 157, 311, 312] and 40 mg twice a day (b.i.d.) [42].

Tolerance following Intravenous Administration

Studies assessing the effects on exercise-induced ischemia proved the concept of very rapid development of tolerance within 24 h of a NTG infusion in dosages of 1.5 mg/h [234], 3 μg/h [300] or cca. 50 μg/min [378]. Similar results

were obtained regarding the pulmonary capillary pressure in patients with acute myocardial infarction receiving 133 μg/min [214]. For low dose NTG infusions, however, data are not as concordant. Whereas one group has not observed tolerance after 60 h of 33 μg/min NTG in patients with acute myocardial infarction [214], others described considerable attenuation following the administration of 45 μg/min in comparable patients [165]. Even at lower infusion rates of NTG (10 μg/min) in patients with exercise-induced angina did rapid attenuation occur [378].

ISDN, infused over 23 h at 4 mg/h in patients with coronary artery disease, did not create tolerance to exercise-induced changes in pulmonary arterial pressure [351]. This may, however be explained by the continuously increasing plasma levels of IS-5-MN originated during the ISDN infusion from 0 (baseline) to 166 ng/ml (after 4 h) up to 558 ng/ml (after 24 h). Although these results were consistent with previous findings [51], a recently published study in coronary patients generated tolerance to exercise parameters within 30 h, infusing ISDN at 5 μg/h [34].

In congestive heart failure, not all patients seem to develop tolerance, even after 72 h of NTG infused at 1.5 μg/kg/min [87].

Tolerance following Transdermal Administration

Although the transdermal application of NTG as ointments and cremes has been well established for over 20 years [140, 179, 267], new delivery systems were designed to 'improve' the transdermal release, providing constant plasma levels for 24 h [144, 168, 225]. In fact, the response of physicians and patients to these patches was 'one of the most remarkable pharmaceutical stories' [2]. While preliminary studies presented encouraging results for patients with angina [122, 148, 278] and congestive heart failure [313], subsequent trials, however, disclosed conflicting findings [48]. Finally, the recently published 'Transdermal Nitroglycerin Cooperative Study' clearly demonstrated in 562 patients the rapid development of tolerance in any of the seven treatment groups (15, 30, 45, 60, 75, 90 and 105 mg/day) [331]. Furthermore, this study also demonstrated the attenuated response to sublingual NTG [311].

For further discussion of this subject, it is important to differentiate between the effects during the first hours after the first patch attachment, the first day after the first attachment and weeks after repeated attachments.

First Attachment. During the first hours, 5 mg/day have not consistently shown beneficial effects. Some authors reported significant anti-ischemic effects [148, 255, 269, 273], whereas others did not [63, 268, 301]. Pooled data analysis of 17 trials in approximately 400 patients revealed a statistically significant increase in exercise duration of 77 s, 4 h after the first attachment of a 5-

mg patch [58]. The 10-mg NTG patches showed significant anti-ischemic effects in most studies [151, 156, 255, 269, 273, 301, 344]. Pooled analysis proved a highly significant increase in exercise duration of 114 s for this dose [58]. The 20-mg patch has remarkable initial anti-ischemic effects [241, 268, 273, 290]. The comparison between oral therapy and NTG patches revealed weaker effects for the patches [268]. Accordingly, for patients with congestive heart failure a minimal effective dose of 60 mg/day has been postulated [162].

Although many authors have reported significant effects at 24 h after the first attachment [5, 122, 290, 313, 344], others have observed a loss of the initially beneficial effects for dosages between 5 and 30 mg [151, 156, 255, 268, 269, 273, 301]. The pooled analysis did not confirm a statistically significant increase in exercise duration 24 h after the first attachment [58].

After Weeks. After 2 weeks of treatment with a 5-mg patch, small but statistically significant effects were observed 5 h after the attachment [279]. Similar data were found at 3–4 h as well as 24 h after a 10-mg patch [132, 223].

In contrast, placebo-controlled trials with initial responsiveness testing demonstrated a complete loss of the anti-ischemic effects after repetitive, continuous attachment, even within the first hours after the second attachment, in patients with coronary artery disease [203, 255, 256, 331] or congestive heart failure [284, 313]. Therefore, the clinical value of conventional nitrate patches has been seriously questioned [2, 250, 337].

Why Is It Difficult to Prove Nitrate Tolerance?

The measurement of plasma levels is crucial to differentiate between tolerance (which occurs at unchanged or even higher plasma levels) and diminishing effects due to decreased plasma levels. Unfortunately, most of the studies did not include plasma level determinations. In 1986, Jordan et al. [163] showed that the diminishing response to NTG develops within 18 h, despite persistently high and adequate plasma levels. This study elegantly demonstrated for the first time that constant plasma levels, as determined, rapidly induce tolerance.

There may be many reasons why nitrate tolerance was not observed in some of the above-mentioned studies with frequent dosing and, therefore, apparently constant plasma levels. First, the study design has to be taken into consideration, since open studies may be sensitive to an inherent bias. Randomized, double-blind studies should be preferred. Whether a placebo control is mandatory or whether it increases the risk of cardiac events remains a controversial and ethical discussion [124, 176].

In some studies with t.i.d. regimens, the single dose and its duration of action might have been too small to generate constant plasma levels with oral NTG [71, 364], oral ISDN or oral IS-5-MN in non-sustained-release form [157].

'Physiologic noncompliance' may be another factor, since tolerance develops rapidly and may be reversed within several hours [61, 67]. Thus, the actual ingestion of each individual tablet is pivotal. Unreliable or irregular ingestions may have blurred the problem of nitrate tolerance in many patients. Unfortunately, in most of the studies documentation of patients' compliance was neglected [10, 68, 71, 126]. Counting the tablets returned or documenting the intake based on patients' diaries is not reliable. The assessment of plasma levels is not feasible in long-term studies on a day-by-day basis. A practical method to check compliance on a daily base is to determine the fluorescence in the patients' urine, attributable to the riboflavin added [319]. One should keep in mind that compliance not only refers to the number of doses swallowed but also to the exact timing of the prescribed dosages. Obviously, it is not easy to ingest the tablets exactly every 8 h for several weeks. Thus, patients may have created a nitrate-poor interval on their own by modifying the study protocol. Accordingly, a t.i.d. regimen with 30 mg dosages of ISDN ingesting the last tablet at 5 p.m. did not generate tolerance [252].

Furthermore, some data suggest that tolerance is not a universal phenomenon, considering that the time course of tolerance development may vary up to 1 week [182, 231, 299]. In some patients tolerance may develop only at the arterial side with maintained venous response [167, 192]. As we have seen, individual analysis reveals that there might be a subset of compliant patients not presenting with full tolerance [319].

Mechanisms of Tolerance Development

For the explanation of nitrate tolerance, reduced absorption, enhanced metabolism or faster elimination of the administered drug or its active metabolites has been ruled out [254, 342].

Nitrate tolerance is a multifactorial phenomenon. Depletion of sulfhydryl (SH) groups, which are essential for the biotransformation of nitrates to nitric oxide (NO), seems to be important. In addition, neurohumoral counterregulatory mechanisms including plasma volume expansion play an increasingly pivotal role in the development of tolerance (table 1).

The SH Depletion Hypothesis and the Role of SH Donators. Theories relating nitrate-induced vasodilatation to prostaglandin synthesis have not been confirmed [100, 194, 226, 249, 347, 362]. It is now well established that relaxation of vascular smooth muscle following the administration of nitrates is accomplished by cGMP. The enzyme responsible for the synthesis of cGMP is soluble guanylate cyclase which is activated by NO [4, 36, 172, 186]. Nitrate tolerance can be traced back to a reduced activation of guanylate cyclase, since the vessels remain responsive to cGMP [146, 186, 233].

Table 1. Possible mechanisms of nitrate tolerance and investigated solutions

Mechanism	Investigated solutions
SH depletion	SH donors (N-acetylcysteine, captopril, methionine)
Counterregulation	
Epinephrine increase	Beta blockers?
Renin-angiotensin-aldosterone increase	ACE inhibitors (captopril, enalapril)
Plasma volume expansion	Fluid restriction, diuretics

To stimulate guanylate cyclase, nitrates require SH groups [232]. As cysteine represents the main SH donor [152, 363], the development of nitrate tolerance may be due to a rapid exhaustion of the 'cysteine pool', i.e. deficiency of reduced SH groups in the vascular smooth muscle with a subsequently reduced production of S-nitrosothiols [153, 186, 346]. For clinical purposes, N-acetylcysteine may be useful. It is converted in vivo to cysteine and therefore is a valid SH donator. The SH depletion hypothesis and the reversal of tolerance by the administration of SH donors is, however, still characterized by conflicting results.

NTG efficacy has been shown to be potentiated in conjunction with N-acetylcysteine in patients with coronary artery disease [149, 150, 211, 363]. Boesgaard et al. [34] recently prevented tolerance after 24 h of infusion of 5 mg ISDN/h using high doses of N-acetylcysteine (2 g i.v. over 15 min followed by 5 mg/kg/h) in patients with coronary artery disease. In patients with severe congestive heart failure, Packer et al. [245] observed the reversibility of induced NTG tolerance (6.4 μg/kg/min over 48 h) 30 min after adding high-dose (200 mg/kg) oral N-acetylcysteine.

Captopril is regarded as another potential SH donator. Although 25 mg captopril t.i.d. provides less SH groups than N-acetylcysteine tested at 200 mg/kg, a substantial enhancement of the efficacy of ISDN was reported after captopril in patients with coronary artery disease [215, 352]. Methionine has also been suggested to be administered as SH donator: 5 mg methionine enhanced the venodilative effect of NTG acutely and restored it in the setting of nitrate tolerance [195, 196].

On the other hand, Parker et al. [253] were not able to reverse tolerance to oral ISDN 15 min after the infusion of 100 mg/kg N-acetylcysteine in patients with coronary artery disease and exercise-induced ischemia. These findings were consistent with previous experimental data [134]. Later on, more disapproving data were published in this context [88, 145]. Perhaps the administration of SH groups may more likely prevent rather than abolish already existing tolerance, although more data are needed to clarify this issue. Anyway, for a wi-

despread clinical use of N-acetylcysteine, lower oral doses would be necessary to avoid considerable gastrointestinal side effects [220].

Bertel et al. [26] indicated that the N-acetylcysteine-related enhanced responsiveness during NTG tolerance is not a reversal of tolerance but rather a nonspecific effect. This supports the hypothesis that NTG may react with N-acetylcysteine extracellularly to form a guanylate-cyclase-stimulating intermediate compound independent of tolerance (S-nitrosocysteine?) [26, 116, 227]. In contrast to NTG, ISDN does not seem to be involved in such an unspecific mechanism [116]. Furthermore, the possible role of other mechanisms such as nitrate-induced direct inactivation of the guanylate cyclase with the subsequent need of its de novo biosynthesis is still undetermined.

The Counterregulation Hypothesis – The Role of Neurohumoral Activation and Plasma Volume Expansion. The concentrations used to produce in vitro vascular tolerance vastly exceeded the typical plasma concentrations of nitrates observed in patients [18]. Furthermore, it became evident that, despite the continuous availability of SH donors, the initial improvement gradually decreased [34]. Therefore, other hypotheses for the mechanism of nitrate tolerance have to be considered, suggesting the activation of compensatory processes involving the sympathetic nervous system and/or the renin-angiotensin-aldosterone counterregulatory mechanisms.

For a long time it has been established that drug-induced vasodilatation stimulates catecholamines and renin [59]. This activation of neurohumoral systems results in vasoconstriction and sodium retention [59, 219, 238, 247]. Whereas animal experiments have failed to demonstrate a further rise in plasma renin levels during long-term application of ISDN [183], many clinical studies observed increased plasma renin activity and plasma volume expansion during the development of nitrate tolerance [97, 199, 224, 245]. NTG, in particular, led to an increase in adrenergic activity (measured as an increase in plasma adrenaline and plasma noradrenaline) as well as to a stimulation of the renin-angiotensin aldosterone system (measured as an increase in plasma renin activity and plasma aldosterone) [224]. Vice versa, the circumvention of nitrate tolerance prevented renin stimulation [244].

The suppression of the nitrate-induced stimulation of the renin-angiotensin-aldosterone system was investigated with different angiotensin-converting enzyme (ACE) inhibitors. The role of captopril as an SH donor (see above) has to be questioned, since even the non-SH-containing enalapril was similarly effective [171]. Therefore, the possible usefulness of ACE inhibitors as an adjunct to nitrate therapy may rather be based on their suppression of counterregulation rather than on SH donation. However, the link between an increased plasma renin and nitrate tolerance has not been consistently shown [91, 171, 238].

The importance of volume expansion during nitrate therapy has been well documented [23, 87, 88, 196, 199, 245] and a considerable weight gain has been noted [171, 196, 245]. Therefore, in patients with severe congestive heart failure diuretics would be essential to potentiate NTG efficacy [353]. Pretreatment with enalapril or captopril prevented a weight increase in healthy volunteers but not in patients with congestive heart failure [66, 171].

Perhaps the development of tolerance occurring within 24 h results from different mechanisms than tolerance developing within weeks.

Solutions to Avoid Tolerance Development

Molsidomine Is Not the Solution

Molsidomine is considered to be a 'nitrate-like' drug. It is the N-ethoxycarbonyl-3-morpholinosydnonimine (SIN-10). Molsidomine itself has no effects on vessels or platelets. It is metabolized in the liver to 3-morpholinosydnonimine (SIN-1) and then readily converted to N-nitroso-N-morpholinoaminoacetonitrile (SIN-1A). SIN-1A carries NO, releasing nitric acid, and is mainly responsible for molsidomine's pharmacological effects. Like nitrates, molsidomine works by stimulation of guanylate cyclase [14].

As compared to nitrates, molsidomine influences hemodynamics and coronary arteries practically identically in experimental settings, in patients with coronary artery disease and in acute myocardial infarction with and without congestive heart failure [14, 70, 84, 270, 293, 308]. Also antiplatelet properties are documented at clinical doses [85].

In contrast to nitrates, molsidomine supposedly activates guanylate cyclase directly, i.e. independently of the presence of SH donors [14, 153, 187, 377]. Therefore, the hypothesis was that if SH group exhaustion is the prevailing mechanism of nitrate tolerance, molsidomine should not induce tolerance.

Unfortunately, many studies with molsidomine in patients with coronary artery disease cannot be interpreted regarding tolerance development, since the administration of 3 times 2mg/day or 3 times 3 mg/day for 8 weeks as well as 6 times 2 mg/day over 4 weeks has not been tested acutely [29, 205]. The only conclusion one can draw from these studies is that there was at least no total loss of action. There might have been, however, an undetected attenuation. In patients with congestive heart failure an unattenuated effect on the resting pulmonary artery pressure after 1 week of 4 times 4 mg/day has been reported [32].

During exercise, however, diminishing effects after 4 weeks of treatment with 3 times 2 mg/day have been demonstrated [240]. These findings are consistent with others, reporting tolerance development to venous vessels following 3

times 2 mg/day [166]. Beyerle et al. [27] have tested 8 mg molsidomine in sustained-release form, given 3 times daily for 4 weeks. Initially, the reduction of ST segment depression at 5 h was weaker as compared to 1 h after the ingestion (51 vs. 88%). After 4 weeks of treatment, the effect at 1 h was unchanged (81%), but the effect at 5 h was less pronounced (34%). This documented decrease of duration of action does preclude tolerance development and should be confirmed in a larger series of patients. One should not forget that a decrease of duration of action was one of the starting points in the discussion about tolerance to ISDN [340]. A clear evidence for total tolerance to molsidomine 8 mg t.i.d has been provided in another randomized, double-blind cross-over study: after 4 days of treatment, the initially positive effects were no longer demonstrable [355]. The authors found 'no marked differences between ISDN and molsidomine'. Furthermore, in the state of nitrate tolerance, the effects of molsidomine are also reduced [356].

These results show that tolerance does also occur with molsidomine and indicate that the role of counterregulatory mechanisms in the development of tolerance has probably been underestimated.

Finally, these days a modified regimen is prescribed by many physicians: ISDN in the morning and molsidomine in the evening. This regimen, however, has never been tested in a controlled trial and therefore must be regarded as an undocumented therapeutic strategy.

Solutions to Nitrate Therapy

Today it is generally accepted that constant plasma nitrate levels induce rapid development of tolerance in the majority of patients. Increasing the dose did not overcome the loss of effect of oral or transdermal application [331, 340]. Therefore, dosing regimens creating constant plasma levels, like ingestions of ISDN or IS-5-MN every 8 h (or more frequently) or the continuous attachment of NTG patches, have to be avoided.

In 1905 Stewart [334] recommended to 'temporarily discontinue the drug for two or more days, at intervals of two or three weeks', thus introducing 'interval therapy' for nitrates. There is no doubt that intermittent therapy is the way out of nitrate tolerance.

Recently, the fear of rebound phenomena was brought up in the context of intermittent nitrate therapy, since an unexpectedly higher treadmill walking time on placebo as compared to either active treatment group just before patch application was observed ('zero-hour effect') [81]. Historically, rebound phenomena are known from workers in the munitions industry, where serious withdrawal phenomena have been reported [180, 190]. In contrast to these extreme, nonclinical conditions, no rebound was apparent in our and others' studies with oral and transdermal applications [78, 92, 135, 238, 239, 246, 250, 265, 287, 291, 314].

Apparently, the degree of fluctuation in plasma levels is more important for the circumvention of tolerance than absolute plasma levels or the sum of the daily administered dose [339]. This is emphasized by the lack of relationship between the total daily dosage and the development of tolerance: on one hand, a relatively low total daily dosage of 60 mg ISDN (20 mg every 8 h) led to a marked reduction in the anti-ischemic effects [21, 257], whereas a total daily dosage of 160 mg ISDN (80 mg, 8 a.m. and 2 p.m.) showed persistent anti-ischemic potency [235, 240]. Therefore, it is not justified to relate 'high-dosage' automatically to 'tolerance'.

Solutions to Oral Therapy

Once-Daily Intermittent Intake of High Dosages in Sustained-Release Form. Since no studies prior to 1982 assessed nitrates with less than t.i.d. dosing, we investigated the hemodynamic and anti-ischemic effects of high-dose ISDN in sustained-release form according to a once-daily or various b.i.d. regimens [319, 321]. The goal of our studies was to determine whether a new regimen might prevent the development of tolerance. In order to achieve the longest possible duration of action of a single tablet, we administered the highest single dosage of ISDN in sustained-release form available at that time (80 mg). Patients were selected according to our standard objective criteria for anti-ischemic studies and only patients with a high likelihood of excellent compliance were enrolled. In addition, we assessed the ingestion of each individual tablet by adding riboflavin to the study medication and checking two urine specimens per day. The determined compliance was 95%, meaning that 95% of each tablet prescribed was actually taken.

Even with every 12 h dosing, development of tolerance occurred. The through plasma IS-5-MN levels were 386 ng/ml, those of IS-2-MN, 37 ng/ml, and those of ISDN, 7 ng/ml [321]. The high plasma levels of ISDN after 12 h may be explained by an inhibited metabolism of ISDN caused by its metabolites [115]. Similar results were obtained for IS-5-MN: like in our studies, the every 12 h ingestion of high dosages in sustained-release form induced tolerance [338].

In contrast, our data for intermittent therapy with once-daily ingestion of 80 mg ISDN in slow release proved the prevention of nitrate tolerance [316, 319, 321]. The peak plasma levels were 485 ng/ml for IS-5-MN, 96 ng/ml for IS-2-MN and 25 ng/ml for ISDN [321]. The trough levels for ISDN and IS-2-MN were essentially zero and for IS-5-MN below 100 ng/ml [33, 321]. During the subsequent years, several other groups have corroborated our concept of once-daily high-dosage ISDN in sustained-release form, showing the prevention of tolerance by providing adequate fluctuations of plasma levels (table 2) [30, 86, 139, 237, 370].

Similar to ISDN, IS-5-MN taken once daily in 40 or 50 mg dosages in sustained-release form prevented tolerance development with trough levels of

Table 2. Prevention of nitrate tolerance with once-daily oral dosages of ISDN or IS-5-MN in sustained-release forms in patients with coronary artery disease (CAD) or congestive heart failure (CHF)

Dosage	Disease	Reference
ISDN		
1 X 80 mg/day	CAD	319
1 X 120 mg/day	CAD	30, 86, 142, 237, 316, 359, 370
1 X 120 mg/day	CHF	139, 366
IS-5-MN		
1 X 40 mg/day	CAD	296
1 X 50 mg/day	CAD	6, 159, 175, 184, 287
1 X 60 mg/day	CAD	221, 235, 296, 338, 365
1 X 100 mg/day	CAD	21, 175, 287, 309, 359

90 ± 12 ng/ml [6, 175, 184, 287, 296]. The once-daily ingestion of 60 mg [221, 235, 296, 338, 365] and even 100 mg of IS-5-MN in sustained-release form [21, 175, 287, 309] did not reveal tolerance development. Conversely, Thadani et al. [341] reported tolerance development for 50 and 100 mg IS-5-MN in sustained-release form after once-daily intake for 1 week (measured 4 h after ingestion) at comparable trough levels [341]. There is currently no reasonable explanation for these findings, unless the development of unstable angina and remarkable shifts in the control group are taken into consideration.

Asymmetric b.i.d. or t.i.d. Dosing. For countries where these high doses in sustained-release form are not (yet) available, an alternative regimen is recommended: 'eccentric or asymmetric' dosing (table 3). As we have demonstrated, the ingestion of 80-mg tablets of ISDN in sustained-release form at 8 a.m. and 2 p.m. results in a good compromise between circumvention of tolerance and maximal possible duration of anti-ischemic protection [321]. Accordingly, asymmetric b.i.d. or t.i.d. dosing with a 12 h washout interval for ISDN has been shown to be effective: 20 mg ISDN in non-sustained-release form administered at 8 a.m. and 1 p.m. prevented tolerance development [286]. 30 mg ISDN in non-sustained-release form ingested b.i.d. at 7 a.m. and noon as well as t.i.d. at 7 a.m., noon and 5 p.m. did not lead to tolerance [252]. Accordingly, similar findings were observed in patients with congestive heart failure [93]. Buccal NTG (3 mg t.i.d. with a nitrate free period of 10 h) also maintained its effects [257].

Symmetric Every 12 H Dosing. 20 mg doses of IS-5-MN in non-sustained-release form taken every 12 h over 4 weeks did not lead to tolerance development, at least tested 1 h after the ingestion [277]. In another study, the same every 12 h regimen was followed by a considerable decrease in the duration of

Table 3. Prevention of nitrate tolerance with asymmetric b.i.d or t.i.d. oral dosages of ISDN or IS-5-MN in patients with coronary artery disease (CAD) or congestive heart failure (CHF)

Total daily dosage	Single dosage	Release form	Intake regimen	Disease	Reference
Asymmetric b.i.d.					
ISDN					
40 mg/day	20 mg	nonsustained	8 a.m. and 1 p.m.	CAD	286
60 mg/day	30 mg	nonsustained	7 a.m. and noon	CAD	252
160 mg/day	80 mg	sustained	8 a.m. and 2 p.m.	CAD	321
IS-5-MN					
40 mg/day	20 mg	nonsustained	8 a.m. and 2 p.m.	CAD	339
Asymmetric t.i.d.					
ISDN					
90 mg/day	30 mg	nonsustained	7 a.m. noon and 5 p.m.	CAD	252
180 mg/day	60 mg	nonsustained	0, 6 and 12 h	CHF	93

action [343]. 40 mg IS-5-MN every 12 h caused 'partial tolerance' [182]. These data are consistent with our previous findings, testing the same dosage regimen with ISDN in sustained-release form [319, 321]. Therefore, the every 12 h intake of 20 or 40 mg IS-5-MN cannot be recommended.

Solutions to Intravenous Therapy

In patients with exercise-induced ischemia tolerance has been prevented by discontinuing the NTG infusion (1.5 mg/h) for 12 h [234]. An infusion-free interval of 12 h was also necessary to prevent tolerance to NTG (6.4 μg/kg/min) in patients with congestive heart failure, whereas an 8-hour interval was not enough [244].

Solutions to Transdermal Therapy

The Continuous-Release Patch. For transdermal delivery systems, various 'patch-free intervals' have been investigated. The following strategies were *not* successful in preventing tolerance development: a 2-hour patch-free interval using 10 mg/day in patients with congestive heart failure [314]; a 4-hour patch-free interval using 10 mg/day for 1 week in patients with coronary artery disease [135, 358] and a 6-hour patch-free interval, using the same dose in similar patients [357]. Even a 10-hour patch-free interval was not helpful with 15 mg/day [275], and a 12-hour patch-free interval did not prevent tolerance development using dosages between 30 and 60 mg/day [229]. Recently, even a patch-free interval of 6 h could not completely avoid some attenuation [155].

In contrast, the removal of a 10 mg patch for 12 h was effective in patients

Table 4. Prevention of nitrate tolerance with continuous-release patches applying different patch-free intervals in patients with coronary artery disease (CAD) or congestive heart failure (CHF)

Patch-free interval	Dosage mg/day	Disease	Reference
16 h	10	CAD	155
12 h	5	CAD	81
	10	CAD	81, 60, 155, 274
	15	CAD	81
	20	CAD	81, 99
10 h	10	CAD	78, 135, 181, 291, 357
	20	CAD	291
8 h	10	CAD	203, 243
	10	CHF	314

with coronary artery disease when tested after 3 days [274] and after 1 week [60] (table 4). In healthy volunteers a patch-free interval of 12 h avoided the weight gain observed during continuous attachment [258]. A 10-hour patch-free interval was effective in patients with coronary artery disease using 10 mg/day [135, 357] or a mean of 16 mg/day [291]. An 8-hour patch-free interval guaranteed full response to 10 mg/day after 1 week in patients with coronary artery disease [203] and after 1 month in patients with congestive heart failure [314].

The minimal necessary patch-free interval seems to be dose-dependent and has to be defined for each dosage used. In the meantime, for most patches the recommendation of a 12-hour patch-free interval should prevent tolerance in most patients.

The Biphasic-Release Patch. Intermittent removal of continuous-release patches carries a major drawback: patients and sometimes even physicians are reluctant to follow this recommendation and just leave the patches on overnight. To facilitate the rational use of patches, a new type of matrix system has been developed [369]. This 16-cm^2 patch containing 10 mg of NTG releases approximately 5 mg over the first 12 h and 2.5 mg over the second half of the 24 h [369]. A similar patch containing 20 mg NTG releases 15 mg/24 h.

Table 5 lists the results published so far. All studies have been performed in patients with documented coronary artery disease and exercise-induced ischemia. For the lower dose with a predicted release of 7.5 mg, results ranged from no tolerance [25] over a 'less marked attenuation' [276] to a decreased duration of action [185]. Applying the higher dose with a predicted release of 15 mg, only one study showed no tolerance [251], whereas others unanimously observed considerable tolerance [236, 295, 324], consistent with findings in healthy volunteers [360]. The 30-mg/day dose also rapidly induced tolerance [125].

Table 5. Biphasic-release patch in patients with coronary artery disease: induction and prevention of nitrate tolerance in relation to the dosage (predicted release per day) and study protocol

Number of patients	Duration of therapy	Test parameters	Determined at	Tolerance	Reference
7.5 mg/day					
28	1 week	Ex-PAP	2 and 24 h	no	25
10	3 days	Ex-ST	2.5, 12 and 24 h	(yes)	276
40	1 week	Ex-ST	2 and 10 h	(yes)	185
15 mg/day					
16	1 week	TWT, time to AP	4, 8 and 12 h	no	251
15	1 week	Ex-PAP, Ex-ST	2 h	yes	236
12	1 week	Ex-ST	1, 4 and 8 h	yes	295
12	2 days	Ex-ST	2 and 10 h	yes	324
30 mg/day					
18	2 days	Ex-ST, Holter-ST	3 and 9 h	yes	125
15 mg/day 90 min off					
12	1 week	TWT, Ex-ST	2 and 10 h	no	318

The tested parameters were exercise-induced (Ex) changes of pulmonary arterial pressure (PAP), treadmill walking time (TWT), time to angina pectoris (AP), exercise-induced ST segment depression (Ex-ST) and Holter-detected ST segment changes. The times at which the test parameters were determined are also listed.

Thus, the continuous attachment of the biphasic-release patch has not convincingly shown a clear advantage over the discontinuous attachment of the continuous release patches at any given dose.

Since the concept of leaving the patch attached overnight is still attractive to patients and physicians, we choose a new approach, removing the biphasic-release patch for only 90 min in the morning [318]. In this placebo-controlled, randomized, double-blind cross-over study, we found an unattenuated effect on treadmill walking time and ST segment depression 2 and 10 h after the attachment, before and after 1 week of treatment without an increase in plasma renin [318]. This interesting concept should be confirmed in a larger series of patients.

Rationale for Using Nitrates

There are many reasons why nitrates should still be used as the fundamental drug in patients with ischemic heart disease (table 6).

Table 6. Reasons why nitrates should still be used today

Nitrates	
1	Are highly effective in angina pectoris
2	Are highly effective in silent myocardial ischemia
3	Show a high responder rate
4	Improve hemodynamics in congestive heart failure
5	Physiologically substitute the vasoactive role of EDRF/NO
6	Show in vivo antiplatelet effects
7	Have only minimal side effects
8	Are well tolerated and may improve prognosis in acute myocardial infarction
9	Are useful in percutaneous transluminal angioplasty
10	Are inexpensive

Nitrates Are Highly Effective in Angina Pectoris

Nitrates are well known to be highly effective in terminating angina pectoris and in the prophylaxis of ischemic chest pain. Nitrates are as effective as beta and calcium channel blockers [50, 86, 111]. In unstable angina and in variant angina with proven coronary spasm, the usefulness of nitrates is unquestioned [209]. During these conditions, nitrates are as effective as nifedipine [147]. Recently, the alleviation of cocaine-induced coronary vasoconstriction by NTG has been reported [39]. Angina, still a major problem with a high prevalence [46], is effectively treated with oral ISDN or IS-5-MN in corresponding equivalent doses [271, 304].

Nitrates Are Highly Effective in Silent Myocardial Ischemia

Although the pathophysiologic mechanisms responsible for the absence of pain during myocardial ischemia are not totally revealed (endorphins?, increased pain threshold?), it is obvious that transient episodes of considerable, asymptomatic ischemia occur in many patients with coronary artery disease [57, 320]. Reports documenting the usefulness of nitrates to abolish silent ischemic episodes include sublingual, oral, intravenous and transdermal applications. As early as in 1975, Winsor and Berger [364] published the beneficial effects of 2.6 mg oral NTG t.i.d. on Holter-detected episodes of ST segment depression, without yet calling it silent ischemia. In 1977, Schang and Pepine [292] found that the hourly administration of 0.4 mg sublingual NTG remarkably reduced the number of ischemic episodes. In patients with vasospastic angina, the infusion of ISDN significantly reduced the number of painless ischemic episodes [83]. The reversibility of wall motion abnormalities was interpreted as a re-

duction of asymptomatic myocardial ischemia [259]. IS-5-MN 20 mg t.i.d. or 50 mg once daily in sustained-release form has also been reported to be effective in silent ischemia [9]. NTG patches were also remarkably effective in the treatment of silent ischemia [125, 229, 279, 298, 315].

As pointed out, nitrates cannot protect for 24 h. Fortunately, in most patients, angina and silent ischemia predominantly occur during the day [79, 230, 361]. A recently published study [181] showed that intermittent transdermal nitrate therapy with a patch-free interval of 10 h is superior to continuous attachment for treatment of silent ischemia and the nightly nitrate-free interval did not lead to increased ischemia in patients with concomitant anti-ischemic medication. In order to optimize the anti-ischemic treatment, beta-blocking or calcium-channel-blocking agents should be added to nitrates whenever possible.

Although there is much evidence that silent ischemia inadversely affects prognosis [130, 283, 349], the vice versa has not yet been proven. It is still unknown whether the pharmacologically induced reduction of silent ischemic episodes improves prognosis. Therefore, although the treatment of silent ischemia makes sense [57, 120], it is not an established form of therapy and therefore not mandatory. Prospectively designed, double-blind trials with strict criteria will substantiate the prognostic usefulness of treatment of asymptomatic episodes.

Interestingly, the anti-ischemic properties of nitrates include antiarrhythmic effects, as recently demonstrated [206] These findings are consistent with previous reports on the antiarrhythmic effects of NTG during myocardial ischemia and reperfusion [335].

Only Few Nonresponders to Nitrates Exist

Diminished venous distensibility and attenuated response to NTG have been observed predominantly in older people [119]. There is some evidence that only a few patients with chronic, stable, exercise-dependent myocardial ischemia poorly respond to low dose ISDN [170], high-dose ISDN [323] and 50 mg of IS-5-MN [138]. As we have seen, coronary patients with insufficient nitrate response are characterized by a less pronounced decrease of LVEDV during exercise. Patients with congestive heart failure may poorly respond to even high dose ISDN [93]. A poor reaction ('resistance') to intravenous NTG in patients with congestive heart failure may be considerably improved by diuretics [353].

Non- or malresponders to NTG patches seem to be more frequent as compared to oral therapy [268]. 10 out of 18 patients were nonresponding to a 20-mg patch [224]. The authors suggested that nonresponse is based on a more pronounced increase in catecholamines or plasma renin. Nevertheless, before

classifying a patient as nonresponder, higher doses should be applied [175, 299].

The reasons why some patients, even despite high dosages, do not respond to nitrates are still unclear. It seems to happen more frequently in patients with severe congestive heart failure than in patients with coronary artery disease [170, 188]. The degree of antianginal response has been related to the acute reaction of the adrenergic and renin-aldosterone system with higher levels of plasma catecholamines, plasma renin activity and plasma aldosterone in nonresponders [224].

Overall, with adequate high dosing of oral nitrates in patients with coronary artery disease, the antianginal response rate in clinical practice is very high.

Nitrates Improve Hemodynamics in Congestive Heart Failure

The first-line goal in the treatment of congestive heart failure is to reduce elevated filling pressures and facilitate ventricular emptying. Venodilatation is an important mechanism in improving the hemodynamics in patients with congestive heart failure [348]. 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 was attributed to passive expulsion of blood, secondary to reduced distending pressure [281, 325].

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 NTG, ISDN and IS-5-MN [51, 53, 80, 107, 108, 131, 139, 143, 192, 218, 245, 297]. Therefore, nitrates are the ideal adjunct medication for most patients with congestive heart failure with and without ischemic heart disease.

Nitrates Compensate for Unopposed Vasoconstriction Due to Endothelial Dysfunction in Atherosclerotic Coronary Arteries

Intact endothelial cells produce a compound which relaxes vascular smooth muscle by releasing cGMP [106]. This previously unidentified substance was therefore called endothelium-derived relaxing factor (EDRF). In 1987, Palmer et al. [248] revealed that EDRF is indistinguishable from NO with its short half-life of 6–50 s. Like endothelial cells, nitrates too release NO.

The EDRF/NO-mediated vasodilatation is provoked by many vasoactive substances such as acetylcholine, histamine and 5-hydroxytryptamine [109]. In addition, shear stress releases EDRF/NO, explaining the marked vasodilatation that follows increased blood flow [133]. On the other hand, coronary arteries

with damaged or absent endothelium show an unopposed ('paradoxical') vasoconstriction to the above-mentioned otherwise potent vasodilators [117, 133]. This inappropriate vasoconstrictor response has been observed in patients with atherosclerotic endothelial dysfunction [202].

In contrast to EDRF/NO-mediated vasodilatation, the nitrate-induced smooth muscle cell relaxation is independent of endothelial integrity [15]. Therefore, it is intriguing to consider nitrates as a physiologic substitute for absent EDRF/NO in patients with coronary artery disease. Endothelial dysfunction is characterized by a marked increase in sensitivity to the constrictor effects of catecholamines which can be reversed by NTG [354]. In patients with early atherosclerosis, even with smooth-looking coronary arteries, increased sensitivity to acetylcholine-induced constriction, still retaining the ability to dilate to NTG was demonstrated [202, 212]. Nitrates may also be of particular importance to prevent unopposed coronary constriction during mental stress [372].

Nitrates Show in vivo Antiplatelet Effects

There is increasing interest in the concept that a part of the antianginal effects of nitrates may be related to their antiplatelet effects [104]. Different nitrates may show different antiplatelet effects [73, 74, 328]. Several studies have reported remarkable antiplatelet effects for NTG and ISDN [73, 82, 307]. The inhibition of platelet thrombus formation by NTG occurs at clinically relevant doses [103]. The antiplatelet efficacy of therapeutic dosages has been found to be greater in vivo than in vitro [73, 327]. One possible explanation is a synergism with prostacyclin at the sites of local prostacyclin production [73]. IS-5-MN has no antiplatelet effects in vitro [85]. Possibly IS-5-MN is transformed by cells other than platelets explaining the in vivo antiplatelet effects [85]. In vivo protocols with IS-5-MN infusions have demonstrated elegantly the inhibition of platelet function [74].

As compared to acetylsalicylic acid, the inhibition of platelet function seems to be smaller, but the different underlying mechanisms suggest the possibility of additive effects [59]. Other explanations for the enhanced in vivo antiplatelet activity are related to the availability of reduced thiols, to direct antiplatelet effects of the mononitrate metabolites or to the interaction with endothelium cells, postulating 'endothelial-cell-dependent antiplatelet nitrate properties' [24, 73]. This may in part be due to the antiplatelet effects of NO itself, elevating platelet cGMP [104]. Recently, it has been shown that EDRF/NO inhibits platelet adhesion to the matrix of cultured endothelial cells [77]. Thus, the intravascular release of EDRF/NO may have an important inhibitory effect on platelets passing close to the endothelium. EDRF/NO, therefore, contributes to the regulatory role of endothelial cells in platelet-vessel wall interaction [77].

There is evidence for a close link between platelets, vasoconstriction and nitrates [189]. The nitrate-induced antiplatelet effect is potentiated by N-acetylcysteine [327].

Thus, nitrates are the ideal substitute for EDRF/NO, not only regarding its role for smooth muscle cell relaxation but also for inhibiting platelet adhesion.

Other Effects

Headache is the most common adverse reaction and usually disappears within a few days (another form of nitrate tolerance) [110]. If headaches persist, noncompliance has to be taken into consideration. This was nicely shown indirectly by munition workers which learned to prevent 'monday-morning headache' by keeping a small pinch of powder in their hat bands to avoid the 'nitrate-free weekend' [180, 190]. Less commonly encountered adverse reactions, such as nausea, vertigo, bradycardia and hypotension, in general also disappear during chronic therapy. Only a few patients, even those fully compliant, continue to suffer from these symptoms.

The only contraindication to nitrates is arterial hypotension, although the ACC/AHA guidelines for early management of patients with acute myocardial infarction recommend to try sublingual NTG even if the systolic blood pressure is below 90 mm Hg in patients with ongoing ischemic pain [136]. In patients with acute infarction and marked bradycardia or tachycardia NTG should be avoided [136].

NO is also involved in the neurotransmission that leads to smooth muscle relaxation in the corpus cavernosum permitting penile erection [264]. Recently, transdermal NTG has been successfully applied to treat impotence [216].

Nitrates Are Useful in Acute Myocardial Infarction and May Prolong Life

In contrast to beta and calcium channel blockers, which are extensively investigated in large multicenter trials, nitrates have always been treated like orphans. This is predominantly due to the fact that nitrates are the oldest group of drugs and, therefore, have not been very well supported by pharmaceutical companies, usually paying for those large trials. Therefore, there are only limited data available on nitrates and prognosis.

Nitrates Alone

Intravenous sodium nitroprusside has been tested in 3 studies and intravenous NTG in 6 trials in over 2,000 patients [45, 101, 114, 164, 262, 374, 375]. The pooled data revealed a 12% mortality rate in the 1,009 treated patients

while the mortality among the 1,004 controls was 18%. This suggests a risk reduction of death for about one third of cases (95% confidence interval: – 18% to – 49%). Noticeably, the risk reduction for NTG seems to be higher than that for sodium nitroprusside (45 vs. 23%). The ACC/AHA guidelines for early management of patients with acute myocardial infarction recommend the use of NTG for patients presenting with ischemic pain [136]. Although the benefit of intravenous NTG is established when the acute myocardial infarction is complicated by congestive heart failure/pulmonary edema, data to recommend NTG infusion in all patients with uncomplicated infarction are considered to be inadequate, at the present time [136].

A retrospective analysis for a period of 11 months in patients with coronary artery disease revealed a mortality of 26% in those without nitrates and one of 10% in those taking nitrates, predominantly ISDN [266]. Altogether, at least 5 trials have been published regarding sublingual or oral treatment [11, 44, 242, 266, 374, 375]. There was an overall 10% short-term mortality among 560 patients randomized to treatment as compared to 12.3% among 521 controls, yielding a risk reduction of 21% (95% confidence interval: + 16 to – 46%).

Taken all intravenous and oral trials together, there were 192 (12.1%) deaths in the nitrate-treated patients as compared to 257 deaths (16.7%) among the controls. This 31% risk reduction (95% confidence interval: – 7 to – 47%) suggests that intravenous NTG and probably oral nitrates reduce mortality when given early to patients with moderate of large myocardial infarctions [375].

Nitrates in Combination

The prospective, randomized V-HeFT-I trial was the first to prove life prolongation by vasodilators [54]. Since, however, a combination of ISDN and hydralazine was used, the question of a prognostic effect of ISDN alone could not be answered. The mortality data for the combination of hydralazine and ISDN in the consecutive V-HeFT-II trial [55] were identical with those of V-HeFT-I, confirming this concept. Eventually prognosis may be enhanced if both V-HeFT-II regimens (hydralazine/ISDN plus enalapril) were used in combination [55]. In an animal model, Bauer and Fung [18] elegantly showed the beneficial interaction between hydralazine and ISDN, a possible explanation why nitrates could have been constantly effective in the V-HeFT trials, despite the fact that ISDN was administered in a dosage that (alone) was likely to produce nitrate tolerance.

Thus, in many studies a beneficial trend for the nitrate-related life prolongation could be observed. Two major prospective trials are currently on their way addressing this issue: GISSI-3 and ISIS-4. In GISSI-3, patients with suspected acute myocardial infarction are randomized 5 h from onset of symptoms to either oral lisinopril (5, then 10 mg/day) or intravenous lisinopril (5–

20 mg/min), then transdermal NTG or both. The 10-mg patch will be applied with a patch-free interval of 10 h [123]. Primary end points are the mortality rates after 6 weeks and 6 months for 10,000 patients in each group. In ISIS-4, patients with acute myocardial infarction are randomized to either oral captopril (6.25 up to 50 mg b.i.d) or 50 or 60 mg IS-5-MN controlled release or both [102]. A total of 40,000 patients will be assigned to the different treatment groups, including magnesium.

Nitrates Are Useful in Percutaneous Transluminal Coronary Angioplasty

The use of nitrates (intracoronary, intravenous or buccal) is highly recommended to reduce myocardial ischemia during percutaneous transluminal angioplasty [95, 161] and to preclude complications either by preventing spasm or by inhibiting platelet aggregation [76, 189]. NTG significantly improves lumen diameter at the site of previous stenosis and prevents spasm after excimer laser atherectomy [19]. On the other hand, intracoronary NTG may significantly decrease the subendocardial-to-subepicardial flow ratio, leading to a possible deleterious effect and failure to relief angina [129, 177].

Anticoagulation with heparin may be less effective with NTG [137, 261]. An NTG-induced antithrombin-III abnormality possibly directly impairs heparin [22]. In contrast, a recently published randomized, double-blind, cross-over trial could not demonstrate an interaction between NTG and heparin, in vitro or in vivo [305]. Another possible interaction has been described for NTG and tissue-type plasminogen activator [213]. Further studies have to be performed to clarify the clinical importance of these interactions.

Using Nitrates Is Economically Wise

As compared to beta blockers or calcium channel antagonists, nitrates are relatively inexpensive. It is interesting to note that ISDN in congestive heart failure significantly reduced the number of required hospitalizations [90].

Rationale for Using a High Dose, Slow-Release, Once-Daily Regimen

As we have first suggested in 1983 [319], intermittent therapy with once-daily high-dose ISDN in sustained-release form prevents the development of tolerance in conjunction with optimal anti-ischemic protection for the day. No other concept in nitrate therapy has been corroborated so unanimously by so many different groups (table 2).

Table 7. Duration of action of a single capsule of 120 mg ISDN in sustained release form according to a randomized, double-blind and placebo-controlled protocol.

	Before ingestion	Time after ingestion		
		2 h	6 h	12 h
120 mg ISDN	2.3±0.8	0.7±0.5*	1.0±0.8*	1.9±0.8*
Placebo	2.5±1.0	2.1±0.9	2.3±0.9	2.5±0.9

The figures represent the exercise-induced ST segment depression at identical work loads before as well as 2, 6 and 12 h after the ingestion. Statistical significance (* $p < 0.05$) refers to the corresponding placebo values. This once-daily regimen warrants a signifcant anti-ischemic protection during the day [data from ref. 322].

Higher Doses Optimize the Duration of Action of a Single Dose

The goal of nitrate therapy is not only to prevent tolerance but also to protect the patient for as many hours as possible with as maximal as possible anti-ischemic effects.

To characterize the duration of action of a single dose, it is not only important to investigate the total time of statistically significant changes, but also to define the duration of the *maximal* effects obtained [350, 368]. Thus, although single dosages of 15–30 mg non-sustained-release ISDN showed statistically significant anti-ischemic effects for 8 h, the maximal effects were observed for only 2–3 h [69, 207, 257, 340]. A single dose of 40 mg ISDN in non-sustained-release form demonstrated considerably less anti-ischemic effects 6 h after the ingestion as compared to 1 h [272]. Similar results have been obtained for IS-5-MN [42, 65, 96, 175, 184, 271, 277, 310–312].

According to the evidence that sustained-release formulations prolong the duration of action of a single dose of ISDN [28, 41, 174, 191, 317], a capsule of 120 mg ISDN was developed. As we have demonstrated, this 120 mg capsule with approximately 6-fold fluctuations of plasma IS-5-MN levels is able to maintain significant anti-ischemic effects up to 12 h, with its effects at 6 h identical to those after 2 h (table 7) [322]. This advantage cannot even be matched by ISDN t. i. d. with no more than 6 h of antianginal benefit [13]. 60 mg IS-5-MN had no effects 12 h after the ingestion [365]. NTG patches showed no effects 12 h after the first attachment [251].

Using molsidomine as a possible alternative to nitrates offers no advantage. There is no reasonable once-daily regimen for molsidomine. Although 8 mg act longer than 2 mg, considerable interindividual differences exist [31]. The single ingestion of 8 mg molsidomine shows significant effects only up to 4 or 5

h [27, 285]. Thus, even 8 mg molsidomine in slow-release form has no significant anti-ischemic effects for 8 h and its effects at 5 h are remarkably less as compared to 120 mg ISDN in slow-release form [27, 285, 322].

Higher Doses Increase the Nitrate Response

Higher plasma levels increase the likelihood of achieving the maximal possible anti-ischemic effect. As we have seen, there is no predictable interindividual relationship between the plasma levels of ISDN, IS-2-MN or IS-5-MN and the degree of the anti-ischemic response [323]. Thus, low plasma levels may be associated with either an optimal or a little anti-ischemic effect. It is important to know that patients with initially poor nitrate response considerably improve with higher doses. This intraindividual dose-response relationship was thoroughly proven by Kenedi et al. [175] and Schneider et al. [299]. Both groups found that increasing oral dosages of ISDN (5, 20, 40 and 80 mg in non-sustained-release form), as well as increasing oral dosages of IS-5-MN (25, 50 and 100 mg in sustained-release form), remarkably enhanced the anti-ischemic effects in those patients who experienced a relatively limited response at lower plasma levels. Consequently, Akhras et al. [7] reported a progressive reduction of angina pectoris with increasing dosages of IS-5-MN. Thus, patients with suboptimal answer to lower doses should not be regarded as 'poorly responding' unless treated with higher doses [215].

Since the anti-ischemic response cannot be predicted from plasma levels, and repetitive stress tests to titrate up to the optimal dose are impractical, it makes sense to recommend intermittently *high* plasma levels to all patients requiring nitrate therapy. Fortunately, nitrates offer an extremely large therapeutic range.

The prolonged duration of action of once-daily, high-dosage sustained-release, the improved patient compliance, the improved quality of life with a single daily administration, and the increased likelihood of maximal anti-ischemic effects are striking reasons to use high single dosages of ISDN or IS-5-MN in sustained-release form. Furthermore, the antiplatelet effects are dose-dependent with higher doses showing more profound antiplatelet effects [169].

Conclusion

Nitrate tolerance is a multifactorial phenomenon and not all of its mechanisms are yet completely understood. Today it is finally accepted that nitrate tolerance to the antianginal/anti-ischemic effects is a clinical problem which can effectively be circumvented by dosage regimens providing intermittent peaks

and valleys of the plasma levels. A continuous anti-ischemic protection is, therefore, not possible. The goal of nitrate therapy, however, is not only to avoid tolerance but also to provide maximal possible anti-ischemic protection for as many hours during the day as possible. After we introduced in 1983 the use of high-dose ISDN in sustained-release form once daily, many investigators corroborated our concept. For the optimal compromise between avoidance of tolerance and a significant 12-hour protection, combined with the advantages of reducing the number of nonresponders and enhanced compliance, the once daily ingestion of a single, high dose in sustained-release form is the rational form of oral nitrate therapy.

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