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J. N. Cohn and R. Rittinghausen

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Clinical Relevance of Nitrate Tolerance

S. Silber

Nitrates have been used for more than 100 years to curtail angina pectoris attacks [15, 54]. There can be no doubt whatsoever about their positive effects in the treatment of acute episodes. However, during the past few years, there has been increasing controversy in discussions concerning the maintenance of nitrate effects when prescribed as long-term therapy. While some groups have shown evidence of either a weakening, or indeed a loss, of efficacy [6, 38, 69, 83], others have not been able to confirm these findings [5, 20, 21, 48, 57, 72, 73, 86]. In summarizing the studies published to date on this subject it is intended here, to present a balanced picture, in order to draw practical conclusions from the comparison of arguments for and against nitrate tolerance.

Definition of Tolerance

An (on the whole clinically orientated) definition of the development of tolerance embraces the weakening or loss of a medicament's effects in a "relatively short period of time" (as distinct from the progression of the presenting disease) despite the maintenance of a constant dosage of the medicament. The term "tachyphylaxis" should not be used in this context as, strictly speaking, it is primarily intended to describe a weakening of the medicament's effects within a few minutes [58]. Concepts such as "partial" or "total" tolerance tend to be confusing because they have different meanings for different authors: On the one hand, they may refer to the variable degree of tolerance developed as defined by a single test parameter, while, on the other hand, they may refer to the number of test parameters affected by the development of tolerance. In considering tolerance, a clear distinction must be drawn, with respect to reduced efficacy, between the degree of efficacy and the duration of efficacy. "True" tolerance refers to a reduction or loss of efficacy directly at the target organ, while "pseudo-"tolerance may develop on the grounds of counter-regulation with continuing effects on that target organ [1]. "Self-tolerance" denotes weakening of a medicament's effectiveness during it's long-term administration; "cross tolerance" leads to a reduction in a medicament's efficacy during long-term treatment with another medication of the same, or of a similar group of substances [1].

Tolerance with Reference to Induced Headaches

Any discussion on nitrate tolerance must make a clear distinction between the different effects. There is unanimous agreement on the development of tolerance with reference to nitrate-induced headaches. Reports agreeing on the partial or total remission of nitrate-induced headaches have become commonplace [18, 26, 35], whereby the reduction in frequency can be shown to take a hyperbolic form [26]. Moreover, those less commonly encountered nitrate-induced symptoms, such as vertigo and nausea, usually diminish during long-term therapy [35]. The above-mentioned undesirable effects show great variations in their individual degree of severity and, as a rule, are not strictly related to the dosage. In a few rare cases, the nitrate-induced headache persists, even under the administration of lower doses of nitrates. However, this must be seen in light of the "unreliable compliance" experienced with some patients.

Tolerance with Reference to the Effects on Blood Pressure and Heart Rate

Reports on the development of tolerance with reference to the *hypotensive effects* are almost as old as the application of nitrates themselves. As early as 1888, Stewart (cited in [81]) criticized nitroglycerin as being a "drug which is often of little service, because, despite intelligent employment, tolerance is too readily established."

It is a fact that the possibility of the development of tolerance with reference to reduction in blood pressure and increase in heart rate, at least at rest, is generally accepted [10, 16, 49]. Following sublingual administration of nitroglycerin, systolic blood pressure (SBP) dropped by a mean of 10 mmHg or by even up to 20% from the initial value [20, 71], while after 4 weeks of long-term therapy, the hypotensive effects had been reduced by an average of 14% (still related to the same initial value) [20, 71]. Following sublingual administration of 5 mg isosorbide dinitrate (ISDN) the SBP initially dropped from a mean of 125 mmHg to 105 mmHg; in contrast, after 3 days' administration of 4×15 mg per day there was no longer any evidence for the hypotensive effects of 5 mg of sublingual ISDN – a clear demonstration of self-tolerance [63]. The oral intake of ISDN in a non-sustained-release form initially, with a dosage of 15 mg, led to a maximum SBP reduction of 20% and, at a dosage of 120 mg, to a maximum reduction of 35% [83]. After only 1 week of therapy with 4×15 to 4×120 mg per day, a marked reduction of the hypotensive effects was shown: Starting with the same initial values, the reduction in SBP had attained a maximum of 15% and, in addition to being affected for a shorter period of time, was no longer related to the dosage [83].

The administration of ISDN in its sustained-release form can be expected to have a reduced initial hypotensive effect. Following the administration of 20 mg ISDN in a sustained-release form, the mean drop in SBP was 4%, after 40 mg it was 8%, and after 60 mg it reached 13% [6]. Eight weeks of 3×1 tablet per day led to a complete loss of efficacy with regard to the hypotensive effects at rest [6, 57]. Similar results were also true for isosorbide-5-mononitrate (IS-5-MN) [38].

In contrast, however, a reduction in the effects of nitrates on the blood pressure during exercise is not uniformly recognizable. While some groups observed a com-

plete loss of efficacy under exercise conditions as well [6, 57], other authors found the hypotensive effects of ISDN to be unchanged after long-term therapy [20, 39]. In acute tests during exercise, IS-5-MN achieved a reduction of approximately 5% in the SBP. However, this reduction could not be underpinned statistically [38].

In the case of nitrate-induced *increase in heart rate* at rest during long-term therapy, reductions in [71], and complete loss of efficacy [6, 57, 82, 83] have been described. In patients during long-term therapy, the further increased heart rate during exercise, initially induced by nitrate, may disappear [6, 39] and it is true that other studies have failed to show any further increase in the heart rate during exercise following nitrate administration in acute tests [39, 57].

Cross tolerance exists between nitroglycerin and ISDN, in terms of the reduction in blood pressure, as well as in terms of the heart rate increase. Following administration of between 4 × 15 mg and 4 × 120 mg ISDN per day for 1 week, the only effects of 0.6 mg nitroglycerin were reducing the SBP by 25% and increasing the heart rate by 30% of the initial effects [82].

Tolerance with Reference to the Antiischemic (Antianginal) Effects

We have "subjective" and "primarily objective" parameters for testing the effects of a medication on myocardial ischemia. Statements relating to the frequency of angina pectoris and the use of nitroglycerin are, to a large extent, subjective; they are documented solely by the patient and are influenced by many variables such as temperature and physical or emotional stress. Any assessment of the patient's exercise capacity – defined as the time interval between the beginning of exercise and the occurrence of angina pectoris – poses a problem, as the exercise capacity can, among other things, be greatly influenced by the testing staff. As a consequence, the exercise capacity parameter can, at the very most, be used in a double-blind study. In the special case of a "tolerance study," however, it is not possible to ensure a blind study with reference to the patient's acute and long-term values, neither is it practicable for the testing staff – as this would require the presence of a different doctor for each exercise test. For these reasons, particularly true here for "tolerance studies," we must stress the importance of comparing parameters which are as "objective" as possible while at the same time maintaining identical levels of exercise. A truly blind evaluation of the tests can only be guaranteed by the subsequent coding of the "acute" and "chronic" values.

The most frequently used noninvasive test parameter is the exercise-induced STsegment-depression, which is easy to determine. In addition to this, there are scintigraphic methods available [77, 78] which enable us to assess the left ventricular ejection fraction during exercise and, at least in patients without prior myocardial infarction, give us an additional indication of the degree of severity of the exercise-induced ischemia. In a minority of studies, the pulmonary arterial pressure during exercise was the objective test parameter [38, 39, 57].

The choice of patients is a factor of decisive importance for each (tolerance) study. The diagnosis of coronary artery disease must be documented by coronary arteriography. Only patients with a clearly interpretable STsegment, without existing STsegment changes even at rest, may be accepted into a study. Clearly, any ad-

ministration of digitalis medication is out of the question. Although patients whose myocardial ischemia cannot be positively influenced by nitrates (nonresponders) are seldom encountered, these patients must be excluded as the absence of efficacy during the long-term phase cannot be described as a "loss of efficacy." Patients with symptoms of variable angina pectoris are unsuitable for tolerance studies on the grounds of the inherent lack of reproducibility. For an exact examination of any tolerance development, the evaluation of all recorded data from every single patient is required, both before and after long-term therapy.

Clinical Studies Showing Evidence of Tolerance to Nitrates with Reference to the Antiischemic (Antianginal) Effects

Table 1 is a compilation of clinical studies which have been able to show evidence of, or at least have led researchers to suspect, the development of tolerance with reference to the antiischemic (antianginal) effects at ingestions of not less than three times per day. The number of patients, the nitrate tested, its dosage, the duration of the long-term phase, as well as the parameters examined can be seen in the table.

In 1969, Goldbarg et al. [32] stated that the combination of ISDN and propranolol was only beneficial by virtue of the beta-blocker, as after 4 weeks of ISDN and a

Table 1. A compilation of clinical studies which either led to the suspicion of or gave evidence of tolerance development with reference to the antiischemic (antianginal) effects of nitrates at dosages not less than three times per day under long-term conditions.

Ref	Original author	Patients *n*	Nitrate	Dosage (mg/day)	Duration (weeks)	Test parameters
[32]	Goldbarg et al. (1969)	21	ISDN, non-sustained release	4 × 10	4	AP frequency Exercise capacity
[3]	Aronow et al. (1970)	20	ISDN, non-sustained release	4 × 5	4	AP frequency Exercise capacity
[50]	Livesley et al. (1973)	18	ISDN, non-sustained release	3 × 20	4	AP frequency Exercise capacity
[6]	Blasini et al. (1980)	9	ISDN, sustained release	3 × 20, 3 × 40	8	AP frequency STsegment
		10	ISDN, sustained release	3 × 60	8	AP frequency STsegment
[83]	Thadani et al. (1982)	12	ISDN, non-sustained release	4 × 15, 30, 60, 120	1	Exercise capacity
[38]	Jansen et al. (1982)	10	IS-5-MN, non-sustained release	3 × 50	4	Pulmonary arterial pressure
[69]	Rudolph et al. (1983)	11	ISDN, non-sustained release	4 × 40	2	STsegment

AP, angina pectoris; ISDN, isosorbide-dinitrate; IS-5-MN, isosorbide-5-mononitrate

placebo, there was practically no difference in the results. Aronov and Chesluk [3] and Livesley et al. [50] reached similar conclusions. Even though any probability of the coincidental presence of nitrate nonresponders (out of a total of 59 patients) is regarded to be extremely low, the absence of data at the beginning of the long-term phase must be stressed, with the result that any development of tolerance can, at most, be presumed.

Moreover, the placebo-controlled, randomized, double-blind, cross-over study published by Blasini et al. in 1980 [6], which showed a total loss of efficacy with regard to the frequency of angina pectoris and the STsegment-depression, was criticized by Abrams since "in this protocol each individual subject was apparently not tested acutely with ISDN" [2]. An additional objection [75], claiming that the point in time chosen for testing following long-term therapy gave the impression of complete tolerance [83], was quashed in a follow-up study by the same group of researchers in which all the patients were examined at the beginning of the long-term phase: Following a 2-week period of 4×40 mg per day of ISDN, 1 h after the oral administration of ISDN, the initial positive effect was no longer demonstrable [69]. Thadani et al. [83] found that, subsequent to 1 week of therapy with between 4×15 mg and 4×120 mg ISDN per day, there was a complete loss of effect 4 h after taking the tablets. However, 2 h after administration, there was a slight "residual effect" on the test subject's exercise capacity.

A reduction in the effects of IS-5-MN has also been described. Following 4 weeks of 3×50 mg per day, the degree of efficacy, when measured by the pulmonary arterial pressure during exercise after the administration of 50 mg, was markedly reduced [38]. A loss of the antiischemic (antianginal) effect was also found in the case of transdermal nitrate application [64].

Cross tolerance between ISDN and nitroglycerin with reference to their antiischemic (antianginal) effects has also been demonstrated. It must, however, be stated that the sublingual administration of nitroglycerin continues to have a positive effect [19] – although when compared with its action before long-term ISDN administration, the effects are reduced to about 50%, even in cases where ISDN has completely failed to act after long-term treatment [69].

Clinical Studies Showing No Evidence of Nitrate Tolerance with Reference to the Antiischemic (Antianginal) Effects

Table 2 shows important data from clinical studies which have failed to show any evidence of weakening or loss of efficacy in patients undergoing long-term oral nitrate therapy with medication of not less than three doses per day.

The unchanged nitrate-induced increase in exercise capacity found in three studies [20, 21, 86] was examined openly and thus the results are not submittable. Lee et al. [48] fulfilled the demands for a double-blind study and found an unchanged positive effect of 3×40 mg on exercise capacity after 4 weeks of medication. Unmodified antiischemic efficacy has also been described for transdermal nitrate application on numerous occasions [14, 23, 30, 65].

Two studies [9, 48] were unable to confirm any cross tolerance between ISDN and nitroglycerin. However, in these studies, where the antianginal effects of ISDN were unchanged, this result was hardly to have been expected.

Table 2. A compilation of clinical studies which showed unchanged antiischemic effects of nitrates at oral dosages of not less than three times per day in long-term studies

Ref.	Original author	Patients *n*	Nitrate	Dosage (mg/day)	Duration (weeks)	Test parameters
[86]	Winsor et al. (1975)	12	GTN, sustained release	3 × 2.6	24	AP frequency Exercise capacity STsegment
[5]	Becker et al. (1976)	10	ISDN, non-sustained release	6–20 × 5	9	STsegment
[21]	Davidov et al. (1977)	25	GTN, sustained release	3–6 × 6.5	12	AP frequency Exercise capacity
[20]	Danahy et al. (1977)	19	ISDN non-sustained release	4 × 20 – 4 × 50	12–40	Exercise capacity
[48]	Lee et al. (1978)	28	ISDN non-sustained release	3 × 40	4	AP frequency Exercise capacity STsegment
[57]	Niederer et al. (1982)	10	ISDN, sustained release	3 × 60	4	STsegment PA
[39]	Jansen et al. (1983)	12	ISDN, sustained release	3 × 20	4	PA
[39]	Jansen et al. (1983)	14	IS-5-MN, non-sustained release	3 × 20	4	PA
[72]	Schneider et al. (1983)	11	ISDN, non-sustained release	6 × 80	4	AP frequency STsegment
[73]	Schneider et al. (1983)	10	ISDN, non-sustained release	6 × 40	4	AP frequency STsegment

AP, angina pectoris; PA, pulmonary arterial pressure; GTN, glyceryl trinitrate (nitroglycerin); ISDN, isosorbide-dinitrate; IS-5-MN, isosorbide-5-mononitrate

Compliance and Dosage Intervals – Possible Explanations for the Controversial Discussion

The application of *various nitrates* cannot be called upon to explain the diverse results obtained, because the development of tolerance has been observed not only for ISDN in different formulations, but also for IS-5-MN, the active antiischemic primary metabolite in ISDN. This tolerance was to have been expected due to the fact that when compared with ISDN, mononitrate has not been able to show any clinically relevant advantages [67, 74, 84]. There is obviously no close relationship between the total *daily dosage* and the development of tolerance as, on the one hand, at a relatively low dosage of 60 mg ISDN per day, a marked reduction in the antiischemic efficacy was observed [6, 83] and, on the other, at a dosage of 480 mg ISDN per day, a persistant antiischemic (antianginal) effect has been described [72].

Neither can the various *times* chosen for the first test after nitrate administration in each individual study – ranging from 30 min to 4 h [6, 38, 48, 69, 72, 86] – even under consideration of the previously mentioned possible foreshortened duration of effect during long-term therapy [75, 83], offer any basis for an explanation of the diverse findings. This is also the case for the various types of ergometric *exercise* selected for the studies such as treadmill [48, 83, 86], step-tests [72, 73], or bicycle ergometry when sitting [20] or semisupine with the legs above the level of the heart [6]. So the type of exercise cannot be related to these discrepancies. The *duration of long-term therapy* cannot account for the controversial results as, on the one hand, after only 1 week of medication a weakened effect was noted [83] and, on the other, even after 40 weeks of nitrate therapy, a persisting and unchanged positive antiischemic effect has been observed [20].

The implementation of a strict, placebo-controlled, randomized, double-blind, cross-over study protocol is not the key answer for the interpretation of the conflicting findings because, even when observing a randomized, double-blind, and cross-over design, there was no evidence of a reduction in efficacy [73], but, on the other hand the development of nitrate tolerance was also observed in an open study [38].

As the analysis of a few studies shows, the *individual degree* of the reduction in efficacy can be very different [38, 78]. Even on the basis of a total loss of efficacy, statistically defined as a nonsignificant difference between the mean values for placebo and nitrate, the effects on a few individual patients may very well be only attenuated [69]. As a consequence of this, the individual degree of tolerance developed must be taken into account particularly in light of the relatively small number of patients participating in practically all the studies (see Tables 1 and 2).

Since nitrate tolerance develops rapidly, i.e., within 1–2 days [7, 18, 19, 63] and is also swiftly reversed [7, 63, 69], the actual ingestion of each single tablet and, consequently, the patient's compliance *(intake reliability),* is pivotal. The unreliable or irregular ingestion of tablets, the probability of which increases with the number of tablets to be taken [85], can draw a veil across the nitrate tolerance problem in practice. Unfortunately, most of the studies omitted to document patient's compliance [3, 5, 14, 20, 21, 23, 30, 50, 57, 83]. Counting the tablets returned, or the documentation of tablet intake on the basis of patients' diaries is also unreliable as, in this manner, any evaluation of compliance lies purely in the hands of the patient. A daily assessment of plasma-levels is just not possible in long-term studies, which is unfortunate, because this is exactly what is needed to answer the question of nitrate tolerance. A practicable method for a daily compliance test would be to determine the fluorescence in the patient's urine attributable to the riboflavin added to the tablets. This scheme would only give results of any value at dosages of one or two tablets per day. At levels of six tablets per day, particularly if in connection with checks at 2-day intervals [72, 73], no conclusions may be drawn concerning the administration of each single tablet.

As a result of the fact that animal experiments have shown evidence of the dependency of tolerance development upon the *dosage interval* [80], and since there have been no clinical studies concentrating on longer dosage intervals, e.g., 12 h or 24 h, we used a randomized and with respect to the dosage interval double-blind study with the administration of 80 mg tablets of ISDN in a sustained-release form to examine the possibility of tolerance development [78]. After 2 weeks, during which on-

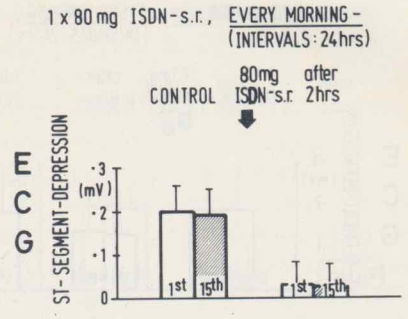

Fig. 1. Effects of a single 80 mg tablet of ISDN in sustained-release form before (1st day) and after (15th day) intake of 1 × 80 mg per day each morning. Test parameters: exercise-induced ST-segment-depression (ECG) and left ventricular ejection fraction during exercise, as determined by radionuclide-ventriculography (RNV)

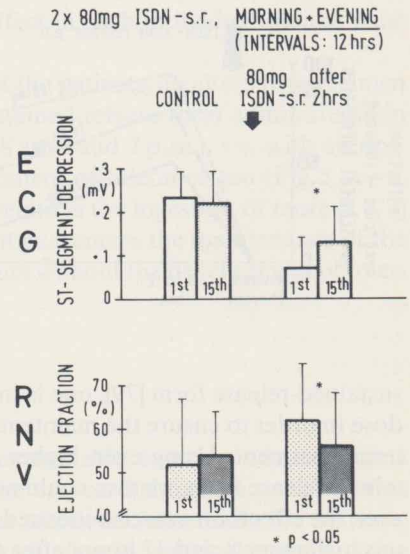

Fig. 2. Effects of a single 80 mg tablet of ISDN in sustained-release form before (1st day) and after (15th day) intake of 2 × 80 mg per day each morning and evening. (See also Fig. 1)

ly one tablet per day was given, the initial positive effects on the exercise-induced STsegment-depression and the left ventricular ejection fraction were demonstrable to the full extent when compared to the initial effects (Fig. 1, $n = 10$). However, a clear reduction in efficacy as measured by both of these parameters was shown after a twice daily (mornings and evenings) administration (Fig. 2, $n = 12$). The objectively evaluated compliance, determined by the riboflavin-urine-fluorescence method, with regard to the ingestion of each single tablet amounted to 95% [78].

Since a dosage interval of 12 h was not sufficient to prevent the development of tolerance, at least in the case of the duration of effect for an 80 mg tablet of ISDN in

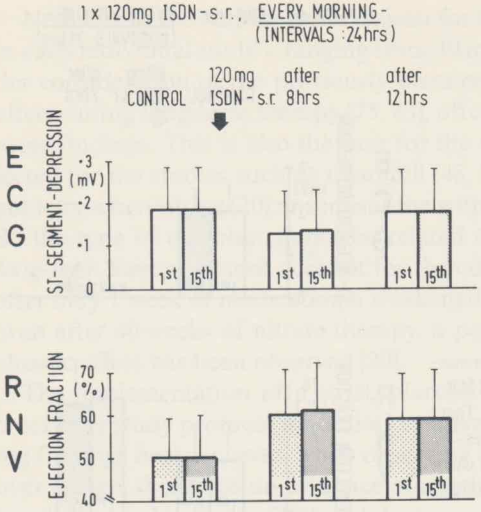

Fig. 3. Effects of a single 120 mg capsule of ISDN in sustained-release form before (1st day) and after (15th day) intake of 1×120 mg per day each morning. (See also Fig. 1)

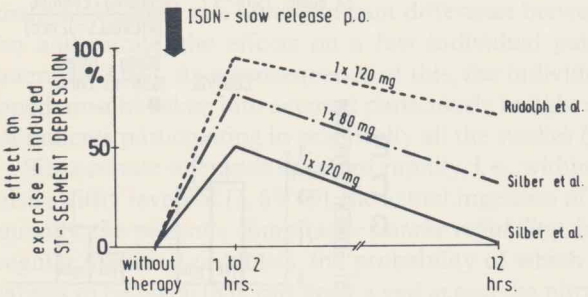

Fig. 4. Comparison of the three studies published to date (70, 79, and this paper) on the antiischemic effects 12 hours after the ingestion of a high single oral dosage of ISDN in sustained (= slow)-release form. The presence and amount of the 12 hours-effects seems to be related to the maximal response 1 to 2 hours after the ingestion

sustained-release form [79], one is initially inclined to favor a single daily high oral dose in order to ensure the maintenance of the full antiischemic effect during long-term treatment. Using even higher single daily dosages of 120 mg ISDN in sustained-release form, we also could not observe any development of tolerance. However, the effects on exercise-induced ischemia, at least when assessed by ECG, were unsatisfactory 8 and 12 hours after the ingestion (Fig. 3, $n = 10$). In contrast to our findings, other authors in a recently published study ([70] $n = 6$) reported excellent results for the antiischemic effects 12 hours after the ingestion of the 120 mg ISDN capsule in sustained-release form of identical formulation. These different findings can easily be explained by taking into account the response 1 to 2 hours after the ingestion: As Fig. 4 shows, the amount of the antiischemic effects 12 hours after the ingestion of a high single oral dosage of ISDN in sustained-release form (80 mg or 120 mg) is clearly related to its maximal effect early after the ingestion: Extremely good responders show highly relevant effects even after 12 hours, whereas patients with initially "medium response" to nitrates have no or minor benefits 12 hours after the ingestion. As a consequence of this variability, chosing the "once-daily high

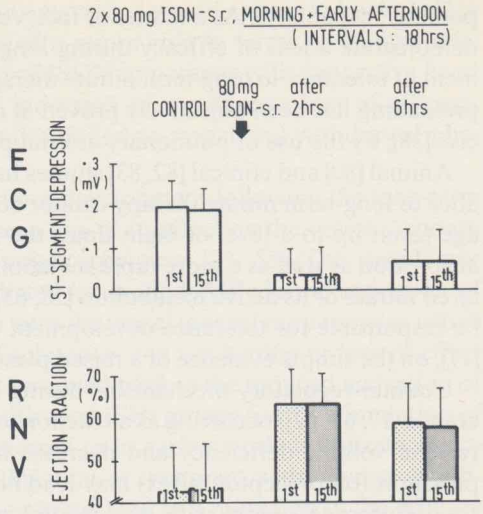

Fig. 5. Effects of a single 80 mg tablet of ISDN in sustained-release form before (1st day) and after (15th day) intake of 2 × 80 mg per day each morning and early afternoon. (See also Fig. 1)

single oral dosage regimen" for chronic treatment to circumvent the development of nitrate tolerance, the testing of the 12-hours effect in each individual patient must be required.

Since this is not practicable in the majority of the patients, an alternative regimen can be used: Using 80 mg ISDN tablets in sustained-release form administered in the morning and in the early afternoon (e.g., 8 a.m. and 2 p.m.), i.e. with an dosage-interval of 18 hours, there was no development of tolerance too (Fig. 5, $n=6$, study is still ongoing). Although this regimen requires the ingestion of more (i.e. 2) tablets each day, it should be favorized, since it guarantees the maintenance of the maximal possible antiischemic effect for 12 hours without the development of tolerance.

Causes of Tolerance Development

The antiischemic (antianginal) effects of nitrates on stable, exercise-induced angina pectoris can be traced back to a reduction in the myocardial oxygen demand. This falls as a result of the reduction in ventricular afterload (essentially the systemic blood pressure), but above all, because of the reduction in ventricular preload due to a drop in the left ventricular (LV) end diastolic pressure or volume [53]. Here, however, the irrefutably demonstrable coronary dilator effects of nitrates [13] (which have been noted both in pre- and poststenotic coronary artery segments as well as in the more severe eccentric stenosed artery segments under resting conditions) to curtail the angina pectoris attacks which are the result of increased oxygen demand, are of no importance [27, 29]. Since the possibility of tolerance development with regard to a reduction in the ventricular afterload has been accepted, and, furthermore, no importance can be attributed to the direct coronary dilation effects within the bounds of exercise-induced ischemia, the loss of nitrate's antiischemic effect must be seen as a decrease in its venous dilation properties (reduced "venous

pooling" capability). As a matter of fact, venous plethysmography has been used to demonstrate a loss of efficacy during long-term nitrate therapy [87]. The development of tolerance to long-term nitrate therapy as seen in the reduction in ventricular preloading has been objectively proven at rest [7], as well as under ergometric exercise [38], by the use of pulmonary arterial pressure measurements.

Animal [80] and clinical [82, 83] studies have shown that the development of tolerance to long-term nitrate therapy cannot be compensated for by increasing the dosage (even up to a level of eight times the initial dose). We must exclude reduced absorption as well as a more rapid metabolism or faster elimination of the administered nitrate or its active metabolites [28, 63] from those causes which might feasibly be responsible for tolerance development under long-term vasodilation treatment [17], on the simple evidence of a raised plasma level during long-term treatment [82].

Counter-regulatory mechanisms during long-term therapy (so-called pseudotolerance [17, 61, 62]) occurring as a reaction to nitrate-induced venous pooling with its relative volume deficiency and decrease in the intracardial and systemic arterial pressures (baroreceptor reflex) may lead both to stimulation of the renin-angiotensin-aldosterone system with its concomitant fluid retention and vasoconstriction, and to a compensatory raised vasoconstrictor tone ("raised sympathetic activity") [47, 59]. The essential difference between "true" and "pseudo"-tolerance becomes clear once the medication is abruptly withdrawn. In the case of a true loss of effect on the vascular smooth muscle there are no changes in the symptoms or hemodynamics, while an interruption of medication in cases of "pseudo"-tolerance may lead to undesirable withdrawal phenomena. In fact, evidence for relevant counter-regulatory mechanisms has been found in dynamite workers and in the pharmaceutical industry who, in days gone by, were exposed to high doses of transcutaneous nitrate due to the lack of adequate safety measures. In approximately 5% of personnel showing no previous signs of coronary disease, typical angina pectoris symptoms, even myocardial infarction and sudden death, were found 30–65 h following the termination of the exposure to nitrate (weekend break) [44, 47, 51]. Coronary spasms in the absence of additional existing fixed coronary arterial stenoses have also been shown to cause angina pectoris [44, 47].

Of course, such extreme withdrawal phenomena can only occur under these extraordinary, nonclinical conditions. Although it is true that patients without heart disease were found to have an increase in the plasma norepinephrine level despite unchanged plasma renin levels, relevant withdrawal phenomena were not found [59]. The problem in assessing the clinical importance of counter-regulatory mechanisms arises from the different circumstances of patients with and without heart disease. In the case of patients with heart failure, there was no incidence of a further increase in plasma norepinephrine with unchanged plasma renin, either during or after withdrawal of continual nitroglycerin administration [59]. These low-level withdrawal phenomena observed were interpreted as an "endogenous vasoconstrictor tone", independent of the renin-angiotensin-aldosterone system and the plasma norepinephrine levels [59]. On the basis of these findings, taken together with the failure of animal experiments to demonstrate a further rise in plasma renin levels during long-term therapy [45], the renin-angiotensin-aldosterone system can hardly be considered responsible for nitrate tolerance. The importance of a nitrate-induced increase in the plasma norepinephrine level must be differentiated from that depen-

dent upon the cardiac disease itself, but in any case, it would appear to be slight [25]. Withdrawal phenomena must be allocated a minor role in terms of clinical relevance. Following the oral administration of ISDN to patients with congestive heart failure and, in spite of the consequent induction of a complete loss of efficacy, abrupt withdrawal of the nitrate medication failed to reveal any withdrawal phenomena [7].

The fundamental mechanism of tolerance development following the long-term intake of nitrates must be looked upon as a loss of its effect on the vessel's smooth muscle, as is seen in tests on isolated vessel specimens [33, 55]. The vasodilator properties of nitrates appear to be mediated by cyclic GMP via the activation of guanylatecyclase [11, 31, 42, 46]. Since in vitro the vessel musculature remains active to cyclic GMP, despite the induction of tolerance, any weakening or loss of effect during long-term nitrate application can be traced back to the reduced activation of guanylatecyclase [42]. Nitrates require sulfhydryl (SH) groups for the stimulation of guanylatecyclase [56]. The SHgroups, referred to in earlier work as "nitrate receptors" [56], whose destruction (e.g., by alkylation or treatment with oxydation substances or "autooxydation" by high-dose nitrates) led to a reduction in the efficacy of nitroglycerin [55] are, according to more recent research, components of thiols, which act in their capacity as "substrate" within the framework of nitrate production for the synthesis of S-nitrosothiols in the smooth muscle cells. As cysteine undoubtedly has the dominant role here [36, 37], the development of nitrate tolerance may possibly be seen as a rapidly occurring exhaustion of the "cysteine store" with the reduced production of S-nitrosothiols [46]. In another study recently published, there was evidence for the enhanced efficacy of intravenously administered nitroglycerin on the systemic and pulmonary capillary pressure when used in conjunction with N-acetylcysteine in patients with coronary artery disease [34]. At the present time, there are no clinical studies dealing with tolerance development dependent upon cysteine infusions. It is possible that the availability of cysteine-bound SHgroups differs with the individual and that it is connected to the individually variable degree of nitrate efficacy despite an identical nitrate dose [34].

As molsidomine, a substance similar to nitrate [4], directly stimulates guanylatecyclase, i.e., independent of thiols [4, 12], the question concerning molsidomine's effect during long-term therapy arises. No assessment can be made of tolerance development under long-term molsidomine intake on the basis of the studies to date, as data were not recorded at the beginning of the study, i.e., neither before 8 weeks of 3×2 mg or of 3×3 mg molsidomine per day, nor 4 weeks of 6×2 mg per day [8, 52]. Since, at the end of the long-term phase, there was still a statistically significant effect on the exercise-induced ischemia, a complete loss of efficacy for molsidomine during long-term therapy appears improbable [8, 52], however, there remains the possibility of a reduction in the antiischemic effect. It is true (certainly for patients with heart failure), that an unchanged reaction of the pulmonary arterial pressure was noted after 1 week of 4×4 mg molsidomine per day [9], but it is also a fact that following 4 weeks with 3×2 mg molsidomine, a significant reduction in molsidomine's effects on pulmonary arterial pressure during exercise was observed [60]. These results are supported by reports of tolerance of the venous vessels to 3×2 mg molsidomine per day after 3 days' intake [41], and throw light on the importance of additional mechanisms of molsidomine effects not yet sufficiently elucidated [68].

Summary and Conclusions

1. While the development of nitrate tolerance with regard to headaches and hypotensive effects is generally accepted, the increasingly controversial discussions of the past few years are centered exclusively on the positive influence on exercise-induced ischemia.
2. Following critical analysis of studies published to date on the subject of nitrate tolerance we can expect a weakening or even loss of effects on exercise-induced ischemia in a high proportion of patients undergoing long-term therapy with a dosage of 3×1 tablets per day.
3. A loss of efficacy may also develop at even relatively low dosages (e.g., 60 mg ISDN per day).
4. In addition to the individually variable degree of tolerance development with relatively low numbers of patients investigated in these studies, "compliance" takes on a pivotal position due to the fact that nitrate tolerance develops rapidly and is swiftly reversed; this implies that the failure to take each single tablet can decisively affect the results.
5. A sufficiently daily "nitrate-free" interval is necessary to prevent the development of tolerance.
6. In cases of relatively high single daily doses (e.g., 80 mg or 120 mg ISDN in sustained-release form), no loss of efficacy develops under oral long-term therapy. Although a high extent of the antiischemic effect may be present in a number of patients 12 hours after the ingestion of an 120 mg capsule ISDN in sustained-release form, this regimen seems to imply considerable inter-individual differences.
7. If a dosage interval of 18 h is applied (e.g., ingestion of 80 mg ISDN in sustained-release form at 8 a.m. and 2 p.m., i.e., in the morning and early afternoon), then we can expect the full antiischemic effect to be maintained with its marked action on exercise-induced ischemia for a period of approximately 12 h under long-term nitrate therapy. In patients suffering angina pectoris symptoms mainly in the afternoon or at night, the tablets can be administered in the afternoon and evening, as appropriate.
8. Since a reduced antianginal effect has also been observed for the transdermal application of nitrates [64], the 24-h effects often postulated [43] for nitrate patches or ointments pose a problem. Assuming adequate dosages in the use of these transcutaneous systems [40], and, insofar as 24-h effects have been proven [66], the present-day knowledge of nitrate tolerance leads us to recommend that the patches should be removed again in the evening or, depending on the symptoms, be used only during the night.
9. In light of the required daily "nitrate-free interval," nitrates should be combined with additional antiischemic substances and in particular with beta-blockers and/or calcium antagonists (naturally under consideration of the contraindications) in the treatment of ischemic heart disease.
10. Long-term antiischemic therapy is desirable both for the prophylaxis of attacks under unforseeable physical or emotional stress and in consideration of spontaneous clinically silent, ischemic episodes [22, 24, 76]. Nitrates continue to form the basis of treatment for exercise-induced ischemia as, in contrast to beta-

blockers and calcium antagonists, they clearly reduce the ventricular preload under stress. However, sufficient weight must be lent to the conditions laid down here for the way in which nitrates should be used.

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