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It is well established that constant nitrate plasma levels, as generated by "q 8 hrs" ingestions as well as by transdermal applications, induce an attenuation or even complete loss of the antiischemic effects during chronic treatment due to the development of tolerance.[1-3] As we have shown first in 1983, the once-daily ingestion of isosorbide dinitrate with its waxing and waning plasma levels prevents the development of tolerance during chronic treatment.[1,2] However, the duration of action of that intermittent dosage regimen was rather limited and inconsistent. To extend the duration of the antiischemic effects of a once-daily dosage, a new formulation, i.e., a capsule containing 120 mg of isosorbide dinitrate in slow release form, was created. This study assessed this newly developed capsule with regard to the antiischemic effects at 2 hours, 6 hours and 12 hours after its ingestion. Additionally, the plasma levels of isosorbide dinitrate and its active metabolites isosorbide-2-mononitrate and isosorbide-5-mononitrate were determined.

Acceptance criteria were based on angiographically proven coronary artery disease (≥75% diameter stenosis of at least 1 of the 3 major coronary arteries) and a history of stable, exercise-dependent angina pectoris. However, because anginal pain is highly subjective and an unreliable parameter for the assessment of myocardial ischemia, we chose the exercise-induced ST-segment depression as the decisive parameter for objective assessment of the antiischemic effects. The details of our standard exercise protocol have been extensively published previously.[1,2] Patients were randomized and given either a single capsule with 120 mg isosorbide dinitrate in sustained-release form as achieved by pellets (Isoket-retard 120™, Pharma Schwarz), or identical-looking placebo capsules with inert pellets. All the capsules were ingested in the presence of the staff. Exercise tests were performed before ingestion (8 A.M.) and repeated 2, 6 and 12 hours after the ingestion. The following day, patients received the complementary capsule according to the randomized, double-blind and crossover protocol (Figure 1). The mean age of our 18 patients was 56 ± 8 years (range 46 to 66). Six patients had 1-vessel, 8 had 2-vessel and 4 had 3-vessel disease. Prior myocardial infarctions were reported in 13 patients (7 anterior, 5 inferior, 1 anterior + inferior wall infarction). Blood samples were drawn and centrifuged according to standard requirements.[2] Analysis of isosorbide dinitrate and its metabolites isosorbide-2-mononitrate and isosorbide-5-mononitrate was performed by a gas chromatographic electron capture method.[4] For statistical analysis, the 2-tailed Wilcoxon test for matched pairs comparing the nitrate values with the corresponding placebo measurements was used. Probabilities were considered significant at the 0.05 level using Bonferroni's adjustment. All data were calculated at the maximal comparable workload and given as mean ± 1 standard deviation.

On the first day, 10 patients received isosorbide dinitrate and 8 patients placebo. There was no carryover effect (variance-analysis) from the first to the second day. Side effects other than nitrate headache were not observed. The exact figures for heart rate, blood pressure and pressure-rate product at rest and during exercise are listed in Table I. The results for the exercise-induced ST-segment depression are also depicted in Table I. The isosorbide dinitrate plasma levels were 17 ± 12, 17 ± 8 and 3 ± 1 ng/ml after 2, 6 and 12 hours, respectively. The isosorbide-2-mononitrate plasma levels were 41 ± 21, 103 ± 18 and 37 ± 13 ng/ml, whereas the isosorbide-5-mononitrate plasma levels were 208 ± 100, 589 ± 139 and 446 ± 127 ng/ml after 2, 6 and 12 hours, respectively. After 24 hours, the plasma levels were 0 for isosorbide dinitrate, 3 ± 2 ng/ml for isosorbide-2-mononitrate and 105 ± 39 ng/ml for isosorbide-5-mononitrate.

To characterize the duration of action, it is important not only to describe the total time range of statistically significant changes, but also to define the duration of the *maximal* effects obtained. Thus, while single dosages of 15 to 30 mg nonsustained isosorbide dinitrate showed significant antiischemic effects for 8

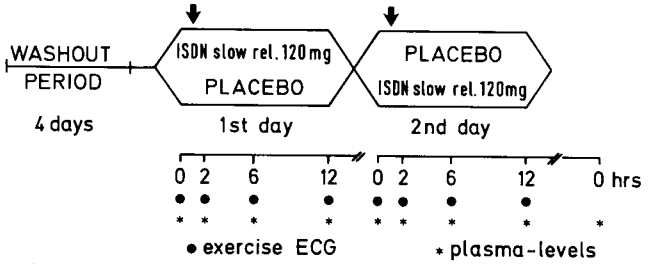

FIGURE 1. Design of the placebo-controlled, randomized, double-blind and crossover study. After a washout period of 4 days with only sublingual nitroglycerin allowed, the 18 patients underwent 4 exercise tests on the first day. After the initial exercise test (usually at 8 A.M. = 0 hours), patients were assigned to ingest either placebo or a single capsule of 120 mg isosorbide dinitrate (ISDN) in slow release form. Exercise tests were repeated in an identical way at 2, 6 and 12 hours after the ingestion. On the second day, patients ingested the complementary capsule and exercise tests were performed as well. Blood samples for the determination of the plasma levels were collected on both days immediately before the exercise tests and 24 hours after the second ingestion.

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TABLE I Clinical Variables Before and After Ingestion of 120 mg Isosorbide Dinitrate in Sustained Release Form (ISDN) or Placebo

	Heart Rate (beats/min)		Systolic BP (mm Hg)		Pressure-Rate Product (mm Hg/min × 1,000)		Diastolic BP (mm Hg)		ST-Segment Depression (mm)	
	Placebo	ISDN	Placebo	ISDN	Placebo	ISDN	Placebo	ISDN	Placebo	ISDN
Before ingestion										
Rest	77 ± 14	75 ± 14	132 ± 13	136 ± 13	10.2 ± 2.4	10.1 ± 2.0	81 ± 13	84 ± 11	—	—
Exercise	137 ± 21	131 ± 24	165 ± 16	175 ± 25	22.5 ± 4.2	22.9 ± 5.8	104 ± 26	111 ± 33	2.5 ± 1.0	2.3 ± 0.8
2 hours after ingestion										
Rest	79 ± 11	88 ± 14*	134 ± 15	117 ± 12†	10.6 ± 2.2	10.3 ± 1.9	84 ± 9	75 ± 11*	—	—
Exercise	136 ± 21	137 ± 20	170 ± 15	158 ± 17*	23.1 ± 4.2	21.6 ± 4.0	102 ± 21	88 ± 13*	2.1 ± 0.9	0.7 ± 0.5†
6 hours after ingestion										
Rest	77 ± 12	86 ± 12*	136 ± 13	116 ± 13†	10.5 ± 1.8	10.0 ± 1.9	82 ± 11*	75 ± 13	—	—
Exercise	137 ± 19	139 ± 17	164 ± 16	163 ± 28	22.3 ± 3.4	22.6 ± 5.2	89 ± 13	98 ± 32	2.3 ± 0.9	1.0 ± 0.8†
12 hours after ingestion										
Rest	73 ± 11	77 ± 11	138 ± 16	127 ± 15*	10.1 ± 1.6	10.0 ± 2.0	87 ± 10	79 ± 13*	—	—
Exercise	138 ± 18	133 ± 18	169 ± 21	157 ± 14*	23.2 ± 3.5	20.8 ± 3.1	102 ± 26	93 ± 18	2.5 ± 0.9	1.9 ± 0.8*

* $p < 0.05$; † $p < 0.005$.

hours, the *maximal* effects were observed for only 2 to 3 hours.[5-7] Because there was much evidence that sustained release formulations prolong the duration of action of a single dosage of isosorbide dinitrate,[8,9] it was our intention to further prolong the duration of action by increasing the content of a single capsule to 120 mg of isosorbide dinitrate. As we have demonstrated in this study, a single dosage of 120 mg of isosorbide dinitrate in sustained release form is able to maintain statistically significant antiischemic effects up to 12 hours and *maximal* effects for at least 6 hours. After 12 hours, the effect on exercise-induced ST-segment depression was less than that obtained after 2 hours and 6 hours (Table I). The antiischemic effect at 12 hours was only 24% as compared with the corresponding value at 2 hours of 67%, despite the more than doubled plasma level of isosorbide-5-mononitrate (446 vs 208 ng/ml), the main active metabolite of isosorbide dinitrate. This metabolite, due to its relatively long half-life of about 6 hours, is considered to be responsible for the duration of action of orally administered isosorbide dinitrate.[10] Because of the placebo group circadian variations can be ruled out; thus, this result might be interpreted as evidence for a very rapid (i.e. within 12 hours) development of nitrate tolerance. As an alternative explanation for our results, the very low plasma levels of isosorbide dinitrate could also be the cause of the lessened antiischemic effects after 12 hours, which would imply that the antiischemic power of isosorbide-5-mononitrate is negligible as compared with isosorbide dinitrate (a statement that contradicts the present experience with pure isosorbide-5-mononitrate).

To warrant the maintenance of the antiischemic properties during long-term treatment, we have recommended since 1983 a regimen using "valleys" with nitrate-poor intervals.[1,2] In the US, the only presently available oral nitrate therapy is low single dosages of isosorbide dinitrate in sustained release form with a relatively short duration of action. In contrast to low single-dose therapy, the ingestion of a single capsule containing 120 mg isosorbide dinitrate in sustained release form exerts its *maximal* antiischemic effects throughout the first 6 hours, with significant, although lessened effects after 12 hours. Thus, in light of this advantage, combined with the superior compliance expected with a once-daily regimen, a modification of the current practice of oral nitrate therapy should be considered.

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