Response to Changing Plasma Concentrations of Isosorbide-Bound NO₂ during Acute and Sustained Treatment with Isosorbide Dinitrate in Patients with Coronary Artery Disease

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Summary

Background: The mechanisms behind development of tolerance to nitrate effects during sustained, asymmetric isosorbide dinitrate (ISDN) therapy are not fully understood.

Hypothesis: The study was undertaken to investigate the changes of the relationships between left ventricular (LV) function and plasma concentrations of ISDN and its vasoactive metabolites (2- and 5-ISMO) during acute and sustained, asymmetric ISDN therapy.

Methods: Left ventricular function and plasma concentrations of ISDN, 2- and 5-isosorbide mononitrates (P-ISDN, P-2- and 5-ISMO) were measured at rest and at supine exercise before and for 4 h after peroral 30 mg ISDN in 15 patients with coronary artery disease, all with initial exercise pulmonary artery wedge pressure (PAWP) > 25 mmHg. Seven patients were untreated (acute group), while eight received 30 mg ISDN b.i.d. for 2 weeks before the invasive study. P-ISDN and the concentration of available isosorbide-bound nitrate (NO₂) in plasma (P-ISDN·2 + P-2-ISMO + P-5-ISMO) (P-NO₂) were used as measures of the nitric oxide (NO) offer to the tissues.

Results: Throughout the study, after administration of medication, all plasma concentrations, in particular P-ISDN, were higher in the chronic than in the acute group. Peak P-ISDN was reached after 15 min in the chronic group and after 25 min in the acute group, while P-2- and 5-ISMO reached maximum only after 40 min in both groups. At rest, the full effect on PAWP was observed after 10 min in both groups, but at markedly higher levels of P-ISDN and P-NO₂ in the chronic group. Afterward, no further changes in PAWP were observed. During exercise, 1 h after medication, PAWP and stroke index to PAWP ratio (SI/PAWP) were normal in both groups. Thereafter, at slowly declining P-NO₂, PAWP rose and SI/PAWP declined toward the initial level in the chronic group, but re-

mained unchanged in the acute group, in spite of higher P-NO₂ and greater NO release in the former.

Conclusions: Patients receiving sustained, asymmetric 30 mg ISDN b.i.d. dosing had the same immediate beneficial effects on LV function during exercise after a morning dose as did untreated patients. However, in spite of higher P-NO₂ and higher rate of NO release during sustained treatment, the effects deteriorated gradually 2 to 3 h after medication. The changes in metabolism and/or distribution of isosorbide-bound NO₂ may possibly be part of the tolerance induced by long-term treatment, even with asymmetric dosing.

Key words: plasma concentrations of isosorbide dinitrate, 2- and 5-ISMO, left ventricular function

Introduction

Tolerance to hemodynamic and anti-ischemic nitrate effects develops rapidly when organic esters are administered continuously, leading to high, constant plasma concentrations.^{1–7} An approach to avoidance of nitrate tolerance has been to allow nitrate-free periods when nitrate plasma concentration drops toward zero. This has been achieved either by application and removal of transdermal nitrate patches or asymmetric dosage regimens with only two dosages per 24 h, and up to 16 to 18 h between the afternoon and next-morning medication.^{8–10} However, even with these treatment strategies it has been shown that isosorbide dinitrate (ISDN) 30 mg given asymmetrically b.i.d. induces significant attenuation of the nitrate effects.^{11, 12}

Studies concerned with the relationship between dosage and response during acute and sustained treatment with ISDN in general have related the effects to the plasma concentrations of the dinitrate only. No studies seem to have dealt with the relationship between left ventricular (LV) response to treatment and the total of isosorbide-bound nitrate (NO₂) in plasma, also including the concentrations of NO₂ in the 5- and 2-isosorbide mononitrates (5-ISMO and 2-ISMO), rapidly formed after the ISDN consumption.

This investigation was undertaken to examine the extent to which differences in the time course of the changes in pulmonary artery wedge pressure (PAWP) and the Frank-Starling curve after acute and sustained, asymmetric ISDN consumption are related to differences in the time course of the plasma

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concentrations of both ISDN (P-ISDN) and its vasoactive metabolites (P-5-ISMO and P-2-ISMO). Since ISDN as well as the mononitrates are prodrugs, the functional changes will be related to both the concentrations of ISDN and the sum of the available isosorbide-bound NO₂ in plasma (P-NO₂), reflecting the potential to release nitric oxide (NO), and to estimates of the rate of NO release. Since the approach to the pharmacologic data is unusual, these will be discussed in some detail.

Materials and Methods

The study comprises 15 male outpatients referred to the laboratory for investigation because of suspicion of ischemic heart disease manifested by fatigue, dyspnea, or vague chest pain. None had characteristic angina pectoris or pulmonary disease. During an incremental ergometer cycle exercise test in the sitting position,¹³ all developed ST-depressions of at least 1 mm (average, 2.8 ± 1.1 mm) in the precordial leads and were referred for diagnostic right heart catheterization.¹² Angiography revealed coronary artery disease in all.

Prior to catheterization, eight patients (63.1 ± 5.1 years, body weight 75.1 ± 8.4 kg, height 176 ± 5.1 cm) were allocated to 14 days of treatment with ISDN (Sorbangil®, Kabi Pharmacia, Uppsala, Sweden) 30 mg asymmetrically b.i.d. (9 A.M. and 3 P.M.) (chronic group). Seven patients (68.9 ± 6.6 years, 77.7 ± 9.8 kg, 176 ± 6.6 cm) were not treated with any medication within the week before catheterization (acute group). The two groups were similar regarding patient characteristics and previous history of cardiac disease.

Right heart catheterization began at 8 A.M. A Swan-Ganz catheter was introduced through the cubital vein and fed into the pulmonary artery for measurements of PAWP. A cannula in the right cubital artery allowed sampling of arterial blood used for determination of plasma concentrations of ISDN (P-ISDN) and its vasoactive metabolites (P-5-ISMO and P-2-ISMO).

Plasma concentrations were measured by gas chromatography according to the method of Morrison and Fung,¹⁴ using a Hewlett-Packard 5710 A gas chromatograph, equipped with ⁶³Ni-ECD (Electron Capture Detector, Avondale, Tex., USA). Lower limits of detection for ISDN, 2-, and 5-ISMO were 2, 5, and 25 nmol/l, respectively. The standard curves were linear in the concentration ranges 2–500 nmol/l for ISDN, 5–1500 nmol/l for 2-ISMO, and 25–3000 nmol/l for 5-ISMO, and the coefficients of variation were better than 8% through the whole concentration ranges.

Patients remained in supine position throughout the study to obtain valid hemodynamic comparisons during the resting and exercise registrations and between registrations. Both at rest and during exercise, all recordings were performed with the legs slightly elevated and fixed to the pedals.

Initial registrations were performed 15 min after instrumentation, with the patients in a steady resting state. Half an hour later, patients performed a bicycle exercise at a constant load, mean 238 ± 33.1 kpm/min (200–300 kpm/min) for 7 min, with measurements beginning 3 min after start of exercise. In accordance with previous experience, the supine exercise load, which had to be tolerable for 7 min, was set to 40% of the max-

imal load for individual patients at the previously performed sitting exercise test. Patients with PAWP > 25 mmHg and ST-depressions > 2 mm during moderate supine exercise were eligible for supplementary ISDN investigation.

Patients received 30 mg ISDN orally 15 min after the first exercise test. New sets of measurements were performed at rest 5, 10, 15, 20, 25, 30, 40, 50, 110, 170, and 230 min after tablet intake and after 60, 120, 180, and 240 min during exercise.

To avoid anxiety and to minimize possible influence from habituation to the procedure during the repeated exercise tests, patients were carefully instructed about the steps of the procedure, both before and continuously during catheterization.

This model with repeated studies several days apart has previously shown high reproducibility of measurements.¹¹

The protocol was approved by the Regional Ethical Committee. Written, informed consent to participate in the study was obtained from each patient.

Calculations

Release of NO: During the initial phase after ISDN consumption, the release of NO was estimated as the rise per min of the total of mononitrates in the total body water, that is, $0.6 \cdot \text{body weight (BW)} \cdot (\text{P-5-ISMO} + \text{P-2-ISMO})$. During the last phase it was estimated as the decline per min of the total of isosorbide-bound NO₂ available in the body water, that is, $0.6 \cdot \text{BW} \cdot (\text{P-5-ISMO} + \text{P-2-ISMO} + 2 \cdot \text{P-ISDN})$. The former estimate does not account for ISDN degraded to nitrate-free isosorbide, that is, the carrier molecule only, and the latter does not consider the possible back diffusion of ISDN from pools outside the body water.

Statistics

The observations are given as means $\pm$ standard deviation. Repeated measures analysis of variance was used for intragroup comparisons, and the Student's *t*-test was used for intergroup comparisons. A *p* value of 0.05 was considered significant.

Due to the small number of patients the validity of all reported conclusions based on the Student's *t*-test were controlled and confirmed with the Mann-Whitney nonparametric test for unpaired data.

Results

Plasma Concentration of Isosorbide Dinitrate and 5- and 2-Isosorbide Mononitrates

Figure 1 shows the mean P-ISDN, P-5-ISMO, and P-2-ISMO after oral consumption of 30 mg ISDN (127 μ mol) in the morning in previously untreated patients (acute group) and in patients with sustained asymmetric treatment (chronic group). Before ISDN consumption, P-ISDN, P-5-ISMO, and P-2-ISMO in the chronic group were 0, 405 ± 140 , and 24 ± 20 nmol/l, respectively.

Plasma concentrations of ISDN in the chronic group rose sharply during the initial 10 min and reached maximum, 407

FIG. 1 Plasma isosorbide dinitrate (P-ISDN), and P-2 and P-5 isosorbide mononitrates (P-2-ISMO and P-5-ISMO) after peroral ISDN 30 mg at rest. ● = Acute group, ○ = chronic group.

nmol/l, 15 min after medication, while ISDN in the acute group had a slower and less pronounced rise, with 211 nmol/l after 15 min ($p < 0.05$) and maximum only after 25 min. After reaching maximum, both curves showed a rapid decline. The rate of disappearance, as reflected by the half-times of the concentrations ($C_{1/2}$), was clearly faster in the chronic group ($C_{1/2}$ 53 $\pm$ 11 min) than in the acute group ($C_{1/2}$ 68 $\pm$ 13 min) ($p < 0.05$). The area under the curve (AUC) for ISDN was 16.9 $\pm$ 6.93 $\mu\text{mol/l}\cdot\text{min}$ in the acute group and 24.4 $\pm$ 9.22 $\mu\text{mol/l}\cdot\text{min}$ in the chronic group ($p = 0.08$), and correspondingly, the clearance (ISDN dose/AUC) was 9.2 $\pm$ 4.9 l/min in the acute group and 6.3 $\pm$ 3.6 l/min in the chronic group.

Also, P-5-ISMO and P-2-ISMO increased rapidly during the first 10 min, clearly most rapidly in the chronic group ($p < 0.05$), but peak concentrations were reached only after 40 min. The peak values were considerably higher than those for ISDN, in particular for P-5-ISMO. The difference between the chronic and acute peak levels was of the same magnitude as the morning remnant of the preceding day's medication in the chronic group. The decline was much slower than that for P-ISDN, particularly for P-5-ISMO. Half-times of the concentrations for P-2-ISMO were the same in both groups (169 $\pm$ 21 and 160 $\pm$ 27 min, respectively), but for P-5-ISMO $C_{1/2}$ was longer in the acute group (425 $\pm$ 43 min) than in the chronic group (355 $\pm$ 74 min) ($p < 0.05$).

FIG. 2 Plasma isosorbide-bound nitrate (P-NO₂) before and after peroral isosorbide dinitrate (ISDN) 30 mg at rest. ● = Acute group, ○ = chronic group.

Available Isosorbide-Bound Nitrate in Plasma

Figure 2 shows time course of the total concentration of isosorbide-bound NO₂ available in plasma (P-ISDN*2 + P-2-ISMO + P-5-ISMO) (P-NO₂), based on the fact that ISDN contains two NO₂ groups per molecule and 5- and 2- ISMO contain one. After a steep rise, most pronounced in the chronic group, a plateau was reached after 15 min in the chronic group and after 20 min in the acute group, lasting until 40 min after administration of the medication. Thereafter, both curves declined at a very slow rate during the last hours of the observation period, most slowly in the acute group.

Assuming that P-NO₂ reflects the concentration of isosorbide-bound NO₂ in the total body water and that this amounts to about 0.6 l/kg BW,^{15,16} the total available isosorbide-bound NO₂ in the body water at maximum, 40 min after ISDN consumption, was 112 $\pm$ 31.6 μmol in the acute group and 131 $\pm$ 46.7 μmol in the chronic group. Thus, of the consumed isosorbide-bound NO₂ (254 μmol), at least 44% in the acute group, and, after deducting the remnants from the preceding medication (17 μmol), 45% in the chronic group was still available for NO release to the tissues, not accounting for the undegraded ISDN pooled outside the body water.

Release of Nitric Oxide

At the end of the maximum plateau of P-NO₂ at 40 min (Fig. 2) ISDN contributed only with a small fraction to the total (Fig. 1), the major part being denitrated or bound/pooled outside plasma and the body water. With a volume of distribution of 0.6 l/kg BW, the total amount of mononitrates formed and distributed in the body water was 80 μmol in the acute and 77 μmol in the chronic group. Thus, without accounting for the ISDN degraded to nitrate-free isosorbide, about 60% of the ISDN consumed (127 μmol) had been degraded in the two groups. The overall release of NO associated with the rise in the mononitrates (see Methods) during the first 40 min after the ISDN intake amounted to 2.1 $\pm$ 0.7 $\mu\text{mol/min}$ in the acute group and 1.9 $\pm$ 0.5 $\mu\text{mol/min}$ in the chronic group (NS). However, corresponding, less accurate estimates at earlier times after the ISDN intake were higher, in particular in the chronic group (Fig. 1).

FIG. 3 Relationship between pulmonary artery wedge pressure (PAWP) and plasma isoribide dinitrate (P-ISDN) at rest, before (Pre ISDN) and 5, 10, 15, 20, 25, 30, 40, 50, 110, 170, and 230 min after peroral ISDN 30 mg. ● = Acute group, ○ = chronic group.

FIG. 4 Relationship between pulmonary artery wedge pressure (PAWP) and plasma isoribide-bound nitrate (P-NO₂) at rest, before (Pre ISDN) and 5, 10, 15, 20, 25, 30, 40, 50, 110, 170, and 230 min after peroral ISDN 30 mg. ISDN = isoribide dinitrate. ● = Acute group, ○ = chronic group.

In contrast, the release of NO from ISDN and mononitrates in the body water (see Methods) during the last hours of the observation period, after the rapid decline of ISDN, but at still high P-NO₂, was only 0.14 ± 0.04 $\mu\text{mol}/\text{min}$ in the acute group and 0.23 ± 0.08 $\mu\text{mol}/\text{min}$ in the chronic group ($p < 0.05$), that is, markedly lower.

The release of NO from 5-ISMO alone was 0.08 ± 0.02 $\mu\text{mol}/\text{min}$ in the acute group and 0.14 ± 0.06 $\mu\text{mol}/\text{min}$ in the chronic group ($p < 0.05$).

Effects on LV Filling Pressure (PAWP) at Rest

Figure 3 depicts the relationship between PAWP and P-ISDN, and Figure 4 that between PAWP and P-NO₂. Figures 3 and 4 show that in both the acute and chronic groups, both with initial PAWP at the upper limit of the normal range, maximal effect was already achieved 10 min after medication, but at widely differing P-ISDN and P-NO₂ levels. At this time, P-ISDN and P-NO₂ were only 155 ± 94 and 1030 ± 490 nmol/l, respectively, in the acute group, in contrast to 387 ± 198 and 2256 ± 946 nmol/l in the chronic group ($p < 0.05$). Furthermore, whereas the initial P-NO₂ in the chronic group (including 405 nmol/l 5-ISMO and 24 nmol/l 2-ISMO) before the morning dose had no effect on PAWP, the same P-NO₂ (including 182 nmol/l 5-ISMO, 75 nmol/l 2-ISMO, and 78.7 nmol/l ISDN) observed 5 min after medication in the acute group was associated with a conspicuous effect (Fig. 4). After the initial effect, considerable variations in P-ISDN and P-NO₂ (Figs. 3 and 4), as well as in 5-ISMO and 2-ISMO (Fig. 1) were not accompanied by any definite further changes in PAWP. The concentration–effect relationship followed a characteristic hysteresis loop.

Effects on LV Function During Supine Exercise

Exercise was performed before the ISDN morning dose and repeated at hourly intervals for 4 h. Thus, exercises under

FIG. 5 Relationships between pulmonary artery wedge pressure (PAWP) and isoribide-bound nitrate (P-NO₂) (A), and between stroke volume index SI/PAWP and P-NO₂ (B) during supine exercise, before (Pre ISDN) and 1 to 4 h after peroral ISDN 30 mg. ● = Acute group, ○ = chronic group.

influence of nitrates were performed after denitration of the major part of ISDN to mononitrates (Fig. 1), after maximal P-NO₂ was reached (Fig. 2), and during a period with slow gradual decline of P-NO₂ and markedly reduced release of NO (see above).

Figure 5 illustrates the time course of the relationship between PAWP and P-NO₂ and between stroke volume index (SI) to PAWP ratio, reflecting the Frank-Starling curve, and P-NO₂. Initially, before the ISDN morning dose, PAWP was markedly elevated, with all individual measurements > 25

mmHg (normally ≤ 16 mmHg), and SI/PAWP was strikingly reduced. One h after the ISDN intake, and simultaneous with a marked rise in P-NO₂, PAWP was normalized in both groups, while SI/PAWP was markedly increased, showing distinctly improved LV function. During the following 3 h, with a gradual decrease in P-NO₂, PAWP and SI/PAWP remained essentially unchanged in the acute group, whereas PAWP rose clearly ($p < 0.001$) and SI/PAWP decreased distinctly ($p < 0.001$) toward the premedication level in the chronic group, despite constantly higher P-NO₂ in the latter. Thus, whereas LV function was unaffected by the decrease in P-NO₂ in the acute group, there seemed to be a concentration–response relationship in the chronic group with higher P-NO₂.

Discussion

This study clearly shows that the applied regimen, with 30 mg ISDN twice daily and 18 h between the preceding and morning dose, is accompanied by partial tolerance with regard to cardiac function. More specifically, it demonstrates the extent to which changes in LV function are related to the potential to release NO from ISDN and the vasoactive metabolites, and also to the net release of NO.

At rest, the initial, rapid fall in PAWP, equal in both groups, took place at markedly lower P-ISDN and P-NO₂ (Figs. 3 and 4) in the acute than in the chronic group, suggesting reduced concentration–response relationship during sustained treatment. However, after the initial 10 min of ISDN influence, neither further rise nor decline of the plasma concentrations was accompanied by corresponding changes in PAWP or reflected differences between the groups. Thus, the data are at variance with previous observations after a single dose of 5-ISMO, suggesting a close relationship between P-5-ISMO and reduction in PAWP.^{17, 18} Neither was there evidence of a close relationship between the estimates of the rate of release of NO, which was high during the first half hour and substantially lower during the following hours, and the changes in PAWP.

During the successive exercises, however, in spite of higher P-NO₂ and a higher rate of NO release in the chronic than in the acute group, LV function deteriorated after initial improvement in the chronic group, but remained unchanged in the acute group. Thus, the data obtained at declining P-NO₂ suggest a relationship between response and concentrations in the chronic but not in the acute group (Fig. 6).

The distinct reduction of the response of LV function to the nitrate supply in the chronic group is at variance with several studies claiming that sustained asymmetric treatment prevents development of nitrate tolerance.^{8–10} However, none of these have investigated the relationships between the combination of plasma ISDN and its vasoactive metabolites on one side and of LV function on the other, described by the Frank-Starling curve.

The finding that even sustained, asymmetric dosing b.i.d. yielded clearly higher P-ISDN levels than acute medication corresponds with studies applying more frequent daily per oral dosings during sustained therapy.^{19–21} This has previously been explained by ISDN accumulation and increased trough

levels,^{19, 21, 22} but is contradicted by the fact that with the actual ISDN doses and 18 h between the preceding and morning ISDN dosage, morning P-ISDN was zero in all patients. Furthermore, the elevation of the P-ISDN levels in the other studies during sustained therapy^{20, 21} were in fact higher than the remnant of the preceding day's ISDN intake. More likely, the elevated level of P-ISDN in the chronic group was due to mechanisms hampering the ISDN degradation, such as accumulation of slowly degrading metabolites of ISDN, in particular 5-ISMO (Fig. 1), and a consequential attenuation of the ability to take up and denitrate ISDN in the liver and/or reduced tissue binding.^{15, 19, 23–25} This is supported by the fact that the clearance of ISDN (dose/AUC) was lower in the chronic than in the acute group in this and a previous study.²² The changes in metabolism and/or distribution of isosorbide-bound NO₂ may possibly be part of the tolerance induced by long-term treatment, even with asymmetric dosing.

With regard to the time course of the plasma concentrations of ISDN, 5-, and 2-ISMO, the present observations deviate conspicuously from most comparable studies. With few exceptions,²⁶ peak P-ISDN during the first 15–45 min after the medication are markedly lower to varying degrees than those in the present study, whereas the subsequent observations are relatively higher and closer to those in this study.^{1, 16, 27–30} Also, the early 2- and 5-ISMO observations are clearly lower than those in this study, whereas the observations during the following hours consistently correspond to the present study.^{16, 26, 27, 30}

In accordance with the markedly higher peaks of P-ISDN, P-2-, and 5-ISMO observed in this study, the apparent volumes of distribution for the consumed ISDN, including also the ISDN not accounted for in the body water, must be lower than those in other studies,^{16, 26, 30} in particular during sustained treatment. This may be ascribed to less intra- or extra-hepatic transformation or reduced tissue binding.²² Likewise, as a consequence of the high P-NO₂, the total available isosorbide-bound NO₂ in the body water, estimated at 30–40 min after ISDN intake, was markedly higher than that reported in previous studies.

Allowing for the different ISDN doses, the marked rise of the mononitrates during the first 40 min after ISDN consumption led to estimates of NO release that were 50% higher than those calculated from other data,^{16, 26, 30} whereas the NO release estimated for the 2–4 h period after the medication, mainly based on the mononitrate decline, was the same in this and in previous studies.^{16, 26, 30} Considering the lower level of P-5-ISMO in this study, the rate of NO release from 5-ISMO alone was of the same magnitude as that calculated for corresponding observation periods after intake of 5-ISMO (20 mg) in other studies.^{31, 32}

The apparently lower rate of NO release, together with the longer half-time of P-5-ISMO in the acute group of this study, may reflect back-diffusion and delayed degradation of ISDN pooled in the tissues.^{15, 19}

The extent to which discrepancies between this and other studies may be ascribed to differences with regard to populations studied, methodological procedures, or unspecified

characteristics of the ISDN formulations, is unclear. It may be noted, however, that this study was performed in patients with coronary heart disease, in the postabsorptive phase after a light morning meal, whereas most other studies have been performed in healthy individuals after an overnight fast. This may have influenced the hepatic first-pass effect.³³

The implications of the term "concentration of available isosorbide-bound NO₂" (P-NO₂) are not unequivocal. Based on three isosorbide-NO₂ compounds, with distinctly different denitration half-lives, its potential to release NO reflected by a given value is reduced with time after ISDN consumption. However, for evaluation of specific aspects of the ISDN metabolism and the consequential circulatory effects, it seems to be a useful tool.

As far as the clinical implications are concerned, the data show that it is not possible to draw definite conclusions as to the adequacy of the nitrate dosing regimen regarding the effects on the heart's performance from isolated determinations of nitrate concentrations.

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