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Plasma Isosorbide Dinitrate Concentrations in Human Subjects after Administration of Standard and Sustained-Release Formulations

D. F. ASSINDER, L. F. CHASSEAUD[x], and T. TAYLOR

Abstract □ After sublingual administration of 5 mg of isosorbide dinitrate, mean plasma concentrations (± *SD*) peaked (8.9 ± 3.1 ng/ml) at 15 min after dosing and declined with a half-life of 30 min. After oral administration of 5 mg, mean concentrations peaked (3.1 ± 0.7 ng/ml) at 30 min and declined with a half-life of 40 min. After oral administration of 20 mg in a sustained-release tablet, mean concentrations initially peaked (1.4 ± 1.2 ng/ml) at 40 min, declining to 0.9 ± 0.5 ng/ml after 8 hr. Mean concentrations were maintained above half the mean peak level during 10 hr. Because of probable rapid first-pass metabolism, the bioavailability of isosorbide dinitrate after administration of the oral dose of the standard tablet was 58% of that from the sublingual dose, and the bioavailability from the sustained-release tablet was 47% of that from the sublingual dose of the standard tablet. The time course of mean plasma concentration data could be described by a one-compartment model; but a more complex model, taking the pass effect into account, probably is needed for a better description of the pharmacokinetics of isosorbide dinitrate.

Keyphrases □ Isosorbide dinitrate—pharmacokinetics, oral and sublingual administration compared, standard and sustained-release tablets compared, humans □ Pharmacokinetics—isosorbide dinitrate, oral and sublingual administration compared, standard and sustained-release tablets compared, humans □ Vasodilators—isosorbide dinitrate, pharmacokinetics, oral and sublingual administration compared, standard and sustained-release tablets compared, humans

The vasodilator isosorbide dinitrate has been in use for many years (1–9), but little has been reported regarding its pharmacokinetics in humans because, in part, of the difficulty in measuring small amounts of the drug in blood. Using a GLC method (10), peak plasma concentrations ranging between 10.5 and 34.5 ng/ml in different subjects were measured at 6 min following a 1.25-mg sublingual dose of isosorbide dinitrate. More detailed studies involving the oral administration of 5.4 mg of ^{14}C-isosorbide dinitrate (11) showed that peak levels of unchanged drug of about 5 ng/ml could be expected (12). However, higher concentrations of the respective mononitrate metabolites were present (12).

Isosorbide dinitrate and other organic nitrates are rapidly metabolized by the glutathione *S*-transferases (13, 14). From studies in animals, Needleman *et al.* (15) concluded that after oral administration of any one of the various organic nitrates, such as isosorbide dinitrate, essentially

none of the parent compound was present in the circulation to relax vascular smooth muscle. Previous work (11), however, showed that, in humans, orally administered isosorbide dinitrate does reach the peripheral circulation intact. Additional evidence is now presented, obtained from studies of standard and sustained-release formulations of the drug.

EXPERIMENTAL

Materials—Standard tablets[1] of isosorbide dinitrate for oral or sublingual administration each contained 5 mg of drug. Sustained-release tablets[1] for oral administration each contained 20 mg.

Drug Administration—Six male subjects[2], 22–39 years old and 57–89 kg, were given one tablet of each formulation of isosorbide dinitrate according to a randomized complete crossover treatment schedule, with about 1 week between dosing.

Following an overnight fast, the oral doses were taken with 100 ml of water and the sublingual doses were retained under the tongue until completely dissolved but were not swallowed deliberately. The subjects fasted for 4 hr following the dose. Blood samples were regularly withdrawn by venipuncture from the antecubital veins into heparinized tubes, and the plasma was immediately separated by centrifugation for rapid analysis.

The blood pressure of each subject was monitored for the first 2 hr after dosing. Decreases in blood pressure occurred after administration of all three formulations but particularly after the sublingual form. The subjects were under continual medical supervision.

Measurement of Drug—Concentrations of isosorbide dinitrate in plasma were measured by GLC using electron-capture detection by a modification[3] of the method of Rosseel and Bogaert (10). Glycerol trinitrate was used as the internal standard; under the conditions employed, it and isosorbide dinitrate were eluted as symmetrical peaks with retention times of 2 and 6 min, respectively. The limit of detection of isosorbide dinitrate in plasma was 0.5 ng/ml. The standard curves were prepared from known amounts of isosorbide dinitrate added to control plasma.

RESULTS

Plasma Concentrations—Fifteen minutes after administration of the standard tablet as a sublingual 5-mg dose, the peak of mean concentrations (±*SD*) was 8.9 ± 3.1 ng/ml (Table I and Fig. 1). Mean concentrations thereafter declined rapidly to 0.8 ± 0.3 ng/ml after 2 hr and were below the limit of detection (<0.5 ng/ml) at 4 hr after dosing. After administration of the standard tablet as an oral 5-mg dose, a peak of mean concentrations of 3.1 ± 0.7 ng/ml was reached at 30 min (Table I and Fig. 1). Mean concentrations declined to 0.7 ± 0.2 ng/ml at 2 hr and were below the limits of detection at 4 hr after dosing. After administration of 20 mg of isosorbide dinitrate as the sustained-release tablet, an initial peak of mean concentrations of 1.4 ± 1.2 ng/ml occurred at 40 min; concentrations remained at about this level during 1–6 hr (Table I and Fig. 1). Thereafter, mean concentrations declined to the limits of detection at about 12 hr after dosing.

After oral or sublingual doses, peak concentrations in individual subjects varied more than twofold. After administration of the 20-mg sustained-release tablet, at least two peak levels in the plasmas of five of the six subjects were measured (Table I). The first peak occurred at 1.5 hr after administration (0.9–3.1 ng/ml), and the second occurred between 4 and 6 hr (1.4–3.0 ng/ml). Three peak levels in the plasma of Subject 4 were measured: at 40 min, 2.2 ng/ml; at 2 hr, 2.1 ng/ml; and at 6 hr, 3.0 ng/ml. Plasma concentrations were maintained at a plateau during approximately 40 min–8 hr after dosing, and the average plateau (steady-state) plasma concentration during this time was 1.4 ng/ml (range of 1.3–1.9 ng/ml). Mean concentrations were maintained above a value of half the average plateau level during 10 hr after dosing; *i.e.*, the mean half-peak value duration time for this formulation was approximately 10 hr. In contrast, the mean half-peak value duration time for the oral dose of the standard tablet was approximately 1 hr, and the ratio, R_Δ, of the half-peak value duration times was 10. The R_c of peak mean concentrations after administration of the sustained-release tablet and the oral dose standard tablet was 1.4/3.1 = 0.45. The retard quotient (R_Δ, R_c) was (10.0, 0.45) for this pair of formulations; therefore, the *in vivo* performance of the sustained-release formulation was fairly good (16).

Table I—Plasma Isosorbide Dinitrate Concentrations (Nanograms per Milliliter ± *SD*, *n* = 6)

Minutes	Route of Administration: Sublingual	Oral	Oral Sustained Release
5	4.2 ± 2.2	—	—
10	8.7 ± 3.8	—	—
15	8.9 ± 3.1	2.4 ± 0.7	0.6 ± 0.5
30	6.5 ± 2.0	3.1 ± 0.7	1.0 ± 1.0
45	4.7 ± 1.5	2.6 ± 0.6	1.4 ± 1.2
60	3.3 ± 1.2	2.0 ± 0.6	1.3 ± 0.7
90	1.7 ± 0.5	1.1 ± 0.3	1.4 ± 0.5
120	0.8 ± 0.3	0.7 ± 0.2	1.4 ± 0.6
240	ND[a]	ND	1.3 ± 0.5
360	ND	ND	1.9 ± 0.8
480	—	—	0.9 ± 0.5
720	—	—	ND[b]

[a] ND = not detected (<0.5 ng/ml). [b] Concentrations (1.6 ng/ml) detected in one subject only.

Bioavailability—The bioavailability from the drug formulations was compared indirectly from the peak plasma concentrations and their times of occurrence. The first peak levels after administration of the sustained-release tablet were much lower (mean 1.8 ± 0.8 ng/ml) and occurred later (78 min) than those after administration of the sublingual dose (9.7 ± 2.1 ng/ml at 12.5 min) or the oral dose (3.3 ± 0.6 ng/ml at 27.5 min) (Table II and Fig. 1). The rates of bioavailability were obviously lowest after administration of the sustained-release tablet, and rates after administration of the oral dose were lower than those after administration of the sublingual dose of the standard tablet.

The extent of bioavailability was estimated by comparing the areas under the plasma concentration–time relationships (Fig. 1), taking the sublingual dose of the standard tablet as a reference. With the sublingual and oral doses of the standard tablet, plasma concentrations were below

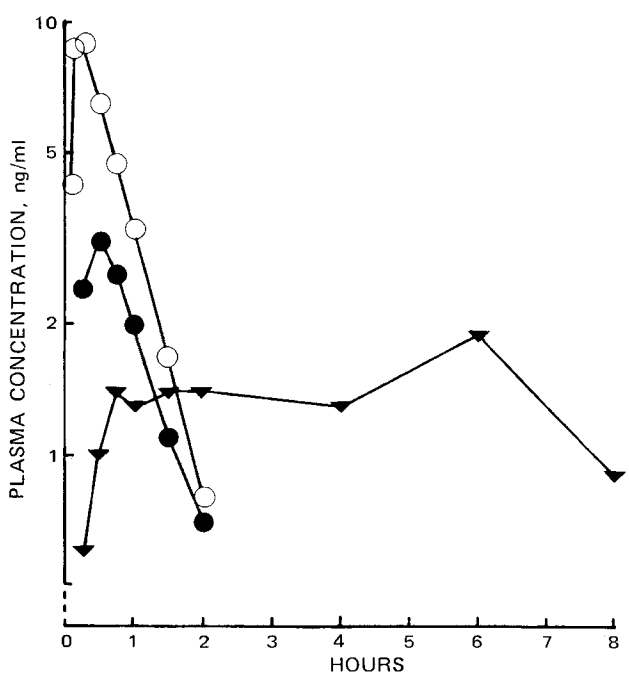

Figure 1—*Mean plasma concentrations of unchanged drug after administration of different formulations of isosorbide dinitrate to human subjects. Key:* ○, *5 mg sublingual;* ●, *5 mg oral; and* ▼, *20 mg oral sustained release.*

[1] Isoket, batches 10421 (standard) and 12463 (sustained release), provided by Pharma Schwarz GmbH, Monheim, Germany.

[2] The subjects were thoroughly screened medically and biochemically soon before and after the studies and were judged to be in good health. The subjects gave their consent to participate after the purpose of the studies and the nature of the drug had been explained.

[3] To be reported elsewhere.

Table II—Peak Isosorbide Dinitrate Concentrations and Their Times of Occurrence in Individual Subjects

Subject	Sublingual		Oral		Oral Sustained Release	
	Peak Level, ng/ml	Minutes	Peak Level, ng/ml	Minutes	Peak Level[a], ng/ml	Minutes[a]
1	7.2	15	3.2	30	3.1	40
2	9.5	10	3.5	45	1.3	90
3	6.9	15	4.1	30	1.7	120–240
4	9.6	10	3.4	15 and 30	2.2	40
5	10.0	10	2.2	30	1.3	30–60
6	15.0	15	3.3	30	0.9	60–90
Mean (±*SD*)	9.7 (±2.1)	12.5	3.3 (±0.6)	27.5	1.8 (±0.8)	78

[a] Initial peak level after administration of the sustained-release tablet containing 20 mg of drug. Several peak levels occurred in plasma of individual subjects.

the limits of detection 4 hr after administration, and areas to 4 hr were equivalent to "areas to infinite time," which are proportional to the fraction of the dose absorbed. With the sustained-release tablet, plasma concentrations were relatively high at the last time of sampling in one subject (12 hr), and comparison of areas to this time may have slightly underestimated the bioavailability from the formulation.

Measured areas under the concentration–time relationships were corrected for dose–body weight variations because unequal doses were administered (Table III). The ratios of corrected areas, with the area after administration of the sublingual dose as reference, provided an estimate of the relative fraction of the dose absorbed into the peripheral circulation and, hence, the bioavailability of isosorbide dinitrate from the standard tablet, oral dose, and the sustained-release tablet. The mean bioavailability from the standard tablet after oral administration was 58% of that from the standard tablet after sublingual administration. So calculated, the mean bioavailability of isosorbide dinitrate from the sustained-release tablet was 47% of that from the sublingual dose of the standard tablet. However, since comparison of areas to 12 hr after administration of the sustained-release tablet may have led to an underestimation of bioavailability, it was likely that a similar fraction of the dose was absorbed from both the sustained-release tablet and the standard tablet after oral administration.

Pharmacokinetics—The half-lives of drug elimination were calculated by least-squares regression analysis of $\log_e$ (concentration) against time from data points on the terminal linear section of the curve (Fig. 1). After sublingual doses, more than 96% of the total variance was accounted for by the regression, and half-lives were adequately estimated from the data. These half-lives were similar in individual subjects, with a mean of 0.5 hr (range of 0.47–0.53 hr; Fig. 1). After oral doses of the standard tablet, more than 93% of the variance was accounted for by the regression, and half-lives were again adequately estimated from the data. The mean half-life after these doses was 0.67 hr, with a wider range (0.47–1.05 hr) than after administration of the sublingual dose. A more prolonged absorptive phase after oral doses may have prolonged the half-lives after oral doses, although the difference in mean half-life after administration by these two routes was not statistically significant ($p > 0.05$).

Inspection of the mean plasma concentrations (Fig. 1) indicated that the data might be fitted to a one-compartment model (17). Accordingly, the rate constants for absorption were calculated by the method of Saunders and Natunen (18) assuming a one-compartment model. After sublingual and oral doses, the mean concentration–time relationships were described by the equations:

$$C_{\text{sublingual}} = 12.25(-e^{-0.2877t} + e^{-0.0229t}) \quad \text{(Eq. 1)}$$

$$C_{\text{oral}} = 5.40(-e^{-0.1093t} + e^{-0.0171t}) \quad \text{(Eq. 2)}$$

respectively. The calculated parameters of the model are given in Table IV; it was assumed that the dose was completely absorbed by the sublingual route and that 58% of the dose was absorbed after oral administration (see *Bioavailability* section).

This model requires a very large "unphysiological" volume of distribution and a high plasma clearance of 10 liters/min. The volume of distribution calculated from the mean data after oral administration (626 liters) was, however, larger than that calculated from data after sublingual administration (443 liters). After oral administration, the volume of distribution, V_D, was calculated for individual subjects both from the model parameters and from the expression V_D = clearance/k_e (where k_e is the elimination rate constant); good agreement was found between the two methods of calculation. The *in vivo* release rate of drug from the sustained-release tablet was calculated to be 1.2 mg/hr.

If the bioavailability of the drug from the sustained-release formulation was similar to that from the standard tablet after oral administration (see *Bioavailability* section), *i.e.*, 58% of the dose was absorbed, then the sustained-release tablet would be expected to supply drug over approximately 10 hr. Inspection of Fig. 1 indicated that plasma concentrations were maintained during 1–8 hr after dosing, in reasonable agreement with the calculated release rate.

Table III—Areas[a] under the Plasma Concentration–Time Relationship to 4 hr after Administration of Sublingual and Oral Doses of the Standard Tablet and to 12 hr after Administration of the Sustained-Release Tablet

Subject	Sublingual	Oral	Oral Sustained Release
1	71.6	62.2	59.0
2	132.7	75.5	50.9
3	87.3	53.9	38.0
4	86.2	59.2	59.2
5	129.7	62.0	44.7
6	190.3	46.0	27.3
Mean (±*SD*)	116.3 (±44.0)	59.8 (±9.8)	46.5 (±12.5)

[a] Corrected for dose–body weight variations. Units of ng × hr/ml/mg/kg.

DISCUSSION

Plasma concentrations of isosorbide dinitrate observed after oral doses (Table I) were in fairly good agreement with those measured using radiotracer methods (11). Concentrations observed after sublingual doses were somewhat lower than those reported by others (10). The plasma half-life of isosorbide dinitrate is short, probably too short to support the role of the drug as a relatively long-acting vasodilator. The pharmacologically active metabolites (19, 20), the two isosorbide mononitrates, also might contribute to drug action. These studies showed (Fig. 1) that the use of a sustained-release formulation may prolong the plasma drug concentrations and, probably, the pharmacological action.

Table IV—Parameters of a One-Compartment Open Model for the Pharmacokinetics of Isosorbide Dinitrate[a]

Parameter	Route of Administration	
	Sublingual	Oral
Absorption rate constant, min^{-1}	0.2877	0.1093
Absorption half-life, min	2.4	6.3
Elimination rate constant, min^{-1}	0.0229	0.0171
Elimination half-life, min	30.3	40.4
Volume of distribution, liters	443	626
Plasma clearance, liters/min	10.15	10.70

[a] Calculated from mean concentration data.

The one-compartment model appeared to describe adequately the data obtained after oral administration, but calculation of the absorption rate constant failed in computing with some sets of data from individual subjects after sublingual administration. It was likely, therefore, that after the absorption phase, a very rapid distribution phase preceded the linear elimination phase of the concentration–time relationships but that there were insufficient early sampling times to allow its detection. A simple one-compartment model, therefore, is probably not adequate to describe the pharmacokinetics of isosorbide dinitrate.

Moreover, isosorbide dinitrate is absorbed completely from the GI tract after oral doses (12). Although the reduced bioavailability of isosorbide dinitrate from the standard tablet after oral administration could have been formulation related, the decreased bioavailability after oral doses probably was due to rapid metabolism by the liver after absorption into the hepatoportal system, the drug being subjected to a considerable first-pass effect as occurs for certain other drugs (21–23). Rapid metabolism also explains the very large volumes of distribution and clearances of isosorbide dinitrate by applying a simple one-compartment model to the data. An adequate model of the pharmacokinetics of isosorbide dinitrate must include a pass effect and can be constructed only from a more intensive study of plasma concentrations of the drug and its metabolites after different routes of administration.

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Systems Approach to Vaginal Delivery of Drugs IV: Methodology for Determination of Membrane Surface pH

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Abstract □ A physical model including a diffusional layer in series with the membrane was developed for studying the possible differences between the pH at the membrane surface and that in the bulk solution. Both the membrane-secreted substances (acids and bases) and buffer constituents in the bulk solutions are assumed to contribute to the surface pH. Equations derived for this situation, together with experimental determinations of the acidic dissociation constant of the secreted material, the total secretion flux, the flux of total secreted acidic species, and the diffusional layer thickness, allow estimates to be made of the pH at the membrane surface. With the rabbit vagina, the membrane surface pH was close to that of the bulk solution in most cases. These results were supported by the fact that the absorption of 1-alkanoic acids in pH 2.2 phosphate buffers was relatively constant over the buffer concentration range of 0.003–0.1 *M* phosphate.

Keyphrases □ Drug delivery, vaginal—membrane surface pH determined, compared to bulk solution pH, rabbits □ pH—membrane surface compared to bulk solution, vaginal drug delivery model, rabbits □ Vaginal drug delivery—model, membrane surface pH determined, compared to bulk solution pH, rabbits

The objectives of the present investigations were to develop suitable methodology in an appropriate animal system to obtain firm baseline data on vaginal absorption, to delineate the general barrier properties of the vaginal mucosa, and to develop quantitative integrated models describing both the release of drug from vaginal devices and the subsequent drug absorption.

The first paper (1) in this series described a method for evaluating drug absorption in the vagina, using the rabbit doe as a prototype animal. A rib-cage-type cell, which provided a closed absorptive compartment in the vaginal tract, was designed and surgically implanted in the rabbit. Drug absorption was determined by perfusing the drug solution through this system and following the time changes in drug concentration in the system. The study showed that the method generally affords good precision