BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 2, 255–263 (1981)

ISOSORBIDE 5-MONONITRATE PHARMACOKINETICS IN HUMANS

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ABSTRACT

When isosorbide 5-mononitrate was intravenously infused at a rate of 4 mg h^{-1} for 2·5 h to five human subjects, its concentrations in plasma increased slowly to 185 ng $ml^{-1} \pm 5$ per cent C.V. at 2·5 h and a steady-state plasma level was not reached during the infusion. When the infusion was discontinued, plasma drug concentrations declined with an elimination half-life of 4·2 h ± 6 per cent C.V. The systemic clearance after the infusion doses was 132 ml $min^{-1} \pm 18$ per cent C.V. and the volume of distribution was 48·4 l ± 16 per cent C. V. After equal oral doses of 10 mg, the peak plasma isosorbide 5-mononitrate concentration of 191 ng $ml^{-1} \pm 16$ per cent C.V. was reached at 1·1 h ± 30 per cent C.V., and plasma levels declined with a terminal half-life of 4·9 h. The complete systemic availability of isosorbide 5-mononitrate indicated that pre-systemic elimination after the oral doses was negligible. A one-compartment open model appeared adequate to describe the plasma level data after intravenous infusion and oral doses. After single oral doses of 10 mg isosorbide dinitrate, the peak plasma concentration of the 5-mononitrate metabolite of 72 ng $ml^{-1} \pm 27$ per cent C. V. occurred at 1·7 h ± 41 per cent C.V. Approximately 50 per cent (range 22–68 per cent) of the oral dose of isosorbide dinitrate circulated in plasma as the 5-mononitrate metabolite. The pharmacokinetics of isosorbide mononitrates are markedly different to those of the parent dinitrate and these differences follow from the greater systemic availability and volume of distribution of the mononitrates.

KEY WORDS Isosorbide 5-mononitrate Isosorbide dinitrate Pharmacokinetics Nitrates Intravenous infusion

INTRODUCTION

The 'long acting' organic nitrate vasodilator isosorbide dinitrate (1,4:3,6-dianhydrosorbitol-2, 5-dinitrate) has been used for many years to treat angina pectoris.[1–3] The dinitrate is biotransformed in animals and man by glutathione

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0142–2782/81/030255–09$01.00

Received 21 November 1980
Revised 13 January 1981

S-transferases to the 2- and 5-mononitrates and to isosorbide.[4-6] Isosorbide 2- and 5-mononitrates share the pharmacological action of the parent drug,[7,8] albeit at lower potencies, and it is probable that the mononitrate metabolites, especially the 5-isomer, contribute to the observed effects and particularly the duration of action of doses of isosorbide dinitrate *in vivo*. The usefulness of isosorbide 5-mononitrate in the treatment of angina pectoris has been reported[9] and the study described in this paper was designed to obtain pharmacokinetic data which would assist the therapeutic use and help in the rational design of clinical trials of this compound.

MATERIALS AND METHODS

Drug formulations

Ampoules of isosorbide 5-mononitrate in solution in sterile isotonic saline (1 mg ml^{-1}), batch 780243, tablets of isosorbide 5-mononitrate each containing 5 mg drug, batch 770753, and tablets of isosorbide dinitrate each containing 5 mg (Isoket®, batch 03852) were supplied by Pharma Schwarz-Monheim GmbH, West Germany. For use, 10 ml of the solution (10 mg) were diluted to 250 ml with sterile isotonic saline for intravenous administration. Analytical standards of isosorbide dinitrate, isosorbide 5-mononitrate and isoidide dinitrate were also supplied by Pharma Schwarz-Monheim GmbH. Glyceryl trinitrate was obtained from a local pharmacy as a solution in ethanol (1 per cent w/v).

Selection of subjects

Six healthy adult male subjects, age range 19–24 years, weight range 64–82 kg were selected and remained under medical supervision during the study. The subjects consented to participate after they had been told of the nature of the drugs, the investigative procedure and the objectives of the study. They were given complete physical examinations, which included ECG and extensive laboratory screening tests, both before and after the study. No other drug was ingested. The study was reviewed and approved by the relevant Ethics Committee.

Only one subject complained of 'nitrate headache' (after the dose of isosorbide dinitrate). During the infusion of isosorbide 5-mononitrate one other subject reported discomforture due to low-grade thrombophlebitis in the right median antecubital vein not used for infusion. This condition, which resolved without treatment, was considered to be a consequence of the fairly intensive blood sampling schedule, but nevertheless this subject was immediately withdrawn from the study and did not receive the oral dose of isosorbide 5-mononitrate.

Dosing schedule and sampling

The subjects were fasted for 12 h before drug administration and for 4 h afterwards. Each received a single oral dose of 2 tablets of isosorbide dinitrate

(total dose 10 mg) together with 100 ml water. One week later, 10 mg isosorbide 5-mononitrate was infused by gravity into an antecubital vein at a rate of 4 mg h^{-1} during 2·5 h (100 ml fluid h^{-1}). This infusion rate was chosen as one which would be typical of those used in therapy. One week later, each subject received a single oral dose of 2 tablets of isosorbide 5-mononitrate (total dose 10 mg) together with 100 ml water.

Blood samples were withdrawn from the antecubital veins (not used for infusion) at several times after the oral doses and also during and after the infusion. Blood cells were removed by centrifugation and the separated plasma was stored at $-20°$ until taken for analysis.

Measurement of plasma concentrations of isosorbide dinitrate and the 5-mononitrate

Plasma concentrations of isosorbide dinitrate were measured by a gas chromatographic method.[10] Calibration lines of peak height ratios of isosorbide dinitrate to the internal standard glyceryl trinitrate were constructed over the range 1–10 ng ml^{-1} and the recovery of isosorbide dinitrate over this range was 88 per cent ±7 S.D. The recovery of the internal standard was 84 per cent ±6 S.D. The coefficients of variation of the means of replicate measurements ($n = 5$) were ±20 per cent at 1 ng ml^{-1} and ±11 per cent at 10 ng ml^{-1}. The standard error of taking the calibration line as a measure of isosorbide dinitrate concentration was 1 ng ml^{-1}. Concentrations of isosorbide dinitrate were measured by reference to a calibration line constructed from plasma containing added isosorbide dinitrate and internal standard and were therefore automatically corrected for small losses in analysis.

Plasma concentrations of isosorbide 5-mononitrate were also measured by a gas chromatographic method. Plasma was washed with *n*-heptane. Isosorbide 5-mononitrate, which remained in the aqueous phase, was extracted twice by diethylether after addition of an internal standard (isoidide 2,5-dinitrate). After evaporation of the pooled ether extracts almost to dryness, the residue was dissolved in ethanol and portions of the ethanolic solution were injected into a gas chromatograph fitted with an electron-capture detector. The 1·5 m × 2 mm i.d. glass column was packed with 10 per cent OV17 on 100–120 mesh Gas Chrom Q support. The carrier gas was argon-methane (9 : 1 v/v) at a flow rate of 50 ml min^{-1}. The instrument temperatures were oven 150°, detector 200° and injector 200°. Under these conditions isosorbide 5-mononitrate and the internal standard were eluted with retention times of 7·5 and 6·5 min respectively.

Calibration lines of peak area ratios of isosorbide 5-mononitrate were constructed over a range of up to 300 ng ml^{-1} from plasma containing added isosorbide 5-mononitrate and internal standard and were therefore automatically corrected for small losses in analysis. The recovery of isosorbide 5-mononitrate (over the range 25–200 ng ml^{-1}) and the internal standard were 84 per cent ±9 S.D. and 94 per cent ±3 S.D. respectively. The coefficients of variation of the mean of replicate measurements were ±25 per cent at 25 ng ml^{-1}

and ±7 per cent at 300 ng ml^{-1}. The limit of detection of concentrations of isosorbide 5-mononitrate was arbitrarily set at 25 ng ml^{-1}, the lowest data point on the calibration line. After administration of the doses of isosorbide dinitrate, drug and metabolite concentrations were assayed separately.

Data processing

Half-lives of the terminal linear sections of the $\log_e$ concentration-time curves were calculated after least squares regression analysis. Areas under the concentration-time curves were calculated by numerical integration and adjusted to infinite time (total areas). Differences between mean areas after administration were tested for statistical significance by paired '*t*'-tests. Pharmacokinetic parameters were calculated using equations discussed by Gibaldi and Perrier.[11]

RESULTS

During the infusion of isosorbide 5-mononitrate at a rate of 4 mg h^{-1}, a 'plateau' plasma concentration was not reached, indicating that steady-state levels were not approached, but a mean of peak levels of 185 ng ml^{-1} occurred at 2·5 h when the infusion was discontinued (Table 1, Figure 1). Thereafter, mean plasma concentrations of isosorbide 5-mononitrate declined during 12 h to 39 ng ml^{-1} and the compound was not detected in plasma withdrawn at 24 h after the end of infusion. After the infusion was discontinued plasma concentrations of isosorbide 5-mononitrate declined monoexponentially with a calculated half-life of 4·2 h (Table 2) and this half-life was therefore interpreted as the elimination half-life of

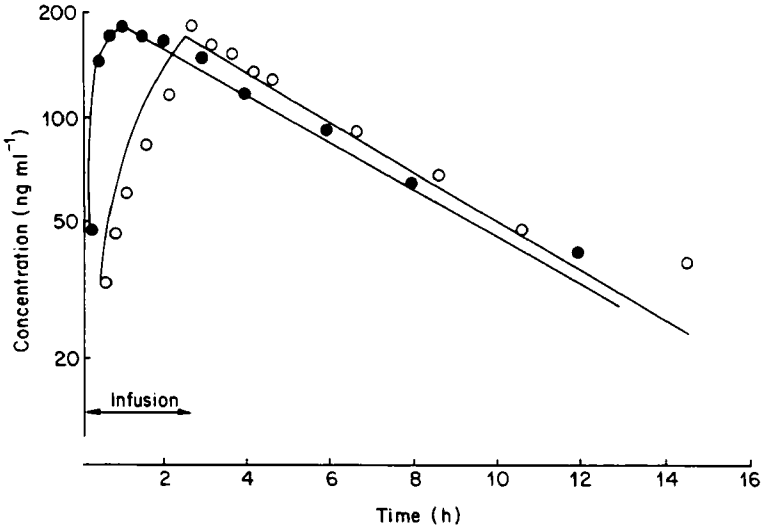

Figure 1. Mean plasma concentrations of isosorbide 5-mononitrate during and after infusion at a rate of 4 mg h^{-1} for 2·5 h (O——O) and after single oral doses of 10 mg (●——●). Semilogarithmic scale. The solid lines represent concentrations predicted by a one-compartment open model

Table 1. Mean plasma concentrations of isosorbide dinitrate after single oral doses of 10 mg, and mean plasma concentrations of isosorbide 5-mononitrate during and after infusion at a rate of 4 mg h^{-1} for 2·5 h, after single oral doses of 10 mg, and after single oral doses of 10 mg of isosorbide dinitrate (equivalent to 8·1 mg isosorbide 5-mononitrate). Coefficients of variation (%) in parentheses

	Isosorbide 5-mononitrate			Isosorbide dinitrate
Time (h)	10 mg infusion dose	10 mg oral dose	10 mg oral dose of isosorbide dinitrate	10 mg oral dose
0·25	ND	47 (89)	11 (62)	2·9 (37)
0·5	32 (13)	142 (29)	25 (58)	6·9 (32)
0·75	46 (24)	173 (23)	50 (43)	6·4 (37)
1	61 (20)	186 (14)	58 (28)	4·1 (37)
1·5	80 (31)	177 (16)	69 (29)	2·4 (61)
2	116 (29)	167 (19)	61 (27)	0·9 (56)
2·5	185 (5)	—	—	—
3	166 (14)	150 (23)	56 (28)	ND
3·25	157 (14)	—	—	—
3·5	151 (16)	—	—	—
4	137 (26)	120 (22)	50 (19)	—
4·5	130 (18)	—	—	—
5	—	—	—	—
6	—	94 (26)	37 (36)	—
6·5	92 (17)	—	—	—
8	—	65 (20)	34 (35)	—
8·5	69 (19)	—	—	—
10·5	48 (10)	—	—	—
12	—	42 (30)	20 (59)	—
14·5	39 (8)	—	—	—

ND = not detected ($<0·5$ ng ml^{-1} isosorbide dinitrate, <25 ng ml^{-1} isosorbide 5-mononitrate).

isosorbide 5-mononitrate. The 'average steady-state level' of 515 ng ml^{-1} was calculated by dividing the infusion rate by the systemic clearance. The systemic clearance of isosorbide 5-mononitrate of 132 ml min^{-1} was calculated by dividing the infused dose by the total area under the plasma concentration-time curve. The volume of distribution of 48 l was calculated by dividing the systemic clearance by the elimination rate constant ($\log_e 2/t_{\frac{1}{2}}$).

After equal oral doses of 10 mg isosorbide 5-mononitrate, the mean of the peak plasma levels of this compound of 191 ng ml^{-1} occurred at a mean time of 1·1 h (Tables 1 and 2, Figures 1 and 2) and the terminal half-life of 4·9 h was similar to that measured after the end of the infusion. The systemic availability of isosorbide 5-mononitrate of 113 per cent was calculated by dividing the total area under the plasma concentration-time curve after the oral doses by that after the infusions, since equal doses were administered by each route (Table 2). The difference between mean areas after administration by each route was not statistically significant ($P>0·05$).

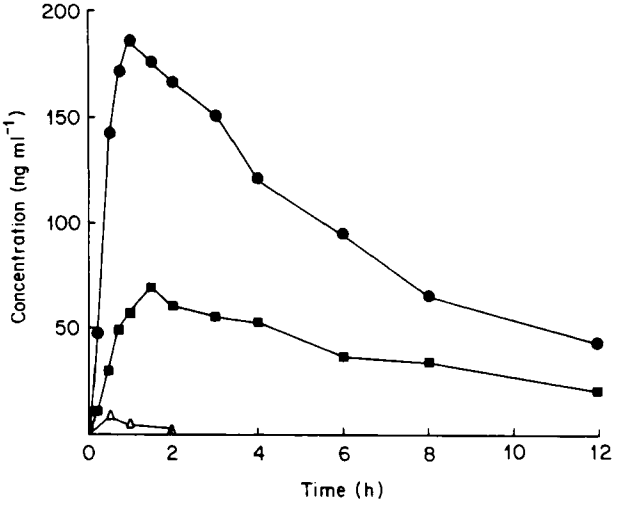

Figure 2. Mean plasma concentrations of isosorbide dinitrate (△——△) and isosorbide 5-mononitrate (■——■) after single oral doses of 10 mg isosorbide dinitrate (equivalent to 8·1 mg 5-mononitrate) and concentrations of isosorbide 5-mononitrate after single oral doses of 10 mg of the 5-mononitrate *per se* (●——●). Linear scale

Table 2. Mean pharmacokinetic parameters of isosorbide 5-mononitrate. Coefficients of variation (%) in parentheses

Parameter	After doses of isosorbide 5-mononitrate	After doses of isosorbide dinitrate
Infusion doses		
Peak level (ng ml^{-1})*	185 (5)	—
Average steady-state level (ng ml^{-1})	515 (16)	—
Systemic clearance (ml min^{-1})	132 (18)	—
Elimination rate constant (h^{-1})	0·164 (6)	—
Elimination half-life (h)	4·2 (6)	—
Volume of distribution (l)	48·4 (16)	—
Total area (ng ml^{-1})	1288 (16)	—
Oral doses		
Peak level (ng ml^{-1})	191 (16)	72 (27)
Time of peak level (h)	1·1 (30)	1·7 (41)
Terminal half-life (h)	4·9 (8)	5·1 (8)
Total area (ng h ml^{-1})	1453 (23)	703 (26)†
Systemic availability (%)	113‡	48†, §

* After infusion for 2·5 h.
† Adjusted for a dose of 10 mg isosorbide 5-mononitrate.
‡ Range 90–129 per cent.
§ Range 22–68 per cent.

When single oral doses of 10 mg isosorbide dinitrate were administered, the mean of the peak plasma concentrations of the dinitrate of 6·9 ng ml^{-1} occurred at 0·5 h, (Table 1, Figure 2) and plasma levels declined with a terminal half-life of 0·6 h. The mean of the peak levels of the 5-mononitrate metabolite of 72 ng ml^{-1} occurred at a mean time of 1·7 h.

The terminal half-life of isosorbide 5-mononitrate, after doses of isosorbide dinitrate, of 5·1 h was similar to that measured after doses of isosorbide 5-mononitrate *per se*. The mean systemic availability of isosorbide 5-mononitrate from the oral dose of isosorbide dinitrate was 48 per cent which indicated that this fraction of the dinitrate (range 22–68 per cent) was converted to, and circulated as, the 5-mononitrate metabolite (Table 2). The difference between mean areas after administration as the 5-mononitrate or as isosorbide dinitrate itself was statistically significant ($P < 0{\cdot}05$).

Using the pharmacokinetic parameters listed in Table 2, the plasma concentrations of isosorbide 5-mononitrate predicted by a one-compartment open model were calculated by the equations:

$$C = \frac{K_0}{VK}(1 - e^{-KT})e^{-Kt} \text{ during and after the infusions}$$

and

$$C = \frac{FD}{V}\frac{K_a}{K_a - K}(e^{-Kt} - e^{-K_a t}) \text{ after the oral doses}$$

Where C is the plasma concentration, F the fraction of the dose D which enters the systemic circulation unchanged (systemic availability), K_0 the infusion rate, V the volume of distribution and K_a and K the rate constants for absorption and elimination respectively. T is the time during infusion (maximum of 2·5 h) and t is the time after infusion and oral doses, but equal to zero during the infusion.[11] A value for K_a of 2·96 h^{-1} was obtained from the mean data after the oral doses by 'stripping' the concentration-time curve. A fairly good visual fit to the observed data was obtained although the predicted levels were consistently higher during the infusion.

DISCUSSION

A one-compartment model seemed to be adequate to describe the pharmacokinetics of isosorbide 5-mononitrate after infusion and oral doses to normal human subjects and in contrast to isosorbide dinitrate,[12] estimates of the terminal half-life of the 5-mononitrate after oral doses were also estimates of the elimination half-life. The high systemic availability of the 5-mononitrate indicated that, again in contrast to isosorbide dinitrate, presystemic elimination processes had negligible effect. A large proportion of oral doses of isosorbide dinitrate circulated in plasma as the 5-mononitrate, and this finding supports the

suggestion that this metabolite contributes to the 'long acting' effects of the parent dinitrate.

The systemic clearance of isosorbide 5-mononitrate was numerically similar to the glomerular filtration rate in man, but this may be coincidental since this compound is known to form a glucuronide conjugate (presumably in the liver) as well as being excreted unchanged in the urine.[6] The volume of distribution approximated that of the total body water, and both volumes of distribution ($r = 0{\cdot}90$, $p < 0{\cdot}05$) and clearances ($r = 0{\cdot}98$, $p < 0{\cdot}01$) were correlated with body weight. The variability of the calculated parameters after the infusion doses was not large; the greatest coefficient of variation (18 per cent, Table 2) was associated with the systemic clearance. As expected, variability of the data was somewhat larger after the oral doses and was largest after administration of the oral doses of isosorbide dinitrate.

Isosorbide 5-mononitrate appeared to be rapidly absorbed, as peak plasma concentrations occurred at approximately 1 h after dosing. Because of the relatively long elimination half-life, plasma concentrations increased only slowly during infusion and plasma levels comparable to the peak levels after oral doses were reached only at 2·5 h after the infusion. Steady-state levels would have been approached (90 per cent) after prolonged infusion for approximately 14 h at the chosen rate of $4\,mg\,h^{-1}$.

The available data on isosorbide 2-mononitrate indicate that the pharmacokinetics of each metabolite are similar, although the elimination half-life of isosorbide 2-mononitrate of 1·8 h is shorter[13, 14] and only approximately 15 per cent of an oral dose of isosorbide dinitrate circulates as the 2-mononitrate metabolite. Differences in the pharmacokinetics of isosorbide dinitrate and the mononitrates appear to be related to their respective systemic availabilities and volumes of distribution. Although the clearances of all three compounds are of similar order, isosorbide dinitrate is poorly available after oral doses and appears to be distributed in a volume which approximates that of the plasma.[12] The mononitrates, in contrast, are completely bioavailable and are distributed in volumes which approximate that of the total body water. Plasma concentrations of the mononitrate metabolites are higher than those of the dinitrate, at least after equivalent oral doses, and remain circulating for considerably longer periods after dosing.

ACKNOWLEDGEMENTS

We thank Drs. N. Pascal and R. Bonn of Pharma Schwarz-Monheim GmbH for their interest and encouragement and for supplies of materials.

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