Influence of Diet on the Single-Dose Pharmacokinetics of Isosorbide 5-Mononitrate and Sustained-Release Isosorbide Dinitrate

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The influence of diet on the single-dose pharmacokinetics of isosorbide 5-mononitrate (IS-5-MN) and sustained-release isosorbide dinitrate (ISDN) was studied in 8 healthy male volunteers. The subjects received either a low-calorie/low-fat diet (LCFD) or a high-calorie/high-fat diet (HCFD) according to a cross-over schedule and were administered the drug in tablet form after breakfast. The study was conducted first in 8 subjects who received a 20 mg IS-5-MN tablet and then in 6 of these individuals who received a 20 mg sustained-release ISDN tablet. After oral doses of IS-5-MN, the plasma drug levels declined monoeXponentially and could be described by a one-compartment open model. There were no significant differences in the pharmacokinetic parameters for IS-5-MN between the LCFD and the HCFD. After administration of sustained-release ISDN, the plasma ISDN levels showed marked variations both between and within individuals. The increase in the mean AUC0–12 values for ISDN with the HCFD was found to exceed 60%, although there was no significant difference between the two diets.

Key words isosorbide 5-mononitrate; isosorbide dinitrate; diet; pharmacokinetics; sustained-release

Organic nitrates have been used extensively in the management of patients with angina pectoris. In Japan, isosorbide dinitrate (ISDN) is the most frequently used nitrate in oral dosage form. However, due to extensive first-pass metabolism, a large proportion of orally administered ISDN is biotransformed to the two main metabolites, isosorbide 2-mononitrate and isosorbide 5-mononitrate (IS-5-MN). In one study in two human subjects, the systemic availability was found to be 3%. In another study, the same investigator found the mean systemic availability of ISDN to be 23% (range 17–26%). As a consequence, ISDN plasma concentrations are very sensitive to changes in the extent of first-pass metabolism, resulting in high intra- and interindividual variances in ISDN blood levels after oral administration. In contrast to ISDN, IS-5-MN, one of the active metabolites of ISDN, does not undergo first-pass metabolism and is completely bioavailable. Thus, IS-5-MN has more predictable plasma concentrations, hemodynamics and clinical effects than ISDN. Oral administration of 20 mg IS-5-MN has previously been shown to be as effective as 20 mg ISDN in sustained-release preparations.

In the last two decades, studies have been performed to investigate the effects of food on the metabolism of drugs, in particular on their bioavailability. Food may affect the extent and rate of absorption, especially of drugs given as sustained-release formulations. Although most drugs are given in conjunction with food, there is very little information in the recent literature about the effects of food on the release profiles of ISDN from sustained-release preparations and the absorption of IS-5-MN from a plain tablet.

We studied the influence of a low-calorie/low-fat and a high-calorie/high-fat diet on the pharmacokinetics of IS-5-MN and ISDN after oral administration of the single standard dose of 20 mg IS-5-MN and 20 mg sustained-release ISDN. Our primary objectives were to assess the influence of any diet-induced physiological changes on the pharmacokinetics of IS-5-MN and ISDN and to obtain pharmacokinetic data regarding IS-5-MN in Japanese subjects which would assist the therapeutic use of this drug.

MATERIALS AND METHODS

Materials The sustained-release ISDN products containing 20 mg of ISDN (Frandol®, lot no. DD392, Toa Eiyo, Ltd., Tokyo, Japan) are tablets consisting of soluble granules and slow-releasing granules coated with wax. Preparations containing 20 mg of IS-5-MN used were plain, uncoated tablets (Itorol®, lot no. DY006, Toa Eiyo, Ltd., Tokyo, Japan). IS-5-MN powder, ISDN powder and isomannide dinitrate used as an internal standard for the determination of ISDN in plasma, were kindly supplied by Toa Eiyo, Ltd. (Tokyo). All other chemicals and solvents used in this study were obtained from standard commercial sources.

In Vitro Dissolution Test The dissolution rates of ISDN from the sustained-release tablets were determined by the following two methods.

a) Rotating basket: The tests were carried out according to JP XII at 100 rpm. The 1st fluid (pH 1.2) for the disintegration test in JP XII was used as the medium during the first 2 h, and then the medium was replaced with JP XII 2nd fluid (pH 6.8).

b) Oscillating basket: The disintegration test device was used with the disk as specified in JP XII. The media used were JP XII 1st and 2nd fluids.

The effects of polysorbate 80 (PS-80) (0.1%) on drug release were investigated. The amount of drug dissolved was determined by the HPLC method, in which the sample solution was filtered (Millex®-HV, 0.45 µm Durapore® membrane) and directly injected.

Subjects Eight healthy male volunteers, ranging from 24 to 45 years of age (mean 28 years), weighing between 53 and 83 kg (mean 63 kg), took part in the study. Six subjects participated in both the IS-5-MN study (1st study) and the ISDN study (2nd study). Age and weight did not differ.

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significantly between the two groups. Each subject received extensive information about the study and gave written informed consent. Ethical approval for the study was obtained from the University Hospital Ethical Committee.

**Study Design** Two independent studies were carried out. Each study had an open, two-way, cross-over design with a 2-week washout period. The study design allowed us to define the pharmacokinetic profiles of IS-5-MN and sustained-release ISDN in direct relation to two specific diets (Table 1).

The subjects abstained from food from 9 p.m. the day before drug intake. They then received a breakfast of the low-calorie/low-fat diet (LCFD) or the high-calorie/high-fat diet (HCFD) according to a cross-over schedule.

In the 1st study, the subjects were given one IS-5-MN tablet and in the 2nd study, were given one sustained-release tablet of ISDN, together with 180 ml of water, at 8 a.m. (0.5 h after breakfast). In both studies, lunch was served 4.5 h later and dinner was served 10.5 h after dosing.

Venous blood samples of 5 ml were collected just before drug intake and 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 h after administration. All blood samples were immediately centrifuged (3000 rpm for 10 min at 0°C) and the separated plasma samples were stored at −20°C until analysis.

**Acetaminophen Study** A study was carried out to examine the influence of the two specific diets on the absorption of acetaminophen. Three volunteers who took part in both the 1st and the 2nd study received five 200 mg acetaminophen tablets (Calonal® O, lot no. 5091T, Showa Yakuhin Kako Co., Ltd., Tokyo, Japan), as described above, 0.5 h after either LCFD or HCFD breakfast, with a 1-week interval. Saliva samples were collected spontaneously by each subject for 2 min into a tube at appropriate intervals for up to 6 h after dosing. The samples were stored at −20°C until assay. The concentrations of acetaminophen in saliva were determined by HPLC. The coefficients of variation of acetaminophen analysis varied from 1.2 to 6.1% over the range 1.0 to 40 μg/ml of acetaminophen. The lower limit of quantitation for acetaminophen was about 100 ng/ml.

**Analytical Method** Plasma concentrations of IS-5-MN and ISDN were measured by gas chromatography with an electron capture detector according to the method of Kato et al. The lower limits of quantitation for IS-5-MN and ISDN were 6 and 0.5 ng/ml, respectively. The interday coefficients of variation for both IS-5-MN and ISDN were less than 10%.

**Pharmacokinetic Analysis** The maximum plasma drug concentration (C_max) and the time to the C_max (t_max) were determined from the highest observed values in the individual plasma concentration–time profiles. The areas under the drug concentration–time curve from zero to 12 h (AUC_0–12) and from zero to 24 h (AUC_0–24) were calculated using the trapezoidal rule. AUC_0–∞ and the mean residence time (MRT) were calculated according to the moment analysis method. A one-compartment open model was fitted to the plasma concentrations of IS-5-MN after administration of IS-5-MN tablets. Estimation of parameters was performed by the nonlinear least-squares method using the program MULTI.

**Statistical Analysis** Paired Student’s t-tests were applied to compare the corresponding parameters between the two diets. Statistical significance was accepted at \( p < 0.05 \).

**RESULTS**

**In Vitro Dissolution Test** Figure 1 shows the dissolution profiles of ISDN from the sustained-release tablets measured by the rotating basket method and the oscillating basket method. The rotating basket method indicated that the drug release rates tended to increase when PS-80 was added to the test medium. The amounts of ISDN released in 8 h from the tablets were 58.9% in the surfactant-free fluid and 80.8% in the fluid containing PS-80.
other hand, revealed that time for 100% dissolution of the IS-5-MN tablets at pH 1.2 was within 5 min.

1st Study The mean plasma concentration–time profiles of IS-5-MN after oral ingestion of a 20 mg IS-5-MN tablet are shown in Fig. 2. The plasma drug levels with both diets declined monoeXponentially and were very similar. Statistically significant difference in the mean plasma IS-5-MN concentrations between the two diets was seen at 0.5 h after dosing, but not at any other sampling times. The mean values of the pharmacokinetic parameters are given in Table 2. The volumes of distribution (Vd) for IS-5-MN were calculated on the assumption of complete bioavailability. 5–8) Paired t-test analysis of the parameters showed that there were no significant differences between the LCDF and the HCDF.

2nd Study The mean plasma concentration–time profiles of ISDN and its metabolite IS-5-MN after oral administration of a single sustained-release tablet are shown for both diets in Figs. 3 and 4. The shape of the individual profiles for ISDN showed considerable variation, both between and within subjects. On average, plasma concentrations of ISDN were higher with the HCFD than with the LCDF. The mean pharmacokinetic parameters of ISDN and IS-5-MN are presented in Table 3. In five

Table 2. Pharmacokinetic Parameters of IS-5-MN after Oral Administration of 20 mg IS-5-MN Tablet

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LCDF</th>
<th>HCFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>tmax (h)</td>
<td>1.3 ± 0.8</td>
<td>1.9 ± 1.0</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>415.2 ± 34.7</td>
<td>369.2 ± 55.0</td>
</tr>
<tr>
<td>AUC0–12 (ng h/mL)</td>
<td>3250.1 ± 335.4</td>
<td>3402.3 ± 633.0</td>
</tr>
<tr>
<td>MRT0–12 (h)</td>
<td>7.4 ± 0.7</td>
<td>8.2 ± 0.9</td>
</tr>
<tr>
<td>k1 (h−1)</td>
<td>3.016 ± 0.208</td>
<td>1.581 ± 0.915</td>
</tr>
<tr>
<td>k12 (h−1)</td>
<td>0.154 ± 0.020</td>
<td>0.148 ± 0.021</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>4.56 ± 0.52</td>
<td>4.78 ± 0.71</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.661 ± 0.119</td>
<td>0.662 ± 0.119</td>
</tr>
</tbody>
</table>

k1: elimination rate constant; t1/2: elimination half-life. For other abbreviations see text. Each value represents the mean ± S.D. of 8 subjects.

Table 3. Pharmacokinetic Parameters of ISDN and Its Metabolite IS-5-MN after Oral Administration of the ISDN Sustained-Release Tablet

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LCDF</th>
<th>HCFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISDN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tmax (h)</td>
<td>2.4 ± 1.2</td>
<td>3.7 ± 2.1</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>7.6 ± 3.9</td>
<td>10.9 ± 4.0</td>
</tr>
<tr>
<td>AUC0–12 (ng h/mL)</td>
<td>32.2 ± 13.3</td>
<td>54.0 ± 22.4</td>
</tr>
<tr>
<td>MRT0–12 (h)</td>
<td>4.1 ± 0.6</td>
<td>4.7 ± 0.7</td>
</tr>
<tr>
<td>IS-5-MN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tmax (h)</td>
<td>4.8 ± 1.3</td>
<td>6.3 ± 1.5</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>99.3 ± 23.6*</td>
<td>125.6 ± 28.7*</td>
</tr>
<tr>
<td>AUC0–24 (ng h/mL)</td>
<td>1293.8 ± 261.3*</td>
<td>1511.2 ± 213.9*</td>
</tr>
<tr>
<td>MRT0–24 (h)</td>
<td>9.2 ± 0.7</td>
<td>9.8 ± 0.7</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.D. of 6 subjects. * is significantly different from paired observations at p<0.05.
of the six subjects, the $AUC_{0-12}$ values for ISDN were larger with the HCFD than with the LCFD. In the other subject, $t_{\text{lag}}$ was longer and $C_{\text{max}}$ was higher with the HCFD than with the LCFD; $AUC_{0-12}$, however, was similar with the two diets. The increase in the mean $AUC_{0-12}$ values for ISDN with the HCFD was found to exceed 60%, although there was no significant difference between the LCFD and the HCFD.

**Acetaminophen Study** Salivary drug levels with the HCFD were not measurable (acetaminophen level < 1 µg/ml) until 15 to 45 min after dosing. This $t_{\text{lag}}$, the time taken to appear in the saliva, and $t_{\text{max}}$ were longer with the HCFD than with the LCFD; however, the differences were not statistically significant (Fig. 5).

**DISCUSSION**

The results of the dissolution test suggested that the release rates of ISDN from the tablets were affected by physiological variables such as bile salts in the digestive fluids and mechanical destructive forces that will arise from digestive actions (grinding or crushing of gastrointestinal (GI) contents), although we could not identify which *in vitro* testing condition was comparable to the destructive force in the GI tract. As many other studies have reported, ingestion of food, particularly of fat, stimulates the secretion of bile. This increase in bile secretion can accelerate the dissolution rates of lipid-soluble compounds and drugs from lipophilic dosage form. The dissolution of ISDN from the sustained-release tablets may be enhanced by both the HCFD itself and the increased secretion of bile salts after HCFD consumption, because in the tablets the slow-releasing granules of ISDN are enveloped with wax and the *in vitro* dissolution rate of ISDN was accelerated by the addition of PS-80. For most sustained-release formulations, the slow release of the drug represents the rate-limiting factor in the process of absorption. As a consequence, the factors directly or indirectly affecting the release rate may influence the absorption of ISDN from the sustained-release tablets.

It is well known that the concomitant ingestion of food may also influence the absorption of a drug by changing the mechanical movement in the GI tract. Absorption is generally altered as a result of a delay in gastric emptying induced by the presence of food as the drug remains in the stomach longer. Prolonged residence in the stomach may have varying effects on drug absorption depending on the drug's solubility, stability in the acidic gastric juices and the lipophilicity of the dissolved molecule. Gastric emptying rates were found to correlate with the nutritive density of the meal. In this study, for acetaminophen, both $t_{\text{lag}}$ and $t_{\text{max}}$ were longer with the HCFD than with the LCFD, although the trends were not significant. As absorption of acetaminophen has previously been shown to be related to the gastric emptying rate, the HCFD may slow gastric emptying of the tablets taken and affect the absorption of ISDN and IS-5-MN.

Administration of the sustained-release ISDN tablets with the HCFD tended to delay $t_{\text{max}}$ to elevate $C_{\text{max}}$ and to increase $AUC_{0-12}$ for ISDN, although these differences were not statistically significant. For both diets, plasma concentrations of ISDN demonstrated consistently high interindividual variations. These large variations of ISDN plasma levels are in accordance with the results of other published studies in which conventional formulations were used, and seem likely to represent greater variations in first-pass metabolism rather than interindividual differences in the drug release from the tablets. The differences between the LCFD and the HCFD may have not been statistically significant because of the large interindividual variability in the pharmacokinetic properties of ISDN. On the other hand, the HCFD significantly increased $C_{\text{max}}$ and $AUC_{0-24}$ for IS-5-MN after administration of ISDN, although these differences were small. And the values of coefficients of variation were about half of the corresponding ISDN values. This is believed to have contributed to the low interindividual variability of IS-5-MN plasma levels.

These results suggest that the absorption of ISDN from the sustained-release tablets may be increased by intake of the HCFD, because Taylor et al. showed that oral doses of ISDN in plain tablet form with a substantial breakfast did not affect the extent of bioavailability of ISDN but significantly reduced its mean $C_{\text{max}}$ value. Increased absorption of ISDN may have been due to increased secretion of bile salts accelerating the release of the drug from the sustained-release tablets, and delayed gastric emptying causing more drug to be dissolved when it eventually enters the small intestine.

The pharmacokinetic parameters for IS-5-MN after oral administration of a 20 mg IS-5-MN tablet presented here were of the same order as those published elsewhere. Intersubject variability was low as indicated by the relatively low standard deviation of most of the calculated kinetic parameters and plasma drug concentrations measured. This was assumed to be because IS-5-MN is rapidly and completely absorbed without any first-pass metabolism. The mean plasma IS-5-MN level at 0.5 h after dosing was significantly lower with the HCFD than with the LCFD. The HCFD had greater tendency to reduce the $k_{b}$ and $C_{\text{max}}$, and to prolong the $MRT_{0-\infty}$ for IS-5-MN. These suggest that slowed gastric emptying may be reducing the rate of drug absorption. It is very likely that
the extent of absorption for IS-5-MN was not significantly altered when the tablet was given with the HCFD, as the AUC_{0-\infty} was very similar with the two diets. IS-5-MN is a hydrophilic drug and its plain tablet showed very fast dissolution in vitro. Thus, the in vivo dissolution of this drug from the tablets with the HCFD may also be comparatively fast.

In conclusion, the absorption of ISDN after administration of the sustained-release tablet studied here appears to be greatly influenced by fatty food intake. In contrast, it appears that a high-fat meal has little effect on the extent of absorption for IS-5-MN from plain tablets. Consequently, the IS-5-MN plain tablet may offer an advantage for clinical use, as its pharmacokinetic profile is predictable and reproducible.

REFERENCES