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Research paper

Pharmacokinetic profile of a new controlled-release isosorbide-5-mononitrate 60 mg scored tablet (Monoket Multitab®)

Armel Stockis[a], Steven De Bruyn[b], Xavier Deroubaix[a], Bernard Jeanbaptiste[a], Edouard Lebacq Jr[c], Fabrice Nollevaux[a], Gianluigi Poli[d,*], Daniela Acerbi[d]

[a]*SGS Biopharma S.A., Wavre, Belgium*
[b]*SGS Biopharma Stuivenberg Research Unit, Antwerp, Belgium*
[c]*SNCP Clinical Pharmacology Centre, La Louviere, Belgium*
[d]*Chiesi Farmaceutici S.p.A., Parma, Italy*

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Abstract

The influences of food, tablet splitting, and fractional dosing on the pharmacokinetics of a new controlled-release double-scored tablet containing 60 mg isosorbide-5-mononitrate (Monoket Multitab®) were investigated in healthy male volunteers. Food interaction was evaluated after single dose administration under fasted conditions and after a standard high-fat breakfast. The effect of tablet splitting was assessed at steady-state, after 5 days of once daily dosing with the tablet taken intact or trisected. The influence of fractional dosing was assessed after 1 and 6 days of daily regimen of 40 mg in the morning (2/3 of a tablet) and 20 mg in the evening (1/3 of a tablet). The pharmacokinetics of isosorbide-5-mononitrate after taking the tablet intact or in three fragments were very similar with a mere 10% increase of maximum plasma concentration (C_{max}) for the latter, while the time to peak (T_{max}) decreased from 5 to 4 h and areas under the concentration vs. time curves (AUCs) were virtually unchanged. Morning trough concentration reached 53 and 46 ng/ml, respectively. Administration of the intact tablet after a high-fat breakfast increased C_{max} by 18% and AUC by 21%, and slightly delayed T_{max} from 5 to 6 h. During fractional dosing, morning and evening C_{max} reached 364 and 315 ng/ml on the first day, and 373 and 300 ng/ml on the 6th day, respectively. The ratio of $AUC_{0-24\ h}$ on the last day to AUC∞ on the first day, was 82.1% (confidence limits 71.7–94.1%) possibly resulting from peripheral volume expansion. The release characteristics of Monoket Multitab® are thus moderately influenced by concomitant intake of food and to a very minor extent by tablet breaking. Fractional dosing allows to achieve lower peak and higher morning trough levels, while total exposure is comparable to that during once daily dosing ($AUC_{0-24\ h,\ s.s.}$ of 5.55 ± 1.78 and 5.71 ± 1.08 μg h/ml).

Keywords: Isosorbide-5-mononitrate; Sustained-release; Angina pectoris; Pharmacokinetics; Drug–food interaction

1. Introduction

Isosorbide-5-mononitrate is an organic nitrate vasodilator that acts by relaxing peripheral vascular muscles and thereby reduces systolic blood pressure. The anti-anginal effect of isosorbide-5-mononitrate and other organic nitrates results from reducing myocardial oxygen demand by causing vasodilatation of the capacitance veins (to decrease preload), thus permitting a reduction in left ventricular volume, and energy expenditure, as well as vasodilatation of the large conductive arteries (to decrease afterload), while increasing myocardial oxygen supply by dilating epicardial coronary arteries [1].

In man, isosorbide-5-mononitrate has an elimination half-life of 4–6 h, and shows complete bioavailability after oral administration [2,3]. Isosorbide-5-mononitrate is cleared from the body almost exclusively by metabolism and the clearance amounts to about 120 ml/min. Only traces of unchanged drug are excreted in the urine. Up to 20% of the administered dose is conjugated to glucuronic acid, whereas the remainder is slowly denitrated to isosorbide, which forms the main metabolic product and is further metabolised to a lesser degree to sorbitol [4,5]. A therapeutic window of plasma isosorbide-5-mononitrate concentrations ranging from a threshold of 100 to a maximum of about 500 ng/ml was proposed on the basis of pharmacodynamic work in healthy volunteers [2,6]. The sigmoid dose–response relationship of isosorbide-5-mononitrate for the fall in pulmonary arterial pressure and increase in workload

* Corresponding author. Chiesi Farmaceutici S.p.A., Via Palermo 26A, I-43100, Parma, Italy. Tel.: +39-0521-279-415; fax: +39-0521-279-889.
E-mail address: g.poli@chiesigroup.com (G. Poli).

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in anginal patients had a $C_{50\%}$ of 365 ng/ml [4]. Tolerance is known to develop when drug concentrations are maintained above a certain critical level, and in particular, when fluctuation of concentrations occurring with usual therapy are not allowed [7]. A nitrate-free period of 8–12 h has been advocated [8]. However, the absence of pre-dose ischaemia rebound in the case of once daily sustained-release (SR) formulation has been attributed to a nitrate-low period instead of a nitrate-free interval [9]. It is recognised that when trough concentrations of about 100 ng/ml are exceeded, tolerance starts to develop, and is fully present when trough levels exceed 300 ng/ml [10,11,12]. The most common dosing regimen is 20 mg two or three times daily for immediate release tablets, and 40 or 60 mg once daily for sustained-release formulations. Once daily SR 120 and 240 mg tablets have also shown their long-term efficacy in stable effort angina up to 12 h post-dose without rebound (zero-hour effect) [13]. Excentric dosing regimens with two split doses in the morning and mid-afternoon, viz., 6–7 h apart, have been advocated by several investigators [11,14,15,16,17,18]. The efficacy of multiple-dose and once daily dosing were not different but the latter regimen was found to provide a better quality of life in large-scale studies [19,20].

The goal for developing this new controlled-release tablet containing 60 mg of isosorbide-5-mononitrate, Monoket Multitab®, was to obtain a formulation exhibiting good absorption, with sufficiently high plasma levels during most part of the day followed by a lower concentration phase in order to prevent nitrate tolerance, while producing a sufficiently long duration of action to allow a once daily regimen. In addition, the tablet was designed to have an oblong shape with two scoring marks allowing to divide it conveniently into either three 20 mg fragments or one 40 mg and one 20 mg fragments. The objectives of the studies reported here were to assess the influence of food intake on bioavailability, to evaluate the impact of tablet splitting on the reproducibility of absorption, and to determine the pharmacokinetic consequences of a fractionated dosing schedule (40 + 20 mg every 12 h).

2. Materials and methods

2.1. In vitro dissolution and tablet splitting

Monoket Multitab® tablets (batch no. 98/0002/0) were submitted to in vitro dissolution tests under five different conditions ($n = 12$): complete tablets either intact or after splitting in three parts along the scores, central or lateral part only, and 2/3 of a tablet. The determinations were performed on a validated Sotax 6-vessel paddle dissolution apparatus operated at 125 rpm and 37°C; each vessel contained 0.5 l of pH 1.2 buffer (2 g NaCl and 7 ml concentrated HCl per litre). Isosorbide-5-mononitrate was determined by reversed-phase (C18) high pressure liquid chromatography (HPLC) with a water/methanol (80:20) mobile phase and 230 nm spectrophotometric detection. The retention time was about 6 min. The dissolved amounts were determined after 1, 4, and 8 h, and were corrected for the actual weight of each individual tablet or part of tablet. The similarity factor $f2$ [21] was computed for each dissolution profile relatively to that of the intact tablet. The accuracy and precision of tablet scoring were also assessed by weighing ($n = 12$) intact tablets, 2/3 tablets, central thirds and lateral thirds, and computing the corresponding means, standard deviations, and coefficients of variation.

2.2. Subjects

The three clinical studies were performed in compliance with the principles of the Declaration of Helsinki and its latest amendment. The experimental protocols and informed consent procedures were approved by registered Medical Ethics Committees (Food interaction and tablet splitting protocols by SNCP Ethics Committee, La Louviere, Belgium; fractional dosing protocol by Independent Ethics Committee (IEC) of City Public Hospitals, Antwerp, Belgium). Healthy male volunteers were selected from the investigator's panel after having undergone a thorough medical examination involving medical history, physical examination, electrocardiogram, and routine laboratory tests. They were aged 20–45 years and had a normal body weight (range: 63–91 kg) for their height (range: 165–189 cm). None of the subjects had received any medication for at least 14 days before the study. After having been informed of the nature and implications of the trial, and before entering the study, all the subjects gave their consent in writing.

2.3. Food interaction protocol

The study was carried out according to a randomised, two-way crossover design in ten subjects. They took a single dose of one Monoket Multitab® tablet either in the fasting state (overnight fast until 4 h post-dose) or after a standardised high-fat breakfast (200 ml of light coffee, two scrambled eggs, four slices of bacon, three slices of bread, 20 g butter and jelly). A washout period of 2 weeks separated the two treatment phases.

Plasma samples were obtained before dosing and 0.5, 1, 2, 4, 5, 6, 8, 10, 12 and 24 h after administration.

2.4. Tablet splitting protocol

The study was carried out according to a randomised, repeated dosing, three periods, and three sequences crossover design in nine healthy subjects. On each of the three study periods, the subjects received one of the following treatments during 5 days: Monoket® 20 mg immediate release tablet three times daily (t.i.d.) at 8.00 am, 1.00 pm and 6.00 pm; Monoket Multitab® 60 mg tablet, taken intact once daily at 8 h; Monoket Multitab® 60 mg divided in three

equal fragments along the scoring marks and taken once daily at 8 h. Ten days separated the end of each period and the beginning of the next one. Plasma samples were obtained at pre-dose on days 1, 3, and 4 and on day 5 at pre-dose and 0.5, 1, 2, 4, 5, 6, 8, 10, 12, and 24 h after administration.

2.5. Fractional dosing protocol

In this study, 12 subjects received two-thirds (40 mg) of one Monoket Multitab® tablet in the morning within 30 min after a standard high-fat breakfast. They received a standard lunch 4 h later, and took the remaining third of the tablet (20 mg) 12 h after the first dose, within 0.5 h after a standard dinner. Serial blood samples were obtained before and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 (i.e., immediately before the evening dose), 12.5, 13, 14, 15, 16, 17, 18, 20, 22, 24, and 36 h after the morning dose. From days 3–7, the subjects returned to the clinic twice daily for morning and evening meals, and supervised dose intake according to the same schedule as on day 1. A second pharmacokinetic profile was obtained on day 8, following the same procedures as on day 1. A total of 44 blood samples were obtained in each subject.

2.6. Sample collection

Blood samples (10 ml in the first two studies, 7 ml in the third study) were obtained by puncture in a vein of the forearm. They were collected into heparin tubes which were immediately chilled and centrifuged ($900 \times g$ for 20 min at 5°C). The plasma was separated and immediately stored at −20°C (two tubes per sample) until submitted for analysis.

2.7. Analytics

Thawed plasma samples (0.25–1 ml) were mixed with isosorbide-2-mononitrate internal standard solution and submitted to double extraction (3 ml × 2) by dichloromethane/diethyl ether (3:5). The organic phase was evaporated to dryness and the residue was taken up into cyclohexane. For the first two studies, plasma concentrations of isosorbide-5-mononitrate were determined by capillary column gas chromatography with ^{63}Ni electron capture detection, using a 25 m × 0.32 mm i.d. OV1701 fused silica column. The analytical method, adapted from published procedures [22] was validated in the range from 5 to 400 ng/ml. Within- and between-series coefficients of variation were <15% across the calibration range. Each batch of study samples included a set of nine calibrators, 25–30 unknown, and three duplicate quality control plasma samples at 20, 100, and 300 ng/ml. In-study quality control samples (QC) recoveries (% found over nominal concentration) were close to 100%, and overall coefficients of variation were <15% at the low level and <10% at the intermediate and high levels.

For the third study, plasma concentrations were determined by liquid chromatography with tandem mass spectrometric detection. Chromatographic separation was achieved on a direct phase silica column (spherical 5 μm particle size, 70 mm × 2 mm internal diameter (i.d.)) using a n-hexane mobile phase containing methanol, isopropanol, and ammonium formate as modifiers. The mass spectrometer (SciEx API 365) was equipped with an ion-spray interface and operated in the negative ion mode. The analytical method was validated in the range from 5 to 600 ng/ml in human plasma. Within- and between-series coefficients of variation ranged from 11.6 and 7.4% at the lower end to 6.4 and 4.5% at the upper end of the calibration range. Overall recovery was close to 100%. Each batch of study samples included a set of seven calibrators, about 40 unknown, and three duplicate quality control plasma samples at 8, 150, and 500 ng/ml. In-study mean QC recoveries were close to 100%, and overall coefficients of variation were <15% at the low level, and <10% at the intermediate and high levels. The absolute extraction yield (response of extracted plasma samples to response of extracted blank plasma spiked with the analyte ratio) of isosorbide-5-mononitrate from human plasma was constant (72 ± 7%) across the range and similar to that of the internal standard (66 ± 7%). Dilution tests indicated that plasma samples could be diluted up to ten-fold in pooled human plasma without significant loss of accuracy. The matrix effect was assessed by analysing augmented samples from different donors ($n = 6$): the mean recovery was 94% of nominal concentration with a coefficient of variation of 10%, indicating a negligible effect. Isosorbide-5-mononitrate was found stable after three successive freeze/thaw cycles, after 24 h at room temperature in reconstituted extracts, and in plasma at −20°C during 6 weeks.

2.8. Pharmacokinetic calculations

The maximum plasma concentration (C_{max}) and the time to peak (T_{max}) were directly obtained from the experimental data, without interpolation. The areas under the concentration vs. time curves (AUC_t) were calculated using the linear trapezoidal method from $t = 0$ to $t = 24$ h post-dose. The apparent terminal elimination rate constants were calculated by log-linear regression over the last data points of each concentration vs. time curve. Extrapolated areas were computed according to the standard formula: $AUC_\infty = AUC_t + C_t/K_{el}$[23]. The apparent plasma elimination half-life, $t_{1/2}$, was calculated as $\ln(2)/K_{el}$. At steady-state, the following parameters were also computed: C_{min} (the lowest concentration in the dosing interval), the ratio of C_{max} to C_{min}, and the percent peak–trough fluctuation ($\%PTF = C_{max} - C_{min}/C_{average}$). The accumulation factor was calculated as the ratio of AUC over the 24 h dosing interval at steady-state to AUC_∞ after single dose intake. Calculations were carried out using the Siphar computer program (Simed, France) for the food interaction, and the tablet splitting studies and Win Nonlin 2.1 (Pharsight Corporation, USA) for the fractional dosing study.

2.9. Statistics

The statistical analysis was carried out employing validated SAS® procedures (version 6.12, SAS Institute, USA). Analysis of variance was performed using the SAS® /STAT GLM procedure. The pharmacokinetic parameters calculated for the different conditions (viz., fed vs. fasted, tablet trisected vs. intact, and steady-state vs. single dose) were statistically compared using univariate analysis of variance [24]. The factors of the model were the sequences, the subjects nested to the sequences, the periods, and the treatments (only the subjects and the treatments for the fractional dosing study). A multiplicative model was assumed, which implied logarithmic transformation prior to the analysis, except for T_{max}. Schuirmann's two one-sided *t*-tests method [25] was used to assess the bioequivalence between the treatment conditions by calculating the standard 90% confidence intervals on the test/reference mean ratio (broken over intact tablets, fed over fasted, steady-state over single dose). The inclusion of the confidence interval within 70–143% for C_{max} and 80–125% for AUC was taken as a demonstration of bioequivalence.

3. Results

3.1. In-vitro dissolution

The in-vitro data shown in Table 1 indicate that the splitting of tablets in two or three parts was highly reproducible with relative standard deviations of 0.8–1.5%. The average weight of the central part was 5% smaller than the lateral parts. The lateral and central parts represented 34 and 32% of the intact tablet, while 2/3 tablet amounted to 66% of the intact tablet on average. Similarity factors *f*2 of each tablet fragment relative to the intact tablet exhibited values between 50 and 100, indicating that dissolution profiles differed by 10% or less [21].

3.2. Tolerability and safety

3.2.1. Food interaction study

Seven subjects suffered from moderate headache with both treatments. The adverse events occurred with an equal frequency and intensity under both treatments. One subject dropped out due to severe headache and nausea after the first treatment (fasted) and was not replaced.

3.2.2. Tablet splitting study

Two subjects dropped out on the second day of the first treatment phase after severe headache subsequent to the intake of Monoket 20 mg t.i.d. and were replaced by two other subjects who completed the full study. Among the other subjects, four suffered episodes of headache of low severity not related to a particular treatment. No subject complained during the second and third treatment phases, indicating a possible accommodation to the medication.

3.2.3. Fractional dosing study

All subjects experienced at least one adverse event. The most frequent were headache (45%), skeletal pain (7%), diarrhoea (7%), and vomiting (6%). The severity was graded as mild in 61% of the cases and moderate in 39%. None of the adverse events were classified as serious or severe. They occurred more frequently on the first day of dosing than during the rest of the study (70 vs. 30%). In particular, vomiting episodes occurred only during the first day. One subject withdrew his consent on day 4 because of moderate but persistent headache, and was replaced by another subject who completed the full study.

3.3. Effect of food on pharmacokinetics

Under fasting and fed conditions, the formulation yielded plasma concentrations characterised by slow absorption pattern with a smooth maximum peak reached within about 6 h after dosing. Individual T_{max} values ranged from 4 to 6 h under fasted conditions and from 4 to 8 h when given with a high-fat breakfast (Table 2). No absorption time lag was detected under either treatment condition. Although the two treatments showed a similar slow release pattern, the administration with food yielded 15–20% lower concentration levels at 1 and 2 h post-dose in most subjects but higher levels thereafter (Fig. 1). Food intake increased the C_{max} by 18%, from 399 to 472 ng/ml on the average, but the 90% confidence interval remained within the enlarged limits for C_{max}. Similarly, $AUC_{24\ h}$ and AUC_{∞} were, respectively, 18 and 21% higher with food than under fasted conditions (Table 2). The differences were statistically significant and the upper limit of the corresponding confi-

Table 1
Dissolution data (arithmetic mean ± standard deviation; $n = 12$) of Monoket Multitab® as intact tablet or as different fractions [a]

Formulation	Weight (mg)	% Dissolved 1 h	% Dissolved 4 h	% Dissolved 8 h	*f*2
Intact tablet	515.5 ± 6.2	31.2 ± 3.9	64.4 ± 1.7	91.7 ± 1.8	
Trisected tablet	515.5 ± 6.2	37.5 ± 6.6	76.3 ± 5.0	97.3 ± 2.0	53.6
Lateral part	174.3 ± 2.1	34.5 ± 7.2	74.1 ± 4.4	96.4 ± 1.8	59.1
Central part	165.7 ± 1.4	37.2 ± 10.8	76.8 ± 6.5	97.8 ± 2.9	52.9
2/3 of tablet	340.3 ± 5.1	32.0 ± 2.8	67.1 ± 2.0	91.1 ± 1.5	85.6

[a] The dissolved amounts are normalised for the actual weight of each individual tablet or part of tablet. Similarity factors *f*2 are relative to the intact tablet.

Table 2
Pharmacokinetic parameters of isosorbide-5-mononitrate after single dose under fasted and fed conditions (arithmetic mean ± standard deviation; for T_{max}: median and range; $n = 9$)[a]

PK parameters	Fasted	Fed	LL90	PE	UL90	CV_w
C_{max} (ng/ml)	399 ± 75	472 ± 87	106.3%	118.2%	131.3%	11.8%
T_{max} (h)	5 (4–6)	6 (4–8)	− 0.5 h	0.75 h	2.0 h	
$AUC_{24\ h}$ (μg·h/ml)	5.22 ± 1.15	6.15 ± 1.25	105.8%	117.7%	131.0%	11.9%
AUC_{∞} (μg·h/ml)	5.57 ± 1.25	6.76 ± 1.49	107.0%	120.9%	136.6%	13.6%
$t_{1/2}$ (h)	5.3 ± 0.4	6.0 ± 0.9	99.1%	111.0%	124.2%	12.6%

[a] LL90 and UL90 are the lower and upper limits of the 90% confidence interval around the geometric mean point estimate PE (arithmetic mean difference for T_{max}) and CV_w is the residual coefficient of variation.

dence intervals exceeded the 125% acceptance limit. The apparent terminal half-life was moderately increased by food intake, from 5.3 to 6 h on average, but the change was not statistically significant ($P > 0.05$).

3.4. Effect of tablet splitting on steady-state pharmacokinetics

The mean plasma concentration profiles of isosorbide-5-mononitrate on the 5th day of once daily administration of Monoket Multitab® as an intact and as a trisected tablet are shown in Fig. 2. They confirm that the slow release absorption pattern was maintained after tablet splitting. The corresponding parameters, calculated point estimates, and their 90% confidence limits are given in Table 3. The area under the curve over the dosing interval was unaffected, with a ratio point estimate of 99.1%, and confidence limits of 92.5 and 106.2%. On the other hand, C_{max} was 10% higher and C_{min} 19% lower for the trisected tablet, entailing thus a 14.6% increase of the peak-through fluctuation (%PTF).

Shortly after administration of 20 mg immediate release tablets, three marked concentration peaks were observed (Fig. 2), with a C_{max} comparable to that of both Monoket Multitab® treatments. The last 20 mg daily dose maintained isosorbide-5-mononitrate plasma levels over 100 ng/ml during the night, with a minimum value about double of that obtained with Monoket Multitab®.

3.5. Effect of fractional dosing on pharmacokinetics

The mean plasma concentration profiles of isosorbide-5-mononitrate on the 1st and 6th day (day 8) of repeated administration of 2/3 Monoket Multitab® tablet at 8 h and 1/3 at 20 h are shown in Fig. 3. After morning administration of 2/3 one Monoket Multitab® tablet (i.e. 40 mg isosorbide-5-mononitrate), the average peak concentration was virtually identical (arithmetic means: 364 and 373 ng/ml) and was reached 5 h (median) after both single and repeated administrations (Table 4). The ratio of steady-state to single-dose C_{max} was 1.04 ± 0.28. $AUC_{0–12\ h}$ was 13% higher at steady-state. The morning trough concentration reached 113 ng/ml on the last day and PTF averaged 103%. After evening administration of the last third of the tablet (i.e. 20 mg isosorbide-5-mononitrate), the average peak concentration was 5% lower at steady-state (arithmetic means: 300 vs. 315 ng/ml), and was reached slightly earlier (median = 3.5 vs. 4 h). The ratio of evening C_{max} at steady-state vs. first day was 1.00 ± 0.34. $AUC_{12–24\ h}$ was almost unchanged (2.43 vs. 2.56 μg·h/ml). Evening trough concentration increased from 150 ng/ml on the first day to 165 ng/ml on the last day. Evening PTF averaged 94%. $AUC_{0–24\ h}$ at

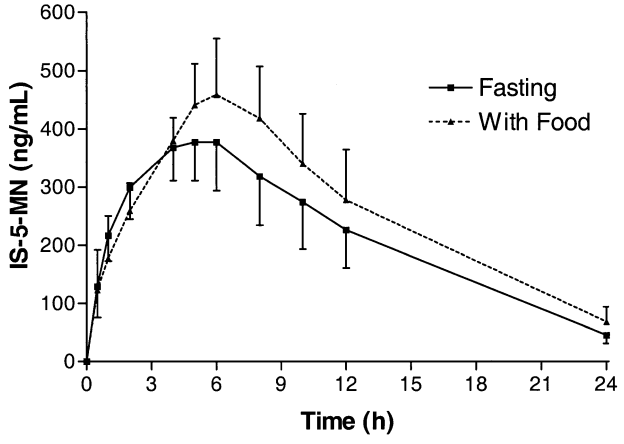

Fig. 1. Mean (±s.d.,$n = 9$) isosorbide-5-mononitrate plasma concentration vs. time after single oral dose administration of Monoket Multitab® in fasting conditions or after a standard high-fat breakfast.

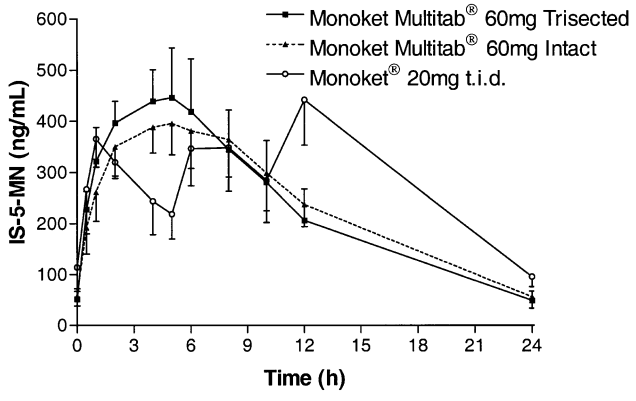

Fig. 2. Mean (±s.d.,$n = 9$) isosorbide-5-mononitrate plasma concentration vs. time on the 5th day of once daily oral administration of Monoket Multitab®, taken intact or trisected or of oral administration of Monoket® 20 mg t.i.d.

Table 3
Steady-state pharmacokinetic parameters of isosorbide-5-mononitrate administered as intact or trisected tablet (arithmetic mean ± standard deviation; for T_{max}: median and range; $n = 9$)[a]

PK parameters	Intact tablet	Trisected tablet	LL90	PE	UL90	CV_w
C_{max} (ng/ml)	425 ± 72	471 ± 88	102.9%	110.1%	117.9%	8.2%
T_{max} (h)	5(2–8)	4(2–6)	− 2.5 h	− 1.0 h	0.0 h	
C_{min} (ng/ml)	53 ± 19	46 ± 16	65.9%	81.1%	99.7%	25.3%
$AUC_{24\ h}$ (μg·h/ml)	5.71 ± 1.08	5.69 ± 1.16	92.5%	99.1%	106.2%	8.3%
$t_{1/2}$ (h)	5.9 ± 0.6	5.6 ± 0.8	86.4%	95.4%	105.4%	12.0%
C_{max}/C_{min}	8.3 ± 1.2	12.2 ± 5.6	107.4%	135.9%	171.9%	28.9%
PTF (%)	158 ± 8	182 ± 29	103.9%	114.6%	126.3%	11.8%

[a] LL90 and UL90 are the lower and upper limits of the 90% confidence interval around the geometric mean point estimate PE (arithmetic mean difference for T_{max}) and CV_w is the residual coefficient of variation.

steady-state was 18% lower ($P < 0.05$) than AUC_∞ after single administration, and the lower limit of the 90% confidence interval, 71.7%, fell below the standard 80–125% acceptance range (Table 4). The 90% confidence interval was within the enlarged 70–143% limits of acceptance for the comparison of morning C_{max} (87–116%), and evening C_{max} (76–115%). The latter interval was broader because of increased variability and PE departure from 100%.

4. Discussion

Using site-specific delivery and gamma-scintigraphic techniques it was shown that isosorbide-5-mononitrate is well absorbed from the stomach and small intestine, while the extent and rate of absorption are progressively reduced in the terminal ileum and in the colon [26,27]. The average transit time from mouth to colon is 6–8 h which represents thus the maximum time for drug release and efficient absorption of a controlled-release formulation of isosorbide-5-mononitrate. In vitro data shown in Table 1 indicate that Monoket Multitab® takes about 8 h to dissolve completely in acidic medium. Since dissolution and release of isosorbide-5-mononitrate is not pH-dependent [5,28], this figure probably approximates the in vivo situation. Further, the in-vitro dissolution profile of Monoket Multitab® is not altered when the tablet is split in two or three parts along the scoring marks, as indicated by the high values achieved by the *f*2 similarity factors [21].

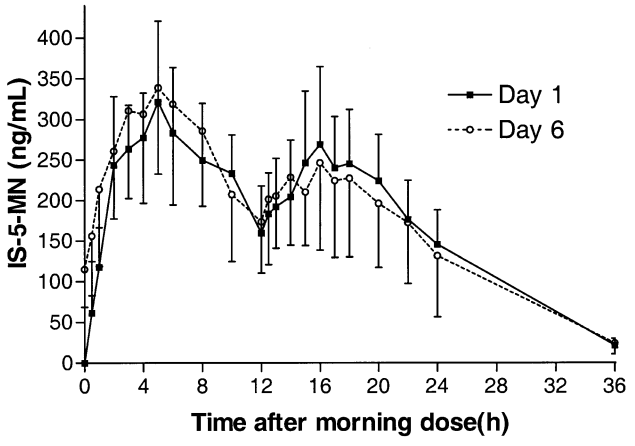

Fig. 3. Mean ($n = 12$) isosorbide-5-mononitrate plasma concentration vs. time on the 1st and on the 6th day (day 8) of fractionated oral administration of Monoket Multitab® (40 mg at 8 h and 20 mg at 20 h).

The moderate (ca ~ 20%) increase in peak concentration and in overall exposure observed after administration of Monoket Multitab® with a high-fat breakfast was significant but probably not large enough to have clinically detectable consequences. The peak time and apparent elimination half-life were unaffected by food. Moderate or non-significant food effects were reported for other sustained-release formulations of isosorbide-5-mononitrate [1,5,29].

At steady-state (Table 3 and Fig. 2), taking the tablet in three fragments instead of intact increased C_{max} by a mere 10%, with negligible effect on T_{max}, AUC, and $t_{1/2}$. The C_{max}/C_{min} ratio and PTF increased from 8.3 to 12.2% and from 158 to 182%, respectively. C_{min}, the minimum concentration over the 24 h dosing interval, remained near 50 ng/ml, i.e. well below the 100 ng/ml cutoff where tolerance begins to develop [2,10].

To modulate the intensity and duration of anti-anginal effect whenever required is the rational basis for introducing a scored tablet that could be divided in three identical 20 mg subdoses. In the third study reported here, we selected the simplest fractional dosing regimen, and compared the single-dose and steady-state pharmacokinetics of Monoket Multitab® given at the dosage of 40 mg at 8.00 a.m. and 20 mg at 8.00 p.m. As expected from the pharmacokinetic profile, the morning peak corresponded approximately to 2/3 of that obtained with the intact tablet, while the evening peak amounted to the sum of the residual concentration near 12 h post-morning dose (about 150 ng/ml) plus 1/3 of the 60 mg peak concentration (about 150 ng/ml). Neither morning nor evening C_{max} was modified upon repeated dosing (Table 4). The morning trough concentration at steady-state, 113 ng/ml on the average, was two-fold higher than with 60 mg once daily dosing, but still low enough to consider that tolerance should remain minimal while offering better anti-anginal protection in the late part of the night. The accumulation factor was smaller than one (point estimate = 82.1%). This phenomenon, already studied by

Table 4
Pharmacokinetic parameters of isosorbide-5-mononitrate (arithmetic mean ± standard deviation; for T_{max}: median and range; $n = 12$) on the 1st and 6th day (day 8) of fractionated dosing (40 mg at 8 h and 20 mg at 20 h)[a]

PK parameters	Day 1		Day 8	
	Morning (40 mg)	Evening (20 mg)	Morning (40 mg)	Evening (20 mg)
C_{max} (ng/ml)	364 ± 84	315 ± 91	373 ± 103	300 ± 96
T_{max} (h)	5 (2–6)	4 (3–6)	5 (3–8)	3.5 (0.5–8)
C_{trough} (ng/ml)	0	150 ± 50	113 ± 48	165 ± 59
$AUC_{12\ h}$ (μg·h/ml)	2.78 ± 0.40	2.56 ± 0.56	3.13 ± 0.99	2.43 ± 0.82
$C_{max,\ s.s.}/C_{max,\ s.d.}$			1.04 ± 0.28	1.00 ± 0.34
PTF (%)			103 ± 22	94 ± 37
$t_{1/2}$ (h)		4.55 ± 0.55		4.98 ± 0.78
$AUC_{24\ h}$ (μg·h/ml)	5.34 ± 0.92		5.55 ± 1.78	
AUC_{∞} (μg·h/ml)	6.50 ± 1.15		6.67 ± 2.34	

PK parameters	LL90 (%)	PE (%)	UL90 (%)	CV_w(%)
$C_{max,\ morning}$ (ng/ml)	87.3	100.4	115.5	19.3
$C_{max,\ evening}$ (ng/ml)	75.8	93.3	114.9	29.0
$AUC_{24\ h,\ s.s.}/AUC_{\infty,\ s.d.}$	71.7	82.1	94.1	11.7

[a] LL90 and UL90 are the lower and upper limits of the 90% confidence interval around the geometric mean point estimate (PE) and CV_w is the residual coefficient of variation.

Parker [30], could be attributed to plasma volume expansion upon repeated dosing. Total exposure, defined as $AUC_{24\ h,\ s.s.}$ (5.55 μg·h/ml, Table 4), was comparable to that observed during once daily dosing (5.71 μg·h/ml, Table 3).

Regarding the safety, the main adverse drug reactions observed in healthy volunteers with the present formulation (headache, dizziness, nausea, vomiting) were identical, and appeared with the same frequency as described previously [3], and generally disappeared with repeated exposure [31,32]. Headache was related to the dose and plasma concentrations, as demonstrated earlier [33] and usually disappeared as the treatment progressed.

5. Conclusions

The release characteristics of Monoket Multitab® are moderately influenced by concomitant intake of food and to a very minor extent by tablet breaking. The slow release pattern is maintained with either 20, 40, or 60 mg. Fractional dosing with 40 mg in the morning and 20 mg in the evening allows to achieve lower peak concentrations and higher morning trough levels while total exposure is comparable to that during once daily dosing. Scored tablets with highly reproducible divisibility should ensure convenience of use and practical adaptation to individual patient requirements.

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