

Pharmacokinetics of sustained-release capsule of 5-isosorbide mononitrate in 20 healthy Chinese young men

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KEY WORDS isosorbide; pharmacokinetics; gas chromatography; delayed-action preparations; cross-over studies; biological availability

ABSTRACT

AIM: To compare the pharmacokinetics of domestic and imported sustained-release capsule of 5-isosorbide mononitrate (5-IM). **METHODS:** A single and 5-d-repeated oral doses of 5-IM 50 mg were performed on 2 groups of 20 Chinese healthy subjects (10 subjects for each group) in a randomized crossover protocol. The 5-IM in plasma were measured by gas chromatography with electron-captured detector method. Data were analyzed automatically by using a CAPP program on a PC computer. **RESULTS:** Fitting the 5-IM concentration-time curves to one-compartment model or following trapezoidal rule, the parameters such as T_{max} , C_{max} , K_e , MRT, and AUC were calculated and there were no significant differences between the two kinds of capsule. The major pharmacokinetic parameters of domestic and imported 5-IM sustained-release capsule with a 5-d multiple dose were respectively: C_{max} (677 ± 103) and (702 ± 76) $\mu\text{g}\cdot\text{L}^{-1}$; T_{max} (5.1 ± 2.0) and (5.6 ± 1.3) h; MRT (11.5 ± 0.5) and (11.4 ± 0.7) h; $\text{AUC}_{0-\infty}$ (12 121 ± 1346) and (12 352 ± 988) $\mu\text{g}\cdot\text{h}\cdot\text{L}^{-1}$. The fraction of drug absorbed *in vivo* was correlated well with the percentage amount of drug released *in vitro* at corresponding time ($P < 0.05$), and the fluctuation indices on d 5 in multiple dose study were not significantly different between the two formulations ($P > 0.05$). The relative bioavailability of the domestic capsule for single and multiple dose

were 96 % ± 11 % and 98 % ± 10 %, respectively.

CONCLUSION: Domestic 5-IM sustained-release capsule showed bioequivalence compared with the imported capsule and provided the same nitrate-low interval in the latter part of the 24-h dosing interval.

INTRODUCTION

5-Isosorbide mononitrate (5-IM) is an active metabolite of isosorbide dinitrate (ID). 5-IM can be more rapidly absorbed than ID by gastrointestinal tract and has a more permanent effect than ID, and it is highly effective in terminating acute attacks of angina pectoris. Many studies with oral dosing of ID or 5-IM at 3 times daily have proved nitrate tolerance in patients with coronary artery disease. As showed in 1983, intermittent therapy with once daily ingestion of 5-IM (40-60 mg) sustained-release capsule was successful in preventing the development of tolerance^[1], so the sustained-release formulation has greatly been adopted in foreign countries to treat angina pectoris and other cardiovascular diseases. In this study we compared the pharmacokinetics between the imported and domestic capsules to see if the two formulations provided the same plasma nitrate profile that incorporated a nitrate-low interval in the latter part of the 24-h dosing interval, during which plasma nitrate levels are sufficiently low to prevent the development of tolerance. This nitrate-low period is best timed to occur during the night when the patient is at the least risk of symptoms.

MATERIALS AND METHODS

Drugs and reagents Domestic 5-IM sustained-release capsule (5-IM-H), (lot No 951201, Huayu Pharmaceutical Factory, Wuxi, China); imported

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controlled capsule (5-IM-S), (lot No 12503, Schwarz Pharmaceutical Factory, Germany), each capsule contained 5-IM 50 mg; detection standard 5-IM (offered by the Third Pharmaceutical Factory of Nanjing); Internal standard isosorbide dinitrate (ID); (lot No 0250-9501, offered by National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China); other reagents used were of AR grade.

Chromatography condition 5-IM was determined by HP5890 gas chromatography with ECD detector and Column BPX5 (made in SGE company). HP3396A data processing integrator was used. High pure (99.99%) He was as carrier gas and N₂ as supplementary gas. Pressure before column was 140 kPa, shunt ratio was 1:10. Temperature was 220 °C for sample intaking, 300 °C for detector, and 130 °C for column.

Subjects Twenty male healthy subjects were all students from Nanjing Medical University. Age: 21.5 ± s 1.1 a; weight: 64 ± 8 kg. Following Helsinki Declaration, they all gave their informed consents. They had no allergic history and stopped using any drugs since 15 d before the test. Cigarette and alcohol were forbidden during trial period. Physical examination and laboratory tests including blood, urine, liver, kidney, and electrocardiogram showed no abnormal findings.

Protocol Twenty volunteers in the single or multiple dose group (each n = 10) entered the study in an open randomized crossover design. In the single-dose study, after a 9-h overnight fast in the hospital, 50 mg of either 5-IM-H or 5-IM-S was given with water 150 mL to each volunteer at 6:30 AM. Antecubital venous blood samples 3 mL were taken before and at 0, 25, 0.5, 1, 3, 5, 8, 12, 16, 24, and 36 h after medication. The blood samples were collected in the Na₂-edetic acid-coating tubes and centrifuged at 3000 × g for 10 min. Plasma was stored at -20 °C until assay. Food was not allowed until 3 h postmedication and volunteers were told to take a rest without strenuous exercise. During the test period they were supplied uniform diets. A crossover study was followed by a washout period of 1 wk.

In the multiple dose study, each volunteer took 50 mg either 5-IM-H or 5-IM-S capsule with 150 mL water every morning at 6:30 AM for 5 consecutive oral doses at a 24-h interval. In the former 4 d, they may have

breakfast 1 h after medication. Three mL venous blood was drawn at 5 and 24 h after every dosing. Volunteers had diet in the diningroom, and regular living was as before. Strenuous exercises were also forbidden. At the fourth night they were hospitalized and fasted for 9 h. The procedure was as that of single dose mentioned above. One wk later a crossover study was repeated.

Assay of 5-IM 5-IM was assayed following the method described previously^[2] except that ID as an interstandard was added in plasma samples.

Validation study The intra-day and inter-day reproducibility were assayed by determining 5-IM in 5 plasma samples with different concentrations for 5 times in a day or in 5 consecutive days. Recovery of standard 5-IM in plasma was also performed.

Pharmacokinetic analysis The concentration-time curves were analyzed with CAPP program (LUO Jian-Ping, *et al.*, the Department of Mathematics, Nanjing Medical University) on Super Personal Computer for K_e and $T_{1/2}$ and adopted HPAUC program (DING Yong, the Department of Mathematics, Nanjing Medical University) to calculate AUC and MRT following trapezoidal rule.

Fluctuation index (FI) The data of C_{max} (putative maximal concentration at 5 h postmedication) and C_{min} (at 24 h postmedication) in single or multiple dose study were used to calculate FI:

$$FI = 2(C_{max} - C_{min}) / (C_{max} + C_{min})$$

Correlation *in vivo* versus *in vitro* Following the Wagner-Nelson equation^[3]

$$f = \frac{C_p + K_e \int_0^t C_p dt}{K_e \int_0^{\infty} C_p dt}$$

and using the NWXG program (DING Yong, the Department of Mathematics, Nanjing Medical University), we got the correlation equations between f (fraction of drug absorbed *in vivo*) and a (%) (percentage amount of drug dissolved *in vitro*) of the two kinds of capsule.

Bioequivalence analysis The relative bio-availability was calculated:

$$F = AUC_{0-\infty 5-IM-H} / AUC_{0-\infty 5-IM-S} \cdot 100 \%$$

To determine whether the two kinds of 5-IMSRC capsule be possessed the same biological effect the parameters including T_{max} , C_{max} , MRT, AUC, and

the logarithm transformation $\ln T_{\max}$, $\ln C_{\max}$, $\ln \text{MRT}$, and $\ln \text{AUC}$ were analyzed with the following methods: ANOVA, Bayesian, Westlake, two one-sided and the rank sum test⁽⁴⁻⁶⁾ through BIO program (DING Yong, the Department of Mathematics, Nanjing Medical University).

RESULTS

Quality control of GC-ECD assay The retention time of ID and 5-IM were 6.7 and 4.2 min, respectively. The peaks were sharp, well-separated and not interfered by plasma (Fig 1).

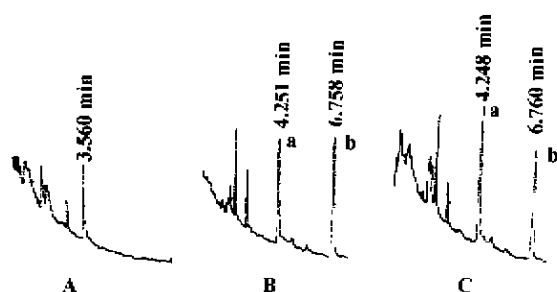


Fig 1. The chromatographies of 5-IM. A: blank plasma. B: standard 5-IM (a) and interstandard ID (b) in blank plasma. C: 5-IM (a) and interstandard ID (b) in plasma after medication.

The calibration curve was linear over the range of $12.2 - 972.8 \mu\text{g}\cdot\text{L}^{-1}$ ($n = 5$). The regression equation is: $A_{\text{standard}}/A_{\text{interstandard}} = 0.2272 + 0.0026X$, $r = 0.9988$. The sensitivity was $1 \mu\text{g}\cdot\text{L}^{-1}$ (plasma extract). The coefficient of variation were 4.93 % - 7.35 % for intra-day and 5.08 % - 5.80 % for inter-day. Recovery coefficient were 81.51 % - 85.56 % (5-IM standard concentrations were 60.8, 486.4, 972.8 $\mu\text{g}\cdot\text{L}^{-1}$, $n = 5$).

Concentration-time course and FI The average concentration-time curves of the two kinds of capsule either in single dose or multiple dose varied concordantly. The FI and the average plasma 5-IM concentration of 5-IM-H and 5-IM-S at 5 h (putative maximal concentration) and 24 h (minimal concentration) after each medication were near to each other (Tab 1).

Pharmacokinetics The time-concentration curves were fitted with one-compartment model. Main pharmacokinetic data between the two kinds of capsule showed no statistical difference (Tab 2). Relative bioavailability was $96\% \pm 11\%$ and $98\% \pm 10\%$ for single and multiple dose group respectively. The $(1 - 2\alpha)$ ($\alpha = 0.05$) confidence limits of the $\ln \text{AUC}$, $\ln C_{\max}$, $\ln T_{\max}$, and $\ln \text{MRT}$ of the two kinds of capsule were shown in Tab 3.

Tab 1. Plasma 5-IM concentration at 5 h (putative maximal concentration) and 24 h (minimal concentration) after each medication following a single and multiple *po* 50 mg of sustained-release capsule (5-IM-H and 5-IM-S) in healthy Chinese, $n = 10$, $\bar{x} \pm s$, ^a $P > 0.05$ compared with 5-IM-S.

	Capsule	Dosing	Concentration/ $\mu\text{g}\cdot\text{L}^{-1}$		FI
			5 h	24 h	
Single dose	5-IM-H	1st	401 ± 74	100 ± 14	1.20
		5-IM-S	403 ± 70	98 ± 25	1.22
	5-IM-H	1st	438 ± 103 ^a	118 ± 24 ^a	1.15
		2nd	484 ± 90 ^a	130 ± 23 ^a	1.16
		3rd	614 ± 113 ^a	144 ± 18 ^a	1.24
		4th	662 ± 102 ^a	142 ± 13 ^a	1.29
Multiple dose	5-IM-S	5th	677 ± 103 ^a	120 ± 18 ^a	1.40
		1st	464 ± 170	110 ± 24	1.23
		2nd	509 ± 151	105 ± 30	1.31
		3rd	576 ± 192	139 ± 24	1.22
		4th	585 ± 177	134 ± 21	1.25
		5th	702 ± 76	118 ± 20	1.42

Tab 2. Parameters of 5-IM after a single and multiple *po* dose of 50 mg of sustained-release capsule (5-IM-H and 5-IM-S) in healthy Chinese. $n = 10$. $\bar{x} \pm s$. * $P > 0.05$ compared with 5-IM-S. " * " represented the parameters fitted by one-compartment model and others were calculated by trapezoidal rules.

Parameter	Single dose		Multiple dose	
	5-IM-H	5-IM-S	5-IM-H	5-IM-S
* K_e/h^{-1}	0.120 ± 0.010 ^a	0.120 ± 0.010	0.120 ± 0.010 ^a	0.120 ± 0.010
* $T_{1/2}/h$	5.7 ± 0.6 ^a	5.7 ± 0.4	5.8 ± 0.5 ^a	5.7 ± 0.5
* T_{max}/h	5.41 ± 0.29 ^a	5.47 ± 0.26	5.30 ± 0.27 ^a	5.3 ± 0.4
T_{max}/h	5.3 ± 2.4 ^a	6.1 ± 2.1	5.1 ± 2.0 ^a	5.6 ± 1.3
$C_{max}/\mu g \cdot L^{-1}$	401 ± 74 ^a	403 ± 70	677 ± 103 ^a	702 ± 76
$AUC_{0-\infty}/\mu g \cdot h \cdot L^{-1}$	7121 ± 957 ^a	7448 ± 1025	12121 ± 1346 ^a	12352 ± 988
MRT/h	11.9 ± 0.6 ^a	11.9 ± 0.6	11.5 ± 0.5 ^a	11.4 ± 0.7
F/%		96 ± 11		98 ± 10

Tab 3. (1 - 2 α) Confidence limits of $\ln AUC$, $\ln C_{max}$, $\ln T_{max}$, and $\ln MRT$ of the two kinds of capsule calculated by two-one side test. $\alpha = 0.05$. (T: 5-IM-H, R: 5-IM-S).

Items	Confidence $\mu T - \mu R$	Limits $\mu T/\mu R$
Single	$\ln AUC$ (-0.1089, 0.0209)	(0.9878, 1.0023)
	$\ln C_{max}$ (-0.0857, 0.0557)	(0.9859, 1.0092)
	$\ln T_{max}$ (-0.0639, 0.0439)	(1.0258, 1.0370)
	$\ln MRT$ (-0.0195, 0.0255)	(0.9921, 1.0103)
Multiple	$\ln AUC$ (-0.0852, 0.0412)	(0.9910, 1.0044)
	$\ln C_{max}$ (-0.0947, 0.0067)	(0.9856, 1.0010)
	$\ln T_{max}$ (-0.0319, 0.0319)	(0.9799, 1.0190)
	$\ln MRT$ (-0.0131, 0.0251)	(0.9946, 1.0103)

Correlation *in vivo* versus *in vitro* A linear relationship existed between f (fraction of drug

absorbed *in vivo*) and a % (percentage amount of drug dissolved *in vitro*). The correlation equations of 5-IM-H were a % = -1.9198 + 112.0071 f ($r = 0.9963$, $P < 0.05$) and a % = -1.7137 + 108.0605 f ($r = 0.9974$, $P < 0.05$) for single dose and multiple dose respectively. Those for 5-IM-S were a % = -2.2011 + 105.5072 f ($r = 0.9981$, $P < 0.05$) and a % = -2.2265 + 101.9469 f ($r = 0.9999$, $P < 0.05$) (Tab 4).

DISCUSSION

We have studied the pharmacokinetics of a new 5-IM sustained-release formulation by using ID as internal standard and taking an imported similar formulation as control, which was developed in foreign countries in recent 10 years.

Tab 4. Correlation of 5-IM-H and 5-IM-S between f (fraction of drug absorbed *in vivo*) and a % (percentage amount of drug dissolved *in vitro*).

		Time/h				
		0.5	1	8	16	
5-IM-H	Single dose	a %	33.19	36.67	81.63	96.93
		f	0.3649	0.4426	0.8400	0.9383
	Multiple dose	a % = -1.9198 + 112.0071 f			$r = 0.9963$	$P < 0.05$
		f	0.3706	0.4547	0.8378	0.9834
5-IM-S	Single dose	a % = -1.7137 + 108.0605 f			$r = 0.9974$	$P < 0.05$
		a %	32.46		79.84	94.88
	Multiple dose	f	0.3702		0.8435	0.9488
		a % = -2.2011 + 105.5072 f			$r = 0.9981$	$P < 0.05$
Multiple dose	f	0.3839		0.8525	0.9946	
	a % = -2.2265 + 101.9469 f			$r = 0.9999$	$P < 0.05$	

The parameters obtained such as $T_{1/2}$ and MRT are close to those reported by Merz-PG^[7]. There was no accumulation of drug during chronic treatment because the accumulation factor for 5-IM was only 1.2 fold in multiple dose than in single dose occurred during the periods of dosing with the two sustained-release capsule (Tab 1). The result was the same as Taylor and Kendall reported^[8-9].

Despite of the well-established benefits of nitrates, the provision of sustained angina prophylaxis has been hindered by the decrease in pharmacological response, nitrate tolerance, that occurs with continuous or high dose administration of nitrates. Tolerance can be successfully overcome by using daily dosing regimen that including a "nitrate-low" interval, a period of 8-12 h each day during which plasma nitrate level is sufficiently low to prevent the development of tolerance^[10-12].

The 5-IM-H and 5-IM-S in our study, therefore, gave the same effective protection from ischemia when the patient was at greatest risk of anginal attack (during the active part of the day), while ensuring that the plasma nitrate concentration fallen below the critical level (about $300 \mu\text{g} \cdot \text{L}^{-1}$) for the development of nitrate tolerance for a sufficient period (8 h) during each 24 h period, furthermore, concentration at $100 \mu\text{g} \cdot \text{L}^{-1}$ may also prevent anginal attack during the night when the patient was at the least risk of symptoms.

According to the ANOVA, furthermore, the main pharmacokinetic parameters of the two capsules in single or multiple dose group were in good agreement with each other. The analysis showed that there was bioequivalence between the two products, so the domestic products had the same biological effects as the imported ones.

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5-单硝酸异山梨醇酯缓释胶囊在中国健康男青年的药物动力学

R972.3

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关键词 异山梨酯; 药物动力学; 气相色谱法; 迟效制剂; 交叉研究; 生物利用度

目的: 比较国产和进口 5-单硝酸异山梨醇酯缓释胶囊在健康人体内的药动学。方法: 20 名志愿者交叉随机分两组, 口服 50 mg, GC-ECD 测血药浓度, 一室模型拟合或梯形法求药动学参数。结果: 多剂量组连续 5 天服国产或进口胶囊, 药动学参数 C_{\max} 分别为 (677 ± 103) 和 $(702 \pm 76) \mu\text{g} \cdot \text{L}^{-1}$; T_{\max} 分别为 (5.1 ± 2.0) 和 (5.6 ± 1.3) h; MRT 分别为 (11.5 ± 0.5) 和 (11.4 ± 0.7) h; $AUC_{0-\infty}$ 分别为

(12 121 ± 1346)和(12 352 ± 988) μg·h·L⁻¹, 两者差异无显著性(P > 0.05). 两种胶囊在服药 16 h 后, 血药浓度降至产生耐受性的阈值浓度以下(< 300 μg·L⁻¹). 两种胶囊体内吸收分数和其体外相应时间的溶出率均呈显著正相关(P < 0.05), 单剂量

和多剂量下国产对进口胶囊的相对生物利用度分别为96 % ± 11 % 和 98 % ± 10 %. 结论: 两种胶囊药动学特点相似.

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