한국임상약학회지 제15권 제2호
Kor. J. Clin. Pharm., Vol. 15, No. 2. 2005

이미그란 정 50 mg에 대한 수마트란 정의 생물학적 동등성 평가

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Evaluation of the bioequivalence of Sumatriptan in healthy volunteers

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수마트립탄은 뇌혈관에 분포되어 있는 5-HT1B/1D수용체에 특이적이고 선택적으로 작용하여 뇌혈관 수축 작용을 나타내어 편두통의 치료에 널리 쓰이는 약물이다. 본 연구는 수마트립탄 제제인 이미그란(50 mg tablet, GSK사)을 대조약으로 하여 시험약인 명인 제약의 수마트란 50 mg정의 생물학적 동등성 평가를 하기 위해 22명의 건강한 지원자를 모집하였다. 지원자를 두 군으로 나누어 1정씩 투여하였고 2×2 교차시험을 실시하였다. 수마트립탄의 혈장 중의 농도를 정량하기 위하여 발리데이션된 HPLC/FD를 사용하였다. 채혈 시간은 투약 전 및 투약 후 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7, 9, 12 시간에 걸쳐 총 12시점에 걸쳐 시행하였다. 생물학적 동등성을 판정하기 위한 파라미터로 12시간까지의 혈장 중 농도 곡선 하 면적(AUC_{12hr})과 최고 혈중 농도(C_{max})를 사용하였다. AUC_{12hr}의 평균은 137.87 ng·ml/hr(시험약)과 130.12 ng·ml/hr(대조약)으로 나타났다. C_{max}의 경우 각 각 29.30 ng/ml(시험약)과 29.25ng/ml(대조약)으로 관찰 되었다. AUC_{12hr}의 경우 로그변환한 평균치 차의 90% 신뢰구간이 log0.95-log1.24이었고, C_{max}의 경우 log0.90-log1.149로 계산되어 두 항목 모두 log0.8 – log1.25이어야 한다는 식품의약품 안전청과 FDA의 기준을 모두 만족시켰다. 이상의 결과를 종합하면 시험약 수마트란 정 50 mg은 대조약 이미그란 정 50 mg에 대하여 생물학적으로 동등한 것으로 판정되었다.

□ **Key words** – Sumatriptan, bioequivalence, HPLC/FD, Sumatran, Imigran®

Sumatriptan succinate, 3-[2-(dimethylamino)ethyl]-n-methyl-1H-indole-5-methane-sulphonamide succinate, is a 5-hydroxytryptamine ($5\text{-}HT_{1B/1D}$) receptor agonist, efficacious in the treatment of migraine.[1)] Sumatriptan has higher binding affinity and selectivity for $5\text{-}HT_{1B/1D}$ receptor binding sites in brain tissue than ergotamine, but is has no affinity for other receptors, such as $5\text{-}HT_{1C}$, $5\text{-}HT_2$, $5\text{-}HT_3$, adrenergic, dopaminergic, muscarinic, or benzodiazepine binding sites.[1,2)] Sumatriptan acts as a vasoconstrictor of dilated intracranial blood vessels and, also as an inhibitor of the pro-inflammentory neutropeptide release which leads to headache relief.[2)]

Sumatriptan is rapidly absorbed after oral single dosing. The plasma half life is about 2 hr. The drug has approximately 14% oral bioavailability. After oral dosing, it is frequently displays more than one peak plasma concentration. This "multiple peaking" gives rise to considerable intersubject variability in time to mean maximum plasma concentration. With the exception of rate of absorption, the pharmacokinetics of sumatriptan is linear over the oral dose range of 25 to 400 mg.[3,4)]

Myung In Pharm. Co., Ltd. (Seoul, Korea) have developed a new formulation of sumatriptan tablet: Sumatran 50mg this study assessed, hence the bioequivalence of this newerly developed formulation with a reference formulation, Imigran® 50mg (GSK Co.,Inc.) in 22 healthy Korean volunteers. Typical bioavailability, including AUC_t (the area under the plasma concentration-time curve from 0 until the last sampling time, 12 hr) and C_{max} (the maximum plasma drug concentration) parameters were compared.

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Materials and Methods

Test and Reference Products

The test product, Sumatran 50 mg (50 mg of sumatriptan succinate, lots no. 351401, Myung-in Pharm. Co., Ltd.) and the reference product, Imigran® 50 mg (50 mg sumatriptan succinate, lots no. VK0005, GSK Co., Inc.) were supplied by tablets.

Subjects and Methods

The 50 mg sumatriptan bioequivalence study involved 22 healthy Korean volunteers with the age from 19 to 28 years (22.50±2.19 years), in weight from 47 to 75 kg (62.96±8.39 kg), and height from 150 to 181 cm (168.75±8.52 cm). All the volunteers were enrolled after passing a clinical examination, including a physical examination and laboratory tests (blood analysis: hemoglobin, hematocrit, WBC, platelets, WBC differential, blood urea nitrogen, total bilirubin, cholesterol, total protein, albumin, alkaline phosphatase, glucose fasting, ALT, and AST, and urine analysis: specific gravity, color, pH, sugar, albumin, bilirubin, RBC, WBC, and casts). Any with potential hypersensitivity to this type of medication, a history of the hepatic, renal, or cardiovascular disease, or chronic alcohol consumption or other medications was excluded. This criteria was applied to elimination the source of variation which can influence the pharmacokinetics of the drug. All the volunteers were retricted not to take using other drugs from at least one week before the study and until the completion of the study. They also refrained from alcoholic beverages and xanthine-containing foods and beverages 48 hr before the study, until the last sampling time. Each volunteer received an oral dose of 50 mg(50 mg×1 tablets) of sumatriptan in a standard 2×2 cross-over design, in randomized order. There was a 1-week washout period. The study was approved by a local ethics committee. All the participants signed a written informed consent, in accordance with the Korea Guidelines for Bioequivalence Tests (KGBT 1998).[5]

The subjects were hospitalized (Sun Obstetrics Hospital, Daejeon, Korea) at 7:00 p.m. the day before drug administration. At 7:00 a.m., the median cubital vein was cannulated and 1 ml of heparinized injectable normal saline solution was flushed into the cannula to prevent blood clotting. The doses were taken at 8:00 a.m. on each dosing day with 240 ml of drinking water. Four hours after oral administration, all the subjects were given standard meals. The subjects were not allowed to take a supine position or to sleep until 4 hr after oral administration. Approximately 7-ml blood samples were collected before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7, 9, and 12 hr after drug administration. The cannula was flushed with 1 ml of heparinized injectable normal saline solution after each blood sampling. The blood sample was centrifuged immediately, and the plasma was frozen at –70°C until the HPLC/FD analysis.

HPLC/FD Assay of Simvastatin in Plasma

The sumatriptan concentration in plasma was analyzed using a reported HPLC/FD method,[6] with slight modification. Briefly, 100 μl of internal standard (terazocin, 2.5 μg/ml) and 500 μl of 1 M-NaOH were added to 1 ml of plasma, followed by a ten-minute liquid-liquid extraction with 7 ml of ethyl acetate. The organic layer was transfered and evaporated to dryness under a gentle nitrogen stream. The residue was reconstituted in 200 μl of methanol and 30 μl was injected onto the column. The mobile phase was a mixture of 0.025 M sodium phosphate buffer (pH 7.5): acetonitrile (80:20, v/v). Analytes were eluted using an LC-10ADvp pump (SHIMADZU, Kyoto, Japan) at 1.2 ml/min. The fluorescense detector (RF-10AXL, SHIMADZU, Kyoto, Japan) excitation wavelength was set 225 nm and the emission wavelength was set at 350 nm. The separation was achieved by using a Zorbax C18 column (150 mm ×4.6 mm, 5 um, Agilent Technologies, Palo Alto, California, USA). The analytical data were processed using CLASS-VP software.

Pharmacokinetic Analysis

The non-compartmental pharmacokinetic parameters were derived using standard methods. C_{max}, was obtained from the concentration-time data. The AUC_t was calcu-

lated using the logarithmic trapezoidal rule and was extrapolated to infinity using the relationship:

$$AUC_{inf} = AUC_t + (C_t/k_{el}) \quad \text{(Eq.1)}$$

where AUC_{inf} is the area under the plasma concentration-time curve from zero to time infinity, C_t is the concentration of the last plasma sample (greater than the limit of quantification LOQ), and k_{el} is the elimination rate constant of the terminal phase.[7]

Statistical Analysis

The following tests or procedures were carried out for AUC_t, and C_{max}. ANOVA was performed using logarithmic transformed AUC_t and C_{max}. Schuirmann's two one-sided *t*-test (*i.e.*, for logarithmic transformed AUC_t and C_{max}) approach was used to test the bioequivalence of the pharmacokinetic characteristics between the products. The range of bioequivalence for the parametric analysis was set to the 80-125%, and the range of equivalence for the non-parametric analysis was set to 20% of the reference mean. All statistical comparisons were made using EquivTest version 1.0 (Statistical Solution Ltd., Sangus, MA, USA).

Results and Discussion

HPLC/FD Analysis

With the HPLC/FD method, no interference was observed in human plasma. The respective retention times for sumatriptan and the internal standard (terazocin) were approximately 3.93 and 6.06 min (Fig. 1). The quantification limit for sumatriptan in human plasma was 5 ng/ml, based on a signal-to-noise ratio of 5.0. The intra- and inter-day coefficients of variation were less than 1.68 and 6.08%, respectively, for the concentration range from 5 to 100 ng/ml.

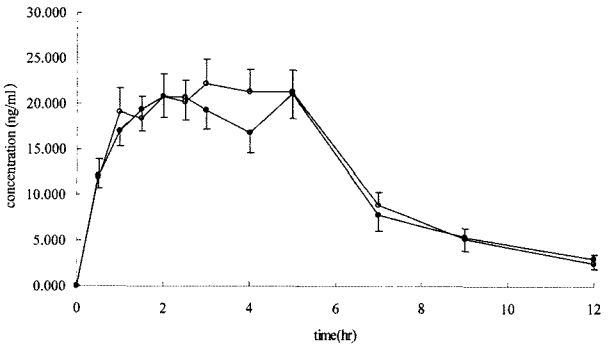

Fig. 2. Mean plasma concentration-time profiles of Imigran® (reference tablet: ●) or Sumatran (test tablet: ○) administration to 22 volunteers. The vertical bars represent the standard error.

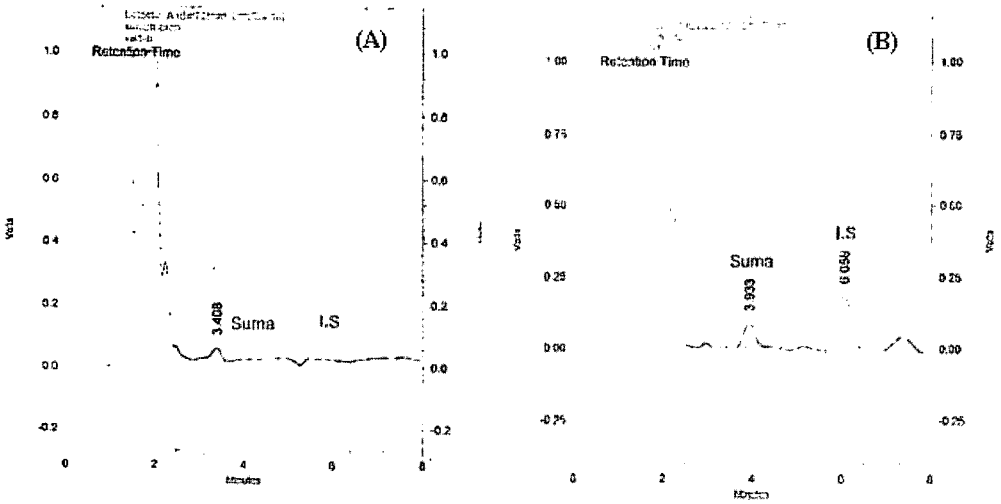

Fig. 1. Chromatograms of sumatriptan and terazocin. (A) double blank plasma, (B) plasma sample equivalent to 17.94 ng/ml from a volunteer 1 hr after the oral dose.

Table 1. Pharmacokinetic parameters of sumatriptan for two brands (mean±S.D., n=22)

Pharmacokinetic parameter	Imigran 50 mg (Reference)	Sumatran 50 mg (Test)
AUC_t (ng·hr/ml)	130.12 ± 84.88	137.87 ± 83.29
AUC_∞ (ng·hr/ml)	155.99 ± 125.32	160.31 ± 115.48
C_{max} (ng/ml)	29.25 ± 12.02	29.30 ± 11.53
T_{max} (hr)	2.80 ± 1.49	2.93 ± 1.42
k_{el} (hr^{-1})	0.23 ± 0.14	0.23 ± 0.17
Cl_{total}/F (L/hr)	572.27 ± 417.27	450.93 ± 674.35

Table 2. Analysis of variance test (α=0.05) for AUC_t (log-transformed) and C_{max} (log-transformed) for the sumatriptan tablets

ANOVA	log-transformed AUC_t (F-value)	log-transformed C_{max} (F-value)
Group or Sequence	3.085(4.351)	0.043(4.351)
Subjects/Group	12.496(2.124)	5.267(2.124)
Period	0.026(4.351)	0.319(4.351)
Drug	1.133(4.351)	0.053(4.351)

Table 3. The 90% confidence intervals and results of Schuirmann's test on the target pharmacokinetic parameters of simvastatin

	Geometric means			90% C.I	Result of Schuirmann's test			
	Test (T)	Reference (R)	T/R		Side I		Side II	
					t	P	t	P
C_{max}	27.366	26.940	1.015	0.90-1.14	3.43	<0.01	4.06	<0.01
AUC_t	113.951	105.087	1.084	0.95-1.23	1.07	<0.01	10.75	<0.01

Clinical Observations

The tolerability of sumatriptan 50 mg medication was acceptable. Clinically relevant or drug-related side effects were not observed in any of the 22 volunteers.

Pharmacokinetic Characteristics

Table 1 shows the pharmacokinetic parameters of simvastatin for the two brands. The mean terminal half-life of sumatriptan of reference and test brands was 3.00±7.09 hr and 5.12±5.39 hr, respectively (mean terminal half-life of two products 4.06±6.31), which were very similar to the results of other previous studies.[3,4]

Standard Bioequivalence Analysis

No significant sequence effect was found for any of the bioavailability parameters, indicating that the cross-over design was properly performed. Significant F-test values were found between subjects and the subjects' nested sequence (SEQ) for AUC_t and C_{max}, indicating substantial inter-subject variation in the pharmacokinetics of simvastatin from the two formulations (Table 2). No significant period effect in AUC_t or C_{max} was detected in this study.

The detailed statistical and bioequivalence analyses of simvastatin for AUC_t and C_{max} under the assumptions of the multiplicative model are given in Table 3. The geometric means of the parameters are given for the test and reference formulations of simvastatin, separately and as combined estimates. The parametric point estimates of the ratio of geometric mean of test and reference products for AUC_t and C_{max} were 0.997 and 0.975, respectively, and the parametric 90% confidence intervals for AUC_t and C_{max} were 0.9510-1.2364 and 0.9029-1.1428 (Table 3), respectively, which were within the commonly accepted bioequivalence range of 0.80-1.25.

In conclusion, the results indicate that the two forms of sumatriptan 50mg is bioequivalent.

Acknowledgment

This study was supported by the contract, "Bioequivalence assessment of sumatriptan 50mg tablets after

administering a single oral dose to healthy Korean volunteers", from Myung In Pharm Co., Ltd., Seoul, Korea.

References

1. Kerry LD, Stephen PC. Sumatriptan-a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the acute treatment of migraine and cluster headache. *Drugs.* 1992; 43: 776-91.
2. Dollery C, Boodis AR, Orme MCL'E, Rawlins MD. Sumatriptan (succinate). Therapeutic Drugs. 2nd edition, London, Churchill Livingstone Publications, 1991; 227-231.
3. Fowler PA, Lacey LF, Keene ON, Thomas M. Effects of prophylactic migraine medications on the pharmacokinetic and pharmacodynamic profiles of sumatriptan. *Cephalalgia.* 1991; 11: 228-9.
4. Cutler NR, Hussey EK, Sramek JJ. Oral sumatriptan pharmacokinetics in the migrainous state. *Cephalalgia.* 1991; 11: 222-3.
5. WK Kang, HY Yun, KI Kwon. Assessing the bioequivalence of 4- and 8-mg benidipine tablets in healthy volunteers after a single oral dose. *J. Clin. Pharm. Ther.* 2005; 30: 85-90
6. Tessier Z, Neirinck L, Zhu Z. High performance liquid chromatographic method for the determination of sumatriptan with fluorescence detection in human plasma. *J. Chromatogr. B.* 2004; 806: 299-303.
7. Milo G, Donald P. Pharmacokinetic, 2nd ed. New York: Marcel dekker, 1985; 294-297.