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Relative Bioavailability of Commercially Available Rifampicin Capsules

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리팜피신캅셀의 생체내 이용율

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The study was performed to compare the dissolution, diffusion and absorption characteristics using Sartorius dissolution and absorption simulator and *in vivo* bioavailability of commercially available rifampicin capsules. Both brands C and F showed similar dissolution patterns and absorption properties through artificial gastric barrier in Sartorius simulator. Diffusion rate constants through the membrane of brands C and F were 3.04×40^{-3} and 2.88×10^{-3} cm/min, respectively. Rifampicin capsules were administered orally to six fasted healthy volunteers according to cross-over design. The pharmacokinetic parameters between brands C and F, maximum plasma drug concentration (C_{max}), the time to reach C_{max}, absorption rate constant and area under the curve ($AUC_{0\text{-}24hr}$), elimination rate constant, and amount of drug excreted in urine were 6.11 and 7.27 μg/m*l*, 2.71 and 1.52 hr, 0.6371 and 1.6456 hr^{-1}, 57.84 and 57.28 μg·hr/m*l*, 0.1891 and 0.1734 hr^{-1}, 119.98 and 119.93 mg, respectively. On the basis of experimental results, it was concluded that the bioavailability of brand C rifampicin capsules was almost the same as that of brand F rifampicin capsules.

Keywords—rifampicin capsules, dissolution, absorption simulation, pharmacokinetic parameter, bioavailability

The rate and extent of absorption of a drug affect the onset, duration and intensity of the pharmacologic response. The major reason for performing bioequivalence studies is that even though drug products which are pharmaceutically equivalent, they may not give the same therapeutic effects in patients at all time[1].

The serum level and pharmacokinetic parameters of rifampicin obtained when intravenously infused at the doses of 300, 450 and 600 mg did not differ to any major extent from those obtained after the same doses were given orally[2-3].

It was reported that single oral co-administration of rifampicin and isoniazid did not affect the serum concentration and half-life of rifampicin significantly, but multiple dosing might affect some hepatic function[4]. The interaction of orally given para-aminosalicylic acid and rifampicin, which

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resulted in a delayed and decreased serum concentration of the latter drug, was probably of significance in the treatment of tuberculosis[5].

The most important factors that may influence the absorption of rifampicin from the gastro-intestinal tract have been known to be the crystal form, the particle size, manufacturing formula and process[6-9]. In this work, therefore, the bioavailability test of both commercially available rifampicin capsules was carried out in healthy volunteers. To compare the bioavailability of both brands of rifampicin capsules accurately, all capsules were administered with the same dose and tested in the same experimental condition.

EXPERIMENTAL

Materials

Rifampicin capsules (brand C, Rifodex® of Chang Kun Dong Co., Ltd.) were prepared using the capsule filling apparatus in our laboratory. One capsule contained 300 mg of rifampicin (as potency), 3.0 mg of sodium laurylsulfate, 5.4 mg of magnesium stearate, 39.2 mg of talc, and lactose to make 600 mg of net weight. The particle size of rifampicin was controlled and the preparation of capsules was done in the same conditions. The physicochemical properties were checked to assure the evaluation of the bioavailability of rifampicin in human. On the other hand, foreign commercial rifampicin capsules (brand F) were obtained from abroad.

Simulation Studies

Diffusion and absorption rate constant, and dissolution characteristics were determined using Sartorius simulator. All experimental operation and calculation were handled in accordance with operating manual.

In Vivo Studies

This study was conducted with six male volunteers in good health screened by laboratory tests including hematology and urine analysis. Their ages were ranged from 24 to 37 years and their weights were between 60 and 75 kg. The subjects were fully informed of the design of this study.

Each person was given no medication for at least 72 hr before the administration of rifampicin capsules. They fasted for 12 hr prior to and 3 hr after drug administration. Each subject was administered in a single oral dose of 600 mg of rifampicin with about 100 m*l* of water.

A catheter was placed in a forearm vein and a continuous drip was maintained for the blood sample, while the subjects were ambulatory. Blank blood was collected beforehand and blood samples were collected by the catheter at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15 and 24 hr after administration. Urine specimens were collected before drug administration and by the following time intervals after administration: 1-2, 2-3, 3-4, 4-6, 9-12, 12-15 and 15-24 hr. Blood samples were collected in heparinized tubes and immediately centrifuged. And then the plasma was taken and immediately frozen. The voided urine was collected and stored in freezer until analysis.

Assay

Ultraviolet-visible spectrophotometer was used to determine the rifampicin concentration in Sartorius absorption simulator. Rifampicin was determined by measuring the absorbance of the aqueous solution at 475 nm.

The concentration of rifampicin in plasma and urine were measured under blind conditions by diffusion method. The test organism was *Bacillus subtilis* (ATCC 6633) and media was Medium 2 of USP XXI.

Data Analysis

The plasma concentration of rifampicin for each subject was modeled using a one compartment model with first-order absorption. The structural model describing the plasma concentration, C at time t is given by;

$$C = \frac{K_a F X_o}{V(k_a - K)} (e^{-Kt} - e^{-K_a t})$$

where K_a and K are apparent first-order sbsorption and elimination rate constants, respectively; F is the fraction of the absorbed to the administered dose (X_o); V is the apparent volume of distribution. Pharmacokinetic calculations were performed by

employing the MULTI computer program[10], where non-linear regression was finished at $(SS_{n-1}-SS_n)/SS_n$ 10 (SS: sum of square). Simplex method was chosen among many algorisms. To obtain accurate K value, weights was set to 2 and the differentiation coefficient was set to 0.001.

RESULTS AND DISCUSSION

Dissolution and Adsorption Simulation

The bioavailability of the active drug in solid dosage form is dependent on several factors. In biologic systems drug dissolution in an aqueous medium is an important condition prior to systemic absorption. Therefore the dissolution and absorption behavior of rifampicin capsules was investigated in the artificial gastric juice and artificial gastric barrier using Sartorius simulator to know if there are any pharmaceutical differences between brands C and F. The dissolution curves of rifampicin capsules in artificial gastric juice are shown in Fig. 1.

Both rifampicin capsules were dissolved within 30 min. And we could not find any significant difference between brands C and F. As shown in Fig. 2, the cumulative amount of rifampicin transported through artificial gastric barrier in Sartorius absorption simulator has no significant difference between brands C and F.

The diffusion constants (Kd) between brands C and F calculated from Fig. 2 were 3.04×10^{-3} and 2.88×10^{-3} cm·min^{-1} respectively, which means that the corresponding gastric absorption fraction was equal to 1.27 and 1.21% per minute in human with a body weight of 70kg.

Oral Absorption

The mean plasma concentration of rifampicin in 6 healthy volunteers after single oral administration of 600 mg dose, determined by the agar-diffusion method, are shown in Fig. 3. The plasma concentration was determined at the indicated time inter-

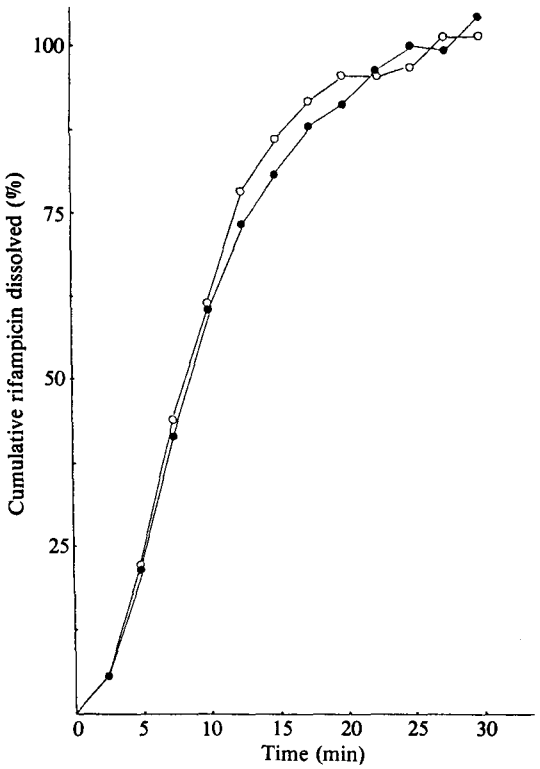

Figure 1—Dissolution characteristics of rifampicin capsules in artificial gastric juice at 37 ± 0.5 °C usingSartorius dissolution simulator. Each point represents the mean of three determinations
Key: ●, brand C and ○, brand F

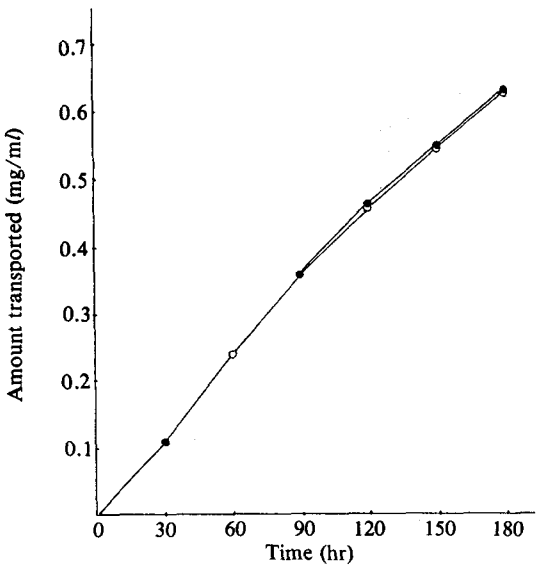

Figure 2—Cumulative amount of rifampicin transported through artificial gastric barrier in Sartorius absorption simulator. Each point represents the mean of three determinations.
Key: ●, brand C and ○, brand F

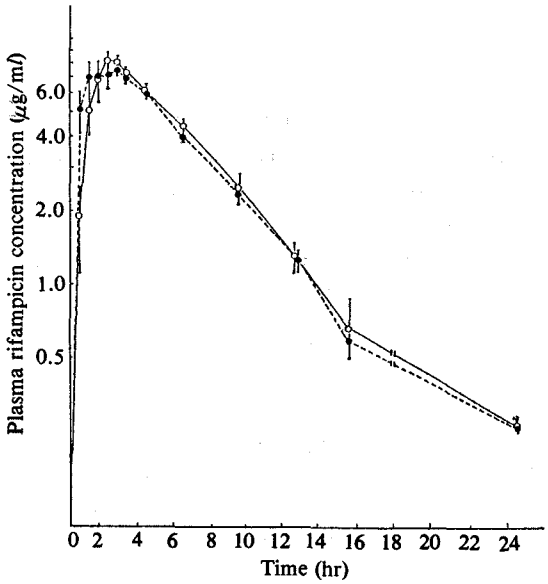

Figure 3—Semilogarithmic plot of plasma concentration of rifampicin after oral administration of 600 mg dose of rifampicin as capsules.
Key: ○, brand C and ●, brand F

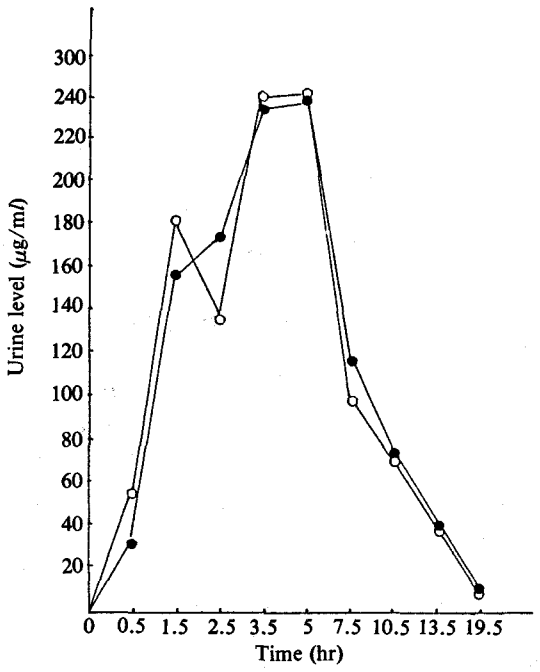

Figure 4—Urine concentration of rifampicin after oral administration of 600 mg dose of rifampicin as capsules.
Key: ●, brand C and ○, brand F

vals for 24 hr after administration. The pharmacokinetic parameters such as absorption rate constant (K_a), elimination rate constant (K), maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}), area under the plasma concentration-time curve (AUC) of brands C and F are summarized in Table I. The C_{max}, T_{max}, and AUC between brands C and F are 6.11 and 7.27 μg/ml, 2.71 and 1.52 hr, 57.84 μg/ml·hr and 57.28 μg/ml·hr, respectively. The C_{max}, T_{max} and AUC did not show any significant differences between brands C and F.

Urinary Excretion

After oral administration, rifampicin was rapidly excreted in urine. The biologically active rifampicin concentrations in urine of brands C and F are shown in Fig. 4. From this figure, it could be seen that the maximum urine levels were reached at 5 hr and its concentrations of brands C and F were 236.6 and 244.3 μg/ml,respectively. The amount of biologically active rifampicin excreted in the urine at the indicated time intervals and its cumulative amount are given in Table II and Fig. 5, respectively. Both brands of rifampicin capsules showed the comparable excretion patterns in the rate and amount.

CONCLUSION

This study was conducted to investigate the physicochemical properties and bioavailability between both commercially available rifampicin capsules. The physicochemical properties, diffusion rate con-

Table I —*Pharmacokinetic Parameters after a Single Oral Administration of 600 mg Dose of Rifampicin Capsules.*

Brand	K_a (hr^{-1})	K (hr^{-1})	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-24} (μg/ml·hr)
C	0.6371±0.3120	0.1891±0.0462	2.71±0.88	6.11±1.24	57.84±4.31
F	1.6456±0.5981	0.1734±0.0203	1.52±0.98	7.27±1.25	57.28±3.00

Parameters are defined in the text. Not significant at $P<0.05$

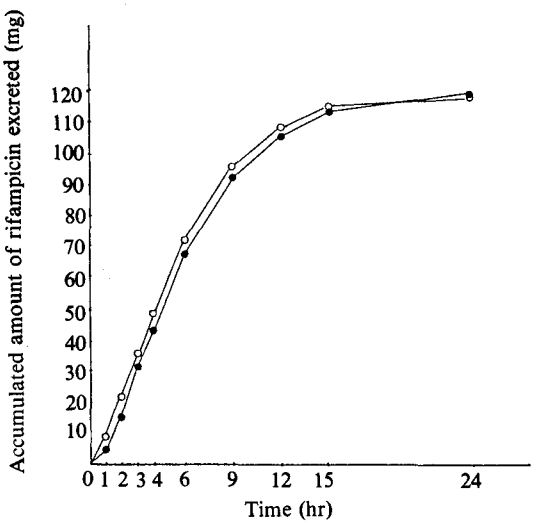

Figure 5—Mean cumulative urinary excretion of intact rifampicin following oral administration of 600 mg of rifampicin as capsules to six normal subjects.
Key: ●, brand C and ○, brand F.

stant and dissolution characteristics in artificial gastric juice were compared to predict the bioavailavility for brand C rifampicin capsules (Rifodex®). Diffusion rate constants were 3.04×10^{-3} and 2.88×10^{-3} cm/min for brands C and F, respectively, and dissolution characteristics and physicochemical properties of the two were almost the same. C_{max} and T_{max} were 6.11, and 7.27 μg/ml and 2.71 and 1.52 hr for brands C and F at 600 mg oral single dose, respectively. Also AUC and the total amount excreted in the urine were 57.84 and 57.28 μg/ml·hr, and 119.98 and 119.93 mg for brands C and F, respectively. Rifampicin was excreted in urine most plentifully between 4 and 9 hr after oral administration and the recoveries in 24 hr from brands C and F were 20.0 and 19.9% for 600 mg dose, respectively. This study did not show statistically significant differences in the bioavailability of the two rifampicin capsules, brands C and F.

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Table II—*Amount (mg) of Rifampicin Excreted in the Urine after a Single Oral Administration of 600 mg Dose of Brand C and F Rifampicin Capsules (300 mg×2 caps.).*

Brand	Subjects	Time (hr)									Total (mg
		1	2	3	4	6	9	12	15	24	
C	Ha	6.57	9.92	11.54	10.34	21.54	25.48	9.69	3.95	1.63	100.66
	Lee	7.84	13.77	15.32	11.30	24.89	31.01	18.89	15.21	16.89	155.12
	Youn	5.73	9.85	19.82	12.70	21.77	21.49	18.13	11.85	6.10	127.44
	Moon	0.05	4.73	17.43	15.86	34.78	31.43	18.72	10.73	7.16	140.89
	Shin	10.17	9.78	13.79	9.55	23.70	19.33	7.20	4.39	2.17	100.08
	Cho	0.55	13.09	16.92	12.28	7.51	17.49	7.51	2.57	1.25	95.66
	Mean	5.15	10.19	15.80	12.01	25.11	24.37	13.36	8.12	5.87	119.98
	±S.E.	±1.65	±1.31	±1.19	±0.91	±2.01	±2.42	±2.36	±2.11	±2.42	±10.15
F	Ha	9.57	12.08	10.44	13.27	25.68	18.89	8.70	2.51	1.15	102.29
	Lee	11.70	17.36	16.03	13.87	31.48	27.85	11.40	8.72	5.50	143.91
	Youn	12.56	14.91	16.35	15.63	19.12	19.35	11.28	5.78	3.63	118.61
	Moon	9.93	15.96	16.63	11.50	22.82	26.39	14.08	9.51	8.69	135.51
	Shin	11.67	12.89	12.67	10.99	21.97	25.67	12.53	7.60	4.48	120.47
	Cho	0.08	1.20	12.05	12.63	21.79	26.09	14.41	7.43	3.09	98.77
	Mean	9.25	12.40	14.03	12.98	23.81	24.04	12.07	6.93	4.42	119.93
	±S.E.	±1.89	±2.38	±1.08	±0.69	±1.76	±1.59	±0.86	±1.02	±1.04	±7.25

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