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:omparative Study of Rifampicin Pharmacokinetics Administered)rally and Intravenously in the Fasted and Non-fasted Rats

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bstract □ Effect of food on the absorption characteristics of oral rifampicin was studied in the fasted rats. ifampicin dissolved in a new cosolvent was also injected to the rats intravenously, and the pharmacokinetic nalysis was performed to explain the effect of food n the gastrointestinal absorption of rifampicin. Rimpicin was absorbed rapidly and completely in the sting state. Food had a profound effect on the garointestinal absorption of rifampicin, i.e., bioavailbility and the extent of absorption were decreased to ss than one-third of the fasting state in the postprndial state. Food seemed to inhibit the absorption and eabsorption of rifampicin in the gastrointestinal tract, ut not the absorption rate constant. Hepatobiliary xcretion seemed to be the major route of elimination, ince the renal clearance accounted for only 8% of the ystemic clearance. Nevertheless, first-pass effect was egligibly small and most of rifampicin absorbed could each systemic circulation. Serum concentration change f oral rifampicin on multiple dosing differed markedly n the fasting and postprandial state, which suggested he need of careful adjustment of dosage regimen in oth states.

Keywords □ Rifampicin, Solubilization, Oral and intravenous study, Pharmacokinetics, Bioavailability, Extent of absorption, First-pass effect, Effect of food, Multiple dosing.

Rifampicin is a semisynthetic derivative of Rifamycin SV which is produced by *Streptomyces mediterranei*. Its antibacterial spectrum includes gram positive and negative bacteria, and antiacidic bacteria[1~3].

The pharmacokinetic studies on intravenous rifampicin[4] and on oral rifampicin[5~6] have been reported in man. But some of them are insufficient and unreliable especially in the absolute bioavailability and extent of absorption following oral administration, since i.v. administration was not studied concurrently. This may be due to the difficulty of i.v. administration of rifampicin on account of its very poor water solubility.

Injectable cosolvent of rifampicin was prepared in this study and injected intravenously to the non-fasted rats. The pharmacokinetic parameters of oral rifampicin were compared with those of i.v. rifampicin. Absorption characteristics of rifampicin were discussed with the i.v. parameters. For example, bioavailability and the extent of absorption of oral rifampicin were determined in the fasted and non-fasted rats using pharmacokinetic parameters from i.v. study.

Effect of food on bioavailability, extent of absorption, absorption rate constant and on serum concentration after multiple dosing were studied in the rats to suggest a rationale for optimizing the dosage regimen according to the prandial state of man.

EXPERIMENTAL METHODS

Materials and Apparatus

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Rifampicin was kindly given by Chong Keun Dang Co. and benzyl alcohol, sodium carboxymethylcellulose (CMC-Na), propylene glycol, mannitol, sodium chloride, heparin, ether, peptone, glucose, yeast extract, beef extract, nutrient broth agar, methanol, sodium hydroxide, potassium phosphate monobasic were of analytical reagent grade or extra pure grade.

Microfuse B from Beckman Co. was used for the centrifugation, and Infusion Pump Model 12H from Natsume Co. was used for infusion to vein, respectively.

Experimental Animals

Male Wistar rats weighing 250~350g from the Experimental Animal Farm of Seoul National University were used in all experiments. Water and commercial chow (Sam Yang Animal Food Inc., Seoul) were given *ad libitum* on the same condition for more than one week before the experiment.

Preparation of Rifampicin Solution for i.v. Injection

To the mixture of benzyl alcohol and propylene glycol (1 : 9), rifampicin powder was added and mixed for 15 minutes vigorously.

Preparation of Rifampicin Suspension for Oral Administration.

90 mg of rifampicin powder was suspended in 30 ml of 0.5 % (v/w) water solution of CMC-Na and stirred with magnetic stirrer to give 3 mg/ml suspension of rifampicin.

Oral Administration of Rifampicin and Blood Sampling.

Under light ether anesthesia, the femoral artery was cannulated with PE-50 polyethylene tubing (Intramedic,® Clay Adams Co.) for blood sampling. After recovery from the ethereal anesthesia, rifampicin suspension was administered orally at a dose of 10 mg/kg with syringe for oral administration. The needle of the syringe was sufficiently thrust into the stomach of th rat, so that the suspension might not be throw up. Blood samples of 0.12~0.15 ml were collec ed at 1, 3, 4, 5, 6, 8, 15 and 22 hr after dru administration from the femoral artery *via* PE-50 catheter. During the blood samplin 1.5 ml of water was orally administered ever five hrs. The rats were kept at spine positio during the experiment. The blood samples wer centrifuged immediately after collection at 3,0C rpm with Microfuge B and 70 μl of serum wa obtained. To this 70 μl of serum, 350 μl (sterilized phosphate buffer (pH 7.0)* was adde and mixed thoroughly and stored at −20°C fo subsequent analysis.

The experiment was performed onto two grou of rats; fasted rats and postprandial rats. Ra of fasted group were fasted for about 20 h before the experiment, but water was free provided during the fast. Rats of postprandi group were fed water and commercial chow *libitum.*

i.v. Injection of Rifampicin and Blood, Uri Sampling

Under light ether anesthesia, the femoral ve and artery were cannulated with PE-50 poly thylene tubings for drug administration a blood sampling, respectively. The ureters we cannulated at 2 cm from both kidneys with PI 10 polyethylene tubings for urine collection. T rats were kept at spine position during the e periment. Infusion of 3 % (w/v) mannitol-sali solution was started more than 1 hr after t operation to allow for recovery from the ether anesthesia. The solution was infused into femoral vein *via* a PE-50 catheter at the consta rate of 1.55 ml/hr. After the steady flux of t urine was attained, rifampicin solution w injected into a femoral vein through a PE- catheter at a dose of 10 mg/kg(=1 ml/k

Blood samples of 200 μl were collected at 1, 3, 4, 5, 6, 8, 15, 20 and 24 hr after the injection from a femoral artery *via* a PE-50 catheter. Urine in each blood-sampling period was collected through the two ureters *via* PE-10 catheters. Blood samples were centrifuged immediately at 3,000 rpm and the serum was obtained. To 70 μl of serum, 350 μl of sterilized phosphate buffer (pH 7.0)* was added and mixed thoroughly and stored at −20°C for subsequent analysis. Urine samples were diluted 10 times with the above phosphate buffer and stored at −20°C for subsequent analysis.

Bioassay of Rifampicin

1) *Preparation of the liquid medium for inoculation*

0.5 g of peptone, 0.25g of beef extract and 0.125 g of sodium chloride were dissolved in distilled water to make 50 ml(pH 6.8∼7.0). It was autoclaved and the autoclaved medium was inoculated with *S. lutea*. The inoculated medium was incubated at 37°C for 16∼18 hrs on the shaker.

2) *Preparation of basal layer and seed layer*

1.0 g of peptone, 0.2 g of glucose, 0.6 g of yeast extract and 0.3 g of beef extract were dissolved in distilled water to make 200 ml(pH 6.8∼7.0) and 6.132 g of nutrient broth agar was added to it to prepare the basal layer. Then it was autoclaved. For the preparation of the seed layer, 1 ml of the liquid medium was added to the 200 ml of the basal layer at 45∼50°C.

3) *Preparation of the solutions for calibration curve*

1.5, 3, 15 and 30 μl of rifampicin stock solution and 2.5 ml of sterilized phosphate buffer (pH 7.0) were added to 0.5 ml of the rat serum to yield solutions of 0.5, 1.0, 5.0 and 10.0 μg/ml respectively. Stock solution of rifampicin was freshly prepared by dissolving 50 mg of rifampicin in 15 ml of methanol and diluting to 50 ml with the phosphate buffer. For the calibration of rifampicin in urine, solutions of the same concentrations were prepared by appropriate dilution of the stock solution with the phosphate buffer.

4) *Preparation of the calibration curve*

After 20 ml of basal layer was spread and set on the sterilized petri dish, 12 ml of seed layer was spread on it to prepare the plate. On this plate, sterilized cylinders were fixed and 200 μl of the calibration solutions were injected into the respective cylinders. They were incubated at 37°C for 16∼18 hrs and the diameters of the inhibition region were measured carefully. Diluted samples of serum and urine were assayed in the same manner.

Interpretation of the Data

The average concentration changes of the rifampicin in the serum after oral administration and i.v. injection were best fitted to the one- or two-compartment model respectively by MULTI program[8].

RESULTS AND DISCUSSION

Solubilization of Rifampicin Powder

Rifampicin powder was well dissolved in the mixture of benzyl alcohol and propylene glycol (1 : 9). The volume ratio (1 : 9) of benzyl alcohol and propylene glycol was decided after confirming the dielectric constant of the cosolvent be 30 like that of methanol, which dissolves rifampicin very well. Dielectric constant of the cosolvent was calculated by the following

* 29.1 ml of 0.2 M-NaOH and 50 ml of 0.2M-KH_2PO_4 was mixed and distilled water was added to it to make 200 ml. pH of the solution was adjusted to 7.0 and the solution was sterilized with autoclave.

equation[9].

$$E_{cosolvent}=\sum\{(E_{each\ solvent})\times(\text{Volume fraction of each solvent})\} \quad \text{(Eq. 1)}$$

where E means dielectric constant. Dielectric constants of benzyl alcohol, propylene glycol and methanol are 13, 32 and 30 respectively. Rifampicin powder was well dissolved in the cosolvent up to 10 mg/ml. To confirm whether rifampicin is deposited after i.v. injection to the rat in the blood pool or not, 1 ml of the solution was added to 18 ml of distilled water or phosphate buffer (pH 7.4) at 37°C, but no changes of the solution state were observed. Therefore, this cosolvent seemed to be more proper than other methods on several papers the for solubilization of rifampicin[4,10~11].

Bioassay of Rifampicin

Fig. 1 is the calibration curves of rifampicin in serum and phosphate buffer (pH 7.0) using *Sarcina lutea* as the microorganism for assay. Relationship between the concentrations of rifampicin and the diameters of inhibition region was linear over the range of 0.5 to 10 μg/ml in both serum and phosphate buffer. Therefore, this method was regarded as the proper assay system. The calibration curve of rifampicin in serum was parallel to that of rifamicin in phosphate buffer (pH 7.0). But the potency of rifampicin in serum was 25% lower than that in buffer. The reason for the decrease of the potency of rifampicin in serum was not revealed yet, but it was supposed to be due to some components of the serum. Calibration curve was prepared each time the samples were assayed.

The concentration of rifampicin in serum can be quantitated by either high performance liquid chromatography (HPLC)[12~14] or detecting ^{14}C-labelled rifampicin[11]. A linear correlation was observed between HPLC and bioassay[5,15~17]. Considering the expense and handling difficulty,

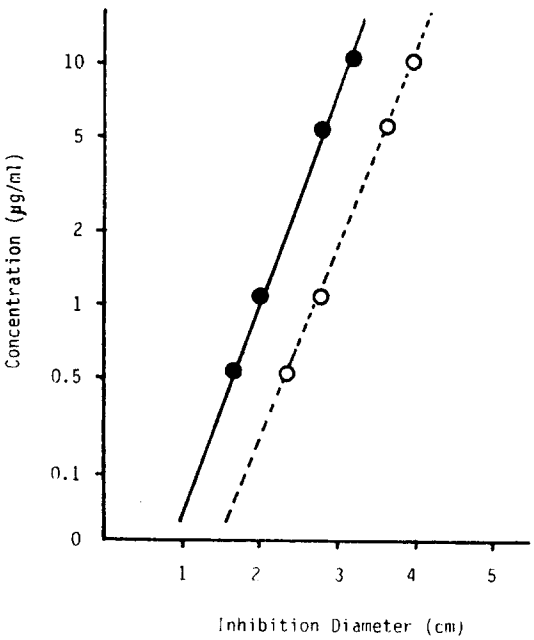


Fig. 1. Calibration curves of rifampicin in serum (solid line) and phosphate buffer (dotted line).

we used the bioassay method and selected *S. lutea* as the microorganism for bioassay like other reports[5,15~17].

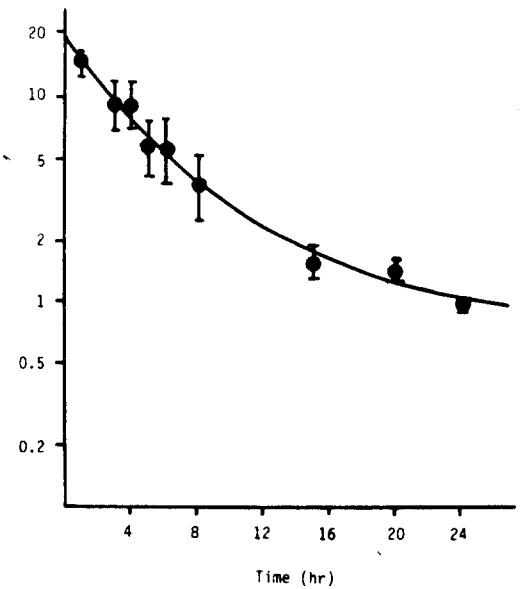
Distribution, Metabolism and Excretion of i.v. Injected Rifampicin

Fig. 2 shows the change of the serum concentration of rifampicin after i.v. injection at a dose of 10 mg/kg to the non-fasted rats. The solid curve in Fig. 2 was drawn by fitting the observed values to two-compartment open model. MULTI program for personal computer by Yamaoka[8] was used in this fitting. As a result, the following equation was obtained for the serum concentration C;

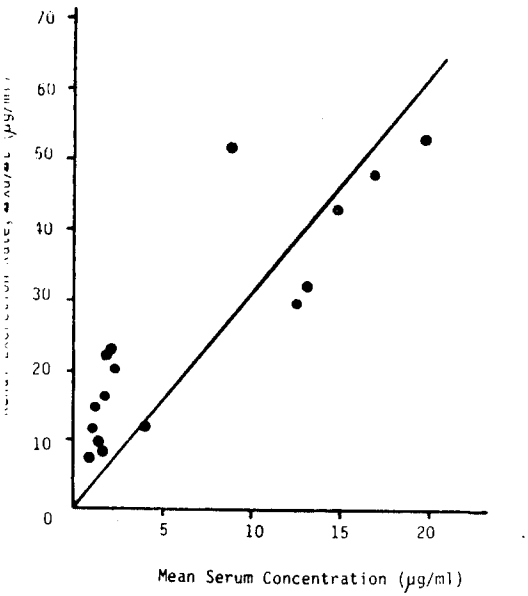
$$C=14.998\ e^{-0.241t}+1.968\ e^{-0.0257t}$$

where t is the time (hr) after the injection.

Fig. 3 shows the relationship between urinary excretion rates and mean serum concentrations of rifampicin after i.v. administration of rifampicin. Since the renal excretion of rifam-



g. 2. Serum concentrations of rifampicin in non-fasted rats following i.v. administration of 10 mg/kg. Solid curve was calculated by MULTI[8] on 2-compartment open model. Each point represents the mean±S.E. of three rats.



g. 3. Relationship between renal excretion rate and mean serum concentration of rifampicin in a rat. Solid line, which means the renal clearance, was calculated from the mean of each slope of each data point.

picin did not show saturation over the concentration ranges in Fig. 3, renal clearance (CL_r) of each rat was calculated as the mean of every (excretion rate)/(mean serum concentration).

Pharmacokinetic parameters of rifampicin following i.v. administration of 10 mg/kg to non-fasted rats are listed in Table I. Conventional two-compartment open model was assumed for the interpretation of the serum concentration data. Table I shows that most part of rifampicin in the body is eliminated by the liver, because renal clearance, CL_r, accounts for only 8 % of the systemic clearance (CL_s) of rifampicin.

Table I. Pharmacokinetic parameters of rifampicin after i.v. administration to the non-fasted rats.

Parameters	Unit	Experimental Values
A	μg/ml	14.998
B	μg/ml	1.968
α	hr^{-1}	0.241
β	hr^{-1}	0.026
$T_{1/2(\alpha)}$	hr	2.876
$T_{1/2(\beta)}$	hr	26.965
V_c	ml/kg	589.41[a]
V_p	ml/kg	318.58[b]
V_{ss}	ml/kg	907.99[c]
$AUC^{0-\infty}$	μg·hr/ml	122.33[d]
CL_s	ml/hr/kg	72.04[e]
CL_r	ml/hr/kg	5.95[f]
CL_{nr}	ml/hr/kg	66.09[g]
k_{21}	hr^{-1}	0.0507
k_{12}	hr^{-1}	0.0938
k_{10}	hr^{-1}	0.1222

Rifampicin was injected intravenously at a dose of 10 mg/kg. *a*) Dose/$(A+B)$, *b*) $V_c \cdot k_{21}/k_{12}$, *c*) V_c+V_p, *d*) calculated by $AUC^{0-24hr}+(C_{24hr}/\beta)$, where AUC^{0-24hr} was calculated by trapezoidal rule, *e*) Dose/AUC, *f*) renal excretion rate/mean serum concentration, *g*) CL_s-CL_r, which means nonrenal clearance[21].

Each value represents the mean of three non-fasted rats.

And from the value of distribution volume at steady-state (V_{ss}), rifampicin was considered to be well distributed to the whole body. Considering that the distribution volume of the central compartment (V_c) was greater than that of peripheral compartment (V_p) and that V_c was much greater than the real volume of the serum, 40 ml/kg[7], the well-strirred organs such as liver or kidney were supposed to be included in the central compartment. This consideration might be supported by the fact that the order of rifampicin concentration in the tissues at postdistributive phase after i.v. injection was reported as follows:[17] liver>kidney≒serum>lung>pancreas.

Absorption, Distribution, Metabolism and Excretion of Orally Administered Rifampicin in the Fasting State and in the Postprandial State

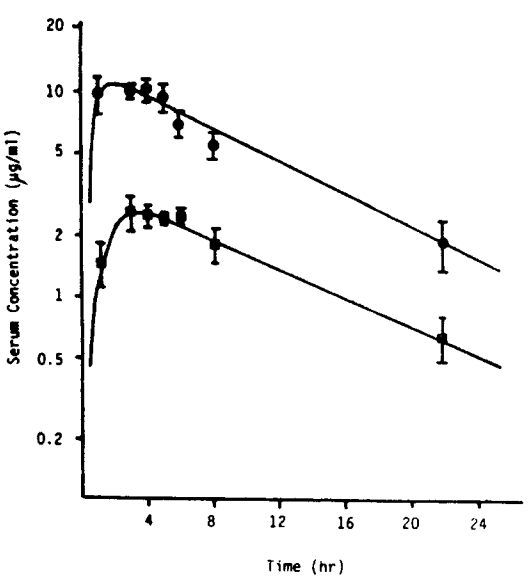


Fig. 4. Serum concentrations of rifampicin in the fasted (•) and non-fasted (▪) rats following oral administration of 10 mg/kg. Solid curves were calculated by MULTI on 1-compartment open model with first order absorption process. Each point represents the mean±S.E. of four (•) or three (▪) rats.

1) *Serum concentration profile of rifampicin follwing oral administration*

The time courses of the serum concentration of orally administered rifampicin are shown in Fig. 4.

Concentrations of rifampicin from the fasted rats were much higher than those from the non-fasted rats. It might be due to the effect of food on the gastrointestinal absorption of rifampicin in the postprandial state. Food often inhibits gastrointestinal absorption of orally administered drugs or gastrointestinal reabsorption of biliary excreted drugs which exhibit enterohepatic circulating characteristics. The fact that biliary excretion of rifamicin is the major route of elimination and that non-renal clearance (CL_{nr}) of rifampicin is very large (Table I) may explain the higher concentrations of rifampicin in the fasted state than in the postprandial state. The effect of food on the absorption of rifampicin was reported to be large especially at low dose [6,18]. The metabolism of rifampicin in the liver was known to be saturated at high dose[6,18]. Therefore, the effect of food on the serum concentration of rifampicin may become smaller after administration of high oral dose, since the saturation of the liver capacity may account for the larger part of the serum concentration of rifampicin.

The time course of the serum concentration of orally administered rifampicin was fitted by MULTI[8] to one-compartment open model with first order absorption. As a result, the following equation was obtained for the fasting state: $C = 13.49 \times (e^{-0.0965t} - e^{-1.6932t})$. For the postprandial state, $C = 3.602 \times (e^{-0.0771t} - e^{-1.0889t})$ was obtained.

2) *Bioavailability of the orally administered rifampicin and the effect of food on it*

Parameters associated with bioavailability are listed in Table II. All of them were read or

calculated from four (fasted group) or three (non-fasted group) experiments.

In spite of its poor solubility in water, rifampicin was rapidly absorbed from the gastrointestinal tract, which was implied by Ka, apparent first order rate constant of absorption, and absoption half-life in Table II.

Maximum concentration (C_{max}) and area under the serum concentration from zero time to infinity ($AUC^{0\to\infty}$) were markedly decreased in the postprandial state. But time to reach maximum concentration (T_{max}) and apparent elimination rate constant (K) did not differ in both states.

Absolute bioavailabity (F) which was calculated in this study as $(AUC)_{oral}^{0\to\infty}/(AUC)_{i.v.}^{0\to\infty}$ was very high (98.4 %) in the fasted state, but it was reduced to less than a half in the postprandial state(29.8 %). The same effect of food on the bioavailability of rifampicin was also reported [6,18]. This may be due to the inhibitory effect of food on drug absorption or reabsorption excreted into small intestine *via* a bile duct as mentioned above[19].

Table II. Bioavailability parameters of orally administered rifampicin (10 mg/kg rat) in the fasted and non-fasted rats.[a]

Parameters	Unit	Fasted (n=4)	Non-fasted (n=3)
C_{max}	μg/ml	10.0	2.7
T_{max}	hr	3.0	3.3
K_a	hr^{-1}	1.693	1.089
$T_{1/2}$ of absorption	hr	0.41	0.64
K	hr^{-1}	0.097	0.077
$T_{1/2}$ of elimination	hr	7.2	9.0
$AUC^{0\to\infty}$	μg·hr/ml	120.34	36.44
Bioavailability (F)	%	98.4	29.8
Extent of absorption (F_{abs})	%	95.1	28.8

a) Expressed as mean. $AUC^{0\to\infty}$ was calculated by $AUC^{0\to 22hr}+C_{22hr}/K$, where $AUC^{0\to 22hr}$ was calculated by trapezoidal rule and C_{22hr} means the serum concentration at t=22hr. F_{abs} was calculated by Eq. 2.

Usually the extent of bioavailability reaches the maximum value, 100 %, only when gastrointestinal absorption is complete and the first-pass effect is negligible. Therefore, it was implied that rifampicin is absorbed almost completely in the fasting state but not so well in the postprandial state, and that rifampicin suffers negligibly small first-pass effect after oral administration.

The elimination rate constant and elimination half-life of rifampicin after oral administration did not differ significantly in the fasted and non-fasted rats, which implies that although the extent of absorption was decreased, but the rate constant of absorption (Ka) of rifampicin was not affected by food, and that it did not take long hours for rifampicin to be absorbed in both states.

The extent of absorption (F_{abs}), which differs from the bioavailability F, means the percent of drug absorbed from gastrointestinal tract to the administered dose, while F means the percent of drug reached to the systemic circulation to the administed dose. F can not exceed F_{abs} on account of first-pass effect that the drug suffers before it reaches the sytemic circulation. F_{abs} was calculated from Eq. 2[20] assuming that there is no other non-renal route of elimination than hepatic metabolism, *i.e.* $CL_{nr}\fallingdotseq CL_h$ for rifampicin.

$$F_{abs}(\%)=F/(1-CL_h/Q_h) \qquad \text{(Eq. 2)}$$

where $(1-CL_h/Q_h)$ means the maximum bioavailability attainable assuming complete absorption. Hepatic clearance CL_h was read to be 66.09 ml/hr/kg from CL_{nr} in Table I and hepatic plasma flow Q_h of the rats was read to be 1,950 ml/hr/kg from the literatures[7,20]. F was read from Table II. As a result, F_{abs} of 95.1 and 28.8 % were obtained for fasted and non-fasted state respectively. It seems from the above results

that the gastrointestinal absorption of rifampicin is almost complete in the fasting state, but very poor in the postprandial state. The fact that $F_{abs} \fallingdotseq F$ means negligible first-pass effect of orally administered rifampicin in both states.

Effect of Food on the Serum Concentrations of Rifampicin Orally Administered to the Fasted and Non-fasted Rats.

Multiple dosing has been generally known to be more effective than single dosing for the therapy. Fig. 5 shows the time course of the serum concentrations of riampicin dosed repeatedly to the rats in the fasting state and postprandial state. Serum concentrations were calculated by Eq. 3[21].

$$C_n = \frac{K_a \cdot F \cdot X_0}{V(K_a - K)} \left[\left(\frac{1 - e^{-n \cdot K \cdot \tau}}{1 - e^{-K \cdot \tau}} \right) e^{-K \cdot t} - \left(\frac{1 - e^{-n \cdot Ka \cdot \tau}}{1 - e^{-Ka \cdot \tau}} \right) e^{-Ka \cdot t} \right] \quad \text{(Eq. 3)}$$

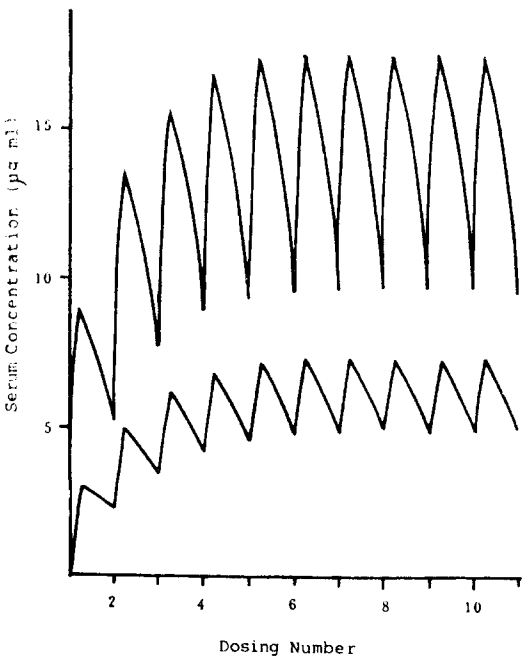


Fig. 5. Serum concentrations of rifampicin on three times-a-day oral administration at a dose of 10 mg/kg in the fasted (above curve) and non-fasted rats (below curve).

where n represents dosing number, τ the dosing interval, t time after dosing ($0 < t < \tau$), X_0 the oral dose and V distribution volume. K, Ka and F were explained previously. All parameters except τ and X_0 were exracted from Table II or I. For the convenience of the consideration, τ and X_0 were fixed to be 8 hr and 10 mg/kg respectively.

Fig. 5 shows that serum concentrations in the fasting state (above curve) were much higher but vibrated in a larger scale than in the postprandial state (below curve).

Considering the above fact that the time course of serum concentration of rifampicin differed markedly according to the prandial state, dosage regimen for man should be designed carefully.

CONCLUSION

Effect of food on the absorption of oral rifampicin was studied in the fasted and non-fasted rats together with i.v. study of rifampicin. Rifampicin solution for i.v. study was prepared by dissolving rifampicin powder in the cosolvent of benzyl alcohol and propylene glycol (1:9).

Phrarmacokinetics of i.v. administered rifampicin could be fitted to two-compartment open model, but that of oral rifampicin to one-compartment with first order absorption process. Well-stirred organs like liver and kidney seemd to be included in the central compartment, since the volume of the central compartment (V_c) exceeded the real volume of the serum. Hepatobiliary excretion was the major route of elimination of rifampicin since the renal clearance (CL_r) accounted for only 8 % of the systemic clearance (CL_s).

Rifampicin was absorbed rapidly and completely from the gastrointestinal tract in the fasted rats. Bioavailability and the extent of

ɔsorption of rifampicin in the non-fasted rats ere less than one-third of those in the fasted ıts. This seemed to be due to the inhibitory fect of food on the absorption and reabsorption f rifampicin in the gastrointestinal tract. But ɔnsidering the fact that K_a and K did not differ ı the fasted and non-fasted rats, food was ɔnsidered to decrease the extent of absorption ut not the absorption rate constant of rifamicin.

Hepatobiliary excretion was the major route of limination. Nevertheless, the first-pass effect of ifamicin seemed to be negligible since bioavaabilty F and extent of absorption F_{abs} were lmost same. Serum concentration of oral ifampicin after multiple dosing differed maredly in the rats of fasted and nonfasted state, vhich suggested the need of careful adjustment f dosage regimen in both states.

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