

CHRONOPHARMACOKINETICS OF RIFAMPICIN

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Abstract: Chronopharmacokinetics of rifampicin was studied in four healthy adult male human volunteers after drug (2.0 g) ingestion at 6.00, 12.00, 18.00 and 24.00 hr. The absorption rate constant was found to be lower and the time to reach peak concentration was longer after drug administration at 24.00 hr than at other dosing times. A second peak was observed in all individual volunteers between 6-12 hr after drug dosing at 24.00 hr. This may be due to the influence of biliary rhythms on the disposition kinetics of rifampicin.

Key words: rifampicin chronopharmacokinetics humans

INTRODUCTION

Many drugs have shown variations in pharmacokinetic parameters with time of administration (1). However there are few reports on these aspects for drugs belonging to the class of ant-infectives or antibiotics (2).

Rifampicin is a drug most commonly used in the treatment of tuberculosis. 25% of the administered drug undergoes biliary excretion and recycling (3). Though reports regarding biliary rhythms are available, their implications on drug disposition kinetics are attempted to a meagre extent (4). In light of this chronopharmacokinetics of rifampicin assumes importance.

METHODS

Subjects

Four healthy adult male human volunteers (weight 51 to 60 kg height 165 to 178 cms and age 22-24 yr) were selected for this investigation. Before each study the volunteers were given a complete medical examination by a physician, a medical history was taken and laboratory tests were performed. Subjects were accepted only after ascertaining their good health. The subjects were not allowed to take any drug 7 days prior to the study. The diet and sleeping time were synchronized 10 days before study. The subjects were informed of all the study details and have given their written consent. The study was approved by a local Ethical Committee.

Protocol

The bioavailability studies were performed on a completely balanced latin square cross over design. A single dose of rifampicin (2.0 g in the form of capsules) was administered orally at one week interval to each subject at 6.00, 12.00, 18.00 or 24.00 hr of circadian clock. After 6 hr fasting, the subjects were administered the drug with 200 ml cold drinking water. No food and drinks were allowed (except water) to be taken by the subjects for three hours after drug administration. Blood samples (3-5 ml) were withdrawn at intervals of 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 5, 7, 10, 12, 15, 20, 24, 30, and 36 hr from median cubital vein. The samples were allowed to clot, serum was separated and frozen at -20°C until assayed.

Estimation of rifampicin in serum : Serum rifampicin levels were estimated spectrophotometrically using butanol-heptane mixture (5). One ml of serum was extracted with 3 ml of butanol : heptane mixture (4:1). The absorbance of organic extract was read at wave length 482 nm on a LKB spectrophotometer against the blank (zero hour serum sample extracted with solvent system) and the concentrations of the rifampicin in the unknown samples were obtained from a standard graph. The % coefficient of variation of this method for estimation of rifampicin at two concentrations 25 and 50 µg/ml in five observations was found to be 2.07 and 2.64 respectively.

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Treatment of bioavailability data : According to a non compartmental pharmacokinetic model, the various pharmacokinetic parameters calculated were : mean residence time (MRT), elimination half-life ($T_{1/2}$), over all elimination rate constant (K_e), total area under the curve ($AUC_{0-\infty}$), apparent volume of distribution (V_d), absorption rate constant (K_a) and total systemic clearance (Cl_s); where as the C_{max} and T_{max} are the observed values.

Statistical analysis of the data : The mean pharmacokinetic parameters were subjected to analysis of variance or paired t-test and the difference between

the treatments was validated at the probability level of $P < 0.05$.

RESULTS

The plots of mean serum concentration versus time after administration of 2.0 g of rifampicin at 6.00, 12.00, 18.00 or 24.00 hr of circadian clock are shown in Fig 1. The means of different pharmacokinetic parameters obtained from serum levels versus time data of individual volunteers are shown in Table I. The mean peak serum rifampicin concentrations (C_{max}) were

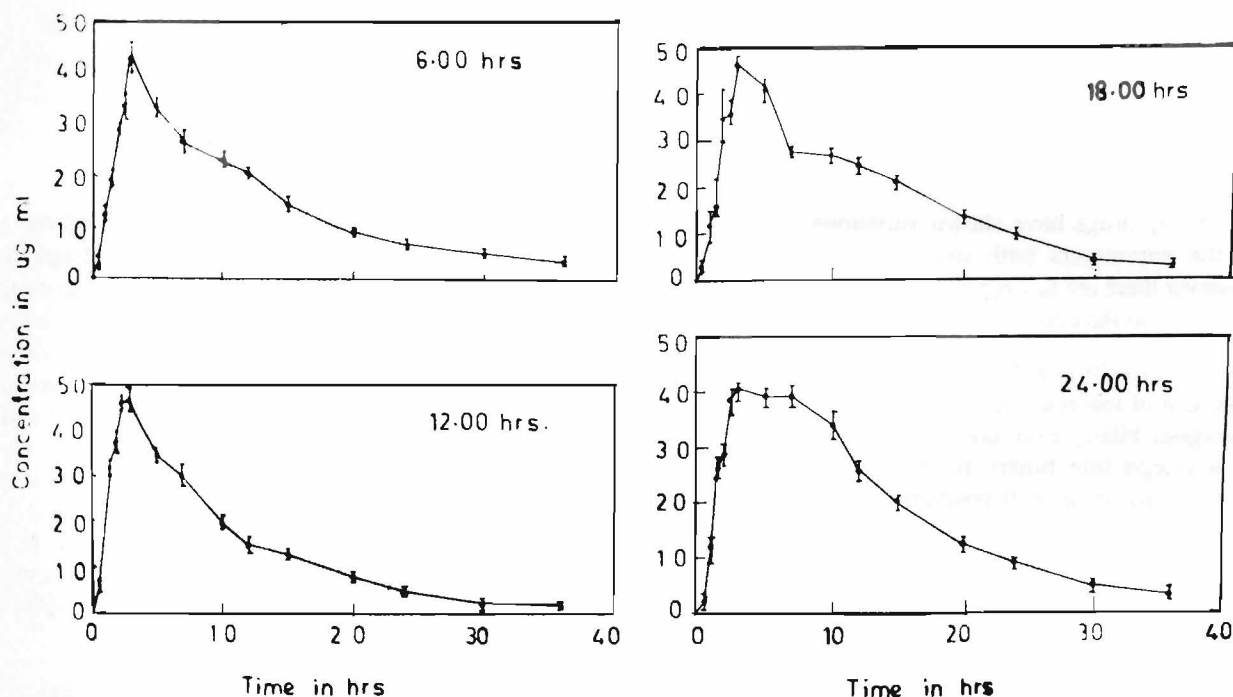


Fig. 1: Mean serum concentration in $\mu\text{g/ml}$ versus time profiles after administration of rifampicin (2.0) orally at 6.00, 12.00, 18.00 and 24.00 hr of the circadian clock.

TABLE I: Pharmacokinetic parameters (MEAN \pm SEM) of rifampicin at 6.00, 12.00, 18.00 and 24.00 hr of circadian clock.

S.No.	Pharmacokinetic parameters	6.00	12.00	18.00	24.00
1.	C_{max} ($\mu\text{g/ml}$)	43.92 \pm 5.92	46.69 \pm 5.36	46.80 \pm 5.79	40.94 \pm 3.65
2.	T_{max} (hr)	2.75 \pm 0.25	2.75 \pm 0.14	3.25 \pm 0.62	5.00 \pm 0.81
3.	K_a (hr^{-1})	1.61 \pm 0.07	1.69 \pm 0.09	1.57 \pm 0.28	0.67 \pm 0.09
4.	K_e (hr^{-1})	0.07 \pm 0.01	0.09 \pm 0.01	0.10 \pm 0.03	0.07 \pm 0.02
5.	$T_{1/2}$ (hr^{-1})	10.24 \pm 1.50	8.08 \pm 1.23	7.32 \pm 0.90	7.84 \pm 0.58
6.	$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{hr}/\text{ml}/\text{kg}$)	10.74 \pm 2.04	9.75 \pm 1.13	11.83 \pm 1.11	12.48 \pm 1.35
7.	MRT (hr)	16.08 \pm 1.72	12.51 \pm 1.89	13.61 \pm 1.10	13.60 \pm 0.82
8.	V_d (l/kg)	0.98 \pm 0.13	0.77 \pm 0.10	0.62 \pm 0.05	0.60 \pm 0.07
9.	Cl _s (ml/min/kg)	1.06 \pm 0.11	1.14 \pm 0.14	0.93 \pm 0.09	0.87 \pm 0.04

slightly lowered and a sustenance in the mean peak levels was observed following the drug administration at 24.00 hr. However, no significant difference was observed between the mean C_{max} values after drug dosing at different clock hr ($F = 0.47, P > 0.05$). The mean time to reach peak concentration (T_{max}) was significantly longer after drug ingestion at 24.00 hr than at other dosing times ($F = 4.01, P < 0.05$). The mean absorption rate constant obtained after drug administration at 24.00 hr was significantly lower than after ingestion at other time points, ($F = 8.79, P < 0.01$).

No significant time dependant variation between the means of other pharmacokinetic parameters (viz; K_e, T_{1/2}, V_d, AUC, Cl_s, MRT) was observed.

Serum rifampicin concentration versus time profiles for drug dosing at 24.00 hr showed two prominent peaks in all individual volunteers (Fig. 2). The first peak appeared between 1-5 hr and second peak between 6-12 hr after drug ingestion. The occurrence of second peak is validated (Table II) by subjecting the concentration of rifampicin just before second peak and at second peak to a paired t-test. Carocella et al (6) applied similar method to validate the occurrence of second peak in serum concentration versus time profiles of digoxin.

TABLE II. Statistical validation of the second peak.

Mean conc before second peak (µg/ml)	Mean conc of second peak (µg/ml)	P value
32.04±3.31	44.88±6.26	P<0.025

Values represent mean ± S.E.M.

DISCUSSION

Circadian changes in the absorption of drugs were reported (7,8,9). The absorption T_{1/2} values of lorazepam (10) and triazolam (11) were thrice and twice lower in the dark phase than in the light phase drug administration respectively. Prolonged T_{max} and lower absorption rate constant observed for rifampicin at 24 hr administration in the present investigation are in parallel with these observations. Temporal changes in the membrane permeability (12), gastric pH (13,14), and gastric motility may be the possible reasons underlying circadian variability in rifampicin absorption.

Goo et al (15) have reported delayed gastric emptying of solids for evening meal than for morning meal. It was thought that the delay in T_{max} in case of drugs like indomethacin and theophylline was due to such a delay in the gastric emptying. Since the subjects

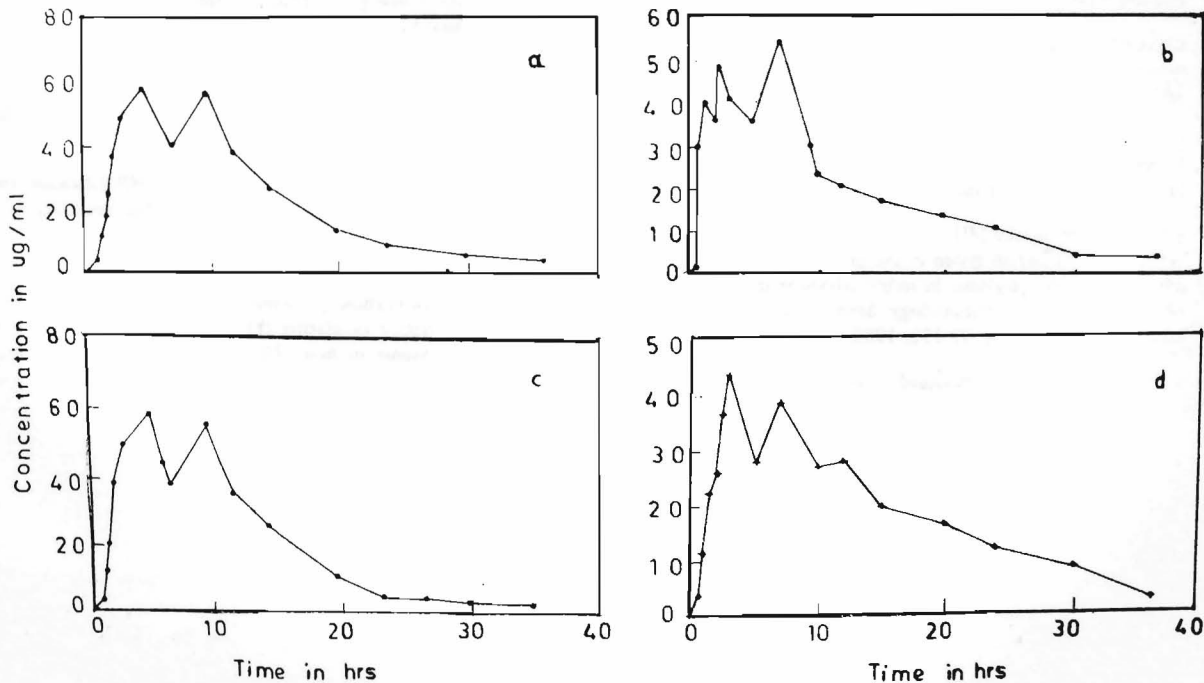


Fig. 2 : Serum concentration in µg/ml versus time profiles after administration of rifampicin (2.0 g) orally at 24.00 hr in four individual subjects a, b, c and d.

in the present study were fasted for 6 hr prior and 3 hr after the drug administration, gastric emptying time differences might not have contributed to the observed variations in the absorption of rifampicin.

Although a second peak in the serum levels of rifampicin was observed in individual subjects, such a phenomenon was not reflected in the mean serum levels which is due to the occurrence of second peak at different times in the individuals. Rifampicin undergoes

enterohepatic circulation. 25% of the drug is handled via this route (3). The time dependent changes in bile output, bile acid concentration (4), and levels of cholecystokinin (16) appear to be responsible for a second peak which was observed in all the subjects after 24.00 hr drug administration. Carocella et al (6) also reported the occurrence of second peak for digoxin and β -methyl digoxin. Results of Carocella et al (6) and ours emphasize the need to investigate biliary rhythms and their implication on drug disposition kinetics.

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