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BIOAVAILABILITY AND DISPOSITION KINETICS OF RIF AMPICIN CAPSULES

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ABSTRACT

Different drug manufactures claim better quality and bioavailability of the similar dosage from of a drug product. In view of this, bioequivalence on the basis of bioavailability and disposition kinetics of rifampicin capsules marketed under the brand names of Rifadin, Rifapin and Rimactane investigated in normal human volunteers. Each drug was given orally and blood levels of active were rifampicin at different times were measured by a microbiological assay procedure. The studies revealed that the abosrption kinetics, bioavailability and disposition kinetics of three brands of rifampicin did not differ from each other significantly in human volunteers.

Introduction

A variable clinical response to one drug administered in the same dosage forms supplied by different drug manufacturers is now a generally accepted possibility. Such a variation in clinical response has been attributed to the differences in bioavailability which is a term used to indicate measurement of both the relative amount of an administered dose of a drug that reaches the general circulation and the rate at which it is absorbed. The measurement of bioavailability under standard conditions for a comparison of a drug in two or more similar dosage forms provides an information about the bioequivalence of the drug products.

Bioavailability and hence, bioequivalence of a drug product are influenced by both the pharmaceutical and biological factors. The in vitro pharmaceutical factors are easy to control than the biological factors. The problems of therapeutic failures or hazards related to bio-equivalence are well documented and warrant testing of important drugs for best clinical results.

A successful short term antitubercular chemotherapy with rifampicin has made this drug popular, hence, it is being marketed under different brand names. In the present study three different brands of rifampicin were studied in healthy human volunteers for bioequivalence. The disposition kinetics parameters were also determined in these experiments.

Material and Methods

The bioequivalence of rifampicin was investigated in 18 experiments on six healthy male volunteers.

Theme commercial capsules of rifampicin marketed under the proprietary brands of Rifadin, Rifapin and Rimactane were procured from the market. Each preparation was randomly designated as A, *B* and C and was tested on each subject on three different occasions with a wash out period of at least one week between each trial.

After an overnight fasting, a control blood sample was drawn from all the subjects by usual venepuncture of the cubital vein. Each one of them was given a dose of 450 mg rifampicin in randomly selected capsules (150 mg capsule x from the formulations with 250 nil of water to swallow the drug. By following completely randomised block design two subjects received each formulation on the trial day. In this way all the six volunteers received the three preparations on three different trial days. The volunteers ate standard breakfast two hours following drug administration.

The venous blood samples were drawn in heparinised centrifuge tubes at 0.5, 1,2, 3, 4, 5, 6, 8, 10, 12 and 24 hours following oral administration. The blood was centrifuged at 3000 RPM for 10 minutes and plasma was separated for the analysis of rifampicin.

Assay of the drug in plasma samples was carried out by microbiological plate method using *Sarcina lutes* A.T.C.C. 9341 as test organism. Pure rifampicin powder was used to prepare the standards in plasma at the concentration of 0.5, 1.0. 2.5, 5.0 and 10.0 µg. ml^{-1}.

The plasma concentration of each drug versus time graph in each subject was drawn separately for the determination of bioavailability and pharmacokinetic parameters (Gibaldi, 1984). The average ± SD values of plasma concentration for the drug A, B and C were calculated in all the six volunteers. A comparison of bioavailability and pharmacokinetic parameters of the drugs A, B and C was performed using Student's t-test, taking one drug as a standard.

Table 1: Bioavailability parameters of three brands of rifampicin investigated in six volunteers following oral dose of 450 mg

Parameters and Units	Average ± SD (n = 6)		
	Drug A	B	C
N µg.ml^{-1}	8.48 ± 2.41	6,52 ± 1.86	7.01 ± 2.10
$C_{\cdot max}$ µg.ml^{-1}	4.37 ± 1.06	4,04 ± 1.46	425 ± 1.02
$t_{\cdot max}$ hour	1.58 ± 041	1.90 ± 0.81	2.01 ± 0.69
$k_{\cdot abs}$ $hour^{-1}$	1.74 ± 0.52*	0.94 ± 0.28	0.99 ± 0.30
$t½_{\cdot abs}$ hour	0.40 ± 0.12*	073 ± 0.20	0.70 ± 0.18
AUC µg.h^{-1}. ml^{-1}	31.5 ± 8.8	30.9 ± 9.3	39.3 ± 8.5

*$P < 0.01$

Results

a) Bioavailability:

The average values of plasma concentration of active rifampicin on a semilogarithmic scale against various time intervals following oral administration of the formulation A, B and C are shown in Figure 1 and the parameters of absorption kinetics are given in Table I. The mean ± SD values of maximum plasma concentration (C_{max}) of bacteriologically active rifampicin for drug A, B and C were 4.37 ± 1.06, 4.04 ± 1.46 and 4.25 ± 1.02 pg. mr^{1}. Statistically, there was no difference between the maximum plasma concentration of the three drugs.

The time (t_{max}) at which drug concentration reached its peak value was determined. It was about one and a half hour for drug A and about two hours for drug B and C. The value of rate constant for absorption K (abs) was higher and half-life ($t_{½}$ (abs) of absorption was shorter for drug a when compared with that of B and C and the difference was significant ($P < 0.01$). However, there was no difference in K (abs) and $t_{½}$ (abs) for drugs B and C (Table 1).The area under plasma concentration versus time curve (AUC) for drug A. B and C revealed average ± SD values 31.5 ± 8.8, 30.9 ± 9.3 and 39.3 ± 8.5 μg. h^{-1}. $m1^{-1}$ respectively. No statistical difference was found between these values (Table 1).

Table 2: Disposition kinetics of three brands of rifampicin investigated in six volunteers following oral dose of 450 mg.

Parameters and Units	Average ± SD (n = 6)		
	Drug A	B	C
B μg.ml^{-1}	5.48 ± 1.75	5.56 ± 2.48	5.40 ± 1.43
β $hour^{-1}$	0.153 ± 0.041	0.149 ± 0.044	0.117 ± 0.023
t ½ hour	4.80 ± 1.20	5.03 ± 1.56	6.09 ± 1.09
Vd 1. kg^{-1}	1.44 ± 0.31	1.52 ± 0.49	1.46 ± 0.45
Cl ml. h^{-1}. kg^{-1}	213 ± 47	208 ± 35	165 ± 33

b) Disposition Kinetics:

The disposition kinetic parameters were determined from the elimination phase following the establishment of absorption and distribution equilibrium. The average ± SD values for the disposition kinetic parameters of rifampicin are shown in Table 2.

The average ± SD values for the extrapolated zero time plasma concentration (B) of the elimination phase for drug A, B and C were 5.48 ± 1.75, 5.56 ± 2.48 and 5.40 ± 143 μg. ml^{-1}, respectively.

The values determined for half-life ($t_{½}$) *were* 4.80 ± 1.20. 5.03 ± 1.56 and 6.09 ± 1.09 hours, for apparent volume of distribution (V) were 1.44 ± 0.31, 1.52 ± 0.49 and 1.46 ± 0.45 1 kg^{-1}, for total body clearnace expressed in ml. h^{-1}. kg^{-1} were 213 ± 47, 208 ± 35 and 165 ± 33 for A, B and C formulations, respectively. Statistically, no difference was found in any of the kinetic parameters between three drugs.

Discussion

Bioequivalents are chemically equivalent drug products which when given in the same dose regimen would result in comparable bioavailability. The bioavailability of drugs is influenced by both the pharmaceutical and biological factors (Wagner, 1975). The pharmaceutical manufacturing units can control the pharmaceutical factors while the biological factors are not under direct control. There are many examples of manufacturing processes that affect the bioavailability and the response to various drugs (Curry, 1977). Several investigations have clearly demonstrated that the kinetic parameters of a drug are best defined in the population and environments where the drug is to be employed clinically (Nawaz, 1983). Recently, the geographical influences on the genetic manifestations through changes in physiological and biochemical variables responsible for a different explanation of homeostasis and drug disposition have been termed as "geonetical" influences (Nawaz & Shah, 1985). To determine how well various pharmaceutical manufacturing units control pharmaceutical factors, we undertook this study using three different formulations of rifampicin.

a) Absorption:

Absorption of rifampicin after oral administration of three brands namely, Rimactane, Rifapin and Madill hardly revealed any difference in the peak absorption times (t_{max}) and peak plasma concentration (C_{max}) in six healthy volunteers.

Orally administered rifampicin is rapidly and totally absorbed (Riess *et al.,* 1970) and the rate of absorption was not dose-dependent (Lecaillon *et al.,* 1981). In the present study, the peak concentration was attained between one to three hours which is similar to the peak concentration time of one to four hours reported earlier. The peak concentration 5.4 μg. ml^{-1} was also comparable to the previously reported value of about 6 pg. ml^{-1} after a similar oral dose of 450 mg. Significant drug concentration persists in the blood for up to 12 hours.

The absorption, and hence the blood concentration of rifampicin may also be affected by the stomach contents. Pre-prandial and post-prandial administration of rifampicin showed significant blood difference in normal volunteers (Riess, 1969) and patients with tuberculosis (Siegler *et al,* 1974). In fasting state or with breakfast, no difference was observed in the length of time during which blood concentration remained above the minimal inhibitory concentration (MIC) for M. *tuberculosis* (Saiegler *et al.,* 1974).

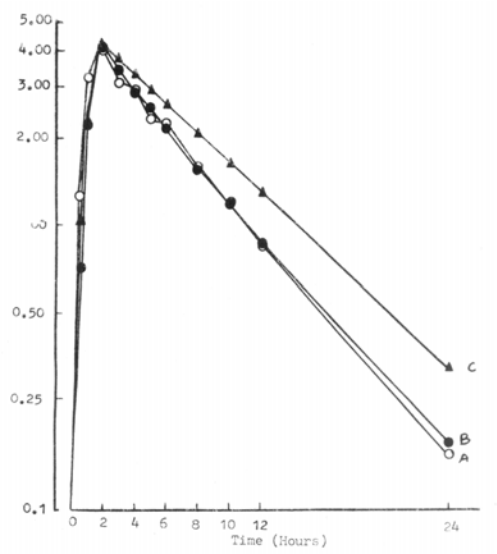

Fig.1: Plasma concentration of three brands of Rifampicin at various time intervals, 450 mg of each brand of drug was orally administered to each of the six volunteers.

Although some workers believe, it is advisable to take rifampicin on an empty stomach Will *et al.,* 1135; Melander, 1978) hut based on our and others data it seems there is no need to insist on this recommendation.

Bioavailability:

The comparative bioavailability parameters of three brands of rifampicin revealed that the drug A was absorbed rapidly (statistically significant) while the drugs B and C were absorbed at an equal rate. However, all the drugs were absorbed within 1-3 hours following oral administration. Such a difference in the rate of absorption may not be of great clinical significance. Area under curve (AUC), though statistically similar, had a relatively higher value 39.3 μg. h^{-1}. ml^{-1} for drug C compared to 31.5 and 30.9 μg. h^{-1}. ml^{-1} for drug A and B, respectively. Thus from these parameters it may be concluded that all the three preparations have similar relative bioavailability and hence, are relatively bioequivalent.

c) Disposition Kinetics:

Zero time plasma concentration (B), the elimination rate constant (β), biological half-life ($t_{½}$), volume of distribution (V_d) and total body clearance (Cl) of rifampicin did not show any difference between the three preparations of the drug. The average values

of biological half-life recorded during the present study were 4.60, 5.03 and 6.09 hogs for the drug A, B and C respectively and are somewhat lunger than the previously reported values 1.53 to 2.78 hours (Keberle *et al.*. 1967). 2.65 to 5.08 hours (Acocella *et al,* 1967) and 3.79 hours (Pawlowska & Pniewski, 1906-1979). The values of half-life of rifampicin compiled by the later author show that the higher doses have longer half-life values although relationship was not linear.

The results of the present study show that statistically there was no significant difference in the absorption kinetics, relative bioavailability and disposition kinetics of rifampicin in the three brands of capsules given in the doses of 450 mg to healthy human volunteers. Thus, in clinical situation any one of these brand of rifampicin maybe prescribed and be reasonably sure that the patient will not have bioavailability problem.

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