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PHARMACOKINETICS OF RIFAMPIN IN THE PRESENCE OF DIPYRONE IN LEPROSY PATIENTS

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SUMMARY

Some pharmacokinetic parameters such as elimination rate, half-life, AUC etc., of rifampin following p.o. administration of rifampin 600 mg. alone and 600 mg. rifampin in combination with 1000 mg. dipyrone were determined in untreated patients of leprosy. Statistical comparison of the mean values of the parameters suggests that the pharmacokinetic behaviour as well as the bio-availability of rifampin are not statistically affected in the presence of dipyrone.

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INTRODUCTION

The pharmacokinetic behaviour of rifampin is reported to be influenced by many factors such as age, stomach contents, hepatic and renal functions (1). A survey of literature reveals that some drugs, like para-aminosalicylic acid and isoniazid affect the g.I. absorption of rifampin (2)(3), as a result of which the serum concentrations of the latter drug are reduced. Dipyrone, an antipyrine derivative is widely used as an analgesic and antipyretic in the patients of leprosy, along with the routinely used anti-leprotic drugs. Antipyrine derivatives are reported to induce hepatic microsomal enzymes and they enhance the metabolism of warfarin and other coumarin anti-coagulants (4) (5) (6).

The present study is undertaken to investigate some of the pharmacokinetic parameters of rifampin in the untreated patients when given alone and in combination with dipyrone orally.

PROCEDURES

Study 1: Following rifampin alone.

(A) Subjects:

All subjects (4 males and 1 female) were untreated patients of leprosy (3 lepromatous and 2 non-lepromatous) aged between 20 and 45 years weighing between 35 and 50 kgs. and had no history of hepatic, renal, cardiac or pulmonary illness.

(B) Experimental design:

After an over-night fasting, each patient was given 600 mg. rifampin (4 capsules of Rimactane-150, Ciba-Geigy Switzerland) along with 200 ml. of water. The subjects were

allowed to take water ad libitum, and all of them were given a uniform diet after 4 hours of drug administration.

(C) Specimen collection:

2 c.c. blood samples were collected from the antecubital vein, after 1/2, 1, 2, 3, 4, 6 and 8 hours after administration of rifampin, were stored in a frozen condition. Urine collected after 1, 2, 4, 6 and 8 hours of administration was measured and a 5 ml. sample was stored in frozen condition.

(D) Analysis of specimens:

Rifampin in serum was estimated microbiologically (7) using cup-plate method and was estimated spectrophotometrically in urine after extraction with Butanol:Hexane (4:1) at 475 nm (8).

(E) Statistical analysis:

Different parameters were compared statistically using statistical t-test (9).

Study 2: Following rifampin in combination with dipyrone:

As the same subjects were used for the interaction study which was undertaken after a week, no drug was given to them during the interval. In the subsequent study the subjects were administered each 600 mg rifampin and 1000 mg dipyrone (2 tablets of 500 mg Analgin, IDPL, India) simultaneously. Blood and urine samples were collected and analysed as mentioned in the rifampin per se study in the patients.

T A B L E - 1

Mean serum concentration (mcg/ml) of Rifampin when Administered alone and in Combination with Dipyrone

Study	Mean (± SEM) Concentration (mcg/ml)						
	Time (Hrs)						
	1/2	1	2	3	4	6	8
Rifampin (600 mg.)	1.70 (0.88)	7.50 (3.33)	8.20 (3.40)	15.00 (3.26)	6.90 (1.46)	5.50 (1.25)	4.20 (0.52)
Rifampin (600 mg.) + Dipyrone 1000 mg.)	1.40 (0.89)	4.20 (1.58)	7.10 (1.60)	8.30 (0.91)	10.10 (2.92)	7.00 (1.53)	4.10 (0.56)

RESULTS

The results are expressed as mean ± SEM (Tables 1,2 & 3). Figure-1 shows the mean rifampin concentration in serum versus time after oral administration of rifampin alone and in combination with dipyrone. It is clear from the profiles that rifampin is well absorbed when given orally to give mean peak concentrations of 15.00 ± 3.26 mcg/ml in 3 hours after rifampin administration and 10.10 ± 2.92 mcg/ml in 4 hours after rifampin given with dipyrone. Results also reveal that peak serum concentration of rifampin attained is faster when it is given alone. Elimination of the drug took place from the serum compartment with a terminal half-lives of 2.17±0.84 hours and 3.30 ± 0.50 hours in the two conditions (Table 2).

The mean areas under the serum concentration - time curve are 55.7 ± 6.3 mcg.hr/ml and 50.6 ± 8.1 mcg.hr/ml respectively following the administration of rifampin alone and in combination with dipyrone.

T A B L E - 2

Observed Plasma Parameters for Rifampin

S1: Study(1): After Rifampin 600 mg. p.o.

S2: Study(2): After Rifampin 600 mg.+Dipyrone 1000 mg. p.o.

Subjects	Peak concentration (mcg/ml)		Peak time (Hrs)		Elimination rate (Hr^{-1})		Serum half-life (Hrs)		AUC 0-8 Hrs. (mcg.hr/ml)	
	S1	S2	S1	S2	S1	S2	S1	S2	S1	S2
T	21.80	4.80	2	3.5	0.380	0.310	1.82	2.24	74.2	20.3
K	21.50	10.00	3	2	0.256	0.150	2.71	4.50	67.5	50.3
P	19.90	9.80	3	4	0.920	0.180	0.74	3.90	48.4	57.9
M	20.60	20.90	1	4	0.920	0.350	0.75	1.96	43.3	67.6
G	10.00	10.00	3	2	0.140	0.180	4.80	3.90	45.2	57.0
Mean (±)	18.76	11.10	2.4	3.1	0.523	0.234	2.17	3.30	55.7	50.6
SEM	2.22	2.64	0.44	0.46	0.166	0.040	0.84	0.50	6.3	8.1

T A B L E - 3

Urinary Recovery of Rifampin

Subject	Cumulative amount (mgs) excreted during					
	0 - 4 Hrs		0 - 6 Hrs		0 - 8 Hrs	
	S1	S2	S1	S2	S1	S2
T	36.0	101.6	40.0	108.0	80.3	112.9
K	34.0	43.2	61.0	71.2	83.4	88.8
P	26.0	28.0	48.6	46.7	62.7	70.2
M	46.0	43.1	80.0	75.8	92.0	97.9
G	48.0	87.7	74.0	101.7	101.3	123.8
Mean (±) SEM	38.0 4.1	60.7 14.3	60.6 7.5	80.7 11.1	83.9 6.5	98.7 9.3

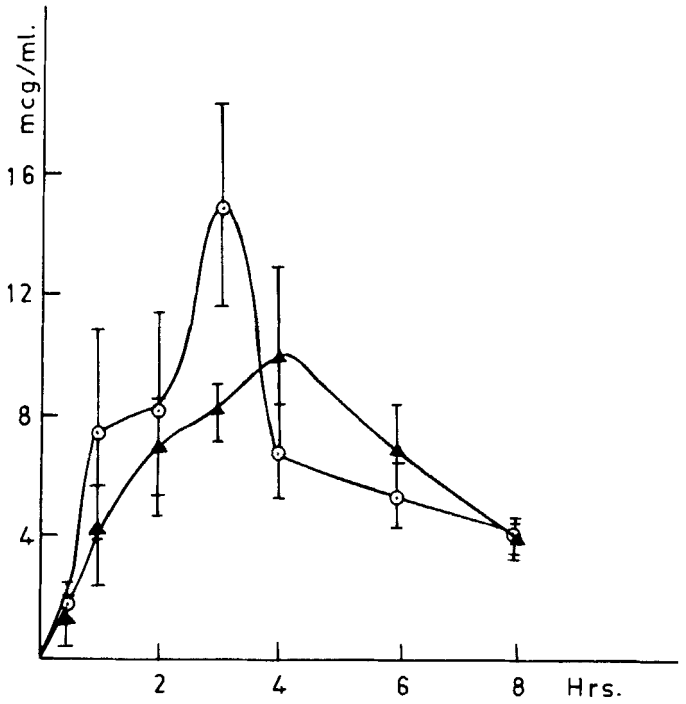

FIGURE-1: SERUM LEVELS OF RIFAMPIN

O——O Following rifampin 600 mg. p.o.

▲——▲ Following rifampin 600 mg. + dipyrone 1000 mg. p.o.

On the average 38.00±4.10, 60.60±7.50 and 83.90±6.50 mgs. of rifampin was excreted cumulatively in urine during 4,6 and 8 hrs. of the administration respectively following rifampin alone. The corresponding cumulative recoveries of rifampin following the combination were 60.70±14.30, 80.70± 11.10 and 98.70±9.30 mgs. respectively in 4,6 and 8 hrs. (Table-3). Mean cumulative amounts of rifampin excreted during these periods reported above were higher when rifampin was given along with dipyrone. However, this increase in excretion was not statistically significant ($P > 0.05$).

DISCUSSION

When two drugs are administered together, they can influence each other at various stages leading to changes in the absorption, distribution, metabolism and excretion. Such influence is more often encountered when they have a common site for absorption, bound to same sites on proteins and tissues, same metabolic pathway or excreted through the common path.

Rifampin, a very potent anti-leprotic drug, is normally prescribed along with other groups of drugs like analgesics, anti-inflammatory agents, vitamins etc., Dipyrone is one of the commonly used analgesics, which is given along with anti-leprotic drugs for managing pains and fever in leprosy. As dipyrone and rifampin have common site of absorption (g.I. route) and common sites of excretion, viz., hepatic and renal routes, it was felt that the pharmacokinetic studies of the anti-leprotic drug would be of great value in leprosy patients when given along with dipyrone.

Our results reveal that higher serum concentration of rifampin was attained in a shorter duration when it was given alone than when given in combination with dipyrone. Similarly the bio-availability of rifampin was higher when given alone than when given in combination. The serum half-life was more when rifampin was given along with dipyrone. The amount of rifampin excreted through urine was enhanced when it was given in combination with dipyrone. As dipyrone was not estimated, it is difficult to explain the mechanism by which dipyrone is enhancing the renal excretion of rifampin without decreasing the half-life.

None of the above values were statistically significant ($P > 0.05$). Our results thus show that the pharmacokinetics and bio-availability of rifampin are not significantly altered when it is given in combination with dipyrone. Statistical analysis of mean serum levels at different time intervals, by using /t/ test reveals that the levels of rifampin administered along with dipyrone are not influenced by the presence of dipyrone.

CONCLUSION

It is evident from the above study that dipyrone 1000 mg. administered orally along with rifampin 600 mg. does not seem to influence the pharmacokinetic behaviour and the bio-availability of rifampin significantly, in untreated patients of leprosy.

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