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PHARMACOKINETIC INTERACTION BETWEEN DAPSONE AND RIFAMPICIN IN LEPROSY PATIENTS.

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Different pharmacokinetic parameters of dapsone and rifampicin following P.O. administration of dapsone 100 mg. alone, rifampicin 600 mg. alone and dapsone 100 mg. plus rifampicin 600 mg. in 7 cases of untreated patients of leprosy were investigated. The blood levels, half-life and $AUC_{0-8\ hrs.}$ of dapsone were significantly reduced with simultaneous increase in plasma clearance when it was administered along with rifampicin. The pharmacokinetic behaviour of rifampicin was, however, not significantly affected in the presence of dapsone.

INTRODUCTION

Rifampicin has been reported to have interactions with many drugs. It reduces the activity of anti-coagu-

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lants[1-3], barbiturates[4-6], oral contraceptives[7], digitalis glycosides[8] and hypoglycaemic agents[9] by increasing their metabolism when administered daily for a few days. Bala krishnan and Seshadri[10] reported that the urinary excretion of dapsone in leprosy patients on long term treatment was enhanced when rifampicin was administered concurrently. Their study was conducted by administering dapsone 100 mg. p.o. daily for 100 days and rifampicin 600 mg. p.o. daily for 15 days. The study however, included only a few pharmacokinetic parameters and more over the influence of this interaction on bio-availability of dapsone was not stressed. No attempt has been made so far to study the influence of dapsone on the pharmacokinetic behaviour of rifampicin. The present investigation thus aims at an elaborate study of the effect of rifampicin on the pharmacokinetics of dapsone and vice versa.

PROCEDURES

Study (I) - Following dapsone alone.

A. Subjects

Total 7 subjects (2 females and 5 males) were untreated patients of leprosy (2 lepromatous and 5 borderline) aged between 25 and 50 years, weighing between 35 and 60 kgs and had no history of hepatic, renal, cardiac or pulmonary illness.

B. Experimental design

After an over-night fasting, each patient was given dapsone 100 mg. (1 tablet of Dapsone, M/s. Burroughs and

Wellcome, India) 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

3 c.c. blood samples were collected from the antecubital vein after 1, 2, 3, 4, 6 and 8 hours of administration of dapsone into vials containing a few crystals of sodium citrate. Urine collected after 1, 2, 4, 6 and 8 hours of administration was measured and 5 ml. sample was taken after mixing it thoroughly. Blood and urine samples were stored in frozen condition. The samples were analysed for dapsone within 24 hours of collection.

D. Analysis of specimens

Dapsone in blood and urine was estimated spectrocolorimetrically[11] at 545 nm.

E. Pharmacokinetic parameters

Half-life ($t_{1/2}$) - From a linear log conc. versus time., plot, the slope was calculated[12].

$$\text{Slope} = [(-k_{el}) / 2.303] \text{ and}$$

$$t_{1/2} = [(0.693) / (k_{el})]$$

Area-under-curve(AUC) - The area was estimated by summing the areas of the trapezoids and triangles under the curve[13].

F. Statistical analysis

Different parameters were compared using statistical t-test[14].

$$t = d / s / \sqrt{n}$$

where d = mean of deviations between the individual values of the studies I & II.

s = standard deviation.

n = number of subjects.

Study (II) - Following rifampicin alone.

Patients of study (I) were used for the study (II) which was undertaken after one week. Each subject was given 600 mg. of rifampicin (4 capsules of Rimactane-150, Ciba-Geigy, Switzerland) p.o. 2 c.c. blood samples, collected at different time intervals were allowed to clot. The serum was decanted immediately and the samples were microbiologically assayed for rifampicin by cup-plate method[15]. Urine collected at the end of 1, 2, 4, 6 and 8 hours of administration was measured, mixed thoroughly and a 5 ml. portion was stored in frozen condition. Rifampicin in urine was estimated colorimetrically[16] after extraction into butanol:hexane (4:1) at 475 nm.

Study (III) - Dapsone in combination with rifampicin.

This study was also done on the same subjects one week after the study (II). The subjects were administered each with 100 mg. dapsone of same batch and 600 mg. of rifampicin p.o. 5 c.c. blood samples were collected and each sample was divided into two portions (3 and 2 c.c.). for the estimation of dapsone and rifampicin respectively. The estimations of dapsone and rifampicin were done as mentioned in the *per se* studies. However, p-amino benzoic acid was incorporated (200 mg/l) in the medium used for the assay rifampincin in serum in presence of dapsone.

RESULTS

The mean (± SEM) blood levels of dapsone following oral administration of dapsone alone and following the administration of dapsone plus rifampicin are represented graphically in Figure 1. The mean (± SEM) serum levels of rifampicin following oral administration of rifampicin alone and following the administration of rifampicin plus dapsone are shown in Figure 2. Different pharmacokinetic parameters such as peak height ($C_{p\ max}$), peak time (t_{max}), half-life ($t_{1/2}$), area-under-curve ($AUC_{0-8\ hrs}$), volume of distribution (V_d) and plasma clearance (Clp) are given in Tables1-4.

The cumulative amounts of dapsone and rifampicin excreted through urine over a period of 8 hours are depicted in Figures 3 & 4 as histograms. Dapsone was well absorbed following its administration, alone and in combination with rifampicin. Dapsone levels following the combination were much lower than those obtained following the administration of dapsone alone. This effect is more marked in the post absorption phase (Figure 1).

It is observed from the Table 1 that the peak concentration of dapsone was decreased in six of the seven subjects. The mean of deviations in individual values is -0.3, which is statistically significant ($P < 0.01$). There was considerable reduction in biological half-life in all the subjects. The mean of deviations is -10.99 which is also significant ($P < 0.01$). The $AUC_{0-8\ hrs}$ in six of seven subjects was also lowered. The mean of deviations in individual AUC values is -4.11 which is statistically

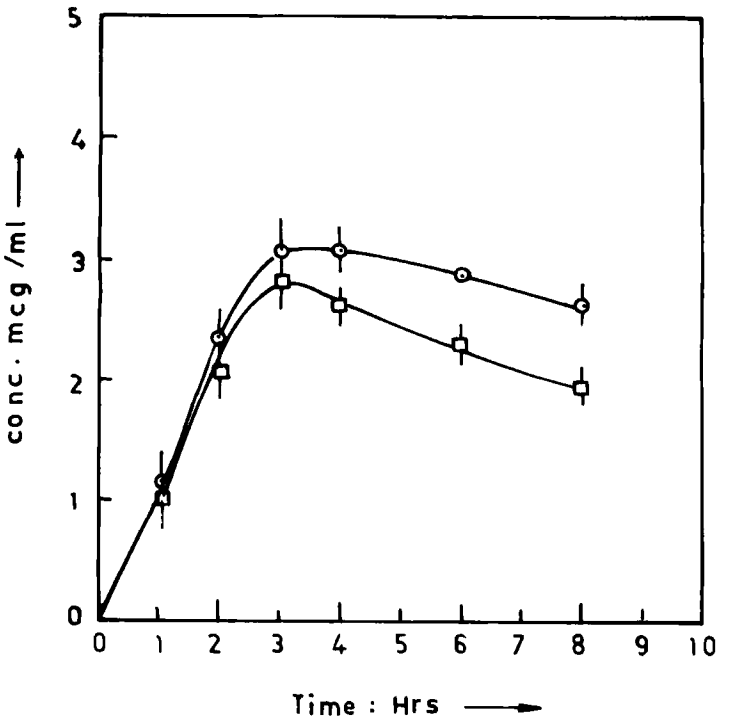

Fig. 1 - BLOOD LEVELS OF DAPSONE IN UNTREATED PATIENTS OF LEPROSY (n = 7)

o—o following the administration of dapsone 100 mg P.O.

□—□ following the administration of dapsone 100 mg + rifampicin 600 mg P.O

significant ($P < 0.01$). The cumulative amounts of dapsone excreted over a period of 4, 6 and 8 hours in all the subjects was enhanced in the presence of rifampicin (Figure 3). The means of deviations in individual values between the two groups during 4, 6 and 8 hours are +1.90, +2.70 and +3.80 respectively and this increase is statistically significant ($P < 0.01$). The plasma clearance of dapsone was also uniformly increased in all the subjects

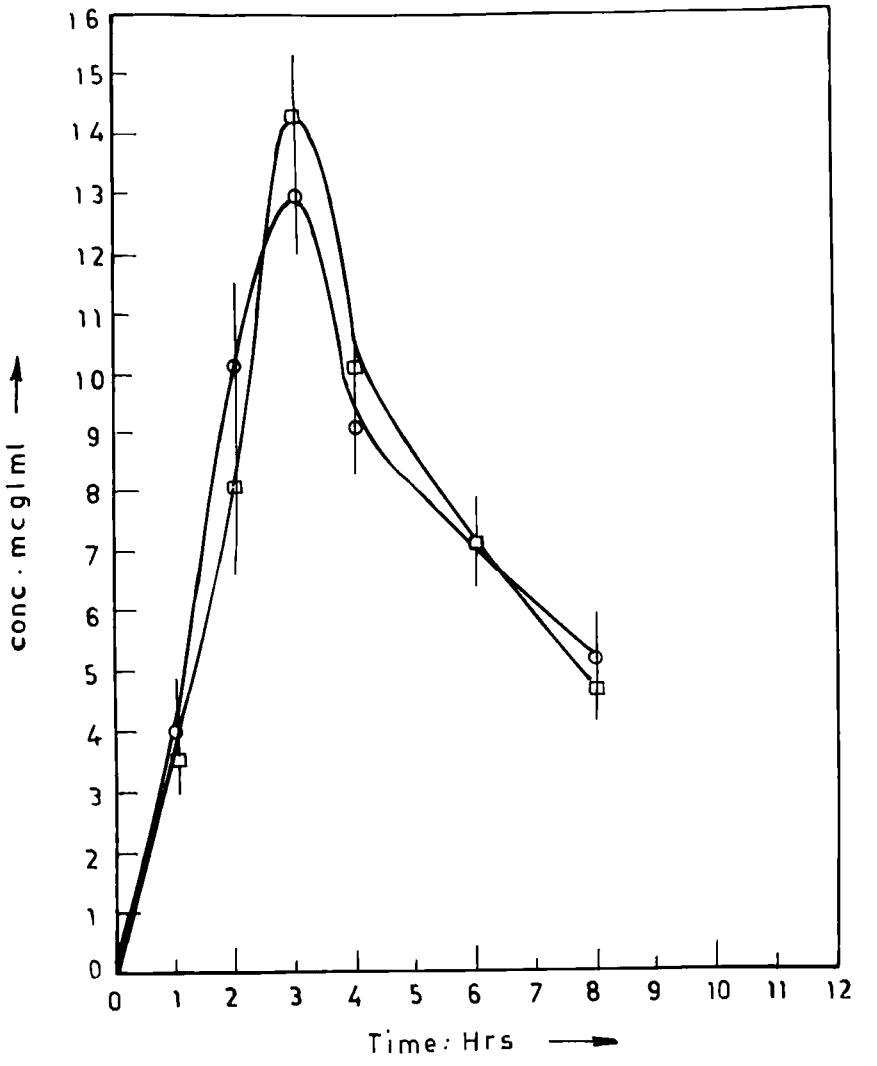

Fig. 2 SERUM LEVELS OF RIFAMPICIN IN UNTREATED PATIENTS OF LEPROSY.

⊙—⊙ following the administration of rifampicin 600 mg P.O

□—□ following the administration of rifampicin 600 mg + dapsone 100 mg. P.O.

TABLE 1

Pharmacokinetic Parameters of Dapsone in Untreated Patients of Leprosy (n=7)

S1 : Study(1) - After Dapsone 100 mg. p.o.
S2 : Study(2) - After Dapsone 100 mg.
Plus rifampicin 600 mg. p.o.

Subject	Peak concentration ($C_{p\ max}$) (mcg/ml)			Peak time (t_{max}) (hrs)			Elimination rate (k_{el}) (hr^{-1})			Half-life ($T_{1/2}$) (hrs)		
	S1	S2	difference	S1	S2	difference	S1	S2	difference	S1	S2	difference
PE	3.1	2.6	-0.5	3	3	0	0.018	0.046	+0.028	36.72	15.20	-21.52
KV	2.8	2.3	-0.5	4	4	0	0.049	0.107	+0.058	14.10	6.48	- 7.62
IT	3.0	2.7	-0.3	3	3	0	0.036	0.072	+0.036	19.00	9.64	- 9.36
JV	3.7	3.5	-0.2	3	3	0	0.023	0.058	+0.035	30.18	11.96	-18.17
BL	4.1	3.8	-0.3	3	3	0	0.042	0.075	+0.033	16.50	9.29	- 7.21
BS	3.2	2.8	-0.4	4	4	0	0.042	0.060	+0.018	16.50	11.49	- 5.01
BSA	2.7	2.8	+0.1	3	3	0	0.049	0.107	+0.058	14.54	6.48	- 8.06
Mean			-0.30			0			+0.0380			-10.99
$s/\sqrt{n}$			0.08			0			0.0057			2.36
			P<0.01						P<0.01			P<0.01

TABLE 2

Pharmacokinetic Parameters of Dapsone in Untreated Patients of Leprosy (n=7)

S1 : Study(1) - After Dapsone 100 mg. p.o.
S2 : Study(2) - After Dapsone 100 mg.
Plus rifampicin 600 mg. p.o.

Subject	Area under curve ($AUC_{0-8\ hrs}$) (mcg.hr/ml)			Absorption rate (k_a) (hr^{-1})			Volume of distribution (V_d) (litres)			Plasma clearance (Cl_p) (litres hr^{-1})		
	S1	S2	difference	S1	S2	difference	S1	S2	difference	S1	S2	difference
PE	19.2	16.0	-3.2	0.17	0.63	+0.46	31.06	35.09	+4.84	0.56	1.64	+1.08
KV	19.1	13.1	-6.0	0.63	0.57	-0.06	33.90	35.20	+1.30	1.66	3.77	+2.11
IT	19.3	15.9	-3.4	0.63	0.63	0.00	29.50	32.31	+2.81	1.06	2.33	+1.27
JV	24.4	18.5	-5.9	0.33	0.49	+0.16	24.41	25.00	+0.59	0.56	1.45	+0.89
BL	24.8	19.4	-5.4	0.40	0.63	+0.29	25.30	19.80	-5.50	1.06	1.49	+0.43
BS	19.8	13.1	-6.7	0.53	0.34	-0.19	27.80	33.60	+5.80	1.17	2.02	+0.85
BSA	14.5	16.3	+1.8	1.16	0.77	-0.39	32.50	26.70	-5.80	1.56	2.86	+1.30
Mean			-4.11			+0.03			+0.58			+1.13
$s/\sqrt{n}$			1.10			0.11			1.75			0.20
			P<0.01			P>0.05			P>0.05			P<0.01

TABLE 3

Pharmacokinetic Parameters of Rifampicin in Untreated Patients of Leprosy(n=7)

S1 : Study(1) - After rifampicin 600 mg, p.o.
S2 : Study(2) - After rifampicin 600 mg.
Plus dapsone 100 mg. p.o.

Subject	Peak concentration ($C_{p\ max}$) (mcg/ml)			Peak time (t_{max}) (hrs)			Elimination rate (k_{el}) (hr^{-1})			Half-life ($T_{1/2}$) (hrs)		
	S1	S2	difference	S1	S2	difference	S1	S2	difference	S1	S2	difference
PE	12.1	13.4	+1.3	3	2	0	0.187	0.231	+0.044	3.71	3.00	-0.71
KV	13.2	14.0	+0.8	2	2	0	0.288	0.188	-0.100	2.41	3.69	+1.28
IT	17.2	14.2	-3.0	3	3	0	0.201	0.108	-0.093	3.45	6.40	+2.95
JV	14.5	16.7	+2.2	3	3	0	0.270	0.178	-0.092	2.56	3.89	+1.33
BL	16.3	18.3	+2.0	2	3	+1	0.230	0.242	+0.012	3.07	2.86	-0.21
BS	15.2	14.7	-0.5	3	3	0	0.260	0.257	-0.003	2.64	2.69	+0.05
BSA	10.5	12.3	+1.8	2	3	+1	0.450	0.242	-0.208	1.53	2.86	+1.33
Mean			+0.66			+0.29			-0.063			+0.86
$s/\sqrt{n}$			0.70			0.18			0.033			0.47
			P>0.05			P>0.05			P>0.05			P>0.05

TABLE 4

Pharmacokinetic Parameters of Rifampicin in Untreated Patients of Leprosy(n=7)

S1 : Study(1) - After rifampicin 600 mg. p.o.
S2 : Study(2) - After rifampicin 600 mg.
Plus dapsone 100 mg. p.o.

Subject	Area under curve ($AUC_{0-8\ hrs}$) (mcg.hr/ml)			Absorption rate (k_a) (hr^{-1})			Volume of distribution (V_d) (litres)			Plasma clearance (Cl_p) (litres hr^{-1})		
	S1	S2	difference	S1	S2	difference	S1	S2	difference	S1	S2	difference
PE	55.9	55.8	- 0.1	0.53	0.58	+0.05	46.4	45.3	- 1.1	8.70	10.47	+1.77
KV	51.3	58.3	+ 7.0	0.77	0.77	0.00	39.9	31.8	- 8.1	11.50	5.97	-5.53
IT	79.9	53.8	-26.1	0.50	0.36	-0.14	35.8	34.3	- 1.5	7.20	6.10	+1.10
JV	53.4	78.0	+24.6	0.50	0.58	+0.08	40.8	28.9	-11.9	11.00	5.14	-5.86
BL	73.7	72.8	- 0.9	0.69	0.69	0.003	34.6	26.4	- 8.2	7.96	6.39	-1.57
BS	53.9	51.7	- 2.2	0.87	0.39	-0.48	25.9	58.6	+32.7	6.74	15.10	+8.36
BSA	50.2	51.2	+ 1.0	0.87	0.50	-0.37	44.4	46.8	+ 2.4	19.97	11.33	-8.64
Mean			+0.47			-0.12			+0.61			-1.79
$s/\sqrt{n}$			5.64			0.08			5.66			2.14
			P>0.05			P>0.05			P>0.05			P>0.05

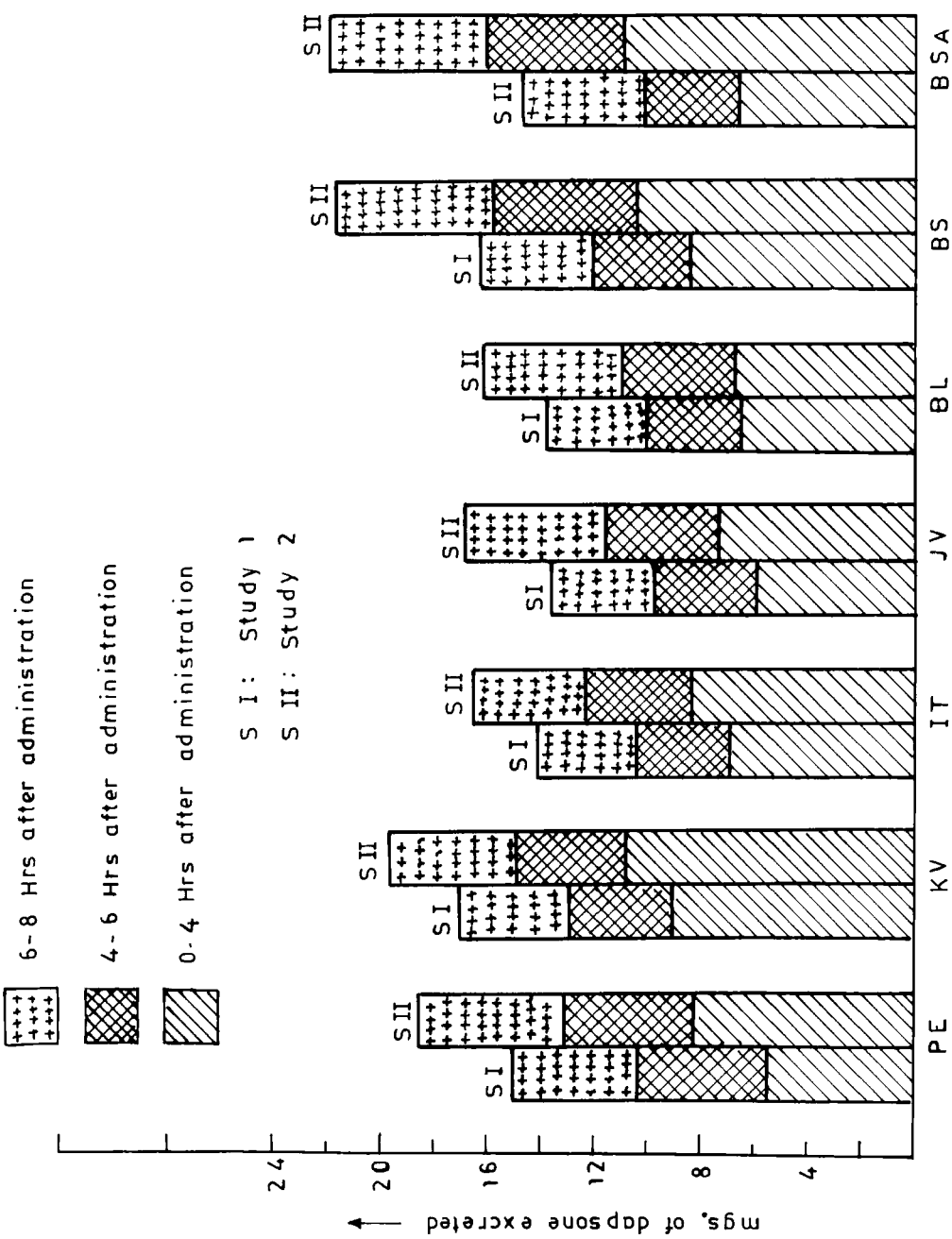

Fig. 3 : URINARY RECOVERY OF DAPSONE

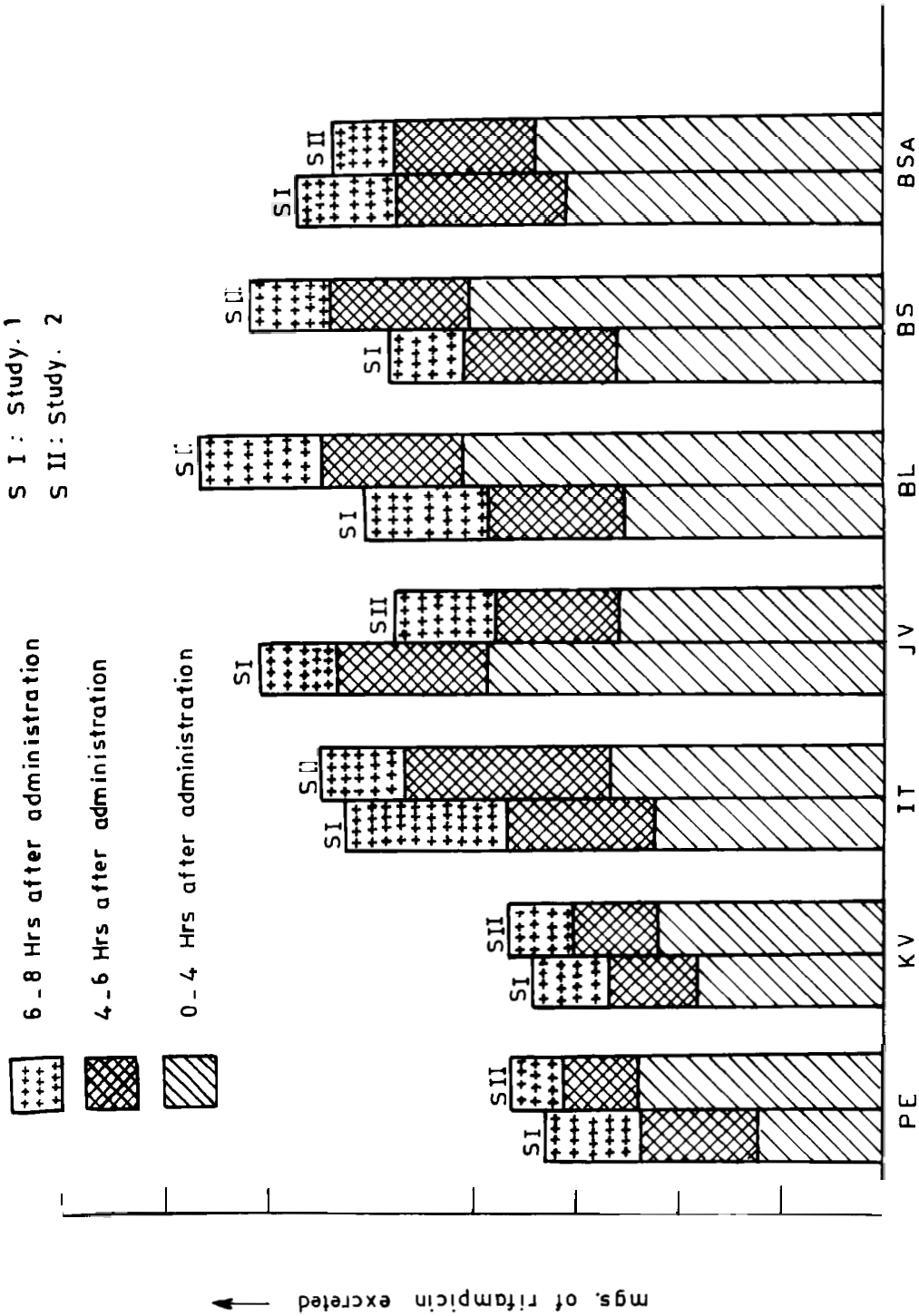

Fig. 4 : URINARY RECOVERY OF RIFAMPICIN

when it was administrated along with refampicin and this enhancement is statistically significant ($P < 0.05$). Absorption rate and volume of distribution of dapsone were, however, not affected significantly in presence of rifampicin ($P > 0.05$).

It is clear from figure 2 that rifampicin was well absorbed in presence of dapsone showing plasma levels comparable with those obtained after the administration of rifampicin alone. It is seen that in both the cases the mean peak levels were achieved after 3 hours of administration. It may be observed from the table that a marginal enhancement in the $C_{p\ max}$, $t_{1/2}$, and V_d of rifampicin was noticed on concurrent administration of dapsone. Similarly a transient fall was also noticed in k_a and Cl_p of rifampicin following the administration of the combination. However, none of the above changes is statistically significant ($P > 0.05$). It is also observed that the urinary excretion of rifampicin was enhanced during 8 hours of administration of the combination (Figure 4) but this enhancement is not statistically significant ($P > 0.05$).

DISCUSSION

From the present study it may be observed that the blood levels including $C_{p\ max}$ of dapsone were very significantly lowered in the presence of rifampicin. The t_{max} of dapsone was unchanged and its rate of absorption was also not affected significantly, which means that rifampicin does not interact with dapsone at the site of absorption. As no significant change is seen in volume of distribution

of dapsone, it is also clear that the distribution of dapsone is not altered in the presence of rifampicin. The urinary excretion of dapsone was very significantly increased on concurrent use of rifampicin, which might be the cause of a significant increase in the plasma clearance, and a significant reduction in half-life and area-under-curve of dapsone. Hence the present study concurs with the previous findings[10].

The peak concentration of rifampicin was enhanced marginally in the presence of dapsone. Slight increase in t_{max} and a transient reduction in the absorption rate of rifampicin were also noticed following the administration of rifampicin-dapsone combination. As these changes are not significant it is clear that they do not interact at the site of absorption. The volume of distribution of rifampicin was slightly enhanced in the presence of dapsone, but this change is also insignificant. The urinary excretion, plasma clearance half-life and $AUC_{0-8\ hrs}$ of rifampicin are not significantly altered in presence of dapsone.

CONCLUSIONS

The blood levels and bio-availability of dapsone may be adversely affected on concurrent administration of rifampicin.

The phrmacokinetics of rifampicin on the otherhand may not be affected in the presence of dapsone.

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REFERENCES

1. J.A. Romankiewicz and M. Erhman, Ann. Int. Med., 82, 224 (1975).
2. R.A. O'Reilly, Ann. Int. Med., 81, 337 (1974).
3. R.A. O'Reilly, Clin. Res., 21, 207 (1975).
4. D.D. Breimer, W. Zilly and E. Richter, Clin. Pharmacol. Ther., 21, 470 (1977).
5. W. Zilly, D.D. Breimer and E. Richater, Europ. J. Clin. Pharmacol., 9, 219 (1975).
6. W. Zilly, D.D. Breimer and E. Richater, Europ. J. Clin. Pharmacol., 11, 287 (1977).
7. D.J. Back, A.M. Breckenridge, F. Crawford, M.Maclever, M.L.E. Orme, B.K. Park, P.H. Rowe and E. Smith, Europ. J.Clin. Pharmacol., 13, 193 (1979).
8. W. Zilly, D.D. Breimer and E. Richater, Clin. Pharmacokinetics, 2, 61 (1977).
9. E.K.G. Syailahti and K.K. Pihalajamaki and E.J.Lisalo, Lancet, ii, 232 (1974).
10. S. Balakrishnan and P.S. Seshadri, Lepr. India., 51, 54 (1970).
11. I.A. Simpson, Int. J. Lepr., 17, 208 (1949).
12. B. Clark, and D.A. Smith, in "An Introduction to Pharmacokinetics", Blackwell Scientific Publishers, Oxford, 1981, p. 10.
13. R.E. Notari, in 'Biopharmaceutics and Clinical Pharmacokinetics', Marcel Dekker, Inc. N.Y., 1980, p. 86.

14. L.K. Randolph and J.L. Ciminera, in 'Remington's Pharmaceutical Sciences' XV edition, A.Osol, eds., Mack Publishing Co., Pennsylvania, 1975, p. 117.

15. A. Bernard, P.J. Diana and A. Kirshbaum, J. Pharm. Sci., 60, 1689 (1971).

16. J.D. Williams, T. Leung, in 'Laboratory Methods in Antimicrobial Chemotherapy, D.S. Reeves, I. Phillips, J.D. Williams and R. Wise, eds., Churchill living stone, Edinburgh, 1978, p. 239.