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DISPOSITION KINETICS OF RIFAMPICIN IN DOGS

Malka Saba, M. Nawaz and Munir Ahmad
Department of Chemistry and Department
of Physiology and Pharmacology,
University of Agriculture, Faisalabad.

The disposition kinetics of rifampicin was investigated in seven dogs. An oral dose of 300 mg rifampicin (150 mg x 2 capsules) was given to each animal. The blood analyses were performed for drug concentration and pharmacokinetic parameters were calculated. The results revealed that absorption half-life was 2.1 $\pm$ 0.27 h and absorption rate constant was 0.36 $\pm$ 0.05 h^{-1}. Elimination half-life was 36.21 $\pm$ 1.76 h and elimination rate constant was o.020 $\pm$ 0.001 h^{-1}. Volume of distribution was 33.21 $\pm$ 4.50 $l.kg^{-1}$ and total body clearance was 0.68 $\pm$ 0.11 $l.h^{-1}$. It was concluded that orally administered rifampicin was rapidly and totally absorbed and the parameters also reflected longer duration of action and persistence of the drug in the body of the dogs.

INTRODUCTION

Many antibacterial drugs are currently produced in commercial quantities and are used for numerous medical applications. Rifampicin is one of the new chemotherapeutic agents. It is synthetically derived from Nocardia meditterranei (previously Streptomyces). Rifampicin has a broad spectrum activity. It is highly active against Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum and certain atypical mycobacteria as well as against many gram positive and gram negative species. Mycobacteria are particulary susceptible to rifampicin and this has led to an extensive use of this compound in the treatment of tuberculosis.

Biodisposition describes the simultaneous effect of absorption and distribution of drug in a biological system and its elimination. The disposition kinetic parameters are used to determine the fate of drug in the body of man or animal on the basis of which optimal therapeutic approach is developed. The present project was designed to investigate the disposition kinetics of rifampicin in dogs after oral administration.

MATERIALS AND METHODS

In order to study the disposition kinetics of rifampicin, experiments were conducted on seven healthy dogs. The body weight of the dogs ranged between 10 and 15 kg (average = 12.43 kg). All the animal were provided with similar conditions of feeding anf watering, In each experiment after restratining the animal, control blood sample was collected before drug administration. A single oral dose of 300 mg rifampicin (150 mg x 2 capsules) was given to each dog. Blood samples were taken in heparinized glass tubes at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 60, 72, 84, 96, 108 hours after drug administration. Plasma was separated by centrifugation and used for analysis. Concentration of rifampicin was determined microbiologically by using Sarcina lutea (ATCC 9341) as a test organism according to the method of Arret et al. (1971).

RESULTS AND DISCUSSION

Plasma concentration of rifampicin against time is shown in Figure I. The plasma concentration versus time data was used for the determination of various absorption and elimination parameters. These are presented in Tables 1 and 2, respectively.

Absorption Parameters: Plasma peak concentration (Cmax) of rifampicin has an average value of 0.73 ± 0.08 $\mu g.ml^{-1}$. The value reported by Lecaillon et al. (1981) is 5.4 $\mu g.ml^{-1}$ which is comparable to the value observed in man (Nawaz, 1988) i.e. 4.04 ± 1.46 $\mu g.ml^{-1}$ but is higher than that found in the present study which may be due to the difference in

Table 1. *Average ± SE of absorption parameters of rifampicin after a signle oral dose of 300 mg to 7 dogs*

Dog No.	B.Wt. kg	N $\mu g\text{-}ml^{-1}$	K_{ab} $hr.^{-1}$	$t_{½ab}$ hr.	Peak Conc. $C_{(max)}$ $\mu g.ml^{-1}$	Peak Time $t_{(max)}$ hr.	AUC / Blood
1	10	0.40	0.35	2.00	0.51	8.00	20.50
2	12	0.42	0.35	2.00	0.54	8.00	25.01
3	12	0.61	0.23	3.00	0.55	8.00	19.78
4	13	1.06	0.35	2.00	1.03	6.00	36.01
5	15	0.86	0.46	1.50	0.86	8.00	31.39
6	10	0.90	0.23	3.00	0.80	10.00	28.83
7	15	0.78	0.58	1.20	0.89	8.00	37.64
Average	12.43	0.72	0.36	2.10	0.73	8.07	28.45
± SE	0.85	0.10	0.05	0.27	0.08	0.38	2.88

Table 2. *Average ± SE of elimination parameters of rifampicin after a single oral dose of 300 mg to 7 dogs*

Dog No.	B.Wt. kg	Dose mg	B $\mu g.ml^{-1}$	β hr^{-1}	$t_{\frac{1}{2}\beta}$ hr	Vd $l.kg^{-1}$	TBC $l.h^{-1}.kg^{-1}$
1	10	300	0.60	0.025	29.00	50.0	1.24
2	12	300	0.62	0.018	39.50	40.3	0.71
3	12	300	0.63	0.017	40.00	40.0	0.69
4	13	300	1.15	0.021	34.00	20.0	0.41
5	15	300	1.00	0.021	33.00	20.0	0.42
6	10	300	0.96	0.019	37.50	31.3	0.58
7	15	300	0.96	0.022	40.50	31.3	0.70
Average	12.43		0.85	0.020	36.21	33.2	0.68
± SE	0.85		0.09	0.001	1.76	4.5	0.11

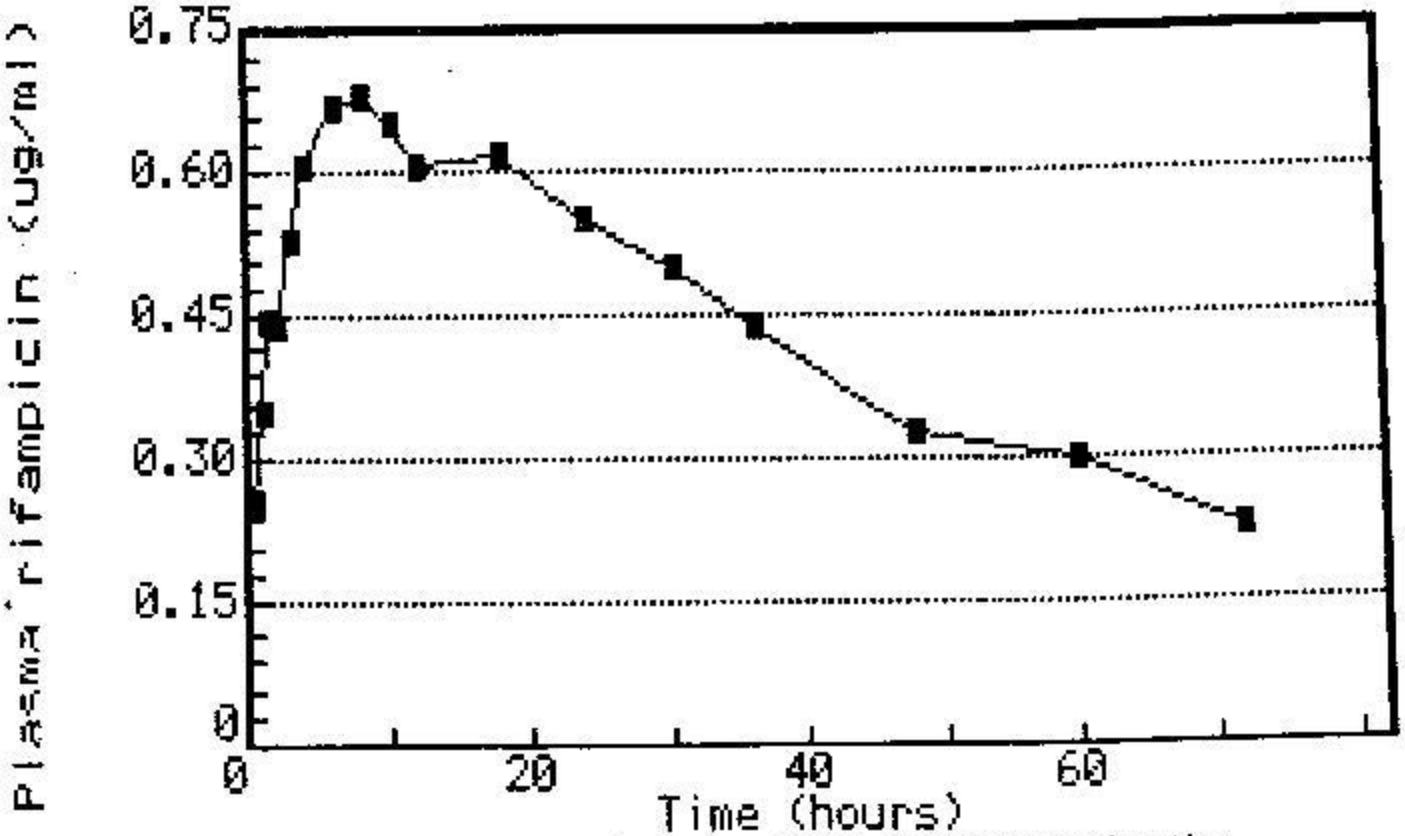

Figure 1. Mean plasma concentration of rifampicin against time in 7 normal dogs following oral administration of 300 mg dose.

the species and dosage level of the drug used in dogs. The average ± SE value for peak absorption time in dogs was 8.07 ± 0.38 h. The peak absorption time (t_{max}) for rifampicin in man has been reported by other workers to be 1.5 -3.0 h (Furesz et al., 1967), 3-4 h (Biya et al., 1982), and 1-4 h (Lecaillon et al., 1981). Yusheng et al. (1983) reported peak absorption time in mice as six hours. The value of peak absorption time found in dogs is somewhat different from man but is nearer to mice.

The rate constant of absorption(k_{ab}) for rifampicin was on an average 0.36 ± 0.05 h. It was reported by Kucers and Bennett (1975) that unlike many other antibiotics rifampicin is lipid soluble and ionizes only to a negligible extent at neutral pH (Seydel, 1970). So the unionization of the drug alongwith its lipid solubility accounts for its rapid absorption. The absorption half-life ($t_{\frac{1}{2}ab}$) in dogs was on an average 2.1 ± 0.27 h, whereas Goodman and Gilman (1975) stated that half-life of rifampicin in man varies from 1.5 -5.0 h. Thus, the absorption half-life of rifampicin in dogs is comparable to that in man. Area under curve (AUC) has an average 28.45 ± 2.88 $\mu g.h^{-1}$ which is comparable to the area under curvein man i.e. 30.9 ± 9.3 $\mu g.h^{-1}.ml^{-1}$ (Nawaz, 1988). The higher area under curve results in higher bioavailability of the drug.

Elimination Parameters: The average value for zero-time plasma concentration (B) is 0.85 ± 0.09 $\mu g.ml^{-1}$. It is quite different from zero-time plasma concentration reported in man (Nawaz, 1988) as 5.56 ± 2.48 $\mu g.ml^{-1}$ and can be due to the species difference. Elimination rate constant (β) has an average value of 0.020 ± 0.01h^{-1} and reflects longer duration of persistence or half-life of rifampicin in dogs. The average biological half-life ($t_{\frac{1}{2}B}$) was 36.21 ± 1.76 h which is somewhat nearer to the elimination half-life value in mice i.e. 20 h (Yusheng et al.,1983). Kiss et al. (1978) stated that enterohepatic circulation of rifampicin makes a major contribution to the prolonged action of the drug. The longer half-life of rifampicin in dogs shows its longer duration of action. The volume of distribution (Vd) of rifampicin was 33.2 ± 4.5 $l.kg^{-1}$ which is quite different from the volume of distribution reported in man (Nawaz, 1988)

as 1.52 ± 0.49 $l.kg^{-1}$. The difference might be due to species variation in extent of protein binding, total body water and total body fat. The total body clearance (TBC) of rifampicin was on an average 0.68 ± 0.11 $l.h^{-1}.kg^{-1}$, being also reflected by the longer biological half-life.

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