

*Original Research Article***BIODISPOSITION KINETICS OF ISONIAZID IN HEALTHY FEMALES**

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ABSTRACT

The aim of the study was to characterize the biodisposition kinetics parameters of Isoniazid after a single oral administration of 150mg tablet Isoniazid. The study was conducted on 6 healthy female volunteers with an average age of 21-22 years and an average body weight of 42-56 kg in the department of chemistry (Biochemistry) university of agriculture Faisalabad, Pakistan. Blood samples were collected after predetermined schedule and drug concentration was determined by using spectrophotometric method. The two compartment model kinetic analysis of plasma isoniazid concentration versus time data revealed estimated values of $t_{1/2}$ β , clearance and volume of distribution to be $7.60 \pm 3.73h$, 4.61 ± 2.69 l/h and $45.45 \pm 22.35L$ respectively. Moreover, the area under curve (AUC), absorption rate constant (k_a) and mean residence time (MRT) were observed to be 38.16 ± 13.76 , 0.76 ± 0.12 and 9.53 ± 4.21 respectively. In conclusion, the pharmacokinetic parameters observed for isoniazid in current study were found to be significantly different from some of the previously reported literature, suggesting that an adequate and rational dosage regimen of drug requires a disposition study of parameters under specific indigenous environment prior to their administration.

Keywords: Isoniazid, Biodisposition kinetics, Female volunteers

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INTRODUCTION

Approximately about one third of the world population has been known to be affected by mycobacterium tuberculosis^[1]. Thereby, it should be considered critical to ensure availability of

the best possible treatment that might reduce the incidences of tuberculosis accounting for millions of disease cases globally. From a century, pyridine-4-carboxylic acid hydrazine commercially known as isoniazid (INH) has been well recognized as an excellent antitubercular drug used as first line therapy for the treatment and a drug of choice for the prophylaxis of tuberculosis. INH dually affects microorganism by acting as bacteriostatic for resting and bactericidal for dividing organism^[2].

Moreover, INH has been also widely used together with rifampicin and pyrazinamide for the^[3]. Many components of mycobacterium tuberculosis have been proposed as possible targets of INH. It inhibits the synthesis of mycolic acid (long-chain branched hydroxylated fatty acids) in mycobacterium tuberculosis^[4]. Although the directly-observed treatment (DOTS) strategy by WHO has resisted the spread and combat tuberculosis, however, the some of the reports have revealed combination of results^[5-7]. This might probably be accounted to various factors including environmental influences on genetics, manifested through biochemical and physiological parameters, affecting the fate of drugs in population (Nawaz et al 1988). Expressions of enzymes responsible effecting its elimination which may differ among individual might also be counted as another aspect contributing for different pharmacodynamic and pharmacokinetic parameters of the drug^[8]. Similarly, biochemical characteristics of body may influence the pharmacokinetic patterns of drug absorption, distribution and elimination. Investigations have shown that biodisposition kinetic parameters were different under indigenous conditions as compared to literature. Thereby, it should be consider critical to set a definite pharmacokinetic outcomes of essential drugs including INH, the first line therapy for treating tuberculosis.

The present project was planned to study the biodisposition of INH in similar population (female volunteers) under local environmental conditions. The purpose of the current analysis was to characterize the pharmacokinetic parameters of INH within the same population under the similar condition to provide an appropriate pharmacokinetic representation that might help predict drug's disposition in a definite community.

MATERIAL AND METHOD

Isoniazid (INH)

The drug used, INH was used as fixed-dose oral tablets of 150 mg manufactured by Sandoz manufactured by Novartis Parma Pakistan LTD, Jamsharo with the brand name of Rimstar.

Volunteers

The study was conducted on 6 healthy female volunteers with an average age of 21-22 years and an average body weight of 42-56 kg in the department of chemistry (Biochemistry) university of agriculture Faisalabad, Pakistan. The volunteers did not receive any medicine at least two weeks prior study. The age, weight, height, blood pressure, and blood glucose for each volunteer was recorded as presented in [Table 1](#). The drug was administered once orally to each volunteer.

Collection and storage of specimen

The blood samples from each volunteer for the determining INH pharmacokinetics were collected at predetermined time intervals (i.e. 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 24). The samples were collected under aseptic condition in heparinized vacuum centrifuge tubes. These

tubes were then centrifuged at 4000rpm for 15min. The collected plasma was then stored at -20°C until further analysis.

Analytical procedure

The frozen samples were thawed at room temperature and INH concentration in these plasma samples was determined by spectrophotometric analysis^[9]. Biodisposition kinetics parameters were calculated following two compartmental models by computer pharmacokinetic software program, APO MV/Pharm, version 3.02, Holland. Biodisposition kinetic parameters of INH after oral administration of 150mg tablets were calculated using plasma concentration versus time data.

RESULT AND DISCUSSION

Plasma concentration

The pharmacokinetic parameters of INH in the studied population were best described using two compartmental model. The plasma concentration of INH versus time for each healthy female volunteer after single oral administration of 150mg INH tablet is shown in Figure 1. Initially a gradual increase in serum drug concentration was observed. The plasma concentration of INH following the oral administration at 0.5 hours was found to be 1.18 ± 0.59 mg/L, however the concentration increased with time and the peak plasma concentration (C_{max}) of 2.08 ± 0.99 mg/L was achieved at T_{max} 2.08 ± 0.43 hours. Notterman^[10] reported that the peak plasma concentrations of INH was achieved within 1 to 2 hours of drug administration that is found to be consistent with the C_{max} achieved in the present study i.e. at T_{max} of 2 to 3 hours. Similarly, Dattani *et al.*^[11] found that peak plasma concentration of INH was reached within 1.5 hours after an oral dose of 200mg INH. Moreover, another investigation was done on male human volunteers to study the pharmacokinetic effects of INH after administration of drug (300 mg) once orally; they observed a t_{max} at 1.17 ± 0.041 hours and C_{max} at 0.164 ± 0.04 mg/l^[12].

Figure 1. Plasma concentration of isoniazid at different time intervals.

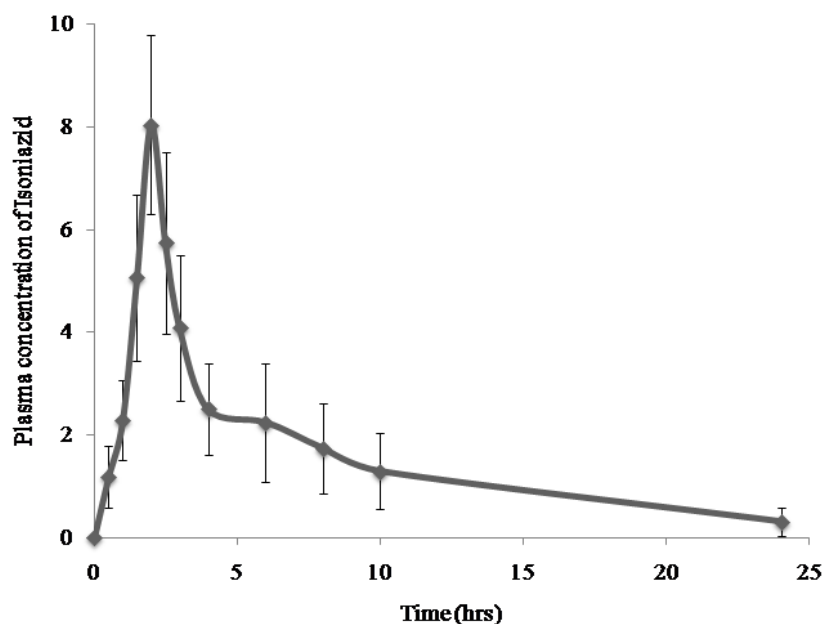


Table 1. Parameters of volunteers.

Parameters	Volunteers						Mean	SD	
	1	2	3	4	5	6			
Age (years)	22	21	23	20	24	23	22.17	1.47	
Body weight (Kg)	56	47	55	42	51	53	50.67	5.32	
Height (Ft)	5.5	5.2	5.1	4.8	5.15	4.9	5.11	0.25	
Blood Pressure	Systolic	110	130	125	120	115	120	120.00	7.07
	Diasystolic	84	85	75	78	84	82	81.33	3.98
Body temperature (⁰ F)	98.7	98.6	98.9	98.5	98.7	98.4	98.63	0.18	
Blood Glucose (mg/dL)	75	73	74	71	79	78	75.00	3.03	

Table 2. Biodisposition kinetic parameters of volunteers after oral administration of 150 mg of isoniazid tablets

Parameters	Volunteers						Mean	SD
	1	2	3	4	5	6		
AUC (h.mg/L)	37.60	15.80	54.00	41.92	49.20	30.42	38.16	13.76
CL (ml/h/Kg)	4.60	9.78	2.48	2.86	3.24	4.71	4.61	2.69
V _d (L)	22.30	77.73	31.77	57.19	25.01	58.71	45.45	22.35
t _{1/2} Phase I (hrs)	0.76	0.88	0.94	1.22	1.01	0.84	0.94	0.16
t _{1/2} Phase II (hrs)	3.36	5.51	8.86	13.87	5.35	8.64	7.60	3.73
MRT (hrs)	5.58	5.78	12.58	16.35	8.88	8.06	9.54	4.20
Absorption Rate constant (K _a)	0.92	0.78	0.75	0.57	0.68	0.83	0.76	0.12
Absorption half-life (hrs)	0.76	0.88	0.92	1.22	1.02	0.84	0.94	0.16
T _{max}	1.91	1.70	2.12	2.42	2.72	1.63	2.08	0.42
C _{max}	5.43	3.02	5.18	4.62	4.68	5.87	4.80	0.99

Disposition kinetics

The calculated mean values (\pm SD) of disposition kinetics of individual volunteer are represented in Table 2. The mean \pm SD volume of distribution after oral administration of 150mg INH in female volunteer was observed to be $45.45 \pm 22.35L$ ($0.92 L/Kg$), which was found to be higher than $0.6L/Kg$ as reported previously^[13]. However, Ramesh *et al.*,^[14] reported that elimination half life (t_{1/2}) of INH when observed ranged from 1.6-6.4h, which is somewhat comparable to present result. In another study ishizaki *et al.*^[15] reported the t_{1/2} of INH ranged between 2.0-2.2 hours, which might be considered lower than the value observed in the present study (i.e. $7.60 \pm 3.73h$).

Moreover, after the oral administration of 150mg INH, the total body clearance revealed to be 4.61 ± 2.69 l/h which when compared is found lower than 5.39 ± 0.43 as reported by Advenier *et al.*^[16]. Correspondingly, as far as the absorption rate constant of INH after the oral administration of the drug is concerned, it was observed to be 0.76 ± 0.12 l/h. However, Ansari *et al.*,^[12] stated the value of absorption rate constant of INH to be 1.57 ± 0.147 .

This divergence of results observed among previous studies conducted and the current investigation for the determination of pharmacokinetic parameters of INH might be due to the difference in doses, drug formulation, environmental conditions and physiological factors e.g. intestinal pH, that may account for the variation observed for the rate of absorption of the drug^[17-19]. Thus, the current results that are significantly different from some of the previously reported literature, suggest that an adequate and rational dosage regimen of drug should be considered that requires disposition studies of parameters under specific indigenous environment prior to their administration.

CONCLUSION AND PERSPECTIVE

To conclude, the present study characterizes the pharmacokinetic behavior of first-line chemotherapeutic agent, INH. The results revealed a clear evidence of variation in the disposition kinetics of INH observed in different population when compared to previous literature, thereby, suggesting that to predict and establish an appropriate population pharmacokinetic model for a drug. Moreover, indigenous investigation of pharmacokinetic parameters should be taken in to account.

In future, the variation in the disposition kinetic parameters of INH observed among the present work and the studies conducted previously should be taken critically in to account. These types of studies require consideration as they may help in depicting and creating a standard therapeutic dosage regimen for therapeutically significant drugs in clinical settings.

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