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SINGLE-DOSE PHARMACOKINETICS OF ISONIAZID AND RIFAMPICIN IN PATIENTS WITH CHRONIC RENAL FAILURE

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Summary. **The pharmacokinetics of Isoniazid and Rifampicin were studied in 18 patients with mild or moderate renal failure (creatinine clearance : 10.1-50.0 ml/min) and 17 patients with severe renal failure (creatinine clearance < 10.0 ml/min) and the findings compared with those in 16 healthy subjects. The renal excretion of Isoniazid, Acetylisoniazid, Rifampicin and Dcsacetylrifampicin was severely inhibited in patients with renal failure. Plasma Rifampicin and Isoniazid concentrations in rapid acetylators were similar in healthy subjects and both the groups of patients. In slow acetylators, plasma Isoniazid concentrations and exposure (AUC) and half-life of the drug, calculated on the basis of these concentrations were appreciably higher in patients than in healthy subjects (P < 0.01); the mean values in the two groups of patients were, however, similar. The correlations between plasma creatinine or creatinine clearance and peak concentration, exposure or half-life of Isoniazid were poor (r < 0.28) in the slow acetylators. These findings suggest that in patients with renal failure, it is not necessary to reduce dosage of Rifampicin or of Isoniazid in rapid acetylators but advisable in respect of Isoniazid in slow acetylators to lessen the risk of toxic reactions.**

Introduction

Kidneys play a major role in the systemic clearance of drugs and their metabolites. In patients with renal failure, the elimination of most drugs being retarded, therapeutic doses as administered to patients with normal renal function could lead to sustained high plasma levels that could be toxic. The dosages of drugs employed for treating tuberculosis in patients with renal failure are still largely empirical, being about half of those administered to patients with normal renal function. Empirical reduction could still lead to toxic plasma levels in patients with severe renal failure, while effective levels may not be attained if there is a mild degree of impairment. The difference could be accentuated in case of Isoniazid where metabolizing enzymes display genetic polymorphism. No information is available, to the best of our knowledge, on the pharmacokinetics of Rifampicin in patients with renal failure and only a few reports concerning Isoniazid[1,2] in combined groups of slow and rapid acetylators with no attempt made to phenotype the patients. We, therefore, undertook a detailed study of single-dose pharmacokinetics of these two drugs in patients with different grades of chronic renal failure, after classifying them as slow or rapid acetylators to devise suitable drug dosage schedules to be administered to such patients. The findings were compared with those in healthy subjects.

Material and Methods

Subjects : Patients reporting to the Nephrology Clinic at the Government General Hospital, Madras, were classified as having mild, moderate or severe renal failure based on creatinine clearance values of 20.1-50.0, 10.1-20.0 and < 10.0 ml/min, respectively. Only patients whose renal failure was stable, as assessed by creatinine clearance determined on three occasions during the preceding week, were admitted to the

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pharmacokinetics study. The healthy subjects were blood relatives of patients admitted for kidney transplantation. The hepatic function, as assessed by AST and ACT activities in plasma was normal in all the subjects.

Determination of acetylator phenotype : The Isoniazid acetylator phenotype was tentatively determined on the basis of salivary concentration of Isoniazid at 5 hours after an uniform oral dose[3] of Isoniazid 100 mg, the criterion for a slow acetylator being a concentration of Isoniazid > 0.41 µg/ml. The classification was later confirmed on the basis of the plasma half-life of Isoniazid (criterion for a slow acetylator : > 2.71 hours) determined during the pharmacokinetic investigation.

Pharmocokinetic study : On the day of the investigation, Isoniazid 7.5 mg/kg and Rifampicin 12 mg/kg (according to the dosage schedule in Table 1) were administered on an empty stomach and blood was collected at 1, 2, 3, 6, 8 and 24 hours. Further, the urine excreted over the period 0-24 hours was collected and its volume measured. Plasma from the blood specimens and aliquots of urine were stored at –20.0C. Plasma concentrations of Isoniazid were determined by the method of Rao *et al*[4] and of Rifampicin by the plate diffusion assay of Dickinson *et a1*[5]. The concentrations of Isoniazid and Acetylisoniazid in urine were determined by the method described earlier[6] and those of Rifampicin and Desacctylrifampicin by a procedure involving the separation of the two compounds by thin-layer chromatography[7]. All the specimens were coded before the estimations were undertaken. Plasma concentrations of urea and creatinine and urine concentrations of creatinine were determined employing an automated blood chemistry analysis system (Beckman 'Astra-8') and creatinine clearance values calculated.

Table 1. *Dosage Schedule*

Body-weight range (kg)	Isoniazid (mg)	Rifampicin (mg)
< 30.0	200	300
30.0-44.9	300	450
45.0-59.9	400	600
> 60.0	500	750

The mean plasma peak concentration was the geometric mean of the highest individual concentrations; exposure was calculated as the area under the time-concentration curve (AUC) from a plot of concentration versus time as linear co-ordinates. The rate constants for elimination and half-life of Isoniazid and Rifampicin were calculated from the terminal phase of the time-concentration curves.

Student's t-test was employed for testing the differences between the mean values.

Results

Sixteen healthy subjects (9 male, 7 female), aged 21 to 52 years with a mean body-weight of 50.3 kg (range : 38-64 kg) and 35 patients with renal failure (19 male, 16 female), aged 15 to 72 years with a mean body-weight of 44.6 kg (range : 31-77 kg) were admitted to the study. The renal failure was mild in 3, moderate in 15 and severe in 17 patients. Since the number of patients with mild renal failure was small, the findings in them were amalgamated with those having moderate renal failure. Of the 51 study subjects, 28 were classified as slow and 23 as rapid acetylators on the basis of the concentration of Isoniazid in saliva; the corresponding numbers based on the plasma half-life of Isoniazid were 32 and 19, respectively (Table 2). The classification was the same by both the procedures in 45 (88%) of the 51

Table 2. Agreement in classification as slow or rapid acetylator between plasma half-life method and Isoniazid concentration in saliva

Based on the salivary method**	Based on the Plasma half-life method*		Total
	Slow	Rapid	
Slow	27	1	28
Rapid	**5**	**18**	**23**
Total	**32**	19	51

* From the terminal phase of the time-concentration curve following an oral dose of Isoniazid 7.5 mg/kg body-weight (criterion for a slow acetylator : > 2.71 hours)

** Based on the salivary concentration of Isoniazid at 5 hours following an oral, uniform dose of Isoniazid 100 mg (criterion for a slow acetylator: > 0.41 µg/ml).

Table 3. Mean values and standard deviations for plasma concentrations of urea and creatinine and creatinine clearance in healthy subjects and patients with renal failure

Group	Acetylator phenotype	Plasma urea (mg/dl)	Plasma creatinine (mg/dl)	Creatinine clearance (ml/min)
Healthy Subjects	Slow (10)*	21.5 + 3.1	0.82+ 0.22	88.1 + 32.8
	Rapid (6)	17.8 + 8.7	0.88+ 0.26	82.6 + 19.0
Mild or Moderate renal	Slow (12)	87.8 + 36.4	4.0+ 1.3	14.4 + 4.9
	Rapid (6)	75.7 + 50.5	3.7 + 1.8	20.9 + 12.8
Severe renal failure	Slow (10)	138.5 + 35.2	5.8+ 1.8	6.5 + 2.1
	Rapid (7)	130.4 + 37.6	6.1 + 2.4	6.8 + 2.4

* Figures in parentheses indicate the number of subjects

subjects. Of the 6 misclassifications, 5 slow acetylators (1 healthy subject, 1 patient with mild or moderate renal failure and 3 patients with severe renal failure) by the plasma half-life procedure were classified as rapid acetylators by the saliva procedure and the converse was true in 1 healthy subject. The numbers of slow and rapid acetylators (by the plasma half-life method) were 10 and 6 among the healthy subjects, 12 and 6 among patients with mild or moderate renal failure and 10 and 7 among those with severe renal failure. The mean plasma concentrations of urea and creatinine and of creatinine, given separately for slow and rapid acetylators are presented in Table 3.

The mean dosages of Isoniazid administered to slow and rapid acetylators among the healthy subjects, patients with mild or moderate renal failure and those with severe renal failure were 7.8 and 7.7, 8.0 and 7.6 and 8.2 and 7.8 mg/kg respectively; the mean dosages of Rifampicin in the 3 groups were 11.6, 11.8 and 12.1 mg/kg, respectively.

The distribution of subjects according to the time at which the highest plasma concentrations of Isoniazid (amalgamating the findings in slow and rapid acetylators, as they were similar) and Rifampicin were attained is presented in Table 4. The rates of gastro-intestinal absorption of both the drugs appear to be similar in all the 3 groups and there appears to be a delay in the absorption of Rifampicin compared with that of Isoniazid.

The geometric mean serial plasma Isoniazid concentrations upto 8 hours in slow and rapid

Table 4. Distribution of healthy subjects and patients with renal failure according to highest concentrations of Isoniazid and Rifampicin at different time points

Group	Drug	No. of subjects with highest concentrations observed at					Total
		1 hr	2 hr	3 hr	6 hr	8 hr	
Healthy subjects	Isoniazid	13	3	-	-	-	16
	Rifampicin	2	11	2	1	-	
Mild or moderate renal failure	Isoniazid	14	4	-	-	-	18
	Rifampicin	4	11	3	-	-	
Severe renal failure	Isoniazid	16	1	-	-	-	17
	Rifampicin	2	13	1	1	-	

acetylators in the 3 groups of subjects are depicted in Figure 1 and those for Rifampicin in Figure 2. The mean concentrations of Isoniazid at 24 hours (not depicted) in slow acetylators among the healthy subjects, patients with mild or moderate renal failure and those with severe renal failure were 0.2, 1.0 and 1.1 μg/ml respectively; the corresponding concentrations in rapid acetylators were 0.1, 0.3 and 0.2 μg/ml, respectively. The mean Rifampicin concentrations at 24 hours in the 3 groups were 0.19, 0.17 and 0.09 μg/ml, respectively. In slow acetylators, the mean Isoniazid concentrations in both groups of patients were higher than those in the healthy subjects from the 3rd hour onwards, the differences attaining statistical significance at 6, 8 and 24 hours ($P < 0.01$); none of the differences in the rapid acetylators was significant ($P > 0.2$). The mean concentrations of Rifampicin were also similar at all time-points in the 3 groups.

The geometric mean values for peak concentration, exposure and half-life for Isoniazid (separately for slow and rapid acetylators) in addition to those for Rifampicin are presented in Table 5. In slow acetylators, the differences between the mean values for peak concentration were not significant; however, exposure to Isoniazid was about 43-56% higher and the half-life 59-85% higher in the two groups of patients than in the healthy subjects ($P < 0.001$ for all). The mean values for all 3 parameters were similar

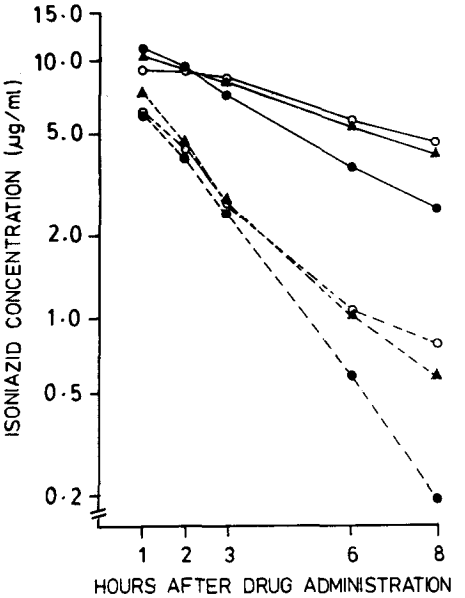

Fig. 1 Serial plasma Isoniazid concentrations in slow acetylators (solid line,——) and rapid acetylators (broken line, – --) among healthy subjects (closed circles, ●), patients with mild or moderate renal failure (open circles, O) and those with severe renal failure (closed triangles, ▲). Maximal SEM values (not shown) were 1.09, 1.06, 1.07, 1.09 and 1.13 μg/ml for plasma concentrations in slow acetylators, and 1.20, 1.17, 1.24, 1.42 and 1.52 μg/ml for those in rapid acetylators at 1, 2, 3, 6 and 8 hours, respectively.

Table 5. Some pharmacokinetic variables of Isoniazid and Rifampicin in healthy subjects and patients with renal failure

Pharmacokinetic variables	Geometric mean (and range) of the values								
	Isoniazid						Rifampicin		
	Slow acetylators			Rapid acetylators					
	Healthy subjects	Mild or moderate renal failure	Severe renal failure	Healthy subjects	Mild or moderate renal failure	Severe renal failure	Healthy subjects	Mild or moderate renal failure	Severe renal failure
Peak concentration μg/ml	11.5 (8.5-15.1)	10.8 (8.0-13.8)	10.6 (9.2-13.6)	6.7 (3.9-11.0)	6.4 (3.1-11.0)	7.6 (5.9-8.8)	15.2 (9.0-27.4)	13.2 (7.0-20.0)	11.8 (5.0-22.2)
Exposure (μg/ml hours)	61 (42-89)	95 (63-140)	87 (42-124)	19 (8-28)	24 (16-42)	24 (16-33)	88 (48-131)	81 (36-138)	71 (36-127)
Half-life (hours)	3.4 (2.7-4.2)	6.3 (4.5-8.4)	5.4 (2.8-7.6)	1.6 (1.0-2.2)	2.1 (1.6-2.7)	2.0 (1.4-2.4)	5.0 (2.1-9.0)	5.1 (2.8-9.0)	4.9 (3.4-9.8)

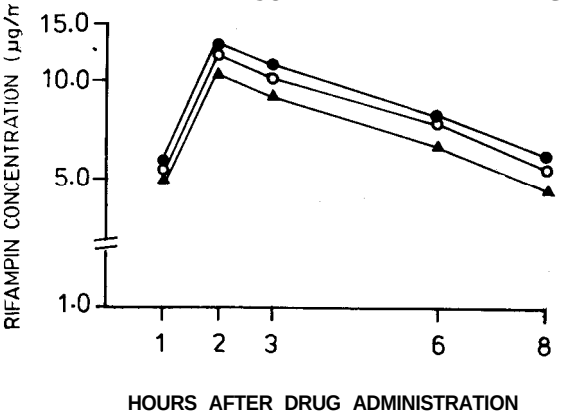

Fig. 2 Serial plasma Rifampicin concentrations in healthy subjects (●—●), patients with mild or moderate renal failure (O—O) and those with severe renal failure (▲—▲). Maximal SEM values (not shown) were 1.46, 1.16, 1.12, 1.11 and 1.12 µg/ml at 1, 2, 3, 6 and 8 hours, respectively.

in the 2 groups of patients. The mean peak concentrations and the mean values for exposure and half-life for Isoniazid in rapid acetylators, and for Rifampicin in both phenotypes were similar in the 3 groups of subjects, and none of the differences was significant (P > 0.2).

The correlations between the renal function parameters such as creatinine clearance, plasma creatinine or urea concentrations, and the pharmacokinetic variables, viz. the mean peak concentration, the exposure and the half-life of Isoniazid were examined in slow acetylators and it was observed that the correlations were poor in all the cases (r < 0.28).

The excretion of Isoniazid and Acetylisoniazid in slow and rapid acetylators and those of Rifampicin and Desacetylrifampicin in urine excreted over a 24-hour period after drug administration (expressed as the % of the dose of drugs excreted) is presented in Table 6. In slow acetylators, the excretion of both Isoniazid and Acetylisoniazid was appreciably lower in the 2 groups of patients than in healthy subjects (P < 0.001 for both); further, the excretion of both the compounds was lower in patients with severe renal failure than in those with mild or moderate renal failure (P < 0.01). In rapid acetylators, the excretion of Isoniazid was lower in patients with severe renal failure than that in healthy subjects (P < 0.01); however, the difference between healthy subjects and patients with mild or moderate renal failure or that between the latter

Table 6. Urinary excretion of Isoniazid Acctylisoniazid, Rifampicin and Desacetylrifampicin in healthy subjects and patients with renal failure

Drug/ metabolite	Acetylator phenotype	Geometric mean and range of proportion of dose (%) excreted in urine (0-24 hours)		
		Heal thy Subjects	Patients with renal failure	
			Mild or moderate	Severe
Isoniazid	Slow	27.0 (11.3-40.4)	12.8 (5.8-18.4)	6.9 (1.5-12.2)
	Rapid	9.1 (2.1-15.7)	4.6 (1.6-14.6)	3.2 (2.0-6.0)
Acetylisoniazid*	Slow	18.1 (13.8-26.3)	6.2 (4.8-16.2)	3.8 (2.3-5.6)
	Rapid	36.6 (30.5-46.8)	11.4 (3.8-51.6)	5.3 (3.8-8.4)
Rifampicin	Both groups	6.3 (2.2-18.7)	1.9 (0.1-5.9)	1.4 (083.0)
Desacctyl-rifampicin	Both groups	3.6 (1.7-9.9)	1.1 (0.1-2.5)	0.7 (0.3-1.7)

*as INH equivalent.

and patients with severe renal failure was not significant ($P > 0.2$). The differences between the 3 groups in the excretion as Acetylisoniazid were significant ($P < 0.05$). The excretion of Rifampicin, either as the unchanged drug or as its primary metabolite, Desacetylrifampicin was significantly less in both the groups of patients than in healthy subjects ($P < 0.001$ for both); the differences between the 2 groups of patients were, however, not statistically significant for either compound ($P > 0.09$).

Discussion

Isoniazid is eliminated from the system by acetylation as well as renal excretion. Earlier investigation [8] in patients with normal renal function had shown that elimination of the drug is predominantly through acetylation (> 90% of the dose ingested) in rapid acetylators while in slow acetylators approximately equal proportions are eliminated through acetylation and renal excretion. Therefore, the plasma concentration and elimination half-life of Isoniazid would be expected to remain largely unaffected by renal failure in rapid acetylators, while the values could be higher in slow acetylators. The results presented in this report show that renal excretion of Isoniazid and Acetylisoniazid is severely inhibited among both phenotypes in patients with renal failure. However, this inhibition results in an increase in the plasma concentrations of Isoniazid (from the 3rd hour onwards) in slow acetylators only, leading to significantly higher exposure and half-life of the drug, while it had no effect on the peak concentration. Surprisingly, no differences were observed between patients with mild or moderate renal failure and those with severe renal failure.

Peripheral neuropathy and hepatitis are the two major reactions that can occur during treatment with Isoniazid. It is possible that their incidence might be altered as a result of the increase in the exposure to Isoniazid that occurs in slow acetylators with poor renal function. Peripheral neuropathy occurs predominantly in slow acetylators and is dose-related[9]. Any increased tendency for it in patients with renal failure could be prevented by administering a small dose (6 mg) of Pyridoxin along with Isoniazid. Among south Indian tuberculosis patients, the incidence of hepatitis is low and similar in slow and rapid acetylators with regimens containing Isoniazid but not Rifampicin[10]; however, with daily regimens of Isoniazid and Rifampicin, the frequency of occurrence of this adverse reaction was substantially higher in slow than in rapid acetylators[11]. An increased risk of hepatitis in slow acetylators with daily regimens of Isoniazid and Rifampicin has been observed by other investigators also[12,13]. **Therefore, in daily regimens with Rifampicin, it may be advisable to prescribe a lower than the standard dosage of Isoniazid to slow acetylators with renal failure, especially to light-weight patients. However, the dosage should not be too low (not below 5 mg/kg, in any case) as that would reduce the peak concentration[14], with which drug efficacy is related. There is also no indication for the reduction of larger doses (15 mg/kg) in intermittent regimens as these are associated with a much lower risk of hepatic toxicity[11].** Since plasma concentrations in rapid acetylator with renal failure are fairly similar to those of healthy subjects, the dose of Isoniazid in these patients should be the same as for patients with normal renal function.

Our recommendation with respect to the dosage of Isoniazid in slow acetylators is not in line with that of Reidenberg *et al*[2] who in their investigation of 8 patients with renal failure did not find any need to reduce the dosage of this drug and Bowersox *et al*[1] who in 10 patients with chronic renal failure did not recommend reduction in the dose of Isoniazid (300 mg) in rapid acetylators and slow acetylators with serum creatinine concentration less than 12 mg/dl. However, in patients with more severe renal failure, they too had suggested that the dose be reduced to 200 mg. Neither of the investigators had classified the patients as slow or rapid acetylators.

Our findings suggest that it is desirable to do acetylator phenotyping of patients to enable the administration of a proper dosage of the drug. Methods based on molar ratios of Acetylisoniazid to Isoniazid in urine are obviously not suitable. And, the determination of the plasma half-life of the drug requires at least 3 collections of blood. We have recently shown that salivary levels of Isoniazid are similar to those in plasma[15] and have successfully used the concentration of the drug in saliva to determine the acetylator phenotype of adults[3] as well as children[16]. In the

current investigation, the agreement between salivary method and the standard plasma half-life of the drug procedure was of the order of 88%. Of the 6 disagreements, 5 classified as slow acetylators by the plasma half-life method were classified as rapid acetylators by the salivary method. If renal failure and consequent retention of Isoniazid were the cause of the disagreement, the converse would have been true and more rapid acetylators would have been classified as slow acetylators by the salivary method.

There was a significant reduction in urine excretion of Rifampicin and Desacetylrifampicin also in patients with renal failure, as compared with healthy subjects. This, however, had no effect on the plasma concentrations of the drug. The elimination of Rifampicin is mainly through hepato-biliary excretion[17] with kidneys playing only a minor role. Even in healthy subjects, only about 10-15% of the dose administered is excreted as the drug and its primary metabolite in urine over a 24-hour period. These findings suggest that there is no need to reduce the dosage of Rifampicin for tuberculous patients with renal failure.

Renal failure on account of tuberculosis is rare[18]. It is not easy to distinguish tuberculous interstitial nephritis from non tuberculous chronic glomerulonephritis on clinical grounds. As has been pointed out in a leading article in *Tubercle*[19], renal failure due to tuberculosis is a distinct possibility where the disease is endemic. The findings reported in this paper could be useful for the management with Isoniazid and Rifampicin of tuberculosis patients with renal failure. Similar studies with other drugs such as Streptomycin, Pyrazinamide and Ethambutol would need to be undertaken as one or more of these drugs are invariably given in combination with Isoniazid and Rifampicin for the treatment of tuberculosis.

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