Pharmacokinetics of isoniazid and rifampicin in patients with renal failure undergoing continuous ambulatory peritoneal dialysis (CAPD)
Running Head : Pharmacokinetic of INH & RMP in renal failure (CAPD)

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Abstract

The pharmacokinetics of isoniazid (INH) and rifampicin (RMP) was determined in 22 renal failure patients, 11 each with low and high membrane permeabilities (LMP and HMP) undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD). Blood samples were collected at different time points following oral administration of INH and RMP. Estimations of INH and RMP in blood were carried out by standard procedures and certain pharmacokinetic variables were calculated based on their concentrations in blood. The INH inactivation status was determined based on salivary levels of INH. The pharmacokinetic variables of INH and RMP did not differ significantly between LMP and HMP groups. The study results suggest that renal failure patients on CAPD may not require reduction in the dosage of RMP or INH in rapid acetylators. Slow acetylators might require dose reduction of INH. Determination of INH inactivation status is important when patients with renal failure and tuberculosis are treated with INH-containing regimens.

Key words: Rifampicin, Isoniazid, Pharmacokinetics, Renal Failure, CAPD

Introduction

Drugs are eliminated from the body by metabolism and excretion. The kidneys play a major role in the excretion of drugs and/or their metabolites. When they fail, such substances may accumulate and cause unwanted side effects. Therapeutic doses as administered to patients with normal renal function could lead to sustained high plasma levels in patients with renal failure and this could be toxic.

We have earlier demonstrated that in patients with chronic renal failure, the dosage of INH may be reduced in slow acetylators of the drug[1]. However, the same may not be applicable to renal failure patients undergoing CAPD. Information on the pharmacokinetics of anti-tuberculosis (TB) drugs is therefore essential in renal failure patients undergoing CAPD, so that drug dosages can be appropriately adjusted. No information is available to the best of our knowledge, on the pharmacokinetics of INH in such patients except for a study report on RMP carried out in two subjects[2]. We, therefore, studied single dose pharmacokinetics of two first-line anti-TB drugs, namely, RMP and INH in patients with end stage renal failure on CAPD having different peritoneal permeability.

Methods

Subject: A total of 22 patients comprising of 13 males and 9 females who were undergoing treatment at the Nephrology Unit of Apollo Hospitals, Chennai were recruited to the study. All the study subjects were suffering from end stage renal failure and were undergoing CAPD. The patients were classified as having LMP or HMP based on peritoneal equilibration test. Those patients who had low or low average were classified as low peritoneal membrane permeability (LMP), and those with high or high average were classified as high membrane permeability (HMP). Patients in the LMP group received 3 exchanges of 2 litres, 8 hours dwell time; while patients in HMP group received 3 exchanges of 2 litres, 3-4 hours dwell time. The hepatic function, as assessed by liver function tests, was normal in all the patients. They were not suffering from any other ailment except renal failure at the time of study.

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The study was cleared by the Ethics Committees of the Tuberculosis Research Centre and Apollo Hospitals, Chennai. The nature of the study and possible side effects of the drugs were explained to the patients and informed written consent was obtained from them before they took part in the study.

Determination of acetylator phenotype

Prior to start of the study, the INH acetylator status was determined in all eligible patients according to the method of Kailasam et al.[3]. A uniform oral dose of INH (100mg) was administered and a sample of saliva was collected exactly at 5 hours after drug administration. The concentration of INH in saliva was determined according to the method of Gurumurthy et al.[4]. The criterion for a slow acetylator was taken as a concentration of INH e″ 0.41 µg/ml.

Conduct of Study

On the day of the investigation, INH (7.5 mg/kg) and RMP (12 mg/kg) (according to the dosage schedule in Table 1) were administered on an empty stomach and blood samples were collected at 1,2,3,6, and 8 hours in heparinised containers. Plasma was separated from all the blood samples and stored at −20ºC until drug estimations were carried out.

Plasma concentrations of INH were determined by the spectrofluorimetric method of Olson et. al. [5], and of RMP by the plate diffusion method of Dickinson et al. [6]. All the specimens were coded before drug estimations were undertaken.

Pharmacokinetic and Statistical Analysis: On each series of plasma INH and RMP concentrations, certain pharmacokinetic variables were calculated. Maximum concentrations (C_{max}) and the time to attain C_{max} (T_{max}) were determined by direct visual inspection of data. The linear trapezoidal rule was used to compute the exposure or area under the time concentration curve (AUC); the elimination rate constant (K_{el}) was calculated from the terminal log-linear decline of concentration; the terminal elinination half-life (t½) was calculated as $0.693/K_{el}$; and $AUC_{0-\alpha}$ was calculated by adding the sum of AUC

obtained from time zero until 8 hour concentration to the last quantifiable concentration (at 8 hours) divided by K_{el}. The plasma clearance (Cl) was calculated as dose/$AUC_{0-\alpha}$.

The pharmacokinetic values were expressed as mean ± standard deviation. Student's t-test (unpaired) was employed for testing the differences between the mean values of the LMP and HMP groups and the significance was taken at the 5% level.

Results

A total of 22 patients comprising of 13 males and 9 females were admitted to the study. Among them, 11 each belonged to the LMP and HMP groups. The mean age and body weight of the patients having LMP were 45.2 years (10-72 years) and 59.3 kg (24-90 kg) respectively. The corresponding values in patients having HMP were 49.8 years (16-67 years) and 58.1 kg (37-86 kg).

The mean dosages of INH administered to patients with LMP and HMP were 7.11 and 7.40 mg/kg bodyweight respectively, while the corresponding values for RMP were 10.69 and 11.20 mg/kg body weight. The numbers of slow and rapid acetylators of INH among patients with LMP were seven and four and with HMP were six and five respectively.

The distribution of patients having LMP and HMP according to the time at which the highest plasma concentrations of INH (amalgamating the findings in slow and rapid acetylators) and RMP were attained is presented in Table 2. The rate of gastro-intestinal absorption of INH appears to be similar in both the groups of patients as evident from the fact that in majority of the patients, peak concentrations were attained within one hour. However, in the case of RMP, there appeared to be a delay in the absorption in patients having HMP compared with that of LMP.

The mean serial plasma INH and RMP concentrations between LMP and HMP groups of patients did not show any statistical significance at all the time points tested. The pharmacokinetic variables calculated based on plasma concentrations of INH and RMP were not different between the LMP and HMP groups (Tables 3 and 4).

Table1 Dosage schedule:

Body-weight range (kg)	Isoniazid (mg)	Rifampicin (mg)
<30	200	300
30.0 – 44.9	300	450
45.0 – 59.9	400	600
≥ 60.00	500	750

Table 2 Distribution of patients based on peak concentrations of isoniazid and rifampicin

Group	Drug	No. of subjects with peak concentrations observed at				
		1 h	2 h	3 h	6 h	8 h
LMP	Isoniazid	6	1	4	-	-
n=11	Rifampicin	3	5	3	-	-
HMP	Isoniazid	6	5	-	-	-
n=11	Rifampicin	2	2	6	1	-

LMP – Low membrane permeability, HMP – High membrane permeability

Table 3 Pharmacokinetics of Isoniazid in patients with different membrane permeability:

Pharmacokinetic Variables	Mean ± SD			
	Slow		Rapid	
%	LMP(n=7)	HMP(n=6)	LMP(n=4)	HMP (n=5)
Peak Concentration (µg/ml)	11.73 ± 2.15	11.71±2.07	7.17±2.51	10.43±5.32
Exposure (0-8) (µg/ml.hours) (0-∞)	69.09±13.85 213.47±55.89	61.17±11.75 139.39±28.00	22.65±9.03 25.78±11.64	34.49±16.80 38.83±19.84
Clearance (ml/min)	6.51±1.12	7.28±1.67	18.36±13.71	15.00±8.13
Half-life (hours)	8.16±1.23	6.15±1.04	2.42±0.75	2.46±0.12

LMP-Low membrane permeability, HMP – High membrane permeability

Table 4 Pharmacokinetics of rifampicin in patients with different membrane permeability:

Pharmacokinetic Variables	Mean ± SD	
	LMP (n=11)	HMP(n=11)
Peak Concentration (µg/ml)	10.37±4.21	10.44±4.00
Exposure (0-8) (µg/ml.hours) (0-∞)	56.49±24.73 172.51±82.11	50.90±20.37 193.19±127.14
Clearance (ml/min)	12.35±4.67	15.61±12.99
Half-life (hours)	6.92±2.05	6.35±1.68

LMP-Low membrane permeability, HMP – High membrane permeability

Discussion

Isoniazid is eliminated from the system by acetylation as well as renal excretion. While elimination of the drug is predominantly through acetylation in rapid acetylators, approximately equal proportions are eliminated through acetylation and renal excretion in slow acetylators[7]. Therefore, exposure and elimination half-life are expected to be higher in slow acetylators. Several studies conducted previously at our centre, both in healthy subject and in patients with pulmonary and extra pulmonary TB have reported half-lives ranging from 2.8 to 3.4 hours for slow and 1.2 to 1.9 hours for rapid acetylators of INH[1, 4, 8-10]. The present study shows that, despite patients undergoing dialysis, plasma concentrations of INH in slow acetylators lead to higher half-life in LMP and HMP groups of patients. However, the mean C_{max} and AUC values in slow acetylators were

almost similar to our previous data [1, 4, 8-10]. The elimination of INH in rapid acetylators did not seem to be affected. It may therefore be advisable to reduce the dosage of INH in slow acetylators with renal failure undergoing CAPD. However, with respect to rapid acetylators of INH, since the pharmacokinetic variables obtained in this study were almost similar to our previous study data, it may not be necessary to adjust drug dosages. This emphasizes the need to determine the INH acetylator status of patients suffering from renal failure and TB, and who require treatment with INH-containing regimens.

Methods to determine INH acetylator status in renal failure patients based on urinary excretion of acetyl INH and INH are obviously not suitable. On the other hand, estimating INH in saliva, collected at a particular time-point, as done in this study can be used to determine the acetylator phenotype in adults[3] as well as in children[11].

Our recommendation with respect to the dosage of INH in patients with renal failure particularly with the slow acetylators is not in line with that of Reidenberg et. al.[12] who in their investigation of eight patients with renal failure did not find a need to reduce the dosage of this drug. A study conducted by Bowersox et. al[13] in 10 patients with chronic renal failure did not recommend reduction in the dose of INH (300mg) in rapid and slow acetylators with serum creatinine concentration less than 12 mg/dl. Neither of the investigators had classified patients as slow or rapid acetylators.

The elimination of RMP is mainly through hepato-biliary excretion[14], with kidneys playing only a minor role. This is evident from this study data where we did not observe any difference in the pharmacokinetic variables between patients with renal failure undergoing CAPD and our previous study data[1, 4, 8-10]. Also no differences were observed in patients having different membrane permeability. These findings suggest that there is no need to reduce the dosage of RMP in patients with renal failure undergoing CAPD. This is in agreement with that reported previously in patients with severe renal failue[1] and also by Woo et. al [2] who observed that in patients with TB on maintenance dialysis, the dosage of RMP need not be reduced.

The risk of developing pulmonary and extra pulmonary TB is increased in patients undergoing peritoneal dialysis, especially in Asia [7, 15, 16]. Since very scanty information is available on the pharmacokinetics of INH and RMP in renal failure patients undergoing CAPD, we have attempted to obtain information on this aspect, and also compare the values between patients with different membrane permeability, namely, LMP and HMP. Although absence of a control group was a limitation of this study, the findings reported in this paper could be useful for the management of renal failure patients undergoing CAPD and suffering from TB, and requiring treatment with INH and RMP.

Acknowledgement

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