ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Comparative Pharmacokinetic Study of Rifampicin and Isoniazid in Intensive and Continuation Phase TB Treatment

AK Jithin[1], MP Narmadha[*1], R Rajasekaran[2], N Murugesh[3] and A Palanisamy[1]

[1]Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode-637205, Tamilnadu, India.
[2]Deputy Director of Health service, Govt Hospital, Erode, Tamilnadu, India.
[3]Dept of Pharmacology, KSR Dental College, Erode, Tamilnadu, India.

ABSTRACT

Altered pharmacokinetics of anti tuberculosis drugs may contribute to an increased risk of tuberculosis treatment failure for TB population.Here we examined and compared the pharmacokinetics of rifampicin and isoniazid in the intensive and continuation phase of tuberculosis treatment.Previously we found that rifampicin and isoniazid exposure was lower in intensive phase treatment when compared to continuation phase.For the study purpose 25 patients each from intensive and continuation phase were included in a government hospital setting. Pharmacokinetic sampling was performed for rifampicin and isoniazid in patients after light breakfast.The assessments were done for 50 tuberculosis patients after careful observation.There is much differences in the area under the concentration- time curves of drugs in plasma from 0 to 8 h(AUC_{0-8}),maximum concentrations of drug in plasma (C max),the time to C max, and half-lives of Rifampicin, Isoniazid were found between intensive and continuation phase tuberculosis treatment. Biological half life of both rifampicin and isoniazid was lowered in both phases of treatment leaving a short exposure of drug.Compared to continuation phase $AUC_{(0-8hrs)}$ of rifampicin was less in intensive phase (32.005µg hr/ml , P= 0.0266*), and AUC of isoniazid also less in intensive phase when compared to continuation phase (35.57µg hr/ml,p=0.1354).The study reveals that there is reduced exposure to rifampicin and isoniazid in intensive phase ,compared to continuation phase. This could be one of the reason for relapse or recurrence of TB.

Keywords: rifampicin, isoniazid, pharmacokinetics, tuberculosis

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Tuberculosis is a highly contagious infection caused by the bacterium Mycobacterium tuberculosis. Tuberculosis can affect anyone with weakened immune systems. Tuberculosis is a major public health problem in India. India accounts for one-fifth of the global TB incident cases. Each year nearly 2 million people in India develop TB, of which around 0.87 million are infectious cases. It is estimated that annually around 330,000 Indians die due to TB. It requires much longer periods of treatment (around 6 to 24 months) to entirely eliminate mycobacteria from the body [1]. The WHO initiated directly observed treatment short-course (DOTS), introducing the administration of standardized short-course chemotherapy regimens with first line drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) under direct observation regardless of drug susceptibility. DOTS treatment is supervised by health workers, community volunteers, traditional birth attendants, and community or religious leaders.

MATERIALS AND METHODS

Study was conducted after acquiring ethical clearance from IEC, of our college Swamy Vivekanandha College of Pharmacy. (IEC/sep/2011/05).Patients taking anti TB medictions both in continuation phase and intensive phase are included in the study. The patients of age between 20-70 years were selected of both sex, were included in the study. Study evaluated the difference in the drug levels between intensive and continuation phase TB treatment .

On the day of pharmacokinetic assessment, patients were administered the standard drug regimen (450mg rifampicin + 600mg isoniazid +600mg ethambutol+ 750mg pyrazinamide) for intensive phase and (450mg rifampicin+600mg isoniazid) for continuation phase with 270 ml water after a light breakfast. Serial venous blood samples were collected from antecubital vein at 0.5hr, 1hr, 2hr, 3hr, 5hr and 8hr after witnessed drug intake. Plasma was separated from blood samples by centrifugation and frozen at -20°C until transport on dry ice for bio-analysis. Plasma drug concentration-analysis was done by reverse phase HPLC method. Both drugs were analyzed simultaneously.

The statistical calculations were done using Graph pad Instat software version 3.01. Results were expressed as mean ± SD or median (range). The statistical significance was taken from P value. P value <0.05 was considered significant.

RESULTS

Pharmacokinetic Study

The study has been designed to detect whether any changes are there in different phases of treatment for TB. A totality of 100 TB patients was screened and 50 patients were selected based on the inclusion and exclusion criteria. Patients of both sex were included, 25 each in intensive phase and continuation phase, from the patients with pulmonary TB alone. The patient were administered the drugs (rifampicin, isoniazid, ethambutol and pyrazinamide)

in hospital setup after light breakfast to avoid gastro intestinal problems which may be occurring if drugs administered in empty stomach. All patients were put under strict observation.

Pharmacokinetics of Rifampicin

While interpreting the results of the study, we realise the difference in various parameters in two phases clearly. Area under curve indicates the amount of drug exposure in patients. Our results show that the total amount of drug available to blood in continuation phase is greater (37.86µg hr/ml) than in intensive phase (32.005µg hr/ml) and the difference is very significant. Both phases demonstrate early tmax achievement to attain peak concentration for rifampicin, and continuation phase patients showed the earliest tmax (1.65 hrs)than intensive phase(1.84 hrs).when these values are compared with officially published tmax values (1-4 hrs),our study results demonstrate to attain tmax quickly in both phases of treatment [2].

Maximum concentration attained in blood plasma from the administered dose will dictate the intensity of action of drug. The expected Cmax range is 7-10µg/ml and this was not achieved in our patients in intensive phase (5.497µg/ml). C max attained in continuation phase was 8.1µg/ml and this is very much within the expected range of C max. Both intensive and continuation phase of treatment show very short half-lives for rifampicin. The normal half-live range is 2-5 hrs, but the patients in continuation phase showed a quicker elimination of rifampicin (1.483 hrs) and intensive phase TB patients also showed shorter half-life.but in comparison with continuation phase, the half-life is slightly lengthened.

Total clearance was increased in both phases of treatment and the increase was more pronounced in intensive phase as compared to reference value 0.30 hr^{-1},two fold increase in elimination rate is found in continuation phase when compared to expected values. All the pharmacokinetic parameters in TB patients are indicative for precision showing good agreement with the values [3].

Pharmacokinetics of isoniazid

Pharmacokinetics of isoniazid in TB patients shows a significant differene between two phases. The total amount of isoniazid in blood was 55.16µg.hr/ml in continuation phase and AUC was less in intensive phase (35.57µg.hr/ml).t max was less than the expected value. Reduction in t max (1.193 hrs) was more in intensive phase when compared to continuation phase (1.55 hrs). Cmax was less in intensive phase when compared to continuation phase. Half-life also was very much reduced in intensive phase. Elimination rate constant is higher in intensive phase (0.647hr^{-1}), compared to continuation phase (0.421 hr^{-1}).

ISSN: 0975-8585

Table 1.Plasma Isoniazid and Rifampicin concentration in patients among intensive and continuation phase TB treatment

	Rifampicin Mean plasma concentration(µg/ml) mean±SD		Isoniazid Mean plasma concentration(µg/ml) mean±SD(SEM)	
Time in hr	**Intensive phase**	**Continuation phase**	**Intensive phase**	**Continuation phase**
0.5hr	1.595±0.13	0.845±0.86	1.8025±0.53	0.27±0.22
1hr	4.005±0.40	4.2±0.32	4.175±1.32	6.165±1.47
2hr	6.43±1.95	8.375±0.03	5.555±5.15	15.225±1.39
3hr	7.705±1.95	6.22±2.07	7.27±9.84	14.325±6.71
5hr	3.241±1.46	5.785±4.33	3.72±4.63	4.695±4.03
8hr	1.42±0.042	1.43±0.08	0.5335±.65	1.325±1.46

Table 2.Pharmacokinetic parameters for rifampicin

Parameters	Intensive phase	Continuation phase	p value
AUC	32.005µg hr/ml	37.86 µg hr/ml	0.0266*
T Max	1.184hrs	1.65hrs	0.0297*
C Max	5.49µg/ml	8.1µg/ml	0.0203*
Half life	2.334hrs	1.483hrs	0.0241*
Volume distribution	47.37 L	25.45 L	0.0780
clearance	14.06L/hr	11.88L/hr	0.0534
Elimination rate constant	$0.296hr^{-1}$	$0.467\ hr^{-1}$	0.1404

*considered significant

Table 3.Pharmacokinetic parameters for isoniazid

Parameters	Intensive phase	Continuation phase	p value
AUC	35.57µg hr/ml	55.16 µg hr/ml	0.1354
T Max	1.93hrs	1.78hrs	0.0415*
C Max	10.66µg/ml	15.10µg/ml	0.0402*
Half life	1.07hrs	1.646hrs	0.1330
Volume distribution	26.07 L	25.83 L	0.0029**
clearance	16.86L/hr	10.87L/hr	0.1354
Elimination rate constant	0.647hr-1	0.421hr-1	0.1328

ISSN: 0975-8585

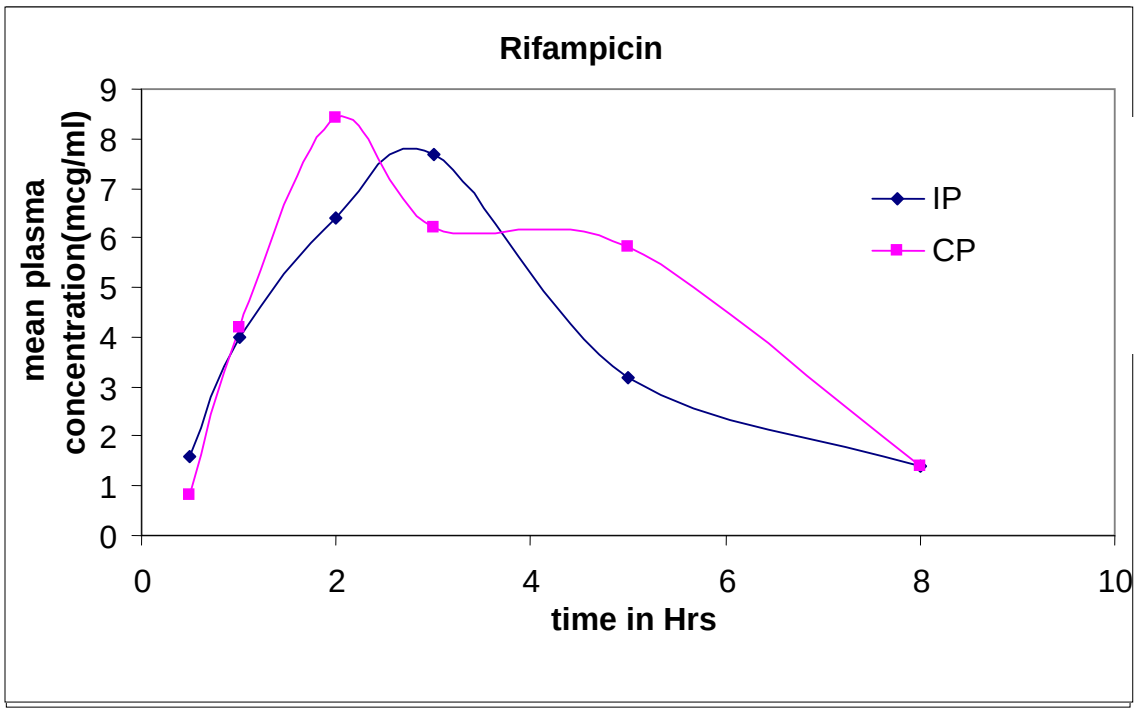

Fig 1 Plasma concentration time profile of rifampicin

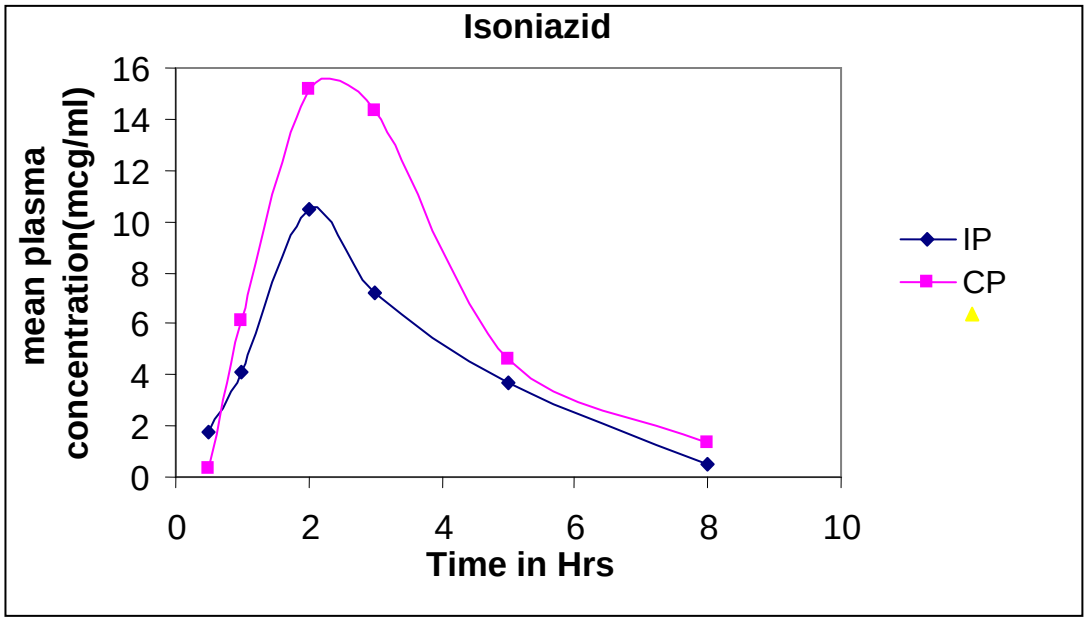

Fig 2 Plasma concentration time profile of isoniazid

ISSN: 0975-8585

DISCUSSION

Influence of therapeutic regimen on pharmacokinetics of rifampicin and isoniazid.

While analyzing the data obtained from 50 study subjects it is found that the drug levels (isoniazid, rifampicin) show marked variation between intensive and continuation phase. The plasma level-time (fig.1) shows the difference in drug kinetics between two phases clearly. Earlier study states that after administration of combined drugs over a period (continuation phase) there is a decrease in biological half life of rifampicin [4]. In both phases rifampicin is eliminated very fast than expected probably due to accelerated metabolism and elimination. Maximum peak concentration achieved is very less when compared to expected concentration, so extent of bactericidal activity may not be clinically sufficient [5].

In isoniazid kinetics time for peak concentration, (1.193hrs, 1.55hrs, $p>0.0001$) maximum peak concentration (10.66mg/ml, 12.10mg/ml, $p>0.0001$) and volume distribution (26.07L, 25, 83L, $p>0.0001$) show significant difference between intensive and continuation phase. Minimum effective concentration of Isoniazid is 3µg/ml, taking this into account, duration of action will last for 4.5 hrs in intensive phase and 5.2 hrs in continuation phase. Total clearance is found to be 16.86L/hr for intensive phase and 10.87L/hr for continuation phase. Elimination rate constant values shows much difference when compared to normal. On considering the values obtained from the graph, we can see that there is a significant lowering of the duration of action in intensive phase when comparing to continuation phase in both rifampicin as well as isoniazid [6].

Four drug combination therapy in intensive phase has influenced through some mechanism for initially quicker absorption than in continuation phase with only rifampicin and isoniazid. Lesser C max than expected value in intensive phase entertains a possibility of hindrance in rifampicin absorption or degradation of absorbed rifampicin by enhanced enzyme induction. Our study results demonstrate short half-lives of rifampicin confirming quick elimination of drugs and it could be due to enzyme induction by rifampicin. This was also reported by a study where they showed a slightly higher half-lifes in TB patients (2.8 hrs),than healthy volunteers (3.11 hrs)[7].

The increased clearance supports the probability of quicker elimination of rifampicin in TB patients. Good agreement in pharmacokinetic profile of rifampicin meaning shorter half-life with increased elimination rate and reduced$AUC_{0\text{-}8}$ is very much evident in our study. This confirms the earlier findings that Rifampicin may be degraded in acidic environment and in addition to rifampicin ability to induce enzyme activity. In the case of isoniazid $AUC_{0\text{-}8}$ was found to be less in our study in intensive phase than continuation phase, indicating the interference of other drugs ethambutol and pyrazinamide [8]. A pilot study conducted in our laboratory showed an $AUC_{0\text{-}5\ hrs}$ of 31.2µg hr/ml and for 8hr we could find AUC of 55.5µg hr/ml and according to study report, $AUC_{0\text{-}12hr}$ was reported as 76.95µg hr/ml [9]. All these results are in agreement with each other. But the results of our study in intensive phase shows very much

reduced AUC when compared to continuation phase, again emphasizing the interference of other drugs [10].

Early t max of isoniazid found in our study is supported by earlier study. C max was found to be 14.83µg/ml in the earlier study [6] and our study shows a value of 12.10µg/ml.This could be because of inter individual variability and the quick elimination of isoniazid. Biological half life of isoniazid was found to be very much reduced in our patients when compared to earlier study in healthy volunteers.

CONCLUSION

Study shows pharmacokinetic variability in intensive and continuation phase TB patients. Reduction in pharmacokinetic parameters found in the study help to suggest the possibility of failure in TB therapy. Hence, future studies may be taken up in larger number of TB patients in different areas of country to assess the uniformity of pharmacokinetics of rifampicin and isoniazid to optimize the therapeutic regimen in intensive phase treatment. With the help of active monitoring of therapeutic regimen.

ACKNOWLEDGEMENT

We take this opportunity to acknowledge Dr. R Rajasekaran, Deputy Director of health services, Govt. Hospital Erode and all staff members in TB centre, Government hospital, Erode for granting permission to interact with patients and for their support during the study.

REFERENCES

[1] Anthony D. Harries et al. Trop Med Int Health 2010; 15 (6): 659–663.
[2] Amrit Guptan, Ashok Shah.et al. Tuberculosis and diabetes: an appraisal. Ind J Tub 2000; 47: 3.
[3] G Acocella, L bonollo, M garimoldi, M Mainardi, LT Tenconi and FB Nicolis. Gut 1972; 13: 47-53.
[4] Shamaila Rafiq, Thahira Iqbal, Amer Jamal. Int J Agric Biol 2010; 12: 391-395.
[5] Chandra Immanuel, Prema Gurumurthy, Geetha Ramachandran, P Venkateshan, V Chandrashekaran and R Prabhakar. Indian J Med Res 2003; 118: 109-114.
[6] Rovina Ruslami, Rob E Aarnoutse, Bachti Alisjahbana et al. Trop Med Int Health 2010; 15(11): 1289-1299.
[7] Indian Journal of Tuberculosis Published quarterly by the Tuberculosis Association of India 2011; 58 (2):
[8] Fact Sheet_tb_2010. www.who.int/tb/publications/2010/factsheet_tb_2010.pdf.
[9] Andrew Robinson, Michael E Kimerling, Penny Philips, Patricia Patterson, Marilyn Hall C. Chest 1998; 113: 1178-1183.
[10] V Roy, U Tekur and K Chopra. In J Tuberc Lung Dis 1995; 3(7): 627-631.