ORIGINAL RESEARCH PAPER
Volume-9 | Issue-2 | February-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

TWO HOURS PLASMA CONCENTRATION OF RIFAMPICIN IN PATIENTS OF NEWLY DIAGNOSED PULMONARY TUBERCULOSIS WITH AND WITHOUT DIABETES MELLITUS ON ANTI TUBERCULOSIS THERAPY– A CROSS-SECTIONAL STUDY.

Pharmacology

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ABSTRACT

Aim: To estimate and compare rifampicin C2hr concentration in newly diagnosed pulmonary TB patients with and without DM on anti-tuberculosis therapy.

Materials and methods: A cross-sectional study was done on 54 newly diagnosed pulmonary TB patients with and without DM on anti-TB drug therapy as per RNTCP.

Sample was collected 2 hours post dose administration. Separated plasma was stored in liquid nitrogen until the analysis. Estimation of rifampicin concentration was done using HPLC.

Result: Rifampicin plasma levels at 2 hours post drug administration (C2hr) were below reference (≥ 8µg/ml) in 24(100%) of diabetics and 23(77%) of non-diabetics.

The mean Rifampicin Plasma C2hr ± SD of diabetic TB patients was significantly lower than the non-diabetic TB patients with values of 3.52±0.96 and 5.79±1.73 µg/ml.

Negative correlation was seen between RBS mg/dl and rifampicin plasma levels in diabetic and non-diabetic TB patients with Pearson correlation coefficient (r) of -0.74, p-value < 0.01 and -0.53, p-value < 0.01 respectively.

Conclusion: Plasma levels of rifampicin were below reference in all of the diabetics and most of non-diabetic TB patients. Higher doses of rifampicin may be required to achieve therapeutic concentration for TB therapy. Therapeutic drug monitoring should be considered for TB therapy in patients of TB with DM as comorbidity.

KEYWORDS

Rifampicin, C2hr levels, Diabetes Mellitus, Tuberculosis

INTRODUCTION

DM poses a great threat to human health as well as a huge socioeconomic burden for governments. The burden of diabetes has steadily increased over the past quarter century in India and across the globe, with India contributing a major part of the global burden. According to the updated data from the international diabetes federation (IDF), the estimated global prevalence of DM reached 8.8% in 2015 and 12% of global health expenditure was due to DM in that same year[1].

Diabetic patients have three times greater risk of developing TB[2]. TB and DM have been described as the "convergence of two epidemics"[3]. Diabetics likely to have slower response to TB therapy [4]. In addition to other complications of treatment, slow response prolongs infectiousness and often extends the treatment duration [4]. The presence of DM affects the outcome of drug treatment negatively, reduces the cure rate, and enhances the risk of relapse and emergence of drug resistance[5].

In Diabetics with TB circulating levels of TB drugs (e.g., rifampicin) are likely to be below the expected therapeutic ranges[4].

Rifampicin is considered the most important 1st line agent against Mycobacterium tuberculosis infection. Because of its potent bactericidal action against Mycobacterium tuberculosis it has remain central agent for TB treatment since 1966. Rifampicin has Tmax of 1.5 to 2hrs and Cmax of 8 to 20 µg/ml [6]. For therapeutic drug monitoring (TDM) of rifampicin in TB treatment, a Cmax of 8–24 mg/L (free plus bound drug) was suggested in the 1990s [7,8].

There are only few studies done in India regarding the effect of DM on the plasma levels of anti TB drugs. So, available data particularly in Indian population is inconclusive with regard to whether DM affects the plasma levels of anti TB drugs.

Considering these facts, present study is planned to estimate and compare rifampicin C2hr concentration in newly diagnosed adult Indian pulmonary TB patients with and without DM.

MATERIAL AND METHODS

A cross-sectional observation study was conducted in J.L.N Medical College and associated hospitals Ajmer, (Rajasthan) after the approval by Institutional Ethical Committee.

Material

Standard drug was purchased from Chromachemie Laboratory Private Limited, Bengaluru. HPLC grade reagents methanol, acetonitrile, water, phosphate buffer were procured from local supplier. Millipore filters of 0.20 µm and 0.45 µm were procured from PG TECH Private Limited Indore.

Instrument

YL9100 HPLC with binary pump, vacuum degasser, UV/VIS detector, enable C18 column and Guard column with YL auto sampler was used in the study.

YL clarity software was used for analysis of the samples. For centrifugation micro centrifuge of Chino Scientific instruments, model CSIM-12 with max speed of 20000 r.p.m was used.

Method

After taking approval from institutional ethical committee, this study was carried out in the department of Pharmacology J.LN Medical College, Ajmer.

54 newly diagnosed pulmonary TB patients with and without DM, out of those registered for the treatment by the department of pulmonary medicine of this college, during the period of 1st November 2018 to 31st June 2019, fulfilling the inclusion criteria were enrolled in the study. They were divided in to two groups.

1st group consisted of 24 pulmonary TB patients with diabetes who were receiving DM therapy at the time of recruitment and they continued to use their anti-diabetic drugs during the study.

2nd group consisted of 30 non-diabetic pulmonary TB patients who were screened for DM and patients with suspicious test results (FBS >100mg/dl) were excluded from the study.

Diagnosis of pulmonary TB was based on clinical symptoms, chest radiological examination, sputum microscopy and culture.

Patients with a comorbid disease (except for DM)) were excluded from the study.

All patients were administered orally first line anti-TB drugs at DOT centre as per RNTCP. 5ml of blood was withdrawn by venepuncture from

each patient at a time point of 2 hours post dose administration at steady state concentration of rifampicin. The blood samples were collected in sodium heparin vials and were immediately centrifuged to obtain plasma. Collected plasma samples were transferred into cryo vials pre dusted with pinch of ascorbic acid which were kept in liquid nitrogen until analysis. On the day of processing, plasma samples were taken out from liquid nitrogen container and thawed at room temperature. One ml of plasma was mixed with one ml of acetonitrile to allow denaturation of protein. The mixture was vortexed for 3 minutes and centrifuged at 3000 rpm for 10 min. Supernatant was neutralized with 0.2ml of 1M NaoH and transferred into pre-labelled HPLC injector vials after filtration through 0.20 µm syringe filters and loaded into HPLC auto sampler. Chromatographic analysis was performed on C18 column protected by guard column. The mobile phase consisted methanol and phosphate buffer (pH 7.4) in the ratio of 75:25.The components of mobile phase were filtered before use through 0.45 µm membrane filter and degassed for 15 minutes. Flow rate was 1.5 ml/min. The eluent was detected by UV detector at 475nm for rifampicin. Mean±SD retention time of rifampicin was 3.52±0.06 minutes.

RESULT

Most of the patients (31.48%) were in 21-30 years of age group and mean age of diabetics (46.95±16.08 years) was significantly higher than the non-diabetics (37.96±16.01 years).

There was significant difference in mean weight (57.16±9.29 vs 50.86±11.64 Kg) and BMI (21.58±3.12 vs19.04±3.91 Kg/m^2) between diabetics and non-diabetic TB patients respectively.

There was no significant difference in gender wise distribution among the diabetics and non-diabetics TB patients.

There was no statistical difference in smoking habits between the diabetics and non-diabetics TB patients.

Mean RBS in diabetic TB patients (194.7±70 mg/dl) was significantly higher than non-diabetics (105.13±15.20 mg/dl) and there was negative correlation between random blood sugar levels and rifampicin plasma levels in TB patients with and without DM with Pearson correlation coefficient (r) of -0.74, p-value < 0.01and -0.53, p-value < 0.01 respectively.

Plasma levels of rifampicin 2 hours post drug administration were below reference in 24/24(100%) of diabetic and 23/30 (77%) of non-diabetic TB patients. Mean plasma levels of rifampicin were significantly lower in diabetics (3.52±0.96 µg/ml) as compared to non-diabetics (5.79±1.73 µg/ml) and DM was found to be associated with decrease levels of rifampicin in TB patients.

Table 1: Comparative data of various parameters of diabetic and non-diabetic TB patients. P value was considered significant at 95% confidence interval (P value less than 0.05).

Patient Characteristics	Diabetic (n=24)	Non-diabetic(n=30)	P value
Unpaired two tail t test			
Age (year)	46.95±16.08	37.96±16.01	0.049(S)
Body wt.(Kg)	57.16±9.29	50.86±11.64	0.034(S)
Height (m)	1.64±0.04	1.63±0.07	0.33(N.S)
BMI(Kg/m2)	21.58±3.12	19.04±3.91	0.012(S)
RBS mg/dl	194.7±70	105.13±15.20	<0.005(S)
Rifampicin Plasma C2hr (µg/ml)	3.52±0.96	5.79±1.73	<0.005(S)
Chi-square test			
No (%) males	20(83%)	20(67%)	0.28(N.S)
No (%) females	4(17%)	10(33%)	
No(%) smokers	13(55%)	8(27%)	0.07(N.S)

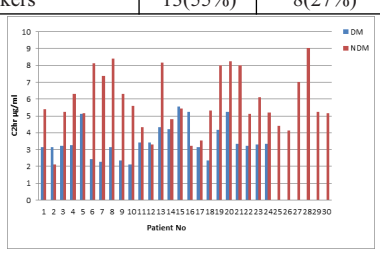

Figure 1 Plasma levels of rifampicin at 2 hours post drug administration in pulmonary TB patients with DM and without DM.

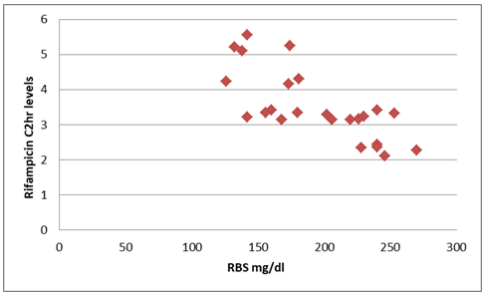

Figure 2 Correlation between RBS and rifampicin plasma levels at 2 hours post drug administration in pulmonary TB patient with DM.

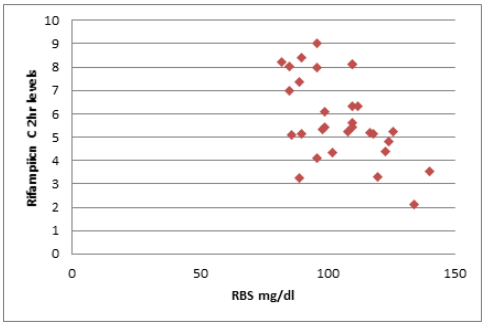

Figure 3 Correlation between RBS and rifampicin plasma levels at 2 hours post drug administration in pulmonary TB patient without DM.

DISCUSSION

In our studies it is seen that rifampicin C2hr plasma levels were below reference in all of the diabetics and most of non-diabetic TB patients. Further there was significant difference in mean rifampicin C2hr levels of diabetics and non-diabetics and DM was shown to be associated with decrease in rifampicin plasma levels. Decrease in Rifampicin plasma levels in diabetics more than non-diabetics has been shown by some but not all previous studies [9-14].

In India Therapeutic drug monitoring of anti-TB drug is not done, so even if patient is at sub-reference plasma levels of rifampicin no dose correction of the drug is done and organism remains exposed to sub-therapeutic concentration of drug which can lead to treatment failure and /or development of drug resistant strains.

In our study, mean RBS level was significantly higher in diabetic TB patients in comparison to non-diabetics Studies have suggested that hyperglycaemic state decreases the release of gastric acid from parietal cells and there by increases the gastric pH. As rifampicin is absorbed at acidic pH, shift in gastric pH due to hyperglycaemia delays rifampicin absorption and there by tend to prolong the Tmax and decrease the Cmax [9]. DM associated hyperglycaemia which can cause reduction in gastric hydrochloric acid secretion resulting in a higher gastric pH leading to decrease in rifampicin absorption could be the reason for low plasma levels of rifampicin. This hypothesis needs confirmation, because gastric pH was not measured in our study.

In our study, mean weight and BMI of diabetic TB patients were significantly higher than the non-diabetics. Similar results were seen in studies done by Nijland HM et al [9] and Aylin Babalik et al[10]. Decrease in plasma levels of rifampicin in diabetics could also be due to increase in the volume of distribution due to greater body weight of diabetic TB patients [10].

The present study also has some limitations.

1. The sample size of the pulmonary TB patients was small.
2. Plasma levels were assessed in blood sample collected 2 hours post drug administration. AUC $_{0\text{-}6\ hours}$ have much better value for comparison of two groups and also additional value in distinguishing patients with delayed absorption.
3. We did not assess relationship between plasma concentration of rifampicin and clinical outcome.
4. Effect of other factors including unexplained variability in rifampicin plasma levels, the effect of co-administrated drugs and the role of genetic polymorphism in low rifampicin plasma levels

were not studied.

CONCLUSION

In the study as the plasma levels of rifampicin at standard rifampicin dose were below reference in most of the TB patients without DM and all of the TB patients with DM; therefore it may be assumed that higher doses may be required to achieve therapeutic concentration, more so in DM patients. Mean plasma levels of rifampicin were significantly lower in diabetics as compared to non-diabetics. However, our study sample size was small and we did not observe the final outcome of the therapy, we strongly suggest that more long term multicentric studies at different levels with therapeutic drug monitoring in TB patients, especially with comorbid condition like DM will certainly help in favourable outcome of the treatment.

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