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Original Article

EFFECT OF DIABETES MELLITUS ON RIFAMPICIN PEAK SERUM CONCENTRATION

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ABSTRACT

Objective: To comparatively analyze the peak serum concentration (Cmax) of rifampicin and to determine the incidence of decreased Cmax between diabetic and non-diabetic adult pulmonary tuberculosis patients.

Methods: A cross-sectional observational study was carried out in the chest and tuberculosis (TB) department of a tertiary care hospital after the approval of the institutional ethics committee. Five millilitre (ml) of blood was withdrawn by venipuncture from each patient at a time point of 2 h post dose administration at steady state concentration (C_{ss}). The separated serum was centrifuged at a rate of 3500 rotations per minute (rpm) for a period of fifteen minutes and the resultant serum was stored at-70 ° C until analysis. Estimation of rifampicin concentration was carried out in Thermo TSQ Ultra (MS/MS) with Shimadzu 20 AD UFLC LC-MS.

Results: The mean (Standard Deviation (SD)) age of the study population was 46.8 (14.2) years. The mean serum C_{max} of rifampicin was significantly less in diabetic patients with pulmonary tuberculosis (p=0.0305). Statistically, a significant difference in the incidence of a decrease in C_{max} was found between diabetic and non-diabetic patients (p=0.0335). Diabetes mellitus was found to be the predominant factor that affects rifampicin C_{max}.

Conclusion: In this study, an effect of diabetes mellitus (DM) on the peak serum concentration of rifampicin was observed. Patients with hyperglycemia levels had significantly reduced levels of rifampicin serum concentrations, thus showing an inversely proportional relationship between blood glucose and rifampicin serum levels.

Keywords: Rifampicin, C_{max}, Diabetes mellitus, Pulmonary tuberculosis, Diabetes and tuberculosis, DM and TB

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INTRODUCTION

The "captain of all these men of death", tuberculosis (TB) has been a menace to the humankind since the ancient time. TB-a serious and highly infectious disease caused by *mycobacterium tuberculosis* is the second leading cause for the high incidence of mortality rates worldwide. TB affects the lungs (Pulmonary tuberculosis-PTB) more commonly than the other parts including pleura, central nervous system, lymphatic system, bone and joints (extra-pulmonary tuberculosis). Hemoptysis, night sweats, loss of appetite and weight loss are the common symptoms of PTB [1, 2].

India is the country of highest TB and diabetes mellitus (DM) burden [3, 4]. According to the world health organization (WHO) 2014 estimates, incidence of 2.5 million cases of active TB was reported to be in India out of 9.6 million cases incident globally. It also adds that "about 40% of the Indian population and one-third of the world's population are infected with the *mycobacterium tuberculosis*, where most of them have a latent infection rather than the active disease" [5, 6].

TB is referred as the top infectious killer disease worldwide [7]. In India, therapeutic success is achieved only in 88% of the treated TB patients, with 4% death, 2% treatment failure and 6% treatment default in patients on anti-tubercular therapy (ATT) [8]. TB is extremely associated with other comorbid conditions like diabetes mellitus, HIV/AIDs, multi-drug and extreme drug resistance [8].

The WHO recommends combination therapies with isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin and other second line agents in intensive and continuous phases for the treatment of pulmonary tuberculosis [9]. Being highly bactericidal, rifampicin forms the nucleus of anti-tubercular therapy. However, the drug is associated with high inter-individual variability, and various clinical, environmental and genetic factors tend to alter the pharmacokinetic profile of rifampicin [10].

Diabetes mellitus has been reported to influence oral rifampicin pharmacokinetics by causing variability in absorption leading to decrease the systemic bioavailability of the drug [11]. Decreased systemic exposure to the drug leads to the emergence of multi-drug resistant bacilli and/or treatment failure [12]. Although several studies have been reported on the pharmacokinetics of rifampicin in tuberculosis patients, the impact of diabetes as a comorbid disease, on the peak serum rifampicin concentration is not addressed in India. Hence this study was carried out with an objective to determine the effect of diabetes mellitus on the peak serum concentration of rifampicin.

MATERIALS AND METHODS

Method

The study was carried out as a cross-sectional observational study in the chest and TB department of a tertiary care hospital. The study protocol was approved by the institutional ethics committee, Sri Ramachandra University (IEC/12/MAR/94/09). The study participants were recruited after obtaining written informed consent. All PTB patients between ages eighteen and sixty-five of either gender were included in the study. Pregnant females with tuberculosis, tuberculosis patients of both genders who were retro-positive were excluded from the study.

Serum collection and storage

Five ml of blood was withdrawn by venipuncture from each patient at a time point of 2 h post dose administration at steady state (C_{ss}). The blood samples were collected in serum separator vacutainers containing clot activator and allowed to stand for 30 min. The vacutainers were shifted to a laboratory for centrifugation after packing with ice bags containing silica gel. The separated serum was centrifuged at a rate of 3500 rotations per minute (rpm) for a period of fifteen minutes, and the resultant serum was stored at-70 ° C until analysis.

Estimation of rifampicin concentration (Srivastava *et al.*, 2012) [13]

The frozen samples were thawed at room temperature, and an aliquot of 200 µl sample was transferred to pre-labeled Ria vials. 50 µl of internal standard (Roxithromycin 1.000 µg/ml) was added and vortexed well-using cyclomixer. 0.400 ml of 100% acetonitrile was added, and the capped vials were re-vortexed in vibramax at 2000 rpm for 10 min followed by centrifugation at 4500 rpm for 10 min at 4 °C. 0.300 ml of supernatant was transferred into pre-labeled injector vials and loaded into LC-MS autosampler. Estimation of rifampicin concentration was carried out in Thermo TSQ Ultra (MS/MS) With Shimadzu 20 AD UFLC LC-MS. ZORBAX Eclipse Plus C18 column of dimensions 4.6 mmx, 150 mm, 5 µm and acetonitrile 10 mmol, ammonium acetate (80:20% v/v) were used as stationary and mobile phases respectively at a flow rate of 1 ml/minute.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 and Graph pad prism 7.0. Pearson's correlation was used to determine the linear dependency of Cmax on individual covariates. Chi-square analysis was used to determine the effect of dichotomous categorical variables. Unpaired student t-test was used to compare two groups. A p-value less than 0.05 were considered statistically significant throughout the study (95% CI).

RESULTS

Forty-five patients who fulfilled the inclusion criterion were recruited in the study. Twenty-five patients were non-diabetic whereas 20 patients were diabetic. The mean (SD) age of the study population was 46.8 (14.2) years. The study participants were constituted of 68.88% male and 31.12% female (fig. 1). The distribution of study population based on their age group is depicted in table 1.

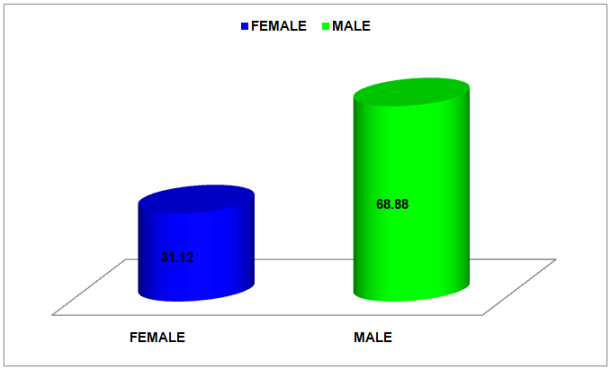

Fig. 1: Gender wise distribution

Table 1: Age-wise distribution

Age	No. of patients N = 45	Percentage (%)
21-30	16	35.5
31-40	11	26.5
41-50	7	13.5
51-60	9	20
>61	2	4.5

The mean (SD) age of males was comparatively higher than that of females with values of 48.7 (10.6) and 43.1 (11.2) respectively (P=0.532). The mean age of non-diabetic TB patients was comparatively higher than that of diabetic patients with values of 46.6 (8.4) and 42.4 (9.2) respectively.

The body weight of about 86.6 % of the patients was less than 50 kg and13.4% of patients was greater than 50 kg. No statistically significant difference in body weight was found between diabetic and non-diabetic patients (P=0.5440). About 51.12% of the patients were smokers and 48.88% were non-smokers. The most commonly prescribed concomitant medications were ranitidine and aluminum hydroxide (36%). The other co-medications prescribed were insulin (34%), paracetamol (18%), theophylline (4%) and supplements (8%). The distribution of study participants based on the RNTCP (revised national tuberculosis control program) treatment (CAT I and CAT II) they received is shown in fig. 2.

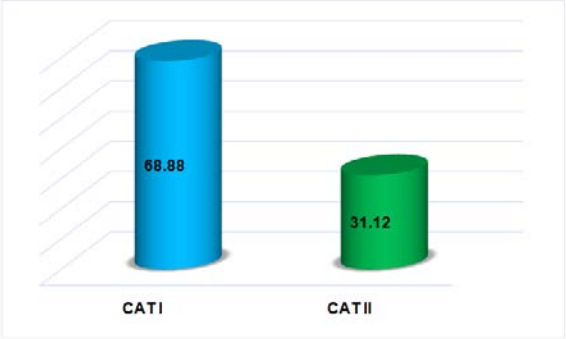

Fig. 2: Distribution based on CAT regimen

Around 55.55% were found to be alcoholic and 44.45% were non-alcoholic. Nearly 68.8% patients had a prior history of TB whereas 31.2% patients had no history of TB. Twenty-five (58%) patients of the study population were non-diabetic, and 20 (42%) were diabetic. Almost 83% of the diabetic patients were on a combination of insulin and metformin. Very few patients received the other oral hypoglycemic medications.

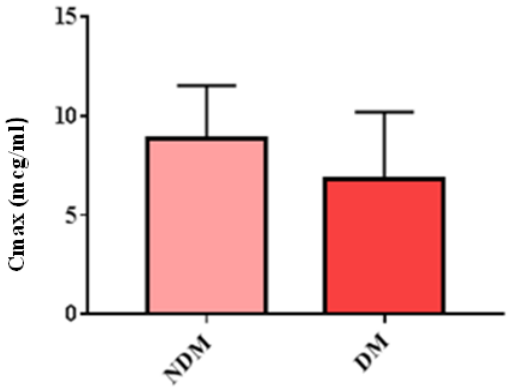

Fig. 3: Comparison of peak serum rifampicin concentration in diabetic (DM) and nondiabetic patients (NDM) with pulmonary tuberculosis (P=0.0305)

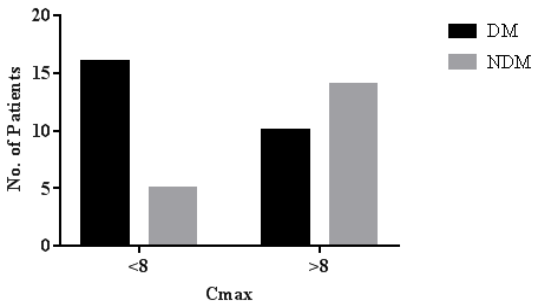

Fig. 4: Incidence of sub-therapeutic peak serum rifampicin concentration between diabetic and non-diabetic patients with pulmonary tuberculosis (P=0.335)

The mean serum C_{max} of rifampicin was significantly less in diabetic patients with pulmonary tuberculosis (P=0.0305) as shown in fig. 3. Statistically, a significant difference in the incidence of a decrease in C_{max} was found between diabetic and non-diabetic patients (P=0.0335) as depicted by fig. 4.

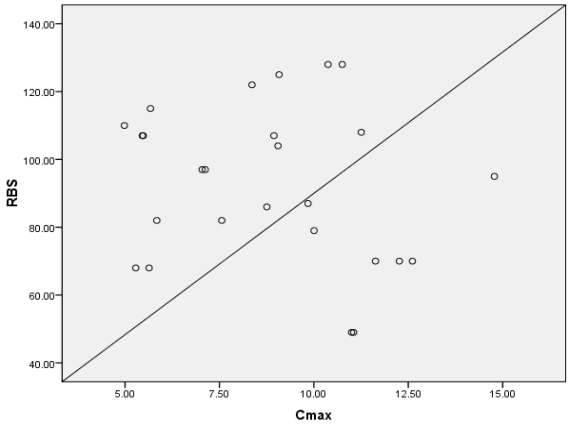

Fig. 5: Correlation of random blood sugar (RBS) and peak rifampicin serum concentration in pulmonary tuberculosis patients without diabetes

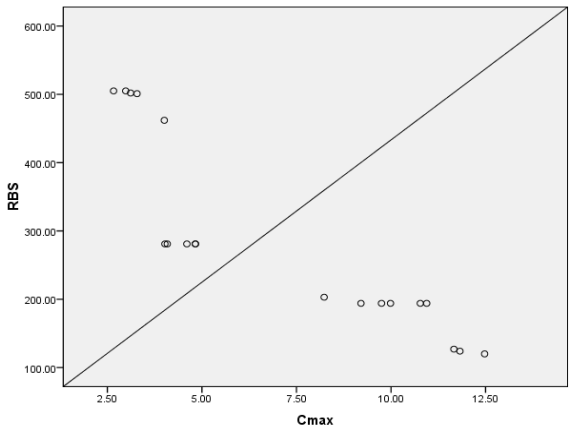

Fig. 6: Correlation of random blood sugar and peak rifampicin serum concentration in pulmonary tuberculosis patients with diabetes

The values of RBS and observed C_{max} of diabetic and non-diabetic patients with pulmonary tuberculosis were correlated using Pearson's correlation. The correlation between RBS and rifampicin Cmax in pulmonary tuberculosis patients without diabetes is shown in fig. 5. The fig. 6 depicts the correlation between RBS and rifampicin Cmax in pulmonary tuberculosis patients with diabetes.

DISCUSSION

This study has examined the effect of diabetes on the peak serum rifampicin concentration in patients with pulmonary tuberculosis, by comparing the expected rifampicin Cmax of patients with PTB only. Peak serum rifampicin concentrations tend to be decreased in pulmonary tuberculosis patients with comorbidity diabetes when compared to PTB patients without diabetes. This is in line with the study carried out by Nijland *et al.* (2006) [12]. The mean age (48.7 y) of the male patients was greater when compared to a similar study conducted by Mendez (2012) [14]. The mean age of PTB patients with diabetes and without diabetes in the present study was in contrast to that conducted by Ruslami *et al.* (2010) [15]. However, our results were similar to Ruslami *et al.* when the statistical significance in body weight between these groups was analyzed [15]. Exposure to rifampicin has been reported to be two-fold lower in diabetic than in non-diabetic patients with tuberculosis during the continuation phase of treatment [14]. Diabetes mellitus was found to be the predominant factor that affects rifampicin C_{max}. Clinical studies suggest that hyperglycemic state decreases the release of gastric acid from parietal cells and thereby increases gastric pH. Being highly pH dependent for solubility and well absorbed from an acidic pH, a shift in the gastric pH due to hyperglycemia delays rifampicin absorption and thereby tend to prolong the t_{max} and decrease the C_{max} [15]. In addition, gastrointestinal ailments such as gastroparesis which are common in chronic diabetics may either delay or impair absorption of rifampicin leading to decreased systemic availability [17]. Univariate analyses were performed to determine the relationship between random blood glucose and rifampicin C_{max}. A near inverse correlation was obtained in diabetic patients (Pearson's correlation=-0.402, P value=0.001); however such a correlation was not observed in non-diabetic pulmonary tuberculosis patients suggesting that the drug absorption is disfavoured only under hyperglycemic conditions and linear relationship does not exist between blood glucose and rifampicin C_{max} (Pearson's correlation=0.006, P Value=0.962). This is similar to the study reported by Nijland *et al.* (2006), Heysell *et al.* (2010) and Heysell *et al.* (2013) [12,16-17]. The RBS vs C_{max} correlation plot of non-diabetic and diabetic PTB patients is shown in fig. 3 and 4 respectively. In addition, the incidence of decreased C_{max} was found to be high in PTB patients with diabetes than patients without diabetes (P<0.0001). These findings suggest that exposure to rifampicin is decreased in PTB patients with comorbid diabetes mellitus, which is in line with that reported by Nijland *et al.* (2006) [12]. Further, linear relationship observed between RBS and C_{max} in diabetic patients was not observed in non-diabetic patients suggesting that decreased in exposure is a direct result of hyperglycemic state and not due to diabetes mellitus as a disease. Further prospective studies to determine the pharmacokinetic profile of rifampicin in PTB patients with diabetic control are required to ascertain whether serum concentrations of rifampicin remain unaltered.

These findings suggest that absorption of rifampicin is decreased due to increase in gastric pH caused by elevated blood glucose level. Therefore, rifampicin administered orally 1-2 h after a carbohydrate-rich meal may not be effectively absorbed. Thus, rifampicin has to be taken in an empty stomach for effective absorption both in diabetic and non-diabetic patients. These findings have to be confirmed in studies involving larger populations.

A sample size of the study population was smaller, the effect of other factors including unexplained variability in peak serum rifampicin concentrations, the effect of co-administered drugs, the role of genetic polymorphism in low rifampicin concentration was not studied and hence were the limitations of the study.

CONCLUSION

In this study, an effect of DM on the peak serum concentration of rifampicin was observed. Patients with hyperglycaemic levels had significantly reduced levels of rifampicin serum concentrations, thus showing an inversely proportional relationship between blood glucose and serum rifampicin levels. However, only the blood glucose levels and body weight were correlated with the concentration of rifampicin, further studies need to be carried out in a larger population in order to rule out the various factors which affect the drug absorption of rifampicin in pulmonary tuberculosis patients with comorbid diabetes.

CONFLICT OF INTERESTS

Declared none

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