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Original Research Article

Comparison of Plasma Rifampicin Concentrations at 0, 2, 4 and 6 Hours in Pulmonary Tuberculosis Patients With and Without Diabetes Mellitus: A Cross-Sectional Study

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Abstract

Introduction: Tuberculosis (TB) continues to be a major global health burden, especially in developing countries. Diabetes mellitus (DM), a rapidly growing non-communicable disease, adversely affects TB outcomes and may alter the pharmacokinetics of anti-tubercular drugs like rifampicin. Subtherapeutic drug levels may contribute to treatment failure and drug resistance.

Aim: To compare plasma rifampicin concentrations at 0, 2, 4, and 6 hours in pulmonary tuberculosis patients with and without diabetes mellitus.

Materials and Methods: This cross-sectional observational study was conducted in the Department of Pharmacology, JLN Medical College, Ajmer, from October 2020 to August 2021. Sixty newly diagnosed pulmonary TB patients were enrolled, including 30 with DM and 30 without DM, all receiving anti-tubercular therapy as per National Tuberculosis Elimination Programme guidelines. Blood samples were collected at pre-dose (0 hour) and 2, 4, and 6 hours post-dose after achieving steady state. Plasma rifampicin levels were estimated using validated reverse-phase high-performance liquid chromatography. Statistical analysis was performed using Student's t-test and Chi-square test.

Results: Mean rifampicin concentrations at 2, 4, and 6 hours were significantly lower in diabetic patients compared to non-diabetics ($p<0.01$). Mean Cmax was significantly reduced in diabetics (3.52±0.96 µg/ml) compared to non-diabetics (5.79±1.73 µg/ml). AUC_{0-6} was also significantly lower in diabetics (15.26±2.27 vs 31.32±7.03 µg·h/ml, $p<0.005$). Subtherapeutic Cmax (<8 µg/ml) was observed in 100% diabetics and 70% non-diabetics.

Conclusion: Diabetes mellitus is associated with significantly reduced plasma rifampicin concentrations in pulmonary TB patients. Therapeutic drug monitoring and dose individualization may be required to achieve optimal therapeutic outcomes.

Keywords: Tuberculosis, Diabetes Mellitus, Rifampicin, Pharmacokinetics, Cmax, AUC, Therapeutic Drug Monitoring.

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Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains one of the leading infectious causes of morbidity and mortality worldwide, particularly in developing countries [1]. Despite global control efforts, TB continues to pose a major public health challenge, with millions of new cases reported annually [2].

India contributes a substantial proportion of the global TB burden, making optimization of treatment strategies a national priority [2]. In recent years, the coexistence of tuberculosis and diabetes mellitus (DM) has emerged as a significant clinical concern. Diabetes, a chronic metabolic disorder characterized by persistent hyperglycaemia, has shown a rapidly increasing prevalence globally and in India [3,4]. Epidemiological studies have demonstrated that individuals with diabetes have approximately three times higher risk of developing active TB compared to non-diabetics [5].

Moreover, TB-DM comorbidity is now more prevalent than TB-HIV coinfection in certain regions [6]. The interaction between TB and DM is bidirectional and detrimental. Diabetes adversely affects host immune responses, leading to higher bacillary load, delayed sputum conversion, and poorer treatment outcomes [7,8]. In addition to immunological alterations, pharmacokinetic changes in anti-tubercular drugs have been proposed as a key factor contributing to suboptimal treatment response in diabetic patients [9].

Rifampicin is a cornerstone drug in first-line anti-tubercular therapy due to its potent bactericidal activity and sterilizing effect [10]. Its therapeutic efficacy is closely related to pharmacokinetic parameters such as peak plasma concentration (Cmax) and area under the curve (AUC) [11]. A Cmax of 8–24 µg/mL is generally considered adequate for optimal therapeutic response [12]. However, several studies have reported reduced plasma concentrations of rifampicin in patients with diabetes, possibly due to altered absorption, increased volume of distribution, and metabolic changes [9,13].

Hyperglycaemia-associated factors such as delayed gastric emptying, increased gastric pH, and gastrointestinal dysmotility may impair rifampicin absorption, leading to reduced bioavailability [14]. Furthermore, higher body mass index in diabetic patients may increase drug distribution volume, thereby lowering plasma drug concentrations [13]. These pharmacokinetic alterations may result in subtherapeutic drug levels, increasing the risk of treatment failure, relapse, and emergence of drug resistance [11].

Despite the clinical significance, limited data are available regarding the impact of diabetes on rifampicin pharmacokinetics in the Indian population, and existing studies show inconsistent findings [9,15]. Therefore, the present study was undertaken to compare plasma concentrations of rifampicin at different time intervals in pulmonary TB patients with and without diabetes mellitus.

Materials and Methods

Study Design and Participants: This cross-sectional observational study was conducted in the Department of Pharmacology in collaboration with the Department of Respiratory Medicine at JLN Medical College and Associated Hospitals, Ajmer, Rajasthan, India, from October 2020 to August 2021. A total of 60 newly diagnosed pulmonary tuberculosis patients were enrolled and divided into two groups: 30 patients with diabetes mellitus (TB-DM group) and 30 patients without diabetes mellitus (TB group).

Diagnosis of pulmonary TB was based on clinical, radiological, and microbiological criteria as per National Tuberculosis Elimination Programme (NTEP) guidelines. Diabetes mellitus was diagnosed based on documented medical history or according to standard diagnostic criteria. Patients aged 18–65 years who were receiving first-line anti-tubercular therapy were included. Patients with HIV infection, hepatic or renal impairment, pregnancy, or those receiving drugs known to interact with rifampicin were excluded.

Drug Administration and Sample Collection: All patients received weight-based fixed-dose combination anti-tubercular therapy as per NTEP guidelines. Blood samples were collected after attainment of steady-state drug levels. On the day of sampling, patients were administered rifampicin under direct observation after an overnight fast.

Venous blood samples were collected at 0 hour (pre-dose), and at 2, 4, and 6 hours post-drug administration. Approximately 3–5 mL of blood was drawn at each time point and collected in heparinised tubes. Samples were centrifuged promptly, and plasma was separated and stored at −20°C until analysis.

Estimation of Plasma Rifampicin Concentration: Plasma rifampicin concentrations were estimated using a validated reverse-phase high-performance liquid chromatography (RP-HPLC) method. The chromatographic separation was carried out using a C18 column with an appropriate mobile phase under standard operating conditions. Detection was performed using a UV detector at a suitable wavelength specific for rifampicin.

The method was validated for linearity, accuracy, precision, and specificity. Calibration curves were prepared using known concentrations of rifampicin, and quality control samples were analysed with each batch to ensure reliability of results.

Statistical Analysis: Data were analysed using appropriate statistical software. Continuous variables were expressed as mean±standard deviation (SD), and categorical variables as percentages. Comparison between the two groups was performed using Student's t-test for continuous variables and Chi-square test for categorical variables.

Pharmacokinetic parameters including peak plasma concentration (Cmax) were calculated by standard method and area under the curve from 0 to 6 hours ($AUC_{0–6}$) were calculated using linear trapezoidal rule. A p-value of <0.05 was considered statistically significant.

Results

A total of 60 patients were included in the study, comprising 30 pulmonary tuberculosis patients with diabetes mellitus (TB-DM group) and 30

without diabetes mellitus (TB group). The baseline characteristics of the study participants are presented in Table 1. The mean age of patients in the TB-DM group was significantly higher compared to the non-diabetic group (p=0.003). Body mass index (BMI) and random blood sugar (RBS) were also significantly higher in diabetic patients. However, gender distribution was comparable between the two groups.

Plasma rifampicin concentrations at different time intervals are shown in Table 2. There was no statistically significant difference in pre-dose (0 hour) concentrations between the two groups. However, at 2, 4, and 6 hours post-dose, plasma rifampicin concentrations were significantly lower in the TB-DM group compared to the TB group (p<0.01).

Pharmacokinetic parameters are summarized in Table 3. The mean peak plasma concentration (Cmax) was significantly lower in diabetic patients compared to non-diabetics (p=0.04). Similarly, the mean area under the curve ($AUC_{0–6}$) was markedly reduced in the TB-DM group, with a statistically significant difference (p<0.005).

Table 1: Baseline Characteristics of Study Participants

Parameter	TB with DM (n=30)	TB without DM (n=30)	p-value
Age (years, mean±SD)	48.97±13.57	38.73±12.37	0.003(S)
Male/Female (n)	22/8	22/8	1.0
BMI (Kg/m2)	22.43±3.85	18.45±2.09	<0.01(S)
RBS mg/dl	194.93±37.85	104.73±9.26	<0.01 (S)

Table 2: Plasma Rifampicin Concentrations (µg/mL) at Different Time Points

Time (hours)	TB with DM (mean±SD)	TB without DM (mean±SD)	p-value
0 hour	0.36±0.26	0.47±0.33	0.146
2 hours	3.05±0.64	6.78±1.78	<0.001
4 hours	3.29±0.54	6.70±1.62	<0.01
6 hours	2.30±0.44	3.85±0.96	<0.01

Table 3: Comparison of Pharmacokinetic Parameters

Parameter	TB with DM (mean±SD)	TB without DM (mean±SD)	p-value
Cmax (µg/mL)	3.52±0.96	5.79±1.73	0.04(S)
Mean AUC_{0-6} of rifampicin (µg.h/ml)	15.26±2.27	31.32±7.03	<0.005 (S)

Discussion

The present study was conducted to compare plasma rifampicin concentrations at different time intervals in pulmonary tuberculosis patients with and without diabetes mellitus. The findings demonstrate that diabetic patients have significantly lower rifampicin concentrations at 2, 4, and 6 hours post-dose, along with reduced peak concentration (Cmax) and overall drug exposure ($AUC_{0–6}$), indicating altered pharmacokinetics in this group.

In the current study, baseline characteristics showed that patients in the TB-DM group were significantly older and had higher BMI compared to the non-diabetic group. These findings are consistent with previous studies that have reported higher age and body mass index among diabetic TB patients [9,13]. Increased BMI may contribute to a larger volume of distribution, thereby reducing plasma drug concentrations [13].

The plasma rifampicin concentrations observed at 2, 4, and 6 hours were significantly lower in diabetic patients. This is in agreement with the study by Ruslami R et al., which reported reduced exposure to rifampicin in TB patients with type 2 diabetes [9]. Similarly, Nijland HM et al. demonstrated that rifampicin concentrations were significantly lower in diabetic patients, suggesting impaired drug absorption or altered pharmacokinetics [13]. Another study by Requena-Méndez A et al. also supported these findings, highlighting reduced rifampicin levels in TB-DM patients [15].

In the present study, no significant difference was observed in pre-dose (0 hour) rifampicin concentrations between the two groups, indicating comparable baseline drug levels. However, the significant reduction in post-dose concentrations suggests that diabetes primarily affects drug absorption and disposition rather than baseline levels.

The mean Cmax in diabetic patients was significantly lower compared to non-diabetics. Although the reduction was modest, it is clinically relevant because rifampicin exhibits concentration-dependent bactericidal activity [11].

Lower peak concentrations may reduce the drug's efficacy and contribute to delayed bacterial clearance. Furthermore, the $AUC_{0–6}$ was markedly reduced in the TB-DM group, indicating decreased overall drug exposure. This finding is particularly important as AUC is a key determinant of

therapeutic success and prevention of resistance [11]. Several mechanisms may explain the reduced rifampicin levels in diabetic patients. Chronic hyperglycaemia is known to cause gastrointestinal autonomic neuropathy, leading to delayed gastric emptying and altered intestinal motility, which can impair drug absorption [14]. Additionally, increased gastric pH in diabetic individuals may reduce the solubility and absorption of rifampicin, a drug that requires an acidic environment for optimal bioavailability [14]. Alterations in plasma protein binding and hepatic metabolism may also contribute to pharmacokinetic variability [9]. Another contributing factor may be the higher body weight or BMI observed in diabetic patients, which can increase the volume of distribution and result in lower plasma concentrations of rifampicin [13]. Furthermore, diabetes-associated microvascular changes may impair drug delivery to tissues, further affecting therapeutic efficacy [7].

The clinical implications of these findings are significant. Subtherapeutic rifampicin concentrations may lead to poor treatment outcomes, including delayed sputum conversion, treatment failure, relapse, and development of drug resistance [11]. Given the increasing burden of TB-DM comorbidity, there is a need to consider individualized treatment strategies in this population. Therapeutic drug monitoring (TDM) may be useful in identifying patients with low drug levels and guiding dose adjustments to achieve optimal therapeutic concentrations [12].

However, routine implementation of TDM in resource-limited settings remains challenging.

Therefore, alternative strategies such as dose optimization or weight-based adjustments may be considered, although further research is needed to establish clear guidelines. The present study has certain limitations. The sample size was relatively small, which may limit the generalizability of the findings. Only rifampicin concentrations were measured, while other first-line anti-tubercular drugs were not evaluated. Additionally, long-term clinical outcomes such as sputum conversion rates and treatment success were not assessed.

Despite these limitations, the study provides important evidence supporting altered pharmacokinetics of rifampicin in diabetic TB patients. The findings highlight the need for further large-scale studies to explore dose optimization strategies and improve treatment outcomes in this high-risk population.

Conclusion

The present study demonstrates that pulmonary tuberculosis patients with diabetes mellitus have significantly reduced plasma rifampicin concentrations at 2, 4, and 6 hours post-dose compared to non-diabetic patients. Both peak plasma concentration (Cmax) and overall drug exposure ($AUC_{0–6}$) were significantly lower in the diabetic group, indicating altered pharmacokinetics of rifampicin in these patients. These findings suggest that diabetes mellitus may adversely affect the absorption and disposition of rifampicin, potentially leading to subtherapeutic drug levels. Given the concentration-dependent activity of rifampicin, such reductions may compromise treatment efficacy and increase the risk of poor outcomes. The study highlights the potential role of therapeutic drug monitoring and individualized dosing strategies in improving treatment outcomes in TB patients with diabetes mellitus.

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