ORIGINAL ARTICLE

Implications of Acetylator Status and Therapeutic Drug Monitoring of Plasma Rifampicin and Isoniazid Concentrations among Indians

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Abstract

Introduction: Low or abnormal plasma concentrations of anti-tuberculosis drugs can be a major reason for treatment failure or the emergence of drug resistance. Acetylator status, which affects drug metabolism, plays a key role in determining drug bioavailability. This study aimed to perform therapeutic drug monitoring (TDM) of rifampicin and isoniazid and to evaluate the correlation between plasma drug concentrations and acetylator status among Indian patients receiving first-line antituberculosis therapy.

Methods: Plasma concentrations of rifampicin and isoniazid were measured using in-house standardized high-performance liquid chromatography methods, while acetylator status was determined by conventional PCR of *NAT2* gene.

Results: Peak concentrations were estimated from 125 patients on first-line tuberculosis (TB) treatment. Among these, 56% exhibited subtherapeutic rifampicin concentrations and 28% had subtherapeutic isoniazid concentrations. Conversely, above normal (potentially toxic) concentrations were seen in 2% and 21% for rifampicin and isoniazid, respectively. Despite receiving the standard TB treatment regimen, only 62% of patients improved clinically, while 38% of patients continued harboring TB signs and symptoms, among which 6 patients (5%) developed rifampicin resistance during the treatment course. About 44% were slow acetylators, followed by 40% intermediate and 16% rapid acetylators. The acetylator status significantly influenced the plasma concentrations of both drugs. Slow acetylators had significantly higher isoniazid concentrations ($p = 0.004$) and lower rifampicin concentrations ($p = 0.01$) as compared to rapid acetylators.

Conclusion: Abnormal concentrations of rifampicin and isoniazid are prevalent and a major concern. Acetylator status influences plasma concentrations of rifampicin and isoniazid. Hence, determining acetylator status and performing TDM could be instrumental in optimizing and improving TB outcomes.

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Introduction

Tuberculosis (TB), caused by *Mycobacterium* species, is one of the oldest known infectious diseases. According to the Global Tuberculosis Report 2022, India is the largest country, accounting for 28% of the total TB cases globally.[1] The treatment for TB requires good patient adherence to combination chemotherapy for a prolonged period. Slow therapeutic response can lead to prolonged infectiousness, extended treatment duration, acquired drug resistance, or recurrence after treatment.[2] The underlying reasons for slow response are diverse, but measurement of serum anti-TB drug concentrations, or therapeutic drug monitoring (TDM), is a potentially useful tool for uncovering the causes of slow response.[2,3]

The bioavailability, pharmacokinetics, and serum concentrations of orally administered antituberculosis drugs can be influenced by several factors, such as patient age, sex, and ethnicity, gastrointestinal disorders, drug formulations, acetylator status, and drug interactions.[4] The *NAT2* gene in humans plays a crucial role in the metabolism of isoniazid. There are a few reports describing the *NAT2* genotype and its association with drug concentrations; however, most of them are from the Western population, and there is limited data on the Indian population.[5] Slow acetylators tend to have increased isoniazid concentrations as compared to intermediate or rapid acetylators.[5] Some studies have also suggested that impaired antimycobacterial drug absorption and bioavailability can delay or lower the cure rates for TB.[6,7] Thus, we aimed to perform TDM of rifampicin and isoniazid in Indian patients suffering from active tuberculosis and on a first-line treatment regimen.

Materials and Methods

Study Participants and Ethical Approval

The study was performed in the biochemistry section of PD Hinduja Hospital and Medical Research Centre with a total of 125 patients (57 males and 68 females) suffering from drug-susceptible TB and on first-line treatment of rifampicin and isoniazid for at least 7 days of therapy. The study protocol was approved by the Institutional Review Board, with written informed consents obtained from all patients prior to enrolment.

The patients were treated with an oral and standard dose of drugs. About 4 mL blood samples (EDTA tube for rifampicin and heparin tube for isoniazid) were collected 2 hours postdose administration (peak concentrations as indicated as C_{max}). The buffy coat from EDTA tubes was used for DNA extraction by the modified Miller et al. method.[8] Plasma was separated, and drug concentrations were analyzed within 1 week to avoid any degradation. Therapeutic ranges for rifampicin were 8–24 mg/L, while those for isoniazid were 3–6 mg/L, as reported in the literature for peak drug concentrations.[2,3]

Drug Level Estimation

The rifampicin and isoniazid concentrations were quantified by an in-house standardized HPLC method. Rifampicin powder (CAS No-13292-46-1) and isoniazid powder (CAS

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No-54-85-3) HPLC grade were obtained from Sigma (St. Louis, MO, USA). The analytical HPLC instrumentation included a Waters 1525 multisolvent delivery system pump and Waters 2487 variable wavelength UV-Vis detector with Empower Version 2 software. MilliQ water was obtained from MilliQ Elix 10® water purification system.

***Rifampicin*:** The separation was performed on a Waters C18 column with a C18 guard column in an isocratic mode at a 1 mL/min flow rate. The mobile phase consisted of 0.05 M dipotassium hydrogen phosphate: acetonitrile in a ratio of 53:47 at pH 4.6, which was adjusted using orthophosphoric acid.[9] Matrix-based calibrators and controls were prepared fresh on the day of assay. A series of working standards with a concentration of 2, 10, 20, 30, and 40 mg/L and the tri-level controls with a concentration of 5, 15, and 35 mg/L were prepared, and protein was precipitated with acetonitrile. The mixture was vortex-mixed and centrifuged at 12,500 rpm for 10 minutes, and 20 µL of the filtered supernatant was injected into the system with UV detection at 340 nm. The method linearity was optimized at 0.2–100 mg/L with the lower limit of detection at 0.1 mg/L. The interday and intraday precision of the controls were within 20% CV. The method is robust, sensitive, and specific for rifampicin.

Isoniazid : The separation was performed on a Waters C8 column with a C8 guard column in an isocratic mode at a 1 mL/min flow rate. The mobile phase consisted of water: methanol in a ratio of 80:20 with 2.5 mL of tetrabutyl ammonium hydroxide and 0.7 mL of 70% perchloric acid. Freshly prepared matrix-based calibrators of concentrations 0.5, 5, 10, 15, and 20 mg/L and tri-level controls of 1, 4, and 17 mg/L were prepared. Plasma proteins were precipitated with para-hydroxybenzaldehyde and trifluoroacetic acid, vortex-mixed, and centrifuged at 14100 rpm for 5 minutes. 20 µL of the filtered supernatant was injected into the system, which passed through the column and a UV detector at 267 nm.[10] The method had a linearity of 0.3–100 mg/L with the lower limit of detection at 0.2 mg/L. The interday and intraday precision of the controls were within 20% CV. The method is robust, sensitive, and specific for isoniazid.

Both the method was validated for all the bioanalytical parameters with an acceptable ± 20% coefficient of variation (CV) for QC samples.[11]

NAT2 Acetylator Status

The *NAT2* acetylator was determined by conventional PCR for the following six SNPs: rs1041983, rs1801280, rs1799929, rs1977730, rs1208, and rs1799931. A web-based server, NAT2PRED, which implements a supervised pattern recognition method to infer NAT2 phenotype from SNPs, was used for the interpretation of acetylator status.[12]

Clinical Outcome

A detailed clinical follow-up was recorded from each patient after 2 months or more of the blood collection to assess their clinical outcome. Compliance was recorded as self-reported or with patient interviews during their clinical follow-up with the treating clinician. As per guidelines from Virginia, patients were regarded as "clinically improved" if they showed an improvement in TB symptoms (i.e., reduced cough/sputum production, no fever, and weight gain), bacteriological reports (TB culture negative), or improvement in imaging reports. Patients with a slow response or no improvement in any of the above factors were classified as "partial responders".[3,13]

Statistical Analysis

Normality testing of the data was performed using the Shapiro–Wilk test. The variables are expressed as mean ± SD when normally distributed and median (range) in all other cases. Statistical analyses (*t*-test and Mann–Whitney test as applicable) and multiple regression analysis for all confounding factors, such as age, weight, dose, etc., were performed using Medcalc version 15.4 software. A p-value <0.05 was considered for statistical significance.

Results

Demographic Details

A total of 125 patients, with a median age of 28 (range, 12–68) years and a median weight of 57 (25–99) kg, were enrolled in the study. Demographic and clinical details of all patients are mentioned in Table 1. None of our patients were suffering from any comorbid conditions such as HIV, while three patients were diabetic.

Table 1: Demographic and clinical details of patients (n = 125)

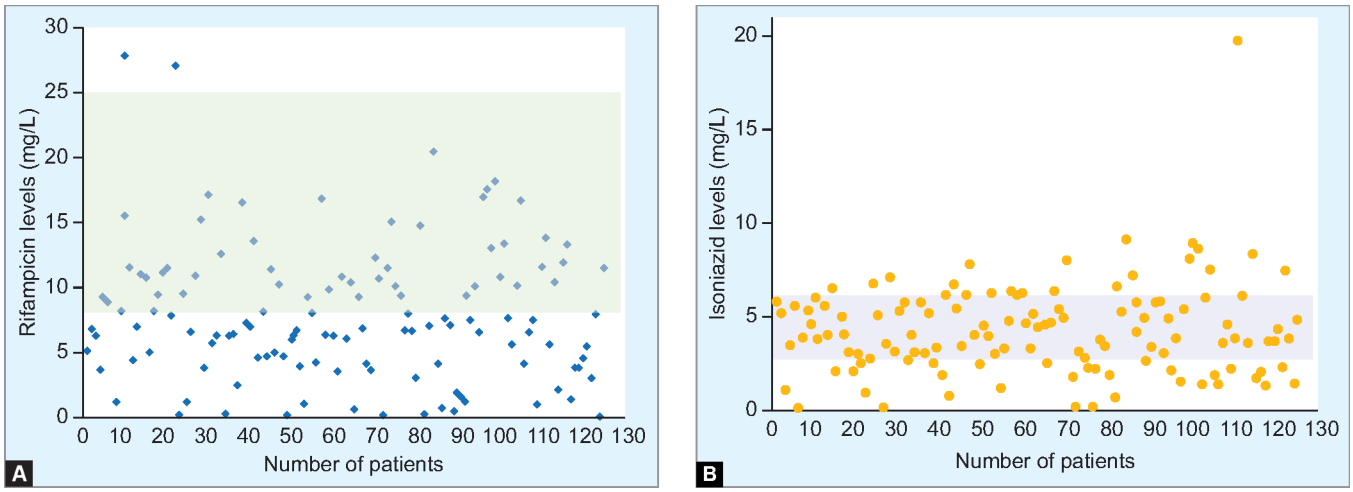
Patient characteristics	
Age in years, median (range)	28 (12–68)
Gender (Female: Male)	68:57
Weight in kg, median (range)	57.0 (25–99)
Site of TB, *n* (%)	
Pulmonary	54 (43)
Glandular	30 (24)
Spine	12 (10)
Other extra-pulmonary sites	29 (23)
Type of therapy*, *n*	
Combination tablets	88 (70)
Single tablets	37 (30)
Medication in mg/day, median (range)	
Rifampicin dose	600 (300–1050)
Isoniazid dose	300 (125–600)
Medication in mg/kg body weight, mean ± SD	
Rifampicin dose	9.91 ± 1.79
Isoniazid dose	5.48 ± 1.31
Rifampicin levels in mg/L, median (range)	7.1 (0.1–27.3)
Isoniazid levels in mg/L, median (range)	4.1 (0.2–19.8)

*Types of therapy refer to either tablets given in Rifampicin and Isoniazid in a single formulation as combination tablets or two different formulations of each drug as single tablets

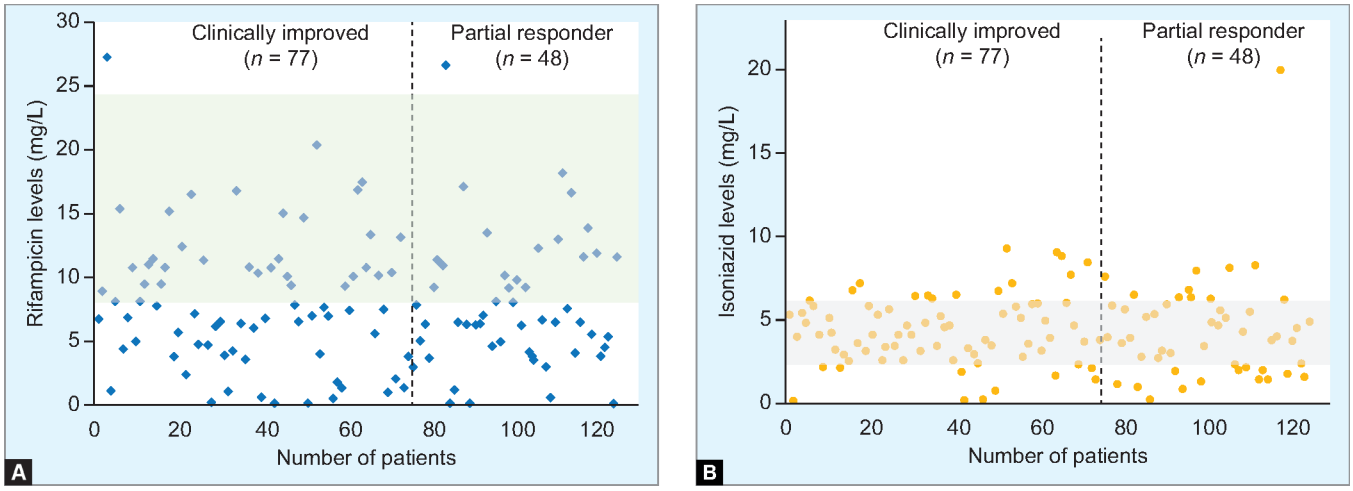
Plasma Rifampicin and Isoniazid Concentrations

Among the study group, on a mean rifampicin dose of 9.91 ± 1.79 mg/kg, a median plasma rifampicin level of 7.1 mg/L was observed. The majority of patients (n = 70; 56%) had peak plasma rifampicin concentrations in the subtherapeutic range, while 53 patients (42%) had therapeutic concentrations and 2 patients (2%) were in the toxic range (Fig. 1A).

The patients were on a mean isoniazid dose of 5.48 ± 1.31 mg/kg and had a median plasma level of 4.1 mg/L. Only 51% (n = 64) of the study group had isoniazid concentrations in the therapeutic range, while the remaining 49% (n = 61) had abnormal isoniazid concentrations. Among these, about 28% (n = 35) had subtherapeutic isoniazid concentrations, while 21% (n = 26) were in the toxic range for isoniazid (Fig. 1B).



Figs 1A and B: Scatter plot representing plasma drug concentrations observed in the study group (*n* = 125): (A) Rifampicin concentrations; (B) Isoniazid concentrations. The shaded boxes represent the therapeutic range of the respective drug



Figs 2A and B: Scatter plots representing plasma drug concentrations observed in the study group (*n* = 125) with clinical outcome: (A) Rifampicin concentrations; (B) Isoniazid concentrations. The shaded boxes represent the therapeutic range of the respective drug

Plasma Drug Concentrations and Clinical Outcome

A detailed clinical follow-up was recorded for all patients after 2 or more months of blood collection. No patient had died during the therapy or follow-up. Among the study group, only 62% of patients (*n* = 77/125) responded well clinically with improving signs and symptoms of TB, while the remaining 38% patients (*n* = 48/125) did not improve or had consistent/worsen conditions. These patients were classified as partial/slow responders to therapy. Figure 2 represents the clinical outcome of all patients with their respective rifampicin and isoniazid concentrations. Six patients (5%) had developed resistance to rifampicin during the course of treatment.

In the entire study group, only 18% of patients (*n* = 23/125) had both the drugs in therapeutic range, while the remaining 82% patients (*n* = 102/125) had either one or both the drug concentrations in the subtherapeutic range or had abnormal normal values.

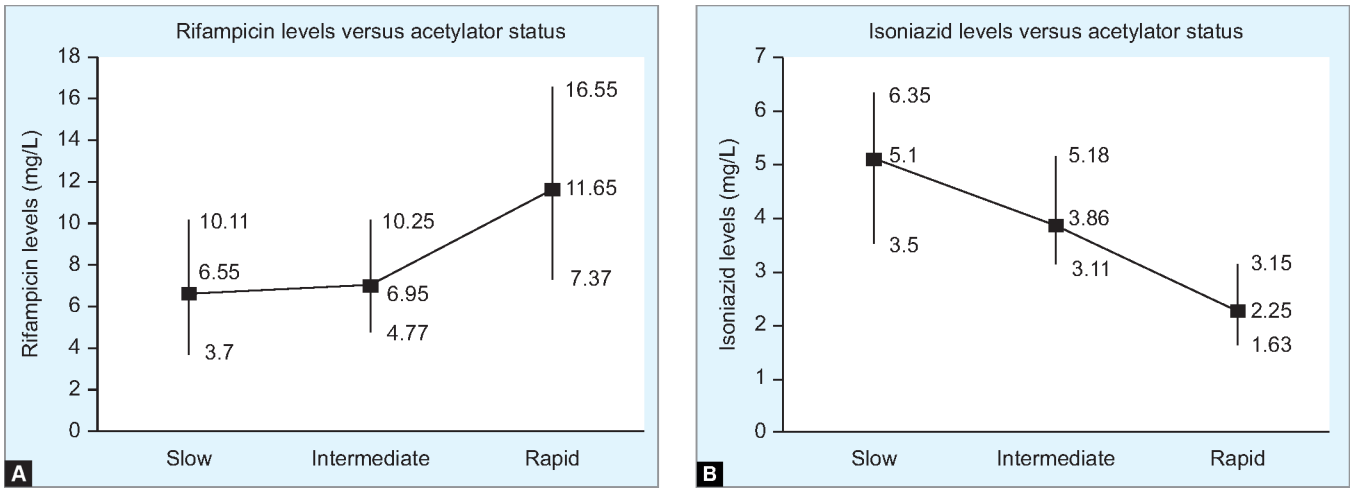
NAT2 Acetylator Status

Based on the genotypes observed from conventional PCR, the acetylator status was determined using the NAT2PRED software. Among the study group, slow acetylators (*n* = 55; 44%) were the most common, followed by intermediate acetylators (*n* = 50; 40%), and rapid acetylators being the least (*n* = 20; 16%). NAT2 acetylator status influences metabolism of isoniazid, thus influencing plasma isoniazid concentrations in the body. Figure 3 shows the trend of plasma concentrations among the acetylator phenotypes. Rapid acetylators had significantly lower isoniazid concentrations as compared to intermediate ($p = 0.01$) and slow acetylators ($p = 0.004$) (Fig. 3B). Whilst on comparing plasma rifampicin concentrations were significantly lower in slow ($p = 0.01$) or intermediate ($p = 0.009$) acetylators as compared to rapid acetylators (Fig. 3A).

The clinical outcome or plasma concentrations may be influenced by several factors such as age, dose, sex, severity and extent of disease, treatment duration, or the immune function of the patient. No statistical significance was seen on multiple regression analyses of confounding factors like age, sex, body mass index, dose in mg/kg, or duration with plasma rifampicin or isoniazid concentrations.

Discussion

An important finding of this study is that abnormal drug concentrations of rifampicin and isoniazid are common and a major concern. We did observe the majority of patients having low rifampicin concentrations, while isoniazid concentrations were varied between low to normal and supratherapeutic (toxic) concentrations. Interpatient variability is a major concern, warranting the need for therapeutic drug monitoring. This is



Figs 3A and B: Correlation of NAT2 acetylator status with (A) plasma rifampicin concentrations and (B) plasma isoniazid levels among slow, intermediate, and rapid acetylators

consistent with our previously reported findings in a smaller sample size study group.[14] In the present study, too, wide interindividual variability in plasma drug concentrations is seen, with about 56% of patients having subtherapeutic rifampicin concentrations, while 28% with low isoniazid concentrations and 21% with above normal isoniazid concentrations. Our results are also in keeping with a number of studies reporting more than 2–48% patients in the subtherapeutic range for isoniazid and 5–92% for rifampicin.[15–18] These variations in drug concentrations could be attributed to several other factors, such as different doses, drug formulations, comorbid conditions, age, weight, sex, or gastrointestinal abnormalities.[18]

In the present study, peak concentrations were estimated at 2 hours postdose administration for plasma rifampicin and isoniazid concentrations. Literature reports of delayed or malabsorption of rifampicin have doubted the 2-hour as a peak level. In such instances, an additional 6-hour level can help distinguish such patients with poor gastric emptying.[2,3,7] To rule out this possibility, in our laboratory, we have performed a 2-hour and a 6-hour plasma rifampicin level estimation in a small subset of patients wherein no cases of delayed or malabsorption were observed (data not shown). Thus, a 2-hour drug level was an appropriate time point to judge the peak rifampicin level.[14] However, if the patient is suspected of a delayed response, an additional 6-hour level could be taken for information on the rate and completeness of absorption.[7,18]

Several studies have linked low concentrations of anti-tuberculosis drugs to treatment failure, delayed diagnosis or therapy, poor adherence, development of multidrug resistance, HIV co-infection, and other comorbid conditions.[4,7,10,19,20] Patients without these risk factors are expected to respond well to the treatment. Patients who show no clinical or radiographic (or other imaging) improvement and continue to have sputum positive for *Mycobacterium tuberculosis* are classified as slow responders.[21,22] The present study observed the relation with plasma drug concentrations and the clinical outcome. About 62% of patients had improved clinically for symptoms of TB, while 38% were slow responders to standard treatment (partial responders). Drug resistance to rifampicin was seen in six patients (5%) despite receiving adequate doses (mg/kg body weight) and attaining therapeutic concentrations of either one or both the drugs. The extent and severity of disease, good compliance, balanced diet, and most importantly, the immune system of the patient play an important role in effective treatment and positive clinical outcome.[3,19,23] Clinical improvement seen in our patients with abnormal drug concentrations could be attributed to any of the above factors.

The data obtained in this study have important clinical implications. The observed wide variability in both rifampicin and isoniazid concentrations is a major concern. This study brings attention to certain points, such as attaining therapeutic drug concentrations may not be adequate to achieve a positive clinical outcome. Other factors marking symptoms of TB also should be closely monitored. Acetylator status strongly influences the metabolism of drugs thus affecting the plasma concentrations in the body.[24] Isoniazid metabolism is impacted by the activity of the polymorphic enzyme NAT2 influencing its elimination rate and possible development of toxic effects. These acetylation polymorphisms could be associated with inter-individual variability in plasma concentration and half-life of isoniazid.[25] Slow acetylators tend to have higher isoniazid concentrations as compared to intermediate and rapid acetylators. In our study, too, we observed slow acetylators had significantly high isoniazid concentrations. Similar findings have been reported in the South Indian population and other ethnic groups.[5,26,27] None of our patients reported hepatotoxicity despite a few patients having high isoniazid concentrations. However, dosage adjustments should be considered to prevent drug-induced liver injuries and to decrease the cost of managing adverse events, especially if patients tend to have above normal isoniazid concentrations.[28] Drug–drug interaction (DDI) is one common factor known to influence plasma concentrations. Rifampicin and isoniazid are also reported to interact with each other, thus reducing the bioavailability of rifampicin in presence of free isoniazid.[29,30] The primary mechanism of the DDI is not yet clear; however, it could be attributed to the excessive hydrazine formation from the hydrolase pathway. Most DDI are pharmacokinetic in nature thus affecting the bioavailability, absorption or metabolism of the drug. Under acidic conditions in solution, rifampicin undergoes hydrolysis to yield 3-formyl-rifamycin SV (3-FRSV) and 1-amino 4-methylpiperazine which is further aggravated in presence of isoniazid.[31] Thus slow acetylator who tend to retain isoniazid for longer durations, have a higher risk for having a decreased bioavailability of rifampicin and hence a poor clinical response. Rifampicin is a potent liver enzyme inducer while isoniazid is an enzyme inhibitor. Most DDI are due to enzyme inducing effect of rifampicin and the combination dosing can lead to synergistic

hepatotoxicity.[32] Fixed dose combinations can therefore be difficult to handle especially in a slow acetylator phenotype as the risk of reduced bioavailability of rifampicin is high in presence of prolonged exposure to isoniazid. Splitting doses can be beneficial with a monitored time gap to help rifampicin attain their peak level at 2 hours followed by isoniazid dose administration. Also, presence of other factors such as liver disease and age can further increase the risk of adverse effects and poor clinical response. One potential limitation is that the study was limited to 125 samples, and the results can be explored further in a larger sample size. Also, drug pharmacokinetics also include accounting for intra-individual variations which could not be evaluated within the scope of this study.

The correlation between NAT2 acetylator phenotype and rifampicin plasma concentrations remains inadequately studied. In our study, we have observed a strong correlation of plasma rifampicin concentrations with slow acetylators versus intermediate or rapid acetylators. For a majority of patients, the standard regimen of drug doses is adequate; however, it is important to improve the clinical condition in patients with abnormal plasma drug concentrations or vulnerable clinical conditions. On a case-by-case basis, assessment of drug concentrations is certainly helpful.

Conclusion

An abnormal plasma concentration of either of the two drugs was seen in more than half of the study group. Variation in drug concentrations can be attributed to several factors, and therapeutic drug monitoring will help optimize the drug doses needed in the treatment regimen. Treatment strategies based on the acetylator status will help clinicians adjust and prescribe separate or fixed dose combinations of dosages to achieve a better bioavailability and metabolism of both drugs. TDM can help identify patients at high risk of treatment failure or delayed response, enabling timely interventions to optimize treatment outcomes.

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Conflict of interest

All authors declare they have no conflict of interest.

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