Analysis of influencing factors on the plasma concentration of first-line anti-tuberculosis drugs-a single-center retrospective cohort study

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Background: The four most commonly used first-line anti-tuberculosis (TB) drugs in clinical practice are isoniazid (INH), rifampicin (RFP), ethambutol (EMB), and pyrazinamide (PZA). The plasma concentration of anti-TB drugs is an important factor influencing the effectiveness of TB treatment. Factors affecting blood concentration of antituberculosis drugs have not been elaborated clearly. The purpose of this study is to investigate the status of plasma concentration of anti-TB drugs, explore the factors influencing anti-TB drug plasma concentration, and guide the rational use of clinical drugs.

Methods: This is a single-center retrospective cohort study. Patients with pulmonary TB received first-line anti-TB drugs in the 309th Hospital of the PLA from June 2014 to September 2018 were investigated. The primary endpoint was factors affecting the anti-tuberculosis drug plasma concentration which were determined by high performance liquid chromatography-mass spectrometry. The factors influencing plasma concentration analyzed by the multiple linear regression model.

Results: A total of 205 patients were included in the study. The rates of patients with substandard 2-hour plasma concentrations of INH, RFP, EMB, and PZA were 45.8%, 54.4%, 37.7%, and 52.9%, respectively. Intravenous administration of INH (P<0.001) significantly increased plasma concentrations compared with oral administration, and its plasma concentration was negatively correlated with blood uric acid levels (P=0.001). RFP 2-hour plasma concentrations were positively correlated with serum albumin levels (P=0.04). EMB 2-hour plasma concentrations were positively correlated with age (P=0.01), dose (P<0.001), and serum creatinine levels (P<0.001). PZA 2-hour plasma concentrations were positively correlated with dose (P<0.001) and total bilirubin levels (P<0.001), and were negatively correlated with blood urea nitrogen levels (P=0.001).

Conclusions: Age, gender, dose, intravenous administration, retreatment, blood uric acid level, serum albumin level, serum creatinine level, total bilirubin level, and blood urea nitrogen level were independent influencing factors of anti-TB drug plasma concentration. During anti-TB treatment, plasma concentration monitoring is essential and helpful to optimize the drug dose and carry out individualized treatment regimen.

Keywords: Anti-tuberculosis drugs; plasma concentration; pulmonary tuberculosis; analysis of influencing factors

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Introduction

According to a report from the World Health Organization (WHO), the annual incidence of tuberculosis (TB) is about 10 million worldwide and China accounts for 9% of all the cases globally. Although the total number of deaths from TB is decreasing globally, it remains one of the top 10 causes of death worldwide (1). Isoniazid (INH), rifampicin (RFP), ethambutol (EMB), and pyrazinamide (PZA) are the most commonly used first-line anti-TB drugs in clinical practice (2). The efficacy of anti-TB drugs is influenced by several factors, including the metabolic status of the tubercle bacilli in the lesion(3), drug resistance, comorbidities (4), drug dose, and serum drug concentration (5). Substandard plasma concentration can lead to bacterial drug resistance (6), disease relapse, or treatment failure (7). It has been reported that about 46% of TB patients failed to achieve sufficient serum concentration of at least one anti-TB drug, and the factors that contribute to substandard blood levels include drug dose, acetyl INH/INH ratio, and creatinine clearance (8). A small sample size (69 patients) (8), lack of multivariate analysis (only univariate analyses) (9,10) have been found in previous studies on the factors influencing the plasma concentration of anti-TB drugs. Factors affecting blood concentration of antituberculosis drugs have not been elaborated clearly.

The purpose of this study was to investigate the plasma concentration status of 4 first-line anti-TB drugs and to explore the determinants of anti-TB drug plasma concentration through multiple linear regression analysis, with an aim to guide rational clinical use, optimize individual patient doses, reduce the drug resistance of anti-TB drugs, and improve the cure rate of TB. We present the following article in accordance with the STROBE reporting checklist (11) (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1341/rc).

Methods

Study design

This single-center retrospective cohort study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) (12). Patient informed consent was waived due to the retrospective nature of the study, and the study was approved by the Medical Ethics Committee of the 309th Hospital of the Chinese People's Liberation Army (PLA). (No. 201607110904). The Medical Support Center of the PLA General Hospital serves all medical centers affiliated, including 309 Hospital.

Study participants

Patients with pulmonary TB admitted to the 309th Hospital of the PLA from June 2014 to September 2018 were retrospectively studied. The inclusion criteria were as follows: (I) ≥16 years; (II) received 4 first-line anti-TB drugs (INH, RFP, EMB, PZA); and (III) taking drugs for at least 5 days before plasma concentration measurement. The exclusion criteria were as follows (met at least one): (I) human immunodeficiency virus (HIV) infection; (II) chronic gastrointestinal disease; (III) taken a compound preparation; (IV) frequent vomiting; or (V) missing important data.

Data collection

Patient demographic characteristics and clinical data were collected from the hospital electronic medical record system. The data collected included: patient demographic characteristics, admission diagnosis, comorbidities (diabetes, abnormal liver function, hyperuricemia, renal insufficiency), primary/recurrent treatment, nutritional status, major symptoms, drug dose, route of administration, plasma concentration at 2 hours after drug administration, biochemical parameters such as liver and kidney function before drug administration, and the use of drugs metabolized through the liver and renal.

The inclusion of the potential factors associated with anti-tuberculosis plasma concentration was based on clinical relevance and previous reports (8-10).

Study endpoints and definitions

The primary study endpoint was factors affecting the plasma concentration of anti-TB drugs. The secondary endpoint was the qualified rate of plasma concentration. All anti-TB drugs were administered on an empty stomach. Venous blood was drawn from patients 2 hours after dosing. Afterwards, the peak concentrations of the 4 drugs (INH, RMP, EMB, and PZA) were measured (13). Evidence from a previous study suggested that INH, RMP, EMB, and PZA reach peak serum concentrations approximately 2 hours after ingestion (13). According to the reference range recommended by the 2021 Expert Consensus on the Clinical Use of Drug Monitoring for Anti-TB Drug Therapy (14), low 2-hour blood levels are defined as follows: INH <3 µg/mL; RMP <8 µg/mL; PZA <20 µg/mL; and EMB <2 µg/mL.

Table 1 Mass spectrometry parameters of 4 anti-TB drugs

Name of drug	Retention time (tR/min)	Ion pair of MRM (m/z)	Optimized declustering potential in positive ion mode declustering potential (DP)	Focus potential entrance potential (EP)	Collision potential collision energy (CE)	Collision cell exit potential (CXP)
INH	2.2	138.0→121.0	44.0	4	22	3
REP	8.4	823.2→791.2	62.0	7	29	7
PZA	4.0	124.1→79.0	37.0	4	23	3
EMB	1.2	205.2→116.1	38.5	4	21	3

TB, tuberculosis; MRM, multiple reaction monitoring; INH, isoniazid; RFP, rifampicin; PZA, pyrazinamide; EMB, ethambutol.

Plasma concentration assay

The samples were analyzed by high performance liquid chromatography-mass spectrometry (15). The chromatographic conditions were as follows: an Agilent Poroshell 120SB C_{18} column (4.6 mm × 50 mm, 2.7 μm) was used as the analytical column, and a ZORBAX SB C18 column (2.1 mm × 12.5 mm, 5 μm) was used as the guard column with 0.2% methanol-0.2% acetic acid solution as the mobile phase, and gradient elution was conducted. The concentration of methanol was set at the following time settings: 0.01 min, 5%; 2.50 min, 17%; 5.00 min, 35%; 6.00 min, 70%; 6.01 min, 80%; 9.00 min, 90%; 9.01 min, 5%; 12.00 min, 5%. The flow rate was 0.5 mL·min^{-1} and the injected volume was 5 μL. The detection was performed by positive multiple reaction monitoring (MRM) with electrospray ionization (ESI). INH's m/z 138.0→121.0, RFP's m/z 823.2→791.2, EMB's m/z 205.2→116.1, PZA's m/z 124.1→79.0, and levofloxacin's m/z 823.2→791.2. The mass spectrometry conditions were as follows: ion source: ion spray of ESI (ion spray); ion spray voltage (IS): 5,000 V; temperature of ion source (TEM): 350 ℃; in-source gas 1 (GS1, N_2): 25 psi; in-source gas 2 (GS1, N_2): 45 psi; curtain gas pressure (Cur Gas): 30 psi. Positive ion mode detection, MRM scanning mode, and other mass spectrometry parameters are shown in *Table 1*.

Statistical analysis

Continuous variables conforming to a normal distribution were expressed as mean ± standard deviation (mean ± SD), otherwise median (IQR) was used to express non-normally distributed variables, and comparisons between two groups were performed by the independent samples *t*-test and non-parametric Mann-Whitney U rank sum test, respectively. Categorical variables were expressed as percentages, and comparisons among groups were performed by the Chi-square test or Fisher's exact probability test. The missing data were handled by mean imputation method. The comparisons were conducted between groups with different gender, whether or not initial therapy, and whether or not with comorbidities.

First, a univariate analysis was performed. Subsequently, multivariate analysis was conducted by using a multiple linear regression model (16). Multicollinearity test was performed before variables were included into the model (17), and variables with variance inflation factor (VIF) greater than 10 were excluded. Then, the variables were screened by stepwise selection, and the variables included in the final model were independent factors. A P value (two side) <0.05 was considered as statistically significant. All statistical analyses were performed by MedCalc Statistical Software version 19.0.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019).

Results

Baseline characteristics of the included patients

A total of 305 patients with pulmonary TB were treated with 4 first-line anti-TB drugs during the study period. Patients were screened in accordance with the inclusion and exclusion criteria, and 205 patients were finally enrolled (*Figure 1*). The median age of the included patients was 26 (IQR, 21–38.5) years, with 151 (73.7%) males and 31 patients (15.1%) on repeat treatment. The doses taken by the included patients are summarized in *Table 1*. The EMB median dose of 1 (IQR, 0.75–1) g did not reach the target dose range, while the median doses of the remaining 3 drugs were in the target range. The substandard rates of patients with 2-hour plasma concentrations for INH, rifampin, EMB, and PZA were 45.8%, 54.4%, 37.7%, and 52.9%, respectively. The baseline characteristics of the included patients are shown in *Table 2*.
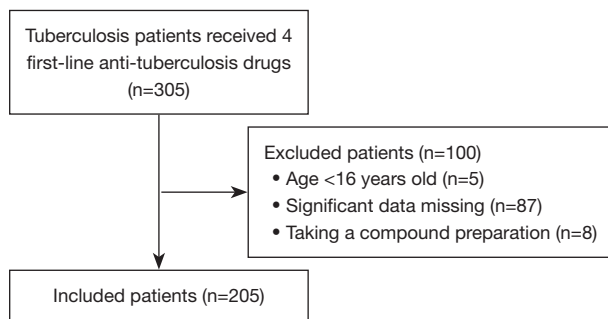
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Figure 1 The patients' inclusion flow chart.

Table 2 Demographic and clinical characteristics of the included patients

Characteristics	Included patients (n=205)
Age (years)	26 (21–38.5)
Male, n (%)	151 (73.7)
Retreatment, n (%)	31 (15.1)
With comorbidities, n (%)	67 (32.7)
Drug dosage	
INH (g/d)	0.4 (0.3–0.4)
RFP (g/d)	0.6 (0.45–0.6)
EMB (g/d)	1 (0.75–1)
PZA (g/d)	1.5 (1.5–1.5)
Biochemical indicators before drug administration	
AST (U/L)	16.8 (12.9–21.8)
ALT (U/L)	15.3 (9.9–21.9)
ALB (g/L)	39.2 (34.9–42.9)
Tb (µmol/L)	10.8 (8.2–16.4)
Cr (µmol/L)	66.3 (51–74.8)
BUN (mmol/L)	4.1 (3.3–5.4)
UA (µmol/L)	355 [274–444]
2-hour plasma concentration	
INH (µg/mL)	3.15 (2.03–4.29)
RFP (µg/mL)	7.66±4.93
EMB (µg/mL)	2.21 (1.56–3.21)
PZA (µg/mL)	19.64±9.14

Data are present as n (%)/median (IQR). INH, isoniazid; RFP, rifampicin; EMB, ethambutol; PZA, pyrazinamide; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; Tb, total bilirubin; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid.

Two-hour serum concentrations of anti-TB drugs and influencing factors

Isoniazid (INH)

The median plasma concentration of INH was 3.15 µg/mL (IQR, 2.03–4.29 µg/mL). The dose (P=0.002) and pre-dose blood uric acid level (P=0.007) were significantly associated with the 2-hour plasma concentrations of INH (*Table 3*) in the univariate analysis. Multivariate analysis demonstrated that intravenous administration (P<0.001) significantly increased plasma concentrations compared with oral administration. Plasma concentrations were negatively correlated with blood uric acid levels (P=0.0012), and the plasma concentrations of INH decreased by 0.002528 µg/mL for every 1 µmol/L increase in uric acid (*Table 4*).

Rifampicin (RFP)

The mean plasma concentration of RFP was 7.66±4.93 µg/mL. Serum albumin levels (P=0.04) were significantly correlated with RFP plasma concentrations in the univariate analysis (*Table 3*). Multivariate analysis demonstrated that 2-hour plasma concentrations of RFP were positively correlated with serum albumin levels (P=0.043), for which plasma concentration of RFP increased 0.09465 µg/mL for every 1 g/L albumin increase (*Table 4*).

Ethambutol (EMB)

The median plasma concentration of EMB was 2.21 µg/mL (IQR, 1.56–3.21 µg/mL). Age (P=0.002), dose (P=0.002), aspartate transaminase (AST) (P=0.03), serum creatinine (P<0.001), and urea nitrogen (P=0.01) were significantly associated with the plasma concentrations of EMB in the univariate analysis (*Table 3*). The results of multivariate analysis suggested that the 2-hour plasma concentrations of EMB were positively correlated with age (P=0.017), dose (P<0.001), and serum creatinine level (P<0.001). The plasma concentration increased by 1.468 µg/mL for each 1 g increase in dose. Serum creatinine increased by 0.001485 µg/mL for each 1 µmol/L increase in plasma concentration (*Table 4*).

Pyrazinamide (PZA)

The mean plasma concentration of PZA was 19.64±9.14 µg/mL. Gender (P=0.03), dose (P<0.001), urea nitrogen (P=0.006), and total bilirubin (P<0.001) were significantly associated with plasma concentrations of PZA in the univariate analysis (*Table 3*). The results of the multivariate analysis demonstrated that plasma concentrations in retreated

Table 3 Univariate analysis results

Drug	Variable	Constant	Coefficient/Mann-Whitney U	F-ratio/test statistic Z	P value
INH	Male		3,618	1.227	0.22
	Age	3.31	0.0439	0.238	0.62
	Retreatment		2,122	1.89	0.058
	Comorbidities		5,071	0.426	0.66
	Malnutrition level	3.41	0.046	0.045	0.83
	Drug dosage	1.79	4.35	9.642	0.002
	Intravenous administration		643.5	0.879	0.37
	ALT	3.40	0.0011	0.03	0.86
	AST	3.42	0.0001567	0.001828	0.96
	ALB	3.86	−0.01119	0.455	0.50
	Cr	3.45	−0.0001978	0.1242	0.72
	BUN	3.51	−0.01159	0.8325	0.36
	UA	4.27	−0.002144	7.2002	0.007
	Tb	3.25	0.01264	0.7691	0.38
RFP	Male		2,697.50	1.394	0.16
	Age	7.18	0.1987	0.4695	0.49
	Retreatment		1,337	0.577	0.56
	Comorbidities		3,150	1.606	0.10
	Malnutrition level	7.95	−0.9621	2.523	0.11
	Drug dosage	5.35	4.3433	0.9586	0.32
	Intravenous administration		1,072	0.481	0.63
	ALT	7.24	0.0239	0.5537	0.45
	AST	7.40	0.01412	0.1296	0.71
	ALB	3.92	0.09465	4.154	0.04
	Cr	7.96	−0.003767	1.6558	0.19
	BUN	7.74	−0.01512	0.07638	0.78
	UA	8.74	−0.002887	1.4583	0.22
	Tb	8.23	−0.04011	1.1820	0.27

Table 3 (*continued*)

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Table 3 (continued)

Drug	Variable	Constant	Coefficient/Mann-Whitney U	F-ratio/test statistic Z	P value
EMB	Male		5,079.00	0.929	0.35
	Age	2.00	0.2034	9.7893	0.002
	Retreatment		3,469.5	1.307	0.19
	Comorbidities		6,292	1.018	0.3
	Malnutrition level	2.53	−0.03567	0.04921	0.82
	Drug dosage	1.30	1.3311	9.3394	0.002
	ALT	2.74	−0.01218	3.1469	0.07
	AST	2.88	−0.01888	4.3411	0.03
	ALB	3.36	−0.02136	2.8786	0.09
	Cr	2.33	0.001587	14.2467	<0.001
	BUN	2.36	0.02381	5.7296	0.01
	UA	2.39	0.0003420	0.3202	0.57
	Tb	2.4835	0.003170	0.09202	0.76
PZA	Male		2,984	2.096	0.03
	Age	18.99	0.2633	0.3233	0.57
	Retreatment		2,105.50	1.771	0.07
	Comorbidities		4,844.00	0.0974	0.92
	Malnutrition level	20.01	−1.2029	1.2855	0.25
	Drug dosage	1.84	12.4745	16.1062	<0.001
	ALT	19.44	0.01134	0.05241	0.81
	AST	19.87	−0.01325	0.04420	0.83
	ALB	18.89	0.01883	0.04160	0.83
	Cr	20.19	−0.004356	2.7130	0.10
	BUN	20.81	−0.1673	7.5994	0.006
	UA	22.15	−0.006429	2.6766	0.10
	Tb	16.04	0.2712	12.6616	<0.001

INH, isoniazid; RFP, rifampicin; EMB, ethambutol; PZA, pyrazinamide; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; Tb, total bilirubin; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid.

patients (P=0.0387) and male patients (P=0.0088) were significantly lower than in primary patients and female patients. PZA 2-hour plasma concentrations were positively correlated with dose (P<0.001) and total bilirubin levels (P<0.001). The plasma concentration increased by 15.1382 μg/mL for every 1 g dose increase, and the plasma concentration increased by 0.2535 μg/mL for every 1 μmol/L increase in total bilirubin level. The 2-hour plasma concentrations of PZA were negatively correlated

with blood urea nitrogen levels (P=0.0013), for which the plasma concentration decreased by 0.1818 μg/mL for every 1 mmol/L increase in urea nitrogen level (*Table 4*).

Discussion

In this study, 205 patients with pulmonary TB treated with first-line anti-TB drugs were included, and the relationships between patient demographic characteristics and major

Table 4 Results of the multivariate analysis

Drug	Independent variables	Coefficient	Std. error	t*	P value	$r_{partial}$	$r_{semipartial}$	VIF
INH	Constant	4.3484						
	Intravenous administration	3.4495	0.7937	4.346	<0.001	0.3007	0.2953	1.015
	Uric acid	–0.002528	0.0007679	–3.292	0.0012	–0.2323	0.2237	1.015
RFP	Constant	3.9292						
	Albumin	0.09465	0.04644	2.038	0.0430	0.1510	0.1510	1.000
EMB	Constant	0.6107						
	Age	0.1538	0.06400	2.402	0.0170	0.1532	0.1453	1.053
	Dose	1.4680	0.4192	3.502	<0.001	0.2205	0.2118	1.008
	Creatinine	0.001485	0.0004190	3.544	<0.001	0.2230	0.2143	1.061
PZA	Constant	–0.7236						
	Dose	15.1382	2.9117	5.199	<0.001	0.3451	0.3242	1.025
	Retreatment	–3.4591	1.6620	–2.081	0.0387	–0.1456	0.1298	1.063
	Gender	–3.6363	1.3734	–2.648	0.0088	–0.1840	0.1651	1.027
	Urea nitrogen	–0.1818	0.05586	–3.256	0.0013	–0.2243	0.2030	1.029
	Total bilirubin	0.2535	0.07234	3.504	<0.001	0.2405	0.2185	1.069

*, the t value is used to judge the significance of each independent variable. If significant, it indicates that the variable has a significant impact on the model. INH, isoniazid; RFP, rifampicin; EMB, ethambutol; PZA, pyrazinamide; VIF, variance inflation factor.

biochemical indicators prior to drug administration and 2-hour plasma concentrations of anti-TB drugs were analyzed by a multiple linear regression model. The results showed that nearly half of the patients had a substandard plasma concentration of at least one drug. Univariate analysis revealed that age, gender, dose, and pre-dose levels of blood uric acid, serum albumin, AST, serum creatinine, urea nitrogen, and total bilirubin were significantly associated with anti-TB drug plasma concentrations. The multivariate analysis showed that age, gender, dose, intravenous administration, retreatment, blood uric acid level, serum albumin level, serum creatinine level, total bilirubin level, and blood urea nitrogen level were independent influencing factors for the plasma concentration of anti-TB drugs.

Relationship with previous studies

Rates of substandard blood concentration of anti-TB drugs

A 2016 meta-analysis (18) conducted a systematic review of 41 studies on 2-hour plasma concentrations of first-line anti-TB drugs, and the combined results showed that the substandard plasma concentration rates of INH, RFP, EMB, and PZA were 43% (95% CI: 32–55%), 67% (95% CI: 60–74%), 27% (95% CI: 17–38%), and 12% (95% CI: 7–19%), respectively. The results of our study are consistent with the above study. The above evidence suggests that substandard plasma concentration of first-line anti-TB drugs are currently not uncommon in clinical settings, which may lead to treatment failure, disease relapse, and drug resistance (13). Therefore, plasma concentration monitoring is essential to optimize the efficacy of anti-TB treatment (19).

Factors influencing the plasma concentration of anti-TB drugs

In a study conducted by Um *et al.* (8) in 2007, 69 patients with pulmonary TB were included and the factors influencing the 2-hour plasma concentration of anti-TB drugs were analyzed by multiple linear regression models. The results showed that drug dose was positively correlated with the plasma concentration, which is consistent with the results of the present study, indicating that the insufficient dose is an important factor that leads to substandard

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blood drug concentration. INH is generally administered orally. However, it can be administered intramuscularly or intravenously in critically ill patients (20). Our study found that intravenous administration significantly increased plasma concentrations compared with oral administration, which may be attributed to the effect of food and the first-pass effect of the liver (21). A large number of previous studies have shown that anti-TB drugs can affect uric acid metabolism in humans, which could result in elevated blood uric acid (22-24). The mechanisms of the interaction between blood uric acid and anti-TB drug metabolism need to be further investigated.

The study showed a positive correlation between RFP plasma concentrations and serum albumin levels, which may be attributed to the albumin binding rate of the drug. A previous study had reported an albumin binding rate of 70–80% for RFP (25), which was higher than other first-line anti-TB drugs. These results suggest that serum albumin is an important factor affecting the serum concentration of RFP, most likely because hypoalbuminemia leads to more clearance of unbound RFP by the liver (26). The relationship between albumin and RFP plasma concentrations in this study is consistent with a previous study (27), and is also in line with the results of a pharmacokinetic study for RFP (28). Future studies are warranted to focus on the relationship between serum total drug concentration and free drug concentration of RFP.

In a 2007 study by Um *et al.* (8), the 2-hour plasma concentration of EMB was significantly correlated with age, dose, and creatinine clearance. In 2019, the results of a study from China confirmed that the plasma concentration of EMB was significantly correlated with dose and creatinine clearance in the univariate and multivariate analyses (27). These results are consistent with our findings in the present study. EMB is a drug excreted through the kidneys, and its excretion decreases concurrently when creatinine clearance decreases, which may explain the negative correlation between its plasma concentration and creatinine clearance. A previous study had shown a positive correlation between the plasma concentration of EMB and age, which is consistent with the present study. This may be caused by metabolic and excretory capacity decreases with age, which can result in a slower decrease in plasma concentration (29). Therefore, the dose of EMB can be appropriately reduced in clinical practice to maintain plasma concentrations in the target range in patients with decreased creatinine clearance or in the elderly.

Two previous studies indicated that the 2-hour plasma concentrations of PZA were significantly higher in female patients than in male patients (8,27), which is consistent with the results of the present study. The mechanism of the discrepancy in plasma concentration of anti-tuberculosis drugs between genders needs further studies. The univariate and multivariate analyses in this study showed that plasma concentrations of PZA were positively correlated with dose and total serum bilirubin levels, which was consistent with previous report (29). When total bilirubin levels are elevated, it indicates that the liver is less able to clear both bilirubin and anti-TB drugs, so blood drug concentration levels may be increased concurrently. When liver function was impaired, PZA doses could be reduced appropriately. Blood urea nitrogen was elevated in response to impaired renal function, which was similar to serum creatinine, while 4–14% of PZA is excreted in urine in prototype form after administration (30), and this may account for the negative correlation between plasma concentrations of PZA and blood urea nitrogen.

Limitations of the study

First, this was a retrospective study. Therefore, there was an insufficient causal relationship between the included variables and drug concentrations, which should be validated in a prospective randomized controlled study. Second, the study excluded a large number of patients with missing data and only analyzed patients with complete data, which may lead to bias. Third, this study did not analyze the relationship between drug concentration, efficacy and patients prognosis, so future studies in this field should expand the endpoints. Fourth, a single time point of 2 hours was used for the determination of plasma concentrations in the study, which may miss the actual peak concentration. Lastly, this single-center study did not have sufficient generalizability of the findings.

Conclusions

In clinical practice, there is a high rate of substandard blood concentration of first-line anti-TB drugs at 2 h post-administration. The multivariate analysis showed that age, gender, dose, intravenous administration, retreatment, blood uric acid level, serum albumin level, serum creatinine level, total bilirubin level, and blood urea nitrogen level were independent influencing factors for anti-TB drug plasma concentration. During anti-TB treatment, plasma concentration monitoring is essential and helpful

to optimize the drug dose and carry out individualized treatment regimen, so as to effectively improve the therapeutic effect and reduce side effects.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1341/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1341/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1341/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of the 309th Hospital of the Chinese People's Liberation Army (PLA) (No. 201607110904) and individual consent for this retrospective analysis was waived.

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