RESEARCH PAPER

Anti-tuberculosis drug concentrations and treatment outcomes among HIV-infected patients with tuberculosis

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Abstract

Introduction: A poor response to tuberculosis (TB) treatment in patients with human immunodeficiency virus (HIV) infection can be related to inadequate adherence or low anti-tuberculosis drug concentrations in serum. Therapeutic drug monitoring (TDM) may be a useful tool to optimize drug therapy in these patients. This study aimed to determine serum concentrations of anti-TB drugs and treatment outcomes in HIV/TB patients.

Material and methods: Twenty-two HIV/TB infected patients were entered into the study. Venous blood was obtained 2 h after a daily dose of isoniazid (INH), rifampin (RIF), and pyrazinamide (PZA). Serum levels of anti-TB drugs were analyzed using high pressure liquid chromatography (HPLC) and compared with published normal ranges. Treatment outcomes were assessed according to World Health Organization (WHO) definitions.

Results: All the patients (median age: 35 years [range 27-57 years], median CD4+: 16 cells/mm^3 [range 5-444 cells/mm^3]) had low or very low serum concentrations of INH and RIF. Serum concentration of PZA was in the reference (normal) range in 5 (22.73%) patients. Of 22 patients, 4 were considered cured, 10 died on TB treatment or during follow-up, 5 relapsed after treatment, and 3 were lost to follow-up.

Conclussions: Low serum concentrations of anti-TB drugs and poor treatment outcomes are common among our patients. Further studies in a wider patient sample are required to explore the association between anti-TB drug concentrations and treatment outcomes.

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Key words: HIV, serum concentration, tuberculosis.

Introduction

Tuberculosis (TB) is the most common serious opportunistic infection and the cause of more than a quarter of deaths among patients with human immunodeficiency virus (HIV) infection [1, 2]. Concurrence treatment of TB and HIV is complex due to some factors such as alteration of drug kinetics, adverse drug reactions, and drug interactions [3, 4].

Oral anti-TB drugs are reliably absorbed by most TB patients without other illnesses. In contrast, TB patients suf-

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fering from HIV do not adequately absorb anti-TB drugs [5]. AIDS may impair gastrointestinal functions that consequently affect drug absorption and treatment outcome [6]. Recent studies reveal that low serum concentrations of rifampicin (RIF) and isoniazid (INH) are common among HIV-TB patients [4]. Gurumurthy *et al*. showed that the rate of urinary excretion of both RIF and INH was significantly lower in HIV-infected patients than in the TB group (non-HIV patients). This issue may lead to drug resistance and treatment failure [7].

The association between serum concentrations of anti-TB drugs and treatment response is still an open issue [4, 8]. It has been suggested that optimizing drug dose using therapeutic drug monitoring (TDM) may lead to a better clinical response than administrating a standard dose [9]. But TB treatment guidelines still consider TDM as an optional strategy because the best approach to implementing TDM on a pragmatic scale remains unknown [10, 11]. The role of TDM for treatment of HIV-TB patients is also controversial [4]. On the other hand, race is an important factor in pharmacokinetics of anti-TB drugs, and serum concentrations of these agents may vary considerably between individuals [12]. Therefore, the current study aimed to determine the blood levels of INH, RIF, and pyrazinamide (PZA) in patients with HIV-TB infection for the first time in our country. Also, the treatment outcomes (according to World Health Organization [WHO] definitions) were evaluated in our patients.

Material and methods

This observational study was carried out during two years in the National Research Institute of Tuberculosis and Lung Diseases, Masih Daneshvari Hospital. The Ethics Committee of the hospital approved the study.

HIV infected patients who were newly diagnosed with pulmonary TB were included in the study. They received daily doses of the standard regimen including INH (5 mg/kg), RIF (10 mg/kg), PZA (25 mg/kg) and ethambutol (15 mg/kg) [13]. Exclusion criteria were highly suspected TB infection of any organs/systems other than the lung, requiring TB treatment longer than 6 months, previously treated for a mycobacterial infection (TB or atypical mycobacterial infection, active or latent), multi-drug resistant tuberculosis (MDR-TB), GFR < 50 ml/min, and hypoalbuminemia.

Age, weight, administered drug dose, liver enzymes, serum creatinine, CD4+, and treatment outcomes were retrieved from the medical records. CD4+ T-cell count (a laboratory predictor of disease progression and survival) less than or equal to 100 cells/mm^3 indicates advance HIV disease and poor treatment outcome [4]. Treatment outcomes were categorized according to the following WHO definitions [14].

Cured: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion. Died: A TB patient who died for any reason before starting or during the course of treatment. Relapse: patients who were declared cured or treatment completed at the end of their most recent course of treatment, and then diagnosed with a recurrent episode of TB. Lost to follow-up: A TB patient for whom no treatment outcome is assigned. This includes cases transferred to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

Informed consent was obtained from all study participants. Blood samples were collected 2 h after drug administration (3-5 days after starting treatment) [6, 10, 15].

Plasma was separated and immediately frozen at –70°C. For injection into the HPLC system, the plasma proteins were precipitated using acetonitrile, zinc sulfate and ammonia. An Agilent HPLC 1200 series (Santa Clara, CA, US) with a C18 reversed-phase column (250.0 × 4.6 mm, 5 μm) and UV spectrophotometry were used. The mobile phase was composed of 75% water and 25% methanol. The UV detector was set at two wavelengths: 254 nm for detection of INH and PZA and 336 nm for detection of RIF. One hundred microliters of the clear supernatant was injected into the system and chromatographic separation was performed at room temperature. Calibration curves were constructed by preparing a series of concentrations of INH (0.5-20 μg/ml), RIF (1-40 μg/ml), and PZA (1.5-60 μg/ml). The concentrations of the samples were quantified by interpolating from the calibration curves.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 for Windows (SPSS, USA). We reported the descriptive results as means ± SD. Correlations between drugs plasma concentrations and age (years), weight (kg), administered drug dose (mg/kg), liver enzymes, serum creatinine, CD4+, and treatment outcomes were assessed using the Spearman rank correlation. Fisher's exact test was used for categorical variables. $P < 0.05$ was considered statistically significant.

Results

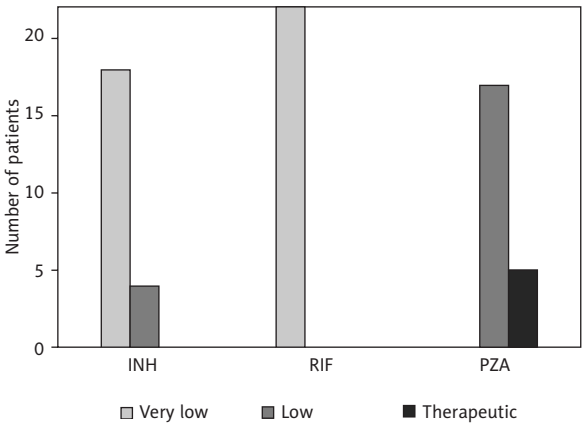
In total, 22 male patients were included in the study. The median age and mean body weight were 35 (range: 27-52) years and 61.18 ± 13.66 kg, respectively. Demographic and clinical characteristics of the patients are shown in Table 1.

Table 2 shows plasma concentrations and doses of INH, RIF and PZA, 2 hours after drug administration. All patients had low or very low serum concentrations of INH and RIF. Serum concentrations of PZA were in the reference (normal) range in 5 (22.73%) patients (Fig. 1). Table 3 shows concurrent drugs, comorbidities, and treatment outcomes of the patients. One patient with isoniazid resistance died and one patient with *Mycobacterium kansasii* infection relapsed after treatment. Other antibiogram results showed

Table 1. Demographic and clinical characteristics of the patients

HIV-TB patients, *n*	22
Patients treated with antiretroviral drugs	5
Age (years), median (range)	35 (27-57)
Body weight (kg), mean ± SD	61.18 ± 13.66
SGPT* (IU/l), median (range)	17 (5-56)
SGOT** (IU/l), median (range)	28.5 (16-81)
Bilirubin total (mg/dl), median (range)	0.4 (0.1-3.5)
Serum creatinine (mg/dl), median (range)	1.0 (0.7-6.4)
CD4+ lymphocyte count (cells/mm^3), median (range)	16 (2-444)
TB type, % (*n*)	
Pulmonary	90.9 (20)
Disseminated	4.54 (1)
Lymph node	4.54 (1)

*TB – tuberculosis, * – alanine transaminase, ** – aspartate transaminase*



INH – isoniazid, RIF – rifampin, PZA – pyrazinamide

Fig. 1. Number of patients with very low, low, and therapeutic levels of three anti-tuberculosis drugs

Table 2. Dose and plasma concentrations of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), 2 hours after drug administration

Patient number	INH			RIF			PZA		
	Dose (mg/day)	Serum level (µg/ml)	Status*	Dose (mg/day)	Serum level (µg/ml)	Status*	Dose (mg/day)	Serum level (µg/ml)	Status*
1	300	0.76	Very low	600	2.33	Very low	1000	23.89	Therapeutic
2	300	1.01	Low	600	3.80	Very low	1500	12.79	Low
3	300	0.92	Very low	600	4.68	Very low	1500	25.13	Therapeutic
4	250	0.81	Very low	450	3.13	Very low	1000	13.37	Low
5	300	0.93	Very low	600	3.84	Very low	1000	16.17	Low
6	250	1.05	Low	450	3.08	Very low	1000	9.63	Low
7	300	0.88	Very low	600	0.00	Very low	1000	16.59	Low
8	300	0.71	Very low	600	0.00	Very low	1000	12.13	Low
9	300	0.78	Very low	600	0.00	Very low	1000	17.64	Low
10	300	0.65	Very low	600	3.79	Very low	1500	22.46	Therapeutic
11	200	0.00	Very low	450	3.03	Very low	1000	12.23	Low
12	300	0.91	Very low	600	3.57	Very low	1000	15.33	Low
13	300	1.09	Low	600	0.00	Very low	1500	6.09	Low
14	250	0.76	Very low	450	0.00	Very low	1000	14.75	Low
15	250	0.00	Very low	450	2.43	Very low	1000	7.88	Low
16	300	0.86	Very low	600	0.00	Very low	1000	8.04	Low
17	300	0.68	Very low	600	2.64	Very low	1500	9.67	Low
18	250	0.84	Very low	450	2.79	Very low	1000	15.55	Low
19	300	0.56	Very low	600	2.39	Very low	1000	7.98	Low
20	300	0.93	Very low	600	0.00	Very low	1000	12.54	Low
21	300	1.25	Low	600	0.00	Very low	1000	23.52	Therapeutic
22	300	0.72	Very low	600	0.00	Very low	1000	25.77	Therapeutic

**INH serum level: therapeutic 3–6 µg/ml, low 1.5–3 µg/ml, very low < 1.5 µg/ml. RIF serum level: therapeutic 8–24 µg/ml, low 4–8 µg/ml, very low < 4 µg/ml. PZA serum level: therapeutic 20–50 µg/ml, low 10–20 µg/ml, very low < 10 µg/ml [8, 31]*

Table 3. Comorbidities, concurrent drugs (used for concurrent diseases), and treatment outcome of the 22 study patients

Patient number	Comorbidities	Concurrent drugs	Treatment outcome
1	Hepatitis C	Ofloxacin, cotrimoxazole	Died (hepatitis C and TB)
2	Hepatitis C, abdominal distension, paraplegia	Azithromycin, cotrimoxazole, fluconazole, warfarin	Died (opium overdose)
3	–	Lamivudine, stavudine, cotrimoxazole, efavirenz	Cured
4	Pneumocystis pneumonia	Zidovudine, lamivudine, efavirenz, cotrimoxazole, omeprazole	Relapse
5	Hepatitis C	Cotrimoxazole, hydroxyzine	Died*
6	Hepatitis C	Cotrimoxazole	Died (bradycardia and respiratory distress syndrome)
7	Immune reconstitution inflammatory syndrome, hepatitis C	Cotrimoxazole	Cured
8	Deep vein thrombosis, cellulitis, depression	Clonazepam	Cured
9	Hepatitis C	Cotrimoxazole	Cured
10	Mild pulmonary embolism, splenomegaly	Metoclopramide, cotrimoxazole, Acetaminophen, ranitidine, metronidazole, ceftazidime	Relapse, died
11	Diabetes mellitus, hepatitis C, lymphadenopathy, oral candidiasis	Salbutamol, ipratropium, beclomethasone, heparin, glibenclamide	Lost to follow-up
12	Pneumocystis pneumonia, hepatitis C, thrombocytopenia	Hydrocortisone, cotrimoxazole, calcium carbonate, vancomycin	Lost to follow-up
13	Generalized edema, bed sore, pericarditis	Cotrimoxazole, fluconazole, meropenem, vancomycin, ranitidine, heparin	Died (generalized edema, bed sore, pericarditis)
14	–	Cotrimoxazole, nystatin, ipratropium, fluconazole	Relapse
15	Hepatitis C, deep vein thrombosis, hydropneumothorax	Cotrimoxazole	Died*
16	Diabetes mellitus, necrotizing fasciitis, oral candidiasis, genital and optical herpes	Calcium carbonate, albumin, allopurinol, ceftriaxone, clindamycin, acyclovir	Died*
17	Pneumocystis pneumonia	Cotrimoxazole	Relapse
18	Hepatitis C	Cotrimoxazole, dextromethorphan, fluconazole	Relapse, died
19	–	Zidovudine, lamivudine, efavirenz, cotrimoxazole, hydroxyzine	Lost to follow-up
20	Hepatitis C	Zidovudine, lamivudine, efavirenz, omeprazole, metoclopramide	Relapse
21	Diabetes mellitus, hepatitis C, nocardiosis	Cotrimoxazole, omeprazole, enoxaparin, insulin, metformin	Relapse
22	Hepatitis C, drug-induced hepatotoxicity	Zidovudine, lamivudine, efavirenz, cotrimoxazole	Died (septicemia)

**There is no information about cause of death.*

that the mycobacterium isolates were sensitive to the antituberculosis medications.

No significant correlations were found between drug plasma concentrations and age, weight, administered drug dose, liver enzymes, serum creatinine, CD4+, or treatment outcomes.

Discussion

In our study, all patients had low serum concentrations of INH, and RIF and only 5 (22.73%) of 22 HIV patients were in the therapeutic range of PZA. Holland *et al.* found 86% of advanced HIV patients with significantly low serum

concentrations of INH, rifamycin, or both drugs [4]. In another study, by Babalik *et al*., anti-TB drug levels of TB patients were frequently below the clinically acceptable range. The patients with low serum drug levels were more likely to have comorbid illnesses (such as HIV), positive smear for a longer time, and lower serum albumin levels [9]. In contrast, Taylor *et al*. found no significant difference between HIV positive and negative patients regarding plasma concentrations of anti-TB drugs [6]. Malabsorption of anti-TB drugs has been reported among HIV-infected patients by measuring drug metabolites and D-xylose excreted in urine [7]. Gurumurthy *et al*. also reported that patients with advanced HIV infection, diarrhea, and evidence of cryptosporidial infection have malabsorption of anti-TB drugs [5]. Malabsorption and low serum concentrations of anti-TB agents may result in treatment failure, relapse, acquired drug resistance and death in non-HIV and HIV infected TB patients [16-22]. In our study, 10 patients died of TB or other complications such as septicemia, opium overdose, and organ dysfunction. Also, 5 patients relapsed with TB after successful treatment. One patient had diarrhea, while 86% had advanced HIV infection that may be associated with malabsorption.

Low serum concentration of anti-TB drugs among our patients could be a risk factor for developing MDR-TB. An increase in rates of MDR-TB and extensively drug resistant (XDR) TB, which are difficult to treat, has been reported by several studies [23]. It has been revealed that the prevalence of MDR-TB is being increased in previously treated Iranian and Afghan patients [24]. Treatment failure and the high number of MDR-TB patients are a danger for public health. TDM appears to be a useful strategy for optimizing pharmacotherapy [25] and overcoming the mentioned concerns related to low serum concentrations of anti-TB drugs [16, 17]. A number of practical and logistic challenges may limit the widespread use of TDM for TB treatment. Therefore, the role of TDM still remains an uncertain issue [10].

There are different opinions about the patients who benefit from a TDM implementation program [16, 20]. Based on the studies, TDM is unlikely to be of benefit for all patients receiving TB therapy [10, 26]. Since TDM is expensive in developing countries, routine measurement of drug concentrations is not accessible in all TB control centers. Identification of patients at risk of low drug concentration has been an important issue in order to prevent drug resistance. A recent study that retrospectively determined the association of serum drug levels with clinical outcomes could not recommend routine TDM for general TB patients [12]. On the other hand, increasing anti-TB drug doses for patients with advanced HIV infection was suggested as an economic strategy instead of TDM by Holland *et al*.

It has been shown that anti-TB drug concentrations are associated with malabsorption [7], alcohol use [16], age [27], sex [16, 27, 28], hypoalbuminemia [29], dose per kg of body weight [27], drug formulation [16, 27, 30], and acetylation polymorphism [17] in tuberculosis patients. However, a direct relationship between treatment response and low anti-TB levels could not be shown by a study that included 413 tuberculosis patients for seven years [12]. Holland *et al*. also did not find any correlation between low drug concentrations and demographic and clinical characteristics in 21 patients with TB and HIV infections [4].

The current study did not show significant correlations between drugs plasma concentrations and age, weight, administered drug dose, liver enzymes, serum creatinine, CD4+, and treatment outcomes. The small sample size and confounding factors (other complications) were our limitations. All patients with HIV-TB infection who met the inclusion criteria during the two years of the study period were examined for anti-TB drug concentrations. Similar studies also had limited numbers of these patients [4, 6, 9]. On the other hand, death (as an outcome) was described according to the WHO definition where a TB patient dies for any reason (other complications) before starting or during the treatment course. Further studies in a wider patient sample (multicenter and long-term studies) are recommended to determine the role of TDM for treatment of HIV-TB patients and the association between anti-TB drug concentrations and treatment outcomes.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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