ผลงานทางวิชาการ

เรื่อง

Low antitubercular drug levels in
newly infected normal hosts

โดย

นางเจียรนัย ขันติพงศ์
ศ.นพ.ชายชาญ โพธีรัตน์
ดร.โกวิทย์ นามบุญมี
ภก.สุนิสา ศิริ
นางพัฒนา โพธิ์แก้ว

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ABSTRACT

Background: Low antitubercular drug level is a risk factor for treatment failures. Antitubercular drug level determination has been suggested for complicated tuberculosis patients, but there has been interest in performing such studies in normal hosts.

Objective: To identify whether there are advantages of routine antitubercular drug level determination.

Materials and methods: We determined drug levels in 15 new normal host Thai tuberculosis patients by using published methods. All patients received the Directly Observed Treatment Short-course including pyrazinamide, rifampicin, and isoniazid.

Results: We started with 15 patients of whom 27% (4 patients) were mycobacteria smear-positive, 33% (5 patients) had low blood levels of pyrazinamide and 87% had low levels of rifampicin. The drug levels in the smear-positive group were lower than in the smear-negative group. All smear-positive patients had a rifampicin levels lower than the therapeutic range.

Conclusions: Antitubercular drug level determination has a potential to identify patients who may be at risk of poor treatment results.

Keywords: Anti-tubercular drug levels, standard short course regimen, Thailand

บทคัดย่อ

ความสำคัญและความเป็นมา

ระดับยารักษาวัณโรคในกระแสเลือดที่ต่ำกว่าปกติ เป็นปัจจัยเสี่ยงต่อการรักษาล้มเหลว ถึงแม้การตรวจวัดระดับยารักษาวัณโรคในกระแสเลือดถูกแนะนำให้ใช้สำหรับผู้ป่วยวัณโรคที่ซับซ้อน แต่การตรวจในผู้ป่วยปกติก็ยังมีความสำคัญ

วัตถุประสงค์

เพื่อแสดงให้เห็นถึงประโยชน์และความสำคัญของการนำวิธีตรวจวัดระดับยารักษาวัณโรคในเลือดมาใช้

กลุ่มตัวอย่างวิธีการศึกษา

คณะผู้วิจัยได้ทำการตรวจวัดระดับยารักษาวัณโรคในเลือดผู้ป่วยชาวไทย ๑๕ คนที่เป็นผู้ติดเชื้อวัณโรครายใหม่ด้วยวิธีที่ผ่านการรับรองและตีพิมพ์เผยแพร่ ผู้ป่วยทุกคนจะได้รับยารักษารักษาวัณโรคโดยวิธีการควบคุมการกินยา (DOT) ซึ่งประกอบด้วยยา pyrazinamide, rifampicin และ isoniazid

ผลการวิจัย

จากการวัดระดับยาในเลือดของผู้ป่วยติดเชื้อวัณโรครายใหม่ ๑๕ คน หลังจากได้รับยาครบสองดือน พบว่าผู้ป่วย ๔ คน (ร้อยละ ๒๗) ยังมีผลสเมียร์เสมหะบวก ผู้ป่วย ๕ คน (ร้อยละ ๓๓) มีระดับยา pyrazinamide ในเลือดต่ำ และ ร้อยละ ๘๗ มีระดับยา rifampicin ต่ำ ระดับยาในเลือดของกลุ่มผู้ป่วยที่มีผลเสมียร์เสมหะบวกน้อยกว่ากลุ่มสเมียร์เสมหะลบ กลุ่มผู้ป่วยที่มีสเมียร์เสมหะบวกจะมีระดับยา rifampicin ต่ำกว่าระดับยาในช่วงสำหรับการรักษา (therapeutic range)

สรุปผลการวิจัย

การวัดระดับยารักษาวัณโรคในกระแสเลือด มีความสำคัญต่อการบ่งชี้ผู้ป่วยที่มีความเสี่ยงต่อการรักษาที่ไม่สัมฤทธิ์ผล (poor treatment)

คำหัส : Anti-tubercular drug levels, standard short course regimen, Thailand

CONTENTS

		Page
ACKNOWLEDGMENTS		I
ABSTRACT (ENGLISH)		II
ABSTRACT (THAI)		III
CONTENTS		IV
LIST OF TABLES		V
CHAPTER I	INTRODUCTION	1
CHAPTER II	OBJECTIVE	1
CHAPTER III	LITERATURE REVIEW	2
CHAPTER IV	MATERIALS AND METHODS	6
CHAPTER V	RESULTS	8
CHAPTER VI	DISCUSSION & CONCLUSION	10
REFERENCES		11

LIST OF TABLES

Page

Table 1. Thailand category I tuberculosis drug regimen 9

Table 2. Mean comparisons of age, weight, TB drug level between men and women of new TB patients 9

Table 3. Relations between treatment drugs level and treatment result among new TB patients 9

Chapter 1

Introduction

Tuberculosis (TB) is a major public health problem worldwide causing 1.7 million deaths in 2010[1]. In order to manage TB, a Directly Observed Treatment Short-course (DOTS) combined with a standard regimen is used as an effective strategy [2]. The main purpose of DOTS is to confirm anti TB drug ingestion and sustain a serum therapeutic range of anti TB drugs. However, because of patient complication and HIV infection, some TB patients show low anti TB drug levels and developed multidrug resistance or delayed responses [3-7]. It has been suggested that blood levels of anti TB drugs should be determined during treatment [8].

Thailand was ranked 17 th on the list of 22 "high-burden" TB countries with 91,374 new TB cases occurring in 2005 [9]. The prevalence of multidrug resistance TB was 1% and 20% among new and previously treated patients [9]. DOTS has been applied in the treatment of TB patients since 1996, and countrywide DOTS coverage was achieved in 2001 [10,11]. However, the successful treatment rate for TB in Thailand was approximately 76% in 2003, slightly lower than the WHO target cure rate of 85% [10]. Causes of treatment failure are probably multiple and low anti TB drug levels are one concern [12,13]. This study was performed to determine advantages of performing serum anti TB drug level determinations in new immunologically normal host Thais.

Chapter 2

Objective

To identify whether there are advantages of routine anti-tubercular drug level determination

Chapter 3

Literature review

Tuberculosis[14]

Tuberculosis (TB) is caused by bacteria (Mycobacterium tuberculosis) that most often affect the lungs. Tuberculosis is curable and preventable.

TB is spread from person to person through the air. When people with lung TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected.

About one-quarter of the world's population has latent TB, which means people have been infected by TB bacteria but are not (yet) ill with the disease and cannot transmit the disease.

People infected with TB bacteria have a 5–15% lifetime risk of falling ill with TB. Persons with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a higher risk of falling ill.

When a person develops active TB disease, the symptoms (such as cough, fever, night sweats, or weight loss) may be mild for many months. This can lead to delays in seeking care, and results in transmission of the bacteria to others. People with active TB can infect 5–15 other people through close contact over the course of a year. Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die.

Who is most at risk TB?

Tuberculosis mostly involved adults in their most productive years. However, all age groups are at risk. Over 95% of cases and deaths are in developing countries.

People who are infected with HIV are 19 times more likely to develop active TB. The risk of active TB is also greater in persons suffering from other conditions that impair the immune system. People with under nutrition are 3 times more at risk. There were globally 2.3 million new TB cases in 2018 that were attributable to under nutrition.

Children, 1.1 million (0–14 years of age) fell ill with TB, and 230 000 children (including children with HIV associated TB) died from the disease in 2018.

Alcohol use disorder and tobacco smoking increase the risk of TB disease by a factor of 3.3 and 1.6, respectively. In 2018, 0.83 million new TB cases worldwide were attributable to alcohol use disorder and 0.86 million were attributable to smoking.

Global impact of TB

TB appear in every part of the world. In 2018, the largest number of new TB cases occurred in the South-East Asian region, with 44% of new cases, followed by the African region, with 24% of new cases and the Western Pacific with 18%.

In 2018, 87% of new TB cases raised in the 30 high TB burden countries. Eight countries accounted for two thirds of the new TB cases: India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh and South Africa.

Symptoms and diagnosis

Common symptoms of active lung TB are cough with sputum and blood at times, chest pains, weakness, weight loss, fever and night sweats. Many countries still rely on a long-used method called sputum smear microscopy to diagnose TB. Trained laboratory technicians look at sputum samples under a microscope to see if TB bacteria are present. Microscopy detects only half the number of TB cases and cannot detect drug-resistance.

The use of the rapid test Xpert MTB/RIF® has expanded substantially since 2010, when WHO first recommended its use. The test simultaneously detects TB and resistance to rifampicin, the most important TB medicine. Diagnosis can be made within 2 hours and the test is now recommended by WHO as the initial diagnostic test in all persons with signs and symptoms of TB.

Diagnosing multidrug-resistant and extensively drug-resistant TB (see Multidrug-resistant TB section below) as well as HIV-associated TB can be complex and expensive. In 2016, 4 new diagnostic tests were recommended by WHO – a rapid molecular test to detect TB at peripheral health centers where Xpert MTB/RIF cannot be used, and 3 tests to detect

resistance to first- and second-line TB medicines. Tuberculosis is particularly difficult to diagnose in children.

Treatment

TB is a treatable and curable disease. Active, drug-susceptible TB disease is treated with a standard 6-month course of 4 antimicrobial drugs that are provided with information and support to the patient by a health worker or trained volunteer. Without such support, treatment adherence is more difficult. Between 2000 and 2018, an estimated 58 million lives were saved through TB diagnosis and treatment.

TB and HIV

People living with HIV are 19 (15-22) times more likely to develop active TB disease than people without HIV. HIV and TB form a lethal combination, each speeding the other's progress. In 2018 about 251 000 people died of HIV-associated TB. In 2018, there were an estimated 862,000 new cases of TB amongst people who were HIV-positive, 72% of whom were living in Africa.

WHO recommends a 12-component approach of collaborative TB-HIV activities, including actions for prevention and treatment of infection and disease, to reduce deaths.

Multidrug-resistant TB

Anti-TB medicines have been used for decades and strains that are resistant to one or more of the medicines have been documented in every country surveyed. Drug resistance emerges when anti-TB medicines are used inappropriately, through incorrect prescription by health care providers, poor quality drugs, and patients stopping treatment prematurely.

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the 2 most powerful first-line anti-TB drugs. MDR-TB is treatable and curable by using second-line drugs. However, second-line treatment options are limited and require extensive chemotherapy (up to 2 years of treatment) with medicines that are expensive and toxic.

In some cases, more severe drug resistance can develop. Extensively drug-resistant TB (XDR-TB) is a more serious form of MDR-TB caused by bacteria that do not respond to the most effective second-line anti-TB drugs, often leaving patients without any further treatment options.

In 2018, MDR-TB remains a public health crisis and a health security threat. WHO estimates that there were 484 000 new cases with resistance to rifampicin – the most effective first-line drug – of which 78% had MDR-TB. The MDR-TB burden largely falls on 3 countries – India, China and the Russian Federation – which together account for half of the global cases. About 6.2% of MDR-TB cases had extensively drug-resistant TB (XDR-TB) in 2018.

Worldwide, only 56% of MDR-TB patients are currently successfully treated. In 2016, WHO approved the use of a short, standardized regimen for MDR-TB patients who do not have strains that are resistant to second-line TB drugs. This regimen takes 9–12 months and is much less expensive than the conventional treatment for MDR-TB, which can take up to 2 years. Patients with XDR-TB or resistance to second-line anti-TB drugs cannot use this regimen, however, and need to be put on longer MDR-TB regimens to which 1 of the new drugs (bedquiline and delamanid) may be added.

In July 2018, the latest evidence on treatment of drug-resistant TB was reviewed by an independent panel of experts convened by WHO. A rapid communication on key changes to recommendations for the treatment of drug-resistant TB has been issued by WHO, to be followed by the release of updated and consolidated WHO policy guidelines later in the year.

WHO also approved in 2016 a rapid diagnostic test to quickly identify these patients. Sixty-two countries have started using shorter MDR-TB regimens. By the end of 2018, 90 countries reported having introduced bedaquiline and 57 countries reported having introduced delamanid, in an effort to improve the effectiveness of MDR-TB treatment regimens.

Chapter 4

Materials and Methods

Population and blood collection

Fifteen normal host laboratory documented newly TB infected patients were enrolled at the Office of 10 Disease Prevention and Control, Anti-TB Association Thailand: Chiang Mai (*ATAT*-Chiang Mai) and Department of Internal Medicine, Faculty of Medicine, Chiang Mai University between October 2008 and September 2010

Patients were treated using DOTS. They received anti TB drugs according to The Thai Guidelines for TB Control [11] (Table1) which included isoniazid (INH), Rifampicin (RIF), pyrazinamide (PZA), and ethambutol for 2 months (initial phase), then INH and RIF for another 4 months (continuation phase). Serum drug level determination was conducted at the end of the initial phase. At the same time, sputum smear microscopy was performed using the Ziehl-Neelsen method. Patients were grouped as smear positive and smear negative. Smear-positivity was used to indicate slow response or unsuccessful treatment. Final treatment results were revealed at the end of the 4-months continuation phase.

The study protocol was approved by the Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Thailand.

Anti-TB drug level determination

At the last day of the initial phase, patients were asked to fast overnight. Venipuncture blood was drawn 2 hours after anti TB drug intake. Each plasma sample was separated by centrifugation and kept at -70° C for further analysis.

Levels of INH, RIF, and PZA were quantified by high-performance liquid chromatography (HPLC) using external standards. Sample pretreatment was modified from Smith et al.[15] and Unsalan et al.[16] methods by using Bondelut C18 extraction cartridges. An HP model 1100 isocratic revered phase HPLC system (Hewlett-Packard, Palo Alto,Calf., USA) fitted with a C8 column and UV-VIS detector was employed. The mobile phase for RIF determination was 80% acetonitrile

with 0.1% trifluoroacetic acid whereas for the INH and PZA determinations was 3% acetronitrile with 0.06% trifluoroacetic acid.

Low levels of anti TB drugs were identified when the anti TB drug level was lower than the therapeutic range (INH < 3 ug/ml, PZA < 20 ug/ml, and RIF < 8 ug/ml.)

Data analysis

All values were arithmetic. Weight adjusted anti TB values were calculated individually before any group mean calculation. Mean comparisons between sex and sputum smear result groups were performed using a Mann-Whitney *U* test. Fisher's exact test was used to determine the relationship between anti TB drug levels and a sputum smear result.

Anti - tubercular drug level determination has a potential to identify patients who may be at risk of poor treatment results.

Chapter 5

Results

There were 15 normal hosts newly infected and enrolled in this study. The mean age was 34.80 years in men and 43.67 years in women (Table 2). Women had a mean weight lower than men (44.33 vs 47.30 kg). There were 4 patients who showed positive smears at the end of the initial phase (Table 3). INH mean levels from the smear-negative group were lower than those from the smear-positive group (8.16 vs 9.16 μg/ml); however, the weight adjusted INH level of the smear-negative group was significantly higher than in the smear-positive group (0.18 vs 0.16 μg/ml/ kg body weight). Similarly, PZA and RIF levels of the smear-negative group were higher than the smear-positive group. The numbers of low antiTB drug level patients was 1 (7%) for INH, 5 (33%) for PZA and 13 (87%) for RIF. The prevalence of smear-positive patients at the end of initial phase was 27%. When subjects were classified according to antiTB drug level and sputum testing result, the prevalence of PZA level < 20 μg/ml and RIF level < 8 μg/ml in the smear-positive group was greater than in the smear-negative group (75% vs 18% and 100% vs 82%, respectively), but this relationship was not significant (Fisher' exact test p = 0.077 and 0.524, respectively) as shown in Table 3.

Table 1. Thailand category I tuberculosis drug regimen

Patient weight (kg)	Dose (mg)			
	Isoniazid (INH)	Pyrazinamide (PZA)	Rifampicin (RIF)	Ethambutol (E)
<40	300	1,000	300	800
40–50	300	1,500	450	1,000
>50	300	1,500-2,000	600	1,200

INH: Isoniazid, RIF: Rifampicin, PZA: Pyrazinamide, E: Ethambutol

Table 2. Mean comparisons of age, weight, TB drug level between men and women of new TB patients

	Men (n = 12)		Women (n = 3)		*p*
	Mean	SD	Mean	SD	
Age (year)	34.80	9.98	43.67	17.10	0.310
Weight (kg)	47.30	6.55	44.33	4.73	0.394
INH (µg /ml)	9.05	3.55	5.90	0.35	0.083
PZA(µg /ml)	22.54	14.21	29.36	13.59	0.563
RIF(µg /ml)	3.95	6.22	3.15	1.54	0.149

Mean comparison was done by Mann-Whitney U test

Table 3. Relations between treatment drugs level and treatment result among new TB patients

		Sputum conversion result n (%)			Fisher's exact *p*
		Convert	Delay convert	Total	
INH	<3 µg /ml	1 (9)	0 (0)	1 (7)	0.733
	>3 µg /ml	10 (91)	4 (100)	14 (93)	
PZA	<20 µg/ml	2 (18)	3 (75)	5 (33)	0.077
	>20 µg/ml	9 (82)	1 (25)	10 (67)	
RIF	<8 µg/ml	9 (82)	4 (100)	13 (87)	0.524
	>8 µg/ml	2 (18)	0 (0)	2 (13)	
Total		11 (73)	4 (27)	15 (100)	

Convert was identified in patient whose sputum acid-fast bacilli was negative whereas delay convert was identified in patient whose sputum acid-fast bacilli was positive by using Ziehl–Neelsen method.

Chapter 6

Discussion and Conclusion

The results of this study showed that smear-positivity was found in four patients at the end of the initial phase treatment. Their INH levels were above the therapeutic range (>3 μg/ml) whereas the RIF levels were low (<8 μg/ml) (Table 3). Smearpositivity appeared after 6 months of treatment in only one patient, whose serum levels of PZA and RIF were lower than in the therapeutic range (<1 and 0.70 μg/ml), but the INH level was higher than in the therapeutic range (9.26 μg/ml).

Discussion and conclusions Unsuccessful TB treatment with low serum antiTB drug levels was reported among a subset of TB patients when the standard Thai short course regimen was used. Thailand has a strategy to increasing use of the standard short course regimen.[3,5] and thus to maximizing cost-benefit advantages.[4,17] Anti-TB drug determination is a sophisticated and costly procedure, requiring a skillful worker and consumes time. It has not yet been included in TB treatment guidelines.[3] TB treatment costs US$100– US$1,000 worldwide and US$750 in Thailand.[1] Cost variation depends on the stage of the disease and will increase for MDR-TB or relapse cases[1]. In 2011, funding for TB treatment worldwide was US$5,000 million[1] and US$648 (12.96%) million was expanded for MDR-TB treatment. TB treatment costs increase as MDR-TB and unsuccessful cases increase. Anti-TB drug levels determination is the one proposed strategy used for MDR-TB and to prevent treatment failures caused by low anti-TB drug levels. This strategy would cost $80 per case and would represent only 10.67% of Thailand's TB treatment costs. The advantage of anti-TB drug level determination was documented among normal host TB patients in Kimerling et al.[18] These patients received DOTS as our subjects and they showed smear-positive sputum within 12 weeks of treatment. The INH level was low in 36% (5/14) of patient and 51% (8/14) of patients showed low levels of RIF, differing from our results. The INH level in our smear-positive sputum subjects was normal (>3 ug/ml) and all smear-positive sputum subjects showed RIF lower than the therapeutic range (Table 3). Kimerling suggested that the early identification of low level anti-TB patients will help to adjust drug regimen and prevent unsuccessful treatment[18]. Therefore, factors that should be of clinical importance are; optimal time to collect blood, the necessity of fasting state, and the effects of other drugs, and alcohol on absorption and metabolism.[18] These factors should be reviewed with care to get optimal conditions for anti-TB drug determination. The limitations of our preliminary study are drug resistant determination in low responders and the small number of subjects. There is need for a larger

study and drug resistant determination on low responders. Patients showing low anti-TB drug levels need to be carefully screened concerning life style and other risk factors that may interfere with the absorption and metabolism of drugs.

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