The Application of the Therapeutic Drug Monitoring (TDM) of First and Second-Line Drugs for Multidrug-Resistant Tuberculosis Patients (MDRTB)

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ABSTRACT

Objective: The study aimed to evaluate the effectiveness, safety, and drug compliance among MDRTB-patients who either undergo therapeutic drug monitoring (TDM) or not to assess the full benefit of TDM related to the disease treatment.

Methods: It was a quasi-experimental design. The study group underwent TDM process to measure serum drug concentrations of pyrazinamide (PZA) and cycloserine (CS), whereas the control group went through the regular process of treatment without taking TDM. All patient information and lab tests were investigated. Descriptive statistics including, frequency, percentage, mean, SD, percentage (s) as well as analytical statistics at confidence interval of 95% ($p<0.05$) including Fisher's Exact test were used.

Results: There were no significant differences between measuring and calculating PZA concentrations throughout 4-month periods ($p>.05$). Overall, the treatment success of MDR-TB among the subjects in both groups were still not satisfied. The common side effects of both medications were reported. Serum concentrations of PZA and cylcoserine were not significantly related to the side effects. Similarly, there was no significant relation between serum concentrations of PZA and drug compliance.

Conclusion: TDM is described as an investigational tool to explore means of improving therapeutic outcomes and reducing toxicity of the current MDRTB medications. Further investigations are still needed.

Keywords: Pyrazinamide (PZA); cycloserine multidrug resistant tuberculosis; therapeutic drug monitoring (TDM)
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INTRODUCTION

Tuberculosis (TB) is one of the causes of deaths around the world.[1] Thailand is ranked 17th of 22 countries having a large number of TB patients via World Health Organization (WHO) since 1998. In 2013, World Health Organization reported the estimated prevalence of tuberculosis in Thailand was 149 per 100,000 population for all forms of TB.[2,3] The most common causes of recent TB epidemic include HIV/AIDS and multi- drug resistant tuberculosis (MDRTB). In Thailand, over the past decade the incidences of MDRTB have been increased among prisoners, and HIV/AIDS infected patients (5-7%).[4] Nevertheless, due to limitations including, lack of sufficient case reports, low access to MDRTB screening, low diagnostic procedure, the total number of MDR-TB cases were miscounted.[5] Diagnosis requires sophisticated laboratories that can perform mycobacterial culture and drug susceptibility test (DST) associated with resistance. Noticeably, treatment involved prolonged use of "second line" anti-TB drugs that are less effective, with narrow therapeutic effect, less tolerated, more toxic, and more expensive than "first line" anti-TB drugs.[6] Under optimum

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program conditions, cure rates for drug susceptible TB exceeds 90 percent; but for MDRTB, cure rates infrequently exceed 70 percent.[7] Inadequate treatment of MDR-TB can allow development of even more lethal strains of MDRTB, such as extensively drug resistant-TB (XDR-TB), which gives substantially lower cure rates.[8] Therefore, there is a possible solution to overcome this called "therapeutic drug monitoring" (TDM). It is the process of obtaining the serum concentration of drugs and modifying the dose based on the results to optimize their therapeutic benefits, while minimizing their risks for side effects or toxicity.[9] TDM has a role and can improve the treatment of TB. Also TDM provides objective information for the clinician to make informed dosing decisions. For the patients who are slow responders, TDM can shorten the time to response to the medications and to determine the adequate plasma concentrations.[10-12]

Due to an unfamiliarity of TDM related to MDRTB in Thailand, there were still some limitations including numbers of experts in TDM skills, knowledge and skills, budget available, and the responsibility of both health workers and patients. The possible solutions includes, the government supports both manpower and budget, the collaboration between health professionals and hospitals set up the standard protocol for TB and MDRTB treatment by integrating TDM as part of the treatment evaluation. Accordingly, the authors had a chance to join the TB team at ITRC, Masan, South Korea in 2009 for the development of a standard TDM protocol of first and second-line drugs for MDRTB patients. The authors aimed to implement the standard protocols of TDM in anti-TB agents for health care professionals to evaluate the effectiveness and toxicity, especially cycloserine (CS) and pyrazinamide (PZA). These two drugs are commonly used for MDRTB treatment in Thailand. For PZA, the concerned issue is involved with its toxicity such as hepatotoxicity which is unknown for its mechanism, but has high severity.[13] For cycloserine, the most common side effects include anxiety, insomnia, suicide, and headache. These symptoms might have interfered with treatment efficacy and caused non-compliance,[14] because the duration of MDRTB treatment is approximately between 12 and 24 months. However, in some cases the duration might be longer depending on some factors including, severity, patient compliance, and treatment efficacy. Thus, there is the possibility the patients might not comply with the treatment which results in treatment failure or relapse. For these reasons, the evaluations of the effectiveness, safety, and compliance between TDM and non-TDM MDRTB patients were conducted.

MATERIALS AND METHODS

Study design

It was a quasi-experimental design. It was 9 month-periods study from January to September 2011.

Study groups

All subjects were diagnosed for MDRTB by following the standard MDRTB guideline protocol, Thailand 2011. The duration of study was 4-month periods for data collection. There were totally thirty-seven MDRTB subjects, who were firstly enrolled into the program. However, there were eventually twenty-four subjects (64%) who went through a completed study process. Causes of cancelation included remote distance from the hospitals, blood sampling rejection, and being prisoners. They were selected into either study or control group via simple random sampling. Eleven were in a study group, the other thirteen were in a control group.

Prior to the study, all subjects were requested to sign the consent forms in which all personal information were confidential. This study was conducted under the approval by Sanpasithiprasong Central Hospital Review Board (Reference no. 305/2553).

Process of data collection

For the study group, therapeutic drug monitoring (TDM) process was started on the hospital visit, where the subjects were scheduled for blood samplings. The blood sampling protocol followed the standard guideline for MDRTB treatment, 2015.[4] Additionally, a personal interview related to side effects and drug compliance was performed. During blood sampling process, the evaluation of serum drug concentration (C_t) should follow drug monogram. PZA and cycloserine blood sampling should be conducted 2 hours after taking the medications for their absorption. All blood samples were tested via High Pressure Liquid Chromatography (HPLC) to detect serum drug concentrations. Later, serum drug concentrations and pharmacokinetic values were analyzed. For the control group, all subjects similarly went through the process without TDM.

Statistical analysis

All findings including demographic data, laboratory tests, pharmacokinetics properties, serum drug concentrations, side effects, and drug compliance of both PZA and cycloserine were evaluated via descriptive statistics. For analytical statistics at confidence interval of 95% ($p<0.05$), Fisher's Exact test was used for the comparison of treatment effectiveness between groups.

Additionally, the comparison of side effects of PZA and cycloserine between groups was analyzed via Fisher's Exact test. Finally, the evaluations of the relations between serum drug concentrations of PZA & cycloserine and side effects as well as drug compliance were investigated via logistic regression analysis. What software and version number were used for statistical analysis?

RESULTS

There were totally 24 (26) subjects (95%) who completed the study. The causes of withdrawal included; accommodation in the remote rural areas, rejected blood sampling process, and staying in the prisons. All details were described in Table 1.

TABLE 1. Demographic data (n=24).

Demographic data	Frequency (%)		p<0.05
	Study (n=11)	Control (n=13)	
Demographic information			
Gender (s)			
Male	7 (63.63)	6 (46.15)	0.895
Female	4 (39.37)	7 (53.95)	
Age (Mean ± SD)	47± 2.72	42 ± 4.72	0.042*
Weight (Mean ± SD)	58 ± 5.4	57 ± 3.8	0.712
Height (Mean ± SD)	168 ± 3.8	165 ± 5.2	0.623
Medical conditions (choose more than 1 answer)			
Hypertension	8 (72.72)	10 (76.92)	0.546
Diabetes	6(54.54)	8 (61.53)	-
Asthma	6 (54.54)	6(46.15)	0.652
Pneumonia	5 (45.45)	4 (30.76)	0.780
Drug allergy history			
Penicillin	0	0	-
Sulfa compounds	0	0	-
Most common reasons for MDRTB treatment (choose more than 1 answer)			
Suspicious of MDRTB	5 (45.45)	8 (61.53)	0.014*
Treatment failure of CAT1	6 (54.54)	8 (61.53)	0.457
Treatment failure of CAT2	5 (45.45)	5 (38.46)	0.712
Treatment failure of other regimens	0	0	-
C/S showed MDRTB	8 (72.72)	7 (53.84)	0.151
DST –resisted to antiTB agents at least 2 agents including INH and RIF	10 (90.90)	10 (76.92)	0.311
HIV test			
Anti-HIV (+)ve	2 (18.18)	1 (7.69)	0.812
Anti-HI (-)ve	9 (81.82)	12 (92.31)	0.032*
Site(s) of TB			
Pulmonary	7 (63.63)	9 (69.23)	0.036*
Extra-pulmonary	3 (27.27)	3 (23.07)	0.199
Both sites	1 (9.1)	2 (7.7)	0.875
Cavity lesion			
Yes	4 (36.36)	6 (46.15)	0.596
No	7 (63.64)	7 (53.84)	0.189

Demographic data	Frequency (%)		p<0.05
	Study (n=11)	Control (n=13)	
Current MDRTB treatment (s)			
6K5OPEZ / 12-18 OPEZ (CAT4(1))	6 (54.54)	8 (61.54)	0.596
6K5 O (P) Et Cs (Z) / 12-18 O (P) Et Cs (Z) (CAT 4(2))	5 (45.45)	5 (38.46)	0.156
second line agents → 2HRE/7HR	1 (9.10)	0	-
Other regimens	0	0	-
Durations of current treatment (-month periods)			
1- to 4- month	0	1 (7.69)	0.365
5- to 8- month	2 (18.18)	5 (38.46)	
9- to 12-month	7 (63.63)	4 (30.76)	
12- to 15-month	2 (18.18)	2 (15.38)	
More than 16-month	0	1 (7.71)	
DOTs			0.14
Yes 4	(36.36)	6 (46.15)	
No 7 (63.64)	7 (53.85)		
Therapeutic Drug Monitoring Availability (TDM)			-
Reason of conducting TDM (choose more than 1 answer)			-
HIV/AIDS infections and received			
GPO-Virs while treating MDRTB	2 (18.18)	N/A	-
Non-compliance	5 (45.45)	N/A	-
Organ impairment	6 (54.54)	N/A	-
Treatment failure			
Failed CAT4(1)	2 (18.18)	N/A	-
Failed CAT4(2)	2 (18.18)	N/A	-
Relapse	0		
Defaults	3(27.27)	N/A	-
Drug Interactions	2 (18.18)	N/A	-
Adverse drug reactions (ADRs)	8(72.72)	N/A	-

Abbreviations: C/S: culture/smear, DST: Drug Sensitivity Test, INH: Isoniazid, RIF: Rifampicin, HIV/AIDS: Human Immunovirus/ Autoimmune Deficiency Syndrome. *Sig at .05

When organ functions were considered including, renal and liver tests during the study, the findings were revealed. For study group, mean blood urea nitrogen (BUN) and serum creatinine (Scr) were within a normal range throughout 4-month periods (7-20 ml/min; 0.6-1.2 mg/dL). Similarly, most subjects had mean values of liver enzymes including, AST/ ALT within a normal range throughout 4-month periods (0-250 U/L/ 0-175 U/L), except case 3 which had slightly high mean values at 2-, and 3-month periods (251 (±7.46)/ 178 (±9.59) U/L, 255 (±4.87)/ 182 (±10.23) U/L, respectively). Regarding control group, both mean values of BUN/ Scr tended to be high between 3- and 4-month periods (26 (±4.23) ml/min/ 1.4 (±0.92) mg/dL; 24 (±2.75) ml/ min/ 2.8 (±0.13) mg/dL, respectively). Also, mean values of AST/ALT were high above normal ranges at 2-, 3-month periods (260 (±12.46)/ 178 (±9.59) U/L; 258 (±20.87) /189 (±22.14) U/L, respectively).

A. The comparison of PZA and cycloserine concentrations between measured and calculated concentrations throughout 4-month periods

The measured concentrations were from TDM process, whereas the calculated concentrations were

from the pharmacokinetic formula. Both measured and calculated PZA concentrations were within therapeutic levels. However, there were no significant differences between measured and calculated PZA concentrations (p>.05), except at 2-month periods (p=.038). For cycloserine, both types of concentrations were not statistically different. However, mean values of calculated cycloserine concentrations were under therapeutic levels compared to those measured concentrations (Table 2).

B. Side effects of PZA and cycloserine between groups throughout *4*-month periods

Some common side effects of PZA were reported including hepatotoxicity by elevatiion of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in both groups. Regarding cycloserine, loss appetite, anxiety, and headache were revealed. Noticeably, a number of side effect cases in the control group were higher than those in the study group (10/13 (76%), 6/11 (54%) respectively)). Additionally, there was no significant difference of side effects of PZA and cycloserine between groups (p=0.3904) (Table 3).

C. Drug compliance between groups

In our study group, there were 3 cases who complied with the treatment and PZA and cycloserine therapeutic levels were favorably reported without any side effects (27.27%). However, only one case in the control group who complied with the treatment reported no side effects (7.69%).

TABLE 2. Comparisons of blood concentrations of PZA and cycloserine between measuring and calculating concentrations - study group.

Agents (Ct (mg/L)	Measuring Conc.		Calculating Conc.		Mean Difference	S.D.	t	p <.05
	Mean	S.D.	Mean	S.D.				
PZA (20-45)								
1-month	33.00	6.76	31.83	6.75	1.16	11.29	0.292	0.779
2-month	38.37	4.71	30.44	6.48	7.92	8.79	2.549	0.038
3-month	40.14	6.17	30.10	7.63	10.04	11.20	2.371	0.055
4-month	34.71	3.90	31.46	6.78	3.25	7.64	1.127	0.303
Cycloserine (20-30)								
1-month	21.60	3.78	14.18	7.57	7.41	8.48	1.955	0.122
2-month	26.80	6.41	13.22	8.42	13.57	11.54	2.630	0.058
3-month	25.40	7.82	13.67	7.98	11.72	9.92	2.642	0.057
4-month	23.00	3.60	14.12	7.76	8.87	8.88	2.234	0.089

Abbreviations: Ct: therapeutic drug concentration, Conc: concentration

TABLE 3. Comparison of side effects of PZA and cycloserine between study and control groups.

The participants	Side effects		Fisher's Exact test	p value*
	Yes Frequency (%)	No Frequency (%)		
Study	6(54.5)	5 (45.5)	1.343	0.39
Control	10 (76.9)	3 (23.1)		

Note: *Fisher's Exact test

TABLE 4. The comparison of the effectiveness of MDRTB treatment between groups.

The participants	Effectiveness of MDRTB treatment		Fisher's Exact test	p value*
	Satisfied Frequency (%)	Unsatisfied Frequency (%)		
Study	-(-)	11 (100)	1.155	0.4761
Control	1 (10)	9 (90)		

Note: *Fisher's Exact test

D. MDR-TB treatment success

When focusing on TDM related to the MDRTB treatment efficacy, the findings revealed most subjects in our study group tended to have both their drug concentrations within therapeutic levels (Table 2). Nevertheless, they experienced some side effects of both medications as well as non-compliance issues. These controversial findings need some explanations (Discussion section). Overall, the treatment successes of MDR-TB among the subjects in both groups were still not satisfied and there was no difference between groups (p =0.4761) (Table 4).

E. The relation between blood concentrations of PZA and cycloserine and the side effects

–study group

Both measured and calculated blood concentrations of PZA were not related to the side effects of the medication (OR=0.97, 95%CI 0.76-1.24 and OR=1.04, 95%CI 0.84-1.27 respectively). Similarly, there was no relation between measured and calculated blood concentrations of cycloserine and the side effects of the medication (OR=1.37, 95%CI 0.69-2.69 and OR=0.82, 95%CI 0.53-1.28 respectively).

F. The relation between drug compliance of PZA and cycloserine and serum drug concentrations – study group

When focusing on the relationship between measured and calculated blood concentrations of PZA and drug compliance, there was no significant relationhip between those two variables in study group (OR=1.03, 95%CI 0.73-1.45 and OR=0.73, 95%CI 0.38-1.38 respectively). For cycloserine, there were only a few subjects prescribed for this medication. Therefore, it was not possible to analyze the data due to a small number of samples.

DISCUSSION

From Table 1 most participants were diagnosed for MDRTB caused by different reasons including, treatment failure, and DST and or C/S results confirmed they had at least two drug resistances such as INH, rifampicin. Normally, the resistance among MDRTB patients can be divided into 2 categories including, '*acquired*-, and *primary*-resistance' which have different resistant pathways.[15-17] Nevertheless, the study did not primarily investigate the cause of MDRTB resistance, so it was unable to confirm the type of the MDRTB resistance. Interestingly, some previous studies found the incidence of MDRTB might relate to those who have a history of drinking and smoking.[15,18] Several studies have reported that persons who drink alcohol in excess are more likely to have treatment interruptions and lead to treatment failure.[19,20] However, our study was not to investigate the relationship between alcohol, tobacco and the effectiveness of MDRTB treatment. Therefore, it was not sensible to discuss this issue.

Regarding the metabolism and excretion of drugs, the common indicators include renal (BUN, Scr) and liver functions (AST/ALT). These indicators varied depending on each patient's physical conditions. The most common side effects of PZA and cycloserine are hepatotoxicity and CNS defect,[41,42] especially when a patient has been treated for a long period (12 to 24 months). Therapeutic drug monitoring (TDM) has been shown to analyze serum therapeutic levels of anti-MDRTB drugs, so the excess levels causing hepatotoxicity could be prevented. Nevertheless, some previous studies revealed some other risk factors including age, HIV infection, alcoholism, and malnutrition could possibly influence the incidence and severity of anti-MDTB toxicity.[40-42,44] the study group using TDM tended to have both normal

kidney and liver functions compared to those in a control group throughout *4*-month periods. However, it might not be sensible to evaluate the correlation between plasma drug levels, organ functions, and drug toxicity, as the subjects in both groups had some inconsistently different demographic information including, age, and HIV infection (p>.05) which might influence the outcomes on this issue.

For MDRTB treatment, the study showed even though serum drug concentrations of MDRTB medications via TDM were in therapeutic levels, the treatment efficacy might not be relatively satisfied. It could be explained by the pathogens which cause MDRTB infection are normally highly resistant types, so they might not be eliminated by the current medications. As a result, in some cases, they might have shown some worse clinical symptoms, with positive smear, and the mortality rate is still high due to treatment failure or relapse.[21,22] Additionally, the similar finding was found in the previous study evaluating serum drug levels of MDRTB medications. The results found a longer duration of negative smear results in TDM groups compared to a control group (p= 0.038).[23] On the other hand, some adequate documents have shown the benefits of therapeutic drug monitoring (TDM) related to the effective treatment, side effect prevention, and good compliance.[3,16,24-27] Recently, the knowledge related to treatment efficacy including, therapeutic drug monitoring (TDM), drug interaction monitoring (DI-M), and adverse drug reaction monitoring (ADR-M) has been written as standard protocols.[28-31]

Recently, therapeutic drug monitoring (TDM) has been found to minimize non-compliance.[25,32-35] However, the authors found serum concentrations of PZA via TDM were not statistically related to drug compliance in the study. It might be explained that some factors including drug toxicity, and socio-economics played a role in the irrelevant findings.[36,37] Therefore, the important message is that TDM should currently be reviewed only as an investigational tool to explore means of improving therapeutic outcomes and possibly reduce toxicity of the current medications.[44]

As MDRTB needs high doses and long treatment duration to eradicate the pathogens, so there is a possibility to develop some side effects. Noticeably, serum PZA concentrations via TDM were not statistically related to side effects of medications, especially hepatotoxicity. The similar incidences were also reported in Korea and Canada.[38,39] The explanation could also be the biochemical mechanism and pathogenesis of drug induced hepatotoxicity (DIH) are not fully understood. For most MDRTB drugs, the relationship between dose and toxicity is unknown.[40] Lastly, dose-related toxicity is not the only possible cause of DIH; idiosyncratic reactions, oxidative stress, or hypersensitivity to MDRTB drugs may also lead to DIH in some cases.[41,42] Interestingly, the findings also revealed the subjects who had a history of chronic disease such as diabetes, and respiratory infections (Table 1), were likely to be more susceptible to develop some side effects of MDRTB medications when compared to those who were not. This finding is similar to some previous studies.[43-47]

The present study has several limitations. First, due to a small number of subjects, so the overall results could not represent the whole picture whether therapeutic drug monitoring (TDM) is related to the key factors involved in MDRTB treatment. A possible way is to adjust the design to be a 'multi-centered' study, so more subjects will be recruited. Additionally, the remaining subjects' demographic data were considered non-homogeneous (e.g., age, reasons for MDRTB treatment) due to a small number of subjects. As a result, it reflected the process of subject sampling. Secondly, during TDM process, there have been several factors which interfered with the accuracy and reliability of the results including, time of blood sampling, time of medication taking, types of specimen containers, and specimen temperature. Adjusting for well controlled procedure for a further investigation is necessary. In this way future studies may achieve more definitive results. Finally, a remote area is one of our study barriers, so, the determination of the convenient areas should be addressed in the criteria to minimize missing subjects.

CONCLUSION

We did not findserum drug concentrations of PZA and cycloserine were directly related either to treatment response, to drug compliance, or to side effects in this study. Due to the results and the limitations of our study, we are not able to recommend a routine TDM for general MDRTB patients except for the suspicion of treatment failure or relapse. The role and usefulness of TDM should be evaluated in further prospective studies.

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REFERENCES

1. World Health Organization. Global Tuberculosis Report 2015. 20th edition. Geneva: World Health Organization 2015.
2. World Health Organization. Global tuberculosis report 2014. Geneva: World Health Organization 2014.
3. Srivastava S, Pasipanodya JG, Meek C, Leff R, Gumbo T. Multidrug-resistant tuberculosis not due to noncompliance but to between-patient pharmacokinetic variability. J Infect Dis 2011;204:1951-9.
4. Bureau of Tuberculosis. Department of Disease Control. MDRTB patient management. Bangkok: Bureau of Tuberculosis. 2015.
5. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization 2014.
6. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. Geneva: World Health Organization 2016.
7. van der Werf MJ, Sandgren A, Manissero D. Management of contacts of multidrug-resistant tuberculosis patients in the European Union and European Economic Area. Int J Tuberc Lung Dis 2012; 16(3): 426.
8. WHO. Multidrug and extensively drug-resistant TB (M/XDR TB): 2010 global report on surveillance and response. Geneva: World Health Organization 2010.
9. Peloquin CA. Therapeutic drug monitoring: principles and applications in mycobacterial infections. Drugs Ther 1992; 22: 31-36.
10. Schumacher GE, Barr JT. Therapeutic drug monitoring: do the improved outcomes justify the costs? Clin Pharmacokinet 2001; 40: 405-9.
11. Alsutan A, Peloquin CA. Therapeutic drug monitoring in treatment tuberculosis: a update. Drugs 2014; 78: 839-54.
12. Van Tongeren L, Nolan S, Cook VJ, FitzGerald JM, Johnston JC. Therapeutic drug monitoring in the treatment of tuberculosis: a retrospective analysis. Int J Tuberc Lung Dis 2013; 17(2): 221-4.
13. Peloquin CA, Jaresko GS, Yong CL, Keung AC, Bulpitt AE, Jelliffe RW. Population pharmacokinetic modeling of isoniazid, rifampin, and pyrazinamide. Antimicrob Agents Chemother 1997; 41(12): 2670-9.
14. Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. Int J Tuberc Lung Dis 2013; 17(10): 1257-66.
15. Mohammad A. Din TE, Maraghy E, Abdel HR, Hay A. Adverse reactions among patients being treated for multi-drug resistant tuberculosis at Abbassia Chest Hospital. Egypt J Chest Dis Tubercu 2015; 64: 939-52.
16. Sotgiu G, Alffenaar JW, Centis R, D'Ambrosio L, Spanevello A, Piana A, et al. Therapeutic drug monitoring: how to improve drug dosage and patient safety in tuberculosis treatment. Int J Infect Dis 2015; 32: 101-4.
17. Roberts JA, Ulldemolins M, Roberts MS, McWhinneyg B, Ungerer J, Patersonh DL, et al. Therapeutic drug monitoring of b-lactams in critically ill patients: proof of concept. Int J Antimicr Agents 2010; 36 332-9.
18. Guastella AJ, Richardson R, Lovibond PF, Rapee RM, Gaston JE, Mitchell P, et al. A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. Boil Pshychiatry 2008; 63: 544-49.
19. A guideline of therapeutic drug monitoring (TDM) for patient care. Pharmacy Unit, Phujchinaraj Central Hospital, Pitsanulok, Thailand. 2013: 15.
20. A guideline of therapeutic drug monitoring (TDM) for patient care. Pharmacy Unit, Phujchinaraj Central Hospital, Pitsanulok, Thailand. 2013: 15.
21. Heysell SK, Moore JL, Keller SJ, Houpt ER. Therapeutic drug monitoring for slow response to tuberculosis treatment in a state control program, Virginia, USA. Emerg Infect Dis 2010; 16: 1546-53.
22. Gandhi NR, Andrews JR, Brust JCM, Montreuil R, Weissman D, Heo M, et al. Risk Factors for Mortality among MDR- and XDR-TB Patients in a High HIV-Prevalence Setting. Int J Tuberc Lung Dis 2012; 16(1): 90-97.
23. Jiehui Li, Joseph N. Burzynski, Yi-An Lee, Debra Berg, Cynthia R, et al. Therapeutic Drug Monitoring for Multidrug-Resistant Tuberculosis Patients. Chest 2007; 126(6): 1770-77.
24. Pasipanodya JG, Srivastava S, Gumbo T. Meta-analysis of clinical studies supports the pharmacokinetic variability hypothesis for acquired drug resistance and failure of antituberculosis therapy. Clin Infect Dis 2012; 55: 169-77.
25. Sime FB, Roberts MS, Tiong IS, Gardner JH, Lehman S, Peake SL, et al. Can therapeutic drug monitoring optimize exposure to piperacillin in febrile neutropenic patients with haematological malignancies? A randomized controlled trial. J Antimicrob Chemother 2015; 70: 2369-75.
26. Gerber JG, Acosta EP. The Potential Role of Therapeutic Drug Monitoring in the Treatment of HIV Infection. Therap Drug Monitor 2002; 10(2): 27-32.
27. Burger DM, Aarnoutse RE, Schapiro JM, Boucher CA, Hekster YA, Therapeutic drug monitoring: an aid to optimising response to antiretroviral drugs?. Drugs 2003; 63(8): 741-53.
28. Thai Hypertension Society: Guidelines in the Treatment of Hypertension 2008: 10.
29. A standard guideline for patient using oral anticoagulants. The Heart Association of Thailand under the Royal Patronage. Bangkok Press, Bangkok 2010: 40.
30. A guideline of therapeutic drug monitoring (TDM) for patient care. Pharmacy Unit, Phujchinaraj Central Hospital, Pitsanulok, Thailand. 2013: 15.
31. Kaewpibal P. Impact of pharmacist on therapeutic drug monitoring utilization for phenytoin, carbamazepine, and valproic acid at Songklanagarind Hospital. Master degree of Pharmacy, Prince of Songklanagarind, Thailand. 2008: 321.
32. Otero MJ, Martin A, Barrueco M, Garcia MJ, Dominguez-Gil A. TDM of theophylline--compliance evaluation. J Clin Pharm Ther 1988; 13(4): 273-80.
33. Walson PD. Therapeutic drug monitoring in special populations. Clin Chem 1998; 44(2): 415-19.
34. Worth LJ, Blyth CC, Booth DL, Kong DCM, Marriott D, Cassumbhoy M, et al. Optimizing antifungal drug dosing and monitoring to avoid toxicity and improve outcomes in patients with haematological disorders. Intern Med J 2008; 38: 521-37.

35. Kenna LA, Labb L, Barrett JS, Pfister M. Modeling and Simulation of Adherence: Approaches and Applications in Therapeutics. The AAPS Journal 2005; 7(2): E390-407.
36. Prasad R. MDRTB: Current status. Indian J Tuberc 2005; 52: 121-31.
37. Ansari MS, Khayyam KU, Sharma M, Alam MS. The contribution of disease and drug related factors to non-compliance with directly observed treatment short course among tuberculosis patients. African Journal of Pharmacy and Pharmacology 2013; 7(35): 2466-73.
38. Van Tongeren L, Nolan S, Cook VJ, FitzGerald JM, Johnston JC. Therapeutic drug monitoring in the treatment of tuberculosis: a retrospective analysis. Int J Tuberc Lung Dis 2013; 17: 221–4.
39. Park JS, Lee JY, Lee YJ, Kim SJ, Cho YJ, Yoon HL, et al. Serum Levels of Antituberculosis Drugs and Their Effect on Tuberculosis Treatment Outcome. Antimicrob Agents Chemother 2016; 60(1): 92–8.
40. Pasipanodya JG, Gumbo T. Clinical and toxicodynamic evidence that high-dose pyrazinamide is not more hepatotoxic than the low doses currently used. Antimicrob Agents Chemother. 2010; 54: 2847–54
41. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. Respirology 2006; 11: 699-707.
42. Sharma SK. Antituberculosis drugs and hepatotoxicity. Infect Genet Evol 2004; 4: 167-70.
43. Chung-Delgado K, Montag AR, Bravo SG, Segovia EV, Montoya AS. Factors associated with anti-tuberculosis medication adverse effects: a case-control study in Lima, Peru. PLoS ONE 2011; 6 (11): e27610.
44. Törün T, Güngör G, Ozmen I, Bölükbaşi Y, Maden E, Biçakçi B, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2005; 9(12): 1373-7.
45. Safwat TM, ElMasry AA, Mohamed AKM, Prevalence of multi drug-resistant tuberculosis at Abbassia Chest Hospital from July 2006 to December 2009. Egypt J Bronchol 2011; 5(2): 124-30.
46. Fouad S, Hassanein KH, Hussein B. Primary Drug Resistance in Newly Diagnosed Cases of Pulmonary Tuberculosis, Thesis submitted for partial fulfillment of the M.Sc. Degree of Chest Diseases and Tuberculosis, Cairo University, 2003.
47. Satyaraddi A, Velpandian T, Sharma SK, Vishnubhatla S, Sharma A, Sirohiwal A, et al. Correlation of plasma anti-tuberculosis drug levels with subsequent development of hepatotoxicity. Int J Tuberc Lung Dis 2014; 18: 188-95.