Prevalence and Risk Factors of Cardiotoxicity in Patients with Multidrug Resistant Tuberculosis Infection Receiving a Shorter All-oral Bedaquiline-containing Regimen

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Abstract

The most important adverse effect of bedaquiline is QT prolongation. There have not been any definitive studies on the prevalence of QT prolongation caused by bedaquiline drugs used in Thailand. Therefore, the purpose of this retrospective chart review study was to estimate the prevalence and risk factors of QT prolongation in patients with multidrug-resistant tuberculosis (MDR-TB) infection who were receiving a shorter all-oral bedaquiline-containing regimen. The data of the MDR-TB patients who received this treatment regimen between June 1, 2020, and December 31, 2021, at the Central Chest Institute of Thailand and Makaruk Hospital were collected. The event of QTc prolongation and risk factors, including QTc baseline, gender, QT prolongation diagnosed by physician, potassium level, comorbidities, and other drugs used in the shorter all-oral Bedaquiline-containing regimen, were recorded. Results showed that, from 33 patients (19 men and 14 women, age 43.24±15.79 years) with multidrug-resistant tuberculosis infection who received treated under this regimen, 27 (81.82%) of the patients received levofloxacin-based regimen, and 2 of the patients (6.06%) had QT prolongation. Other factors that may contribute to the development of QT prolongation are hypokalemia and other drugs used in this regimen. This study may lead to the development of a risk assessment tool for monitoring QT prolongation in patients who receive the shorter all-oral bedaquiline-containing regimen.

Keywords: QT prolongation, bedaquiline, hypokalemia, multidrug-resistant tuberculosis, risk factor

Introduction

MDR-TB is a serious communicable disease and a problem in Thailand's public health system because it takes a long time to heal and there is a chance of missing treatment. The necessity to use multiple drugs in parallel, which can often cause adverse drug reactions, affects the consistency of treatment. As a result, the success rate of treating patients with MDR-TB is low. A treatment regimen with a short healing time has been developed (Department of Disease Control, Division of Tuberculosis, 2020; Borisov et al., 2017; Pym et al., 2015). This treatment regime is a new way of categorizing the assortment of drugs used in a treatment based on the efficacy and safety of each individual drug and addresses the methods for organizing drug regimens and the selected drugs, based on the new drug classification model that has been developed in the study. In addition, proactive drug monitoring and active drug safety management of TB drugs are also important, to be able to identify problems that may arise from the treatment and provide prevention or treatment in a timely manner. This would result in reducing the potential harm to the patient and increasing the likelihood that the patient will cooperate until the end of the treatment.

Treatment of multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) with a short-term oral regimen containing bedaquiline is recommended in patients with MDR/RR-TB who have not been treated with a second line of a shorter all-oral bedaquiline-containing regimen for more than 1 month and tested with non-

resistance to the drug group Fluoroquinolones (Department of Disease Control, Division of Tuberculosis, 2020). Common side effects of bedaquiline have been reported in multidrug-resistant pulmonary tuberculosis regimens (Deoghare, 2013). The most common side effects of the short-term oral formulation are nausea (30%), arthralgia (26%), headache (22%), hemoptysis (14%), chest pain (9%), and anorexia (7%), and rash (6%). Another important cardiovascular adverse effect is QT prolongation (Deoghare, 2013). QT prolongation is the prolongation of the QTc interval. The QTc interval is the count of Q wave to T wave, which is associated with ventricular depolarization. If this section is longer, the heart beats slower, but if this section is shortened, it makes the heart beat faster. Normal values are generally less than 440 msec, with the highest cut-off in males being 440 msec, while in women 470 msec. Anything that extends the QTc interval to greater than 500 msec can lead to serious arrhythmia, torsade's de pointes, with a risk of sudden cardiac arrest, and death. QT prolongation is caused by a variety of drugs, including levofloxacin, moxifloxacin, clofazimine, and bedaquiline. The main mechanism for QT prolongation is where these drugs inhibit the human ether-a-go-go-related gene (hERG)-potassium channel in myocardial cells resulting in delayed birth action potential repolarization and prolongs QTc interval (Patel et al., 2019; Nachimuthu; Boutjdir et al., 2015; Assar, & Schussler, 2012; Ponte, Keller, & Girolamo, 2010; Roden, 2004). The proposed structured and toxicity relationship is that the Naphthalene ring, a structure with high lipophilicity (logP=7.25), enables to bind well to hERG-K+ channels in myocardial cells. In addition, basic nitrogen is a structure that can lose electrons in the pH of the human body (pKa = 9.6) and then generates Pie-cations at aromatic sites, thereby increasing the binding affinity to the hERG-K+ channel (Patel et al., 2019).

According to the study of Jing-Tao Gao et al. (Abdelwahab et al., 2021), treatment with A short-term oral regimen containing bedaquiline for 167 days showed an incidence of QT prolongation in 287 of 1162 patients, representing 24.7% (Abdelwahab et al., 2021). A study by Borisov, Filippov, Ivanushkina, Ivanova, & Litvinova, 2016 showed that treatment by a short-term oral regimen containing bedaquiline for a median duration of 168 days showed an incidence of QT prolongation of 24 in 248 patients, representing a 9.7% (Borisov et al., 2017). There has not been such valuable information in Thailand even though this medication is used more frequently than previously.

In addition, previous studies have reported that other factors associated with QT prolongation in patients with multidrug-resistant pulmonary tuberculosis are levofloxacin, moxifloxacin, clofazimine, short-term oral regimens containing bedaquiline, ischemic heart disease, hypokalemia (<3.5 mmol/L), low serum magnesium (<1.5 mmol per liter) (Noori et al., 2022; Abdelwahab et al., 2021; Nachimuthu et al., 2012; Briasoulis, Agarwal & Pierce, 2011; Widimsky, 2008; Roden, 004). This information about the risk factors associated with QT prolongation will enable well-planned patient monitoring strategies. Therefore, this study has 2 main objectives. First, to study the prevalence of QT prolongation in patients with multidrug-resistant pulmonary tuberculosis from the use of a short-term oral regimen containing bedaquiline and the second was to study the risk factors of QT prolongation in patients with multidrug-resistant pulmonary tuberculosis from the use of a mentioned regimens.

Methods and Materials

Research design

Retrospective chart review

Population and sample collection

Population: Patients with multidrug-resistant pulmonary tuberculosis who had bedaquiline exposure data.

Sample group: Patients with multidrug- resistant pulmonary tuberculosis who had data on bedaquiline exposure from June 1, 2020, to December 31, 2021, at Makaruk Hospital. Kanchanaburi Province and the Central Chest Institute.

Inclusion criteria:

1. All patients who were diagnosed with multidrug-resistant pulmonary tuberculosis for whom bedaquiline-containing short-term oral therapy was available.

2. Patients with multidrug-resistant pulmonary tuberculosis without resistance to fluoroquinolone containing regimens.

Exclusion criteria

1. Patients had QT prolongation before bedaquiline administration.

1.1 QTc interval is greater than 450 for men.

1.2 QTc interval is greater than 470 for women.

2. Death from causes other than QT prolongation.

3. Patients who discontinued bedaquiline for causes other than QT prolongation.

4. Patients with congenital long QT syndrome (ICD-10: I45.81).

The characteristics of patients that were recorded at baseline were age and gender, and potassium levels, medication regimens and baseline QTc were recorded at baseline with outcomes also recorded. The event of QT interval was recorded after receiving betaquiline administration.

Data analysis

To analyze the prevalence of QT prolongation in patients receiving a short-term oral regimen containing bedaquiline in the form of period prevalence. The prevalence calculation formula is as follows:

$$\text{Prevalence} = \frac{\text{total number of patients with new and old QT prolongation}}{\text{Patients receiving Bedaquiline at the time}}$$

Other variables were reported by descriptive statistics (Mean $\pm$ SD, percentage). The risk factors were evaluated according to the literature reviewed and the patient's medical records.

This study was approved by the ethical committee of both centers. In addition, it was also approved by the university ethical committee (COE 65022-036).

Results

1. Patient characteristics

General information about the patient

From collecting data from Makaruk Hospital and the Central Chest Institute, the results were as follows.

Makaruk Hospital: A total of 26 patients were enrolled in a short-term oral regimen containing bedaquiline, 20 of whom did not meet the study criteria and 6 people who met the inclusion criteria: 3 males and 3 females.

The Central Chest Disease Institute: A total of 27 patients were enrolled in a short-term oral regimen containing bedaquiline, of which 27 met the inclusion criteria, 16 males and 11 females.

Looking at the general data of the study population based on the inclusion criteria in the study, it can be seen that a total of 33 subjects met the inclusion criteria. A total of 33 subjects met the inclusion criteria and participated in the study, with 57.58% being males and 42.42% being females, and the mean age being 43.24±15.79 years, as shown in Table 1.

Table 1 Patients' characteristics of 2 setting

Characters	Results (N=33)
Age	
Mean (SD)	43.24(15.79) years
Range	27-79 years
Gender (N, (%))	
Male	19(57.58)
Female	14(42.42)
Potassium level (SD)	3.9(0.36) mM
Medication regimens (N, (%))	
Levofloxacin based.	27(81.82)
Moxifloxacin based.	6(18.18)
Clofazimine based.	33 (100)
Baseline QTc	428.58(37.64) msecs
Hypokalemia (%)	2 (6.06)

Two patients (6.06%) had hypokalemia during QT prolongation, but no comorbidities contributing to QT prolongation were found.

From Table 2 and Table 3, it was found that baseline potassium levels and QTc values of Makarak Hospital were higher than those experienced at the Central Chest Disease Institute of Thailand.

Table 2 Patients' characteristics of the Central Chest Institute of Thailand

Characters	Results (N=27)
Age	
Mean (SD)	39.11(13.31) years
Range	20-73 years
Gender (N, (%))	
Male	16(59.26)
Female	11(40.74)
Potassium level (SD)	3.87(0.36) mM
Medication regimens (N, (%))	
Levofloxacin based.	25(92.59)
Moxifloxacin based.	2(7.40)
Clofazimine based.	27 (100)
Baseline QTc (SD)	424.19(39.57) msecs

Table 3 Patients' characteristics of Makaruk Hospital

Characters	Results (N=6)
Age	
Mean (SD)	61.83(12.94) years
Range	41-79 years
Gender (N, (%))	
Male	3(50)
Female	3(50)
Potassium level (SD)	4.02(0.49) mM
Medication regimens (N, (%))	
Levofloxacin based.	2(33.33)
Moxifloxacin based.	4(66.67)
Clofazimine based.	6 (100)
Baseline QTc (SD)	448.33(18.84) msecs

2. The prevalence of QT prolongation

Analysis of the patient data attained during the study period identified two cases of QT prolongation from a total of 33 patients who met the inclusion criteria and participated in the study.

$$\text{Prevalence} = \frac{\text{total number of patients with new and old QT prolongation.}}{\text{Patients receiving Bedaquiline at the time.}}$$

The prevalence of QT prolongation was 6.06% in patients receiving regular doses of bedaquiline (400 mg daily for the first 2 weeks and 200 mg 3 times weekly for a total of 22 weeks) as shown in Table 4.

When focusing on the prevalence of QT prolongation at the Chest Institute of Diseases, it was found that the prevalence of QT prolongation was 3.7% in patients receiving regular doses of bedaquiline (400 mg daily for the first 2 weeks and 200 mg 3 times weekly for a total of 22 weeks). The prevalence of QT prolongation at Makaruk Hospital was 16.67% in patients receiving regular doses of bedaquiline (400 mg daily for the first 2 weeks and 200 mg 3 times weekly for a total of 22 weeks) as presented in Table 5-Table 6.

Table4 The prevalence of QT prolongation in patients taking a short-acting oral regimen containing bedaquiline in 2 setting

Total number of participants	33
Participant who had QT prolongation	2
Prevalence	6.06

Table 5 The prevalence of QT prolongation in patients taking a short-acting oral regimen containing bedaquiline. At the Central Chest Institute of Thailand

Total participants	27
Participant who had QT prolongation	1
Prevalence	3.7

Table 6 The prevalence of QT prolongation in patients taking a short-acting oral regimen containing bedaquiline at Makaruk hospital

Total number of participants	6
Participant who had QT prolongation	1
Prevalence	16.67

3. The relevant risk factors and QT prolongation

After patients received a short-term oral regimen containing bedaquiline, QT prolongation was assessed among all patients in this study (33 patients). We also screening of risk factors according to the literature review. One case of the Central Chest Institute of Thailand, both of which had hypokalemia with the use of clofazimine and a fluoroquinolone class of drugs. which may promote QT prolongation.

A male patient from the Central Chest Institute of Thailand who had multidrug-resistant tuberculosis received a short-term regimen containing bedaquiline with a baseline QTc of 271 msec. In the third month, the patient had QTc prolongation with a QTc value of 528 and hypokalemia (3.2 mmol/l). When the serum potassium level was restored to the normal range, the QTc value returned to the normal range of 384 msec within the next six days. When the serum potassium level was restored to the normal range, the QTc level dropped back to the normal range of 384 msec over the next six days.

A female patient from Makaruk Hospital who was a multidrug-resistant tuberculosis patient received a short-term regimen containing bedaquiline. In the third month, QT prolongation with a QTc of 538 msec was associated with hypokalemia at 3.17 mmol/l. Upon discontinuation of bedaquiline, the patient's QTc decreased by month 9, the patient's QTc was 498 msec.

Discussion

This study was conducted retrospectively from medical records in patients with multidrug-resistant pulmonary tuberculosis at Makaruk Hospital and the Central Chest Institute. The data was collected from 1 June 2020 to 31 December 2021. Because we collected data before and after receiving the short course bedaquline regimens, we can be confident that fluoroquinolone is not a risk factor for QT prolongation in this case. Furthermore, according to the literature (Nachimuthu et al., 2012), fluoroquinolone has an uncommon influence on QT prolongation.

This study's prevalence of QT prolongation differs from that of Borisov et al. (2017), who obtained information from prospective data on adverse events related to a bedaquiline-containing tuberculosis regimen. QT prolongation was found in 24 of 248 individuals. It reflected a prevalence of 9.7%, which was greater than the prevalence found in this study. This could be owing to the large number of patients involved and the longer duration of the Sergey E. et al investigation. Furthermore, these groups exhibited stronger resistance to fluoroquinolones than our research, which increased the likelihood of prescribing bedaquiline-containing regimens.

Two cases of QT prolongation were reported after a short-term oral regimen containing bedaquiline, with a prevalence of 6.06%. The prevalence in the Central Chest Institute of Thailand was 3.7%, while the prevalence of Makaruk Hospital was 16.67%. The prevalence of the two places was quite different. This may be due to the difference in the number of participants in the two settings.

Because access to patient information is difficult at Makaruk Hospital, the prevalence of QT prolongation was higher. In the past, 26 patients were using short-term regimens. One patient died of unknown causes. One patient could not follow up on treatment. A further 18 patients were able to access information in the medical records of the study, and only six of the study participants met the criteria for entry. The QTc of patients at

Makaruk Hospital was higher than the baseline QTc of patients at the Central Chest Institute. This may be a factor contributing to the higher prevalence of QT prolongation at Makaruk Hospital.

The significance of this study is the early reporting of the present prevalence situation of adverse medication reactions to bedaquiline, which is often used in MDR-TB in Thailand. This data is valuable for adverse drug reaction monitoring. Based on our information, three months of monitoring was recommended because QT prolongation occurred during the first three months of drug treatment in both cases. The study's limitation was that it was conducted during the COVID-19 outbreak. The number of patients was insufficient to conduct a statistical analysis of the risk factors linked with QT prolongation. Furthermore, bedaquiline was rarely utilized at the time because it was only mentioned in the Thai tuberculosis treatment policy for 1-2 years. More prospective studies should be conducted.

Conclusion and Suggestions

The prevalence of QTc prolongation was 6.6%. The founded risk factor was hypokalemia. This prevalence study may lead to the development of a risk assessment tool for monitoring QT prolongation in patients who received a shorter all-oral bedaquiline-containing regimen and 3 months of monitoring is suggested.

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