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ANALYSIS OF QTC PROLONGATION DUE TO BEDAQUILINE IN TUBERCULOSIS PATIENTS – A RETROSPECTIVE STUDY.

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Abstract

Introduction: Bedaquiline should be administered under direct observation along with standard MDR-TB regimen. Recommended dose is 400 mg once daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks. After 24 weeks of Bedaquiline therapy, MDR-TB regimen should be continued as per national TB treatment guidelines. The observed prolongation of the QT interval and potentially fatal cardiac arrhythmia may or may not be related to interference with membrane associated cation transports.

Aims and objective: To analyze QTc Prolongation in patients who received Bedaquiline in District tuberculosis center at Rajkot.

Material and method: All the patient who received and actively followed and developed QTc prolongation as Adverse Drug Reaction were included in the study. Demographic parameters and detailed information about ECG changes due to QTc Prolongation was noted from patient treatment sheet. Interim analysis was done in this study. Adverse drug reactions data was collected in Adverse Drug Reaction(ADR) form (version 1.3) by Indian Pharmacopoeia Commission. The ADR related data can be accessed through - https://vigiflow-in.who-umc.org.

Result: Total 30 patient who received Tablet Bedaquiline were included in the study. Out of which 18 (60%) were males and 12 (40%) were females, Mean age of patient was 28.3 (years) ± 11.6 SD, Mean weight of patient was 48.2 (kg) ± 5.6 SD and 2 patient died due to cardiac arrest.

Statistical analysis: Descriptive analysis like mean, standard deviation and percentage was done using excel office version 2016.

Conclusion: Long QTc prolongation was noted more among male patients weighing 41 to 50 kg. Among all the participants, majority were having QTc prolongation and two death were observed during treatment of Bedaquiline. The patients will be further followed up for outcome analysis.

Keywords: Bedaquiline, QTc interval, adverse effect.

Introduction

Tuberculosis (TB) is a major threat to world health. After HIV/AIDS, it is the most common cause of death from an infectious disease worldwide. One of the major obstacles to TB control is the emergence of mycobacterial resistance to anti-tuberculous chemotherapy.[1] Tuberculosis is a chronic granulomatous disease and it continues to remain a major

health problem in developing countries. Burden of Tuberculosis in India still very high. The Revised National Tuberculosis programme for Cure and Prevention of TB was launched in 1997. [2]. In the year 2016 new drug bedaquiline was added to multi drug resistant TB(XDR). The outcome of MDR-TB patients has remained suboptimal. In a recent meta-analysis, reported cure rate for MDR-TB patients was about 54% to 64%.[3] Bedaquiline is recommended as 400 mg once daily for 2 week followed by 200 mg thrice weekly for 22 week(total of 24 weeks). Hospitalization is done for a minimum of 2 weeks and sometimes longer as required. Subsequently, patients are referred to their respective DOT sites for continuing the treatment. The sputum cultures, ECG monitoring and blood tests are done as per the bedaquiline guidelines. After 24 weeks of bedaquiline therapy, second line drugs are continued as per National tuberculosis treatment guidelines. (Isoniazid, Pyrazinamide, Moxifloxacin and Pyridoxine).The QT interval in ECG, represents the depolarization and repolarization of the ventricles and is usually corrected for heart rate (QTc). Previous studies have shown that women have a reduced repolarization reserve and greater susceptibility to the QTc prolongation to some drugs .[4]The observed prolongation of QT Interval and potentially fatal cardiac arrhythmia may or may not be related to interference with membrane associated cation transport, Specifically Potassium transport in cardiomyocytes secondary to cationic amphiphilic properties, an issue that requires investigation.[4 QT intervals and heart rate at all sites and heart rate measured by ECG machine. Bazett's formula continues to be the most commonly used formula for QT rate correction in spite of the fact that it severely overcorrects at high heart rates. [6] The present study was planned to observe QTc interval at various time points of drug administration and analyse any prolongation in patients who have received bedaquiline in District Tuberculosis Center (DTC) at Rajkot.

Material and methods

Study design and population

This was a retrospective descriptive study conducted at District Tuberculosis Centre and Civil Hospital, Rajkot. The population consisted of all the patients who were initiated bedaquiline as per selection criteria of RNTCP program, all patients were actively followed and observed for QTc prolongation as adverse drug reactions. QTc A Schiller CP300 electrocardiograph (Schiller Healthcare India Pvt. Ltd., Mumbai, India) was used to automatically calculate QT intervals and heart rate at all sites and heart rate correction was performed using the Fridericia formula. [5] .All reactions were also reported in pharmacovigilance program of India by ADR monitoring Centre, PDUMC, Rajkot between January 2019 to March 2020.

Ethical approval:

Ethical approval was obtained from the institutional ethics committee prior to start of this study.

Data collection

Demographic parameter, comorbid condition, past medical/medication history, relevant laboratory test, drug details and detailed information about ECG changes due to QTc Prolongation was noted from patient treatment information sheet. QTc was reported by a calibrated 12 lead ECG machine which gave the reading by Bazett's formula. Interim analysis was done for 2 months in this study Adverse drug reactions data was collected in Adverse Drug Reaction(ADR) form (version 1.3) by Pharmacovigilance program of India. Reaction terminology was confirmed with Medical Dictionary for Regulatory Activities (MedDRA) in vigiflow. The ADR related data can be accessed through - https://vigiflow-in.who-umc.org

Outcome variables:

Suspected ADRs were assessed for causality, preventability and severity using WHO causality assessment scale & Naranjo algorithm, modified Schumock & Thornton's criteria and modified Hartwig's criteria

respectively. WHO causality assessment scale incorporates causality terms based on different assessment criteria. . The association between suspected drug & Reaction was assessed as probable.[7] The degree of association of an ADR with a drug was done with the help Naranjo algorithm which involves assigning score to a set of questions. The total score for a particular ADR was calculated and the association was termed into one of the category– probable (score 5-8) .[8] Modified Schumock and Thornton's criteria have section namely probably preventable each consists of three questions.[9] Severity of the identified ADRs was assessed at different levels, ranging between 1 and 7.Level 7 considered as severe ADRs. [10]

Statistical analysis:

Descriptive analysis like mean, standard deviation and percentage was done using excel office version 2016.

Results

A total 30 patients who received tablet bedaquiline were included in the study. The mean age of the patient was 28.3 ± 11.6 years and mean weight was 48.2 ± 5.6 kg. Majority of patients developed QTc interval prolongation within 24 hours. Most common comorbid condition was diabetes and HIV. Severity of QTc prolongation was found more in male (60%) as compared to females (40%). Majority have long QTc (84%) as compared to possible long (13%). Considering sex wise distribution , majority have long QTc interval in males (57%) and in females (27%). (Table-1)

Regarding preventability, majority have probably preventable (84%) QTc prolongation.. As shown in Table-2 majority of patients belonged to weight group of (41-50) kg. As this was interim analysis, So out of 30 patient 28 patients (93%) are still under treatment and 2 Patient were died due to cardiac arrhythmia.

Table 1: Severity and Preventability assessment of QTc Prolongation

Gender	**Male**	**Female**	**Total**
Number	18 (60%)	12(40%)	30 (100%)
Normal QTc	0	1 (3%)	1 (3%)
Possible long	1 (3%)	3 (10%)	4 (13%)
Long QTc Interval	17 (57%)	8 (27%)	25(84%)
Probably Preventable	17 (57%)	8 (27%)	25 (84%)
Not Preventable	1 (3%)	4 (13%)	5 (16%)

Table 2: Assessment between QTc Prolongation and Weight

Weight(Kg)	**Normal**		**Possible Long**		**Long**	
Range	M	F	M	F	M	F
30-40	-	-	-	-	1	1
41-50	-	-	**1**	**3**	**9**	**5**
51-60	-	1	-	-	7	2

Discussion

Bedaquiline is a novel drug which is used for treatment of pre-XDR and XDR TB patients as per RNTCP guidelines under CAP (Conditional Access Programme) at the National Institute of Tuberculosis & Respiratory Diseases. Even small average increases in the QTc may translate to a substantial number of patients developing drug-induced long QTc syndrome when treating a large population.[11] However, little is known about the QTc effects of standard first-line drugs, because initial studies for these drugs were performed before it became customary to assess QTc prolongation effects in advance of introducing a new medicine to the market .[11]

Our result showed that mean age of the patient was 28.3 years which was almost similar to study done by Singla N et al and Udwadia JF et at receptively. [12,13] Our finding observed that more males (60%) affected as compared to females (40%) which was also similar to study done by Singla et al. [12] but opposite to study done by Udwadia et al in which more females were effected.[13] Majority of our patients received concomitant regimen was isoniazid, pyrazinamide, moxifloxacin and pyridoxine means sensitivity to isoniazid was maintained which was opposite to finding of the study where 100% patients were resistant to isoniazid.[13] Most common comorbid condition was diabetes and HIV which was similar to study done by Marks et al. [14]

Our result showed that majority have long QTc (84%) as compared to possible long (13%) which was opposite to study where QTc prolongation between 480 & 500 Ms were reported in 37 patients and 500> Ms in 13 patients.[12] Considering sex wise distribution , majority have long QTc interval in males (57%) and in females (27%) this can be correlated by the study which state that two new QTc formulas we developed both minimized the bias in the upper normal limits of QTc and enabled establishment of improved criteria for prolonged QT for both sexes and all ages from 5 to 89 years.[15]

Our result observed that QTc prolongation are preventable, a careful monitoring of the patient. As this was interim analysis, Out of 30 patient 28 patients (93%) are still under treatment and 2 Patient were died due to cardiac arrhythmia. The main safety concern of Bedaquiline is cardio toxicity. The QTc prolongation was detected through routine monitoring with regular electrocardiography. There are 47 (16.45%) deaths reported in the study, most of these were due to poor general condition at the onset of treatment.[12]

Unfortunately, as limited information was provided on the frequency of ECG monitoring, we cannot provide additional evidence regarding the ideal monitoring frequency. Nevertheless, we can confirm the current recommendation to perform ECG before starting bedaquiline and at least at weeks 2, 4 and every following month. [16] The management of cardio toxicity needed timely ECG, electrolyte testing and correction of electrolytes. Training the treatment supporters in recognizing the commonly occurring adverse reactions and referring the patient to appropriate treatment facility providing timely action can lead to greater adherence to treatment and reduction in loss to follow-up and prevent ADR.[12]

Conclusion

Long QTc was observed more among male weighing 41 to 50 kg and mortality was presented in two patients. Adverse reactions do occur with these regimens but are preventable. It requires strengthening of infrastructure in terms of training the peripheral staff for early identification and management of common adverse drug reaction and making ECG and electrolyte testing available. Also needed is developing coordination and linkages mechanisms for timely referral and management of adverse drug reactions.

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