- **Article title: QT changes of unforeseen implications and bedaquiline: an observational study**
- **Short running title:.** Bedaquiline induced QT changes
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- *The authors confirm that the Principal Investigator for this paper is Sandip Mukhopadhyay (and Dr. Rupam Kumar Ta Co-investigator) and had direct clinical responsibility for patients.*

- **Ethical disclosure:**

  "The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. Anonimysed data of human subjects were collected without personal identifier from patients records with permission from the Hospital authority

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What is already known about this subject'

Bedaquiline might be linked to QT prolongation (occasional reports from the Clinical trials)

'What this study adds':

In the real world patients of MDR and XDR TB, Bedaquiline causes alarmingly high numbers of QT prolongation events in first two weeks. It may also cause QT reduction in a subset of patients. All such changes must be monitored intensively as these may lead to unknown serious consequence.

Title: QT changes of unforeseen implications and bedaquiline: an observational study

- **Abstract:**

Background: Bedqauiline (BDQ) is a relatively new agent for multidrug (MDR) and extremely drug resistant (XDR) TB. It is important to look for cardiac safety and the bizarre adverse reactions after initiation of the drugs from the real world studies.

Methods: An observational study was conducted on the institutionalized MDR and XDR patients under the conditional access program of BDQ in India. Daily ECG, adverse events and change in laboratory values for first two weeks were recorded with mortality and serious adverse events till first three months of initiation of BDQ containing regimen.

Results: Among the total of 49 patients, nausea (n=33) was the most reported side effect. Though a mean rise of QTcF (12%) was noted after 14 days, individually, both prolongations (QTcF >440 ms) and shortening (from baseline values) of QTcF were noted in 95.92% (n=47) and 89.8% (n=44) patients. Three distinct QT patterns noted in ECG were, a) initial rise then fall (n=8), b) initial fall then rise (n=9) and c) rise followed by further rise (32). There was no serious adverse event leading to drug withdrawal or mortality in the first three months.

Conclusions: Prolongation of QTcF occurs in alarming numbers during first two weeks of BDQ therapy as well as shortened QT. However, BDQ was otherwise tolerated well by the real world MDR & XDR-TB patients in short term. Intensive ECG and clinical monitoring is recommended to detect possible serious implications of such ECG changes in the long term.

- **Keywords:** Bedaquiline, MDR-TB, XDR-TB, QT prolongation, QT reduction, adverse events, tuberculosis, nausea, short term safety

Title: QT changes of unforeseen implications and bedaquiline: an observational study

Introduction:

Drug resistant tuberculosis (DR-TB) is now a threat to the global community with rifampicin resistant, multi-drug resistant TB (MDR-TB) with resistance to both rifampicin and extensive drug resistant TB (XDR-TB) where resistance is found to rifampicin, isoniazid and fluoroquinolones (FQ). It was found that 20% of the previously treated cases and 3% newly diagnosed cases are MDR-TB. XDR-TB is now reported from 105 countries and approximately 9.7% MDR-TB patients are actually XDR.[1] Only 50% MDR-TB patients could be treated successfully. It was also found that MDR-TB constitutes 1/3 of the total deaths from antimicrobial resistance globally.[2] Bedaquiline, delamanid and pretomanid are three new antimicrobial agents which are potential weapons to fight the antimicrobial resistance of the TB bacilli.[3] Bedaquiline (BDQ), a diaryquinoline class of antimicrobial, was the first anti-mycobacterial agent to be developed in several decades. This new drug demonstrated inhibitory action against the proton pump for ATP Synthase of *Mycobacterium sp*.[4] A number of studies had been conducted in different parts of the world with BDQ and demonstrated a better 'sputum conversion' with BDQ-combining regimens compared to non-BDQ regimens.[5–11] Moreover, BDQ-containing regimens were also found to be more cost-effective than other injectable-containing regimens and can reduce total health provider treatment expenditure.[12]

Bedaquiline received approval in the USA from the Food and Drug Administration in 2012, in Europe in 2014 from the European Medicines Agency and later in South Korea, South Africa, India, the Russian Federation and Peru by the 2014-15.[13–15] It should be remembered that the drug received an accelerated approval in the USA after phase 2b study.[16] Considering higher number of deaths in the BDQ arm, the drug received a black-box warning from US-FDA though the deaths could not be related to BDQ.[17] Though the drug appeared to be a

great hope in the DR-TB patients, is still very new in most of the countries and there is limited pharmacovigilance data and data from phase 4 trials. BDQ has some intricate risks like possible cardiac toxicity due to its action on the hERG potassium channels, possibilities of hepatic damage, phospholipidosis as well as potential drug interactions.[18]

Cardiac safety is still a grey area with BDQ that needs evaluation. The 'idiosyncratic, bizarre or novel' reactions that may occur in initial phase of treatment when the body responds to the new compound 'acutely', often remains undetected in clinical trials and needs detection from the real world studies.[19] TB burden is high in India with 27% of the global TB cases and MDR-TB in 14% previously treated and 2.4% new patients.[1,20] BDQ had been incorporated into the Revised National Tuberculosis Control Program (RNTCP) in 2016 in India for MDR-TB cases in a conditional access program.[20] Therefore, the present study has been planned to elicit a safety report on bedaquiline on the DR-TB patients during their 'institutionalized treatment phase' under the 'conditional access program' in India which can allow daily intensive ECG monitoring and daily adverse effect data collection from the real world patients.

Materials and Methods:

This study was a descriptive observational study a period of one year from August 2018 on the DR-TB patients under bedaquiline therapy at the DR-TB Center of a Tertiary Care Medical College Hospital located at Eastern part of India and followed the STROBE guidelines. The study commenced after receiving approval from the Institutional Ethics Committee and the administrative authority of the hospital. Data of all the MDR & XDR-TB patients receiving their first bedaquiline therapy under the conditional access program of the Revised National TB Control program (RNTCP) in the above mentioned center were

collected in the study. The data collection and storage was anonymized and hence a 'waiver of consent' was obtained from the Institutional Ethics Committee for this research.

As per the protocol of the conditional access of bedaquiline in the RNTCP, the 'eligible' DR-TB patients selected for bedaquiline therapy were admitted in the DR-TB centers for initial 15 days of treatment or longer in cases of special situations.[21] All MDR-TB patients with additional resistance to fluoroquinolones received the bedaquiline containing regimen containing *6 months BDQ+ 6-12 months Kanamycin (Km), Ethionamide (Eto), Cycloserine (Cs), Pyrazinamide (Z), Linezolid (Lzd), Clofazimine (Cfz) to be followed by 18 months of "Eto-Cs-Lzd-Cfz"*. The regimens used for XDR-TB were *6 months BDQ+ 6-12 months of Capreomycin (Cm), Ethionamide (Eto), Cycloserine (Cs), ethambutol (E), Pyrazinamide (Z), Linezolid (Lzd), Clofazimine (Cfz), followed by 18 months of "Eto-Cs-Lzd-Cfz-E". Same dose of BDQ were used in MDR and XDR TB (supplementary appendix Table S1).* All the patients received oral pantoprazole 40 mg twice daily, domperidone 10 mg thrice daily and vitamine b complex tablets once daily and paracetamol 500mg on p.r.n. basis.

The baseline data collection was primarily a) demographic and baseline clinical data, b) baseline laboratory data including renal function, liver function, blood sugar and a list of other investigations are done routinely before starting the treatment, and c) Baseline ECGs.

In the two weeks, the data collection consisted a) daily clinical and laboratory data b) the reported adverse events and c) daily ECG. During this period the patients are closely monitored daily by team of nurses, healthcare workers and attending Physicians. There were also unscheduled visits in cases of emergencies. Data of all such rounds and visits, laboratory investigations and ECG are recorded on real-time basis. Adverse events records of the patients were noted.

ECG data for each day of the two weeks were evaluated for QT prolongation and other significant changes during this time. As the absolute QT values alter due to heart rate, a

'corrected QT' (QTc) value is calculated from the observed QT values. 'Corrected QT' interval could be obtained using Bazette's formula (QTcB) or Friedricia's formulam(QTcF). The Bazette's formula however has its own limitations. As per the RNTCP guideline for BDQ usage, the corrected QTcF should be looked at as reference for using, monitoring or withholding bedaquiline during the course of treatment involving Friedricia's formula.[22] Values above 440 ms are considered as prolonged QTcF and >500 ms is indicated for cessation of therapy. Corrected QT by Friedricia's formula (QTcF) is calculated as $\boldsymbol{QTcF = QT / 3\sqrt{(RR\ Interval)}}$ where *RR Interval = 60 / Heart rate.*[23]

All adverse events, reported as well as obtained from laboratory parameters and ECG recordings, were analyzed for causality by WHO-UMC scale. Record mortality and serious adverse events during this period was also recorded.

After these two weeks the patients are generally discharged and allowed to take medication at their home. A follow up at three months were considered to record serious adverse event or mortality beyond the institutionalized period.

Statistical analysis:

All obtained data were tabulated and descriptive statistics were applied. The statistical differences in mean QTcF values among day 1, day 7 and day 14 of bedaquiline therapy were tested using Repeated Measures ANOVA test. All statistical tests were performed using IBM SPSS ver. 20.0.

Results:

Total 49 patients were recruited in this study and had a relatively younger age with mean age of 38.63±1.63 years. Gender distribution was predominantly skewed with male more than 65%. Most of them were smokers (Table 1a).

Laboratory parameters were included both haematology and blood biochemistry. Apart from complete blood count, liver function, renal function, lipid profile and serum electrolytes were routinely done at baseline in all the patients. All these parameters were mostly within normal limit except a number of cases for low haemoglobin value (Table 1b).

A. **General and Patient reported adverse events:** A total of 124 patients' reported adverse events or symptoms were recorded during the 14 days in-hospital period. Nausea was the most commonly reported complaint (n=33) followed by headache (n=30) and arthralgia (n=28) (Table 2a). Nausea was also reported as 'most troubling symptom'. There were also reports of other complaints like diarrhea, anorexia, chest pain and hemoptysis. However, all these adverse events were of milder severity (grade 1 or 2).

B. **ECG changes:** A total 686 ECG recordings were evaluated from the 49 patients for for QTcF value and any other changes during the two weeks. QT changes remained varied; often bidirectional that included both prolonged and shortened QT in the same patient.

   B.1: QT prolongation: An overall 17.13% (72 ms) mean rise of QTcF over the baseline was noted and was statistically significant ($p < 0.001$). Total 95.92% (n=47) patients had prolonged QTcF of >440 ms from during day 2-14 of bedaquiline therapy (278 observations).

   There were 69 observations of QTcF values >500 ms. Overall 61.22% (n=30) patients had developed QTcF >500 ms during day 2-14. The incidence of such value was maximum on day 14 (n=9) (Figure 1). All values of QTcF within normal range (<440 ms) were found in only 2 patients.

   B.2: QT reduction: At least one or more value of QTcF below the baseline (mean 4.7 and median of 3 values per patient) was noted in 44 (90%) patients during these two

weeks. Such lowering varied from 1 episode to all 13 episodes in some patients of ECG recording during day 2-14.

B.3: QT patterns: On further analysis of data, the QTcF values were found to follow three distinct trends: 1) initial rise then fall (n=8), 2) initial fall then rise (n=9) and 3) rise followed by further rise (n=32) (Figure 2a, 2b, 2c and Figure 3). A subgroup analysis was carried out in these patients (supplementary appendix Table S2 and Table S3). Though majority patients had shown only rising trend (n=32) of QTcF value, fall in QTcF at some point of time (subgroups 1 & 2) was noted in 34.7% patients which was an appreciable number (n=17). Such fall in QTcF value was not a result of stopping any drug or adding any new therapy. The distribution commonly reported adverse events among these subgroups are shown in table 2b.

C. Causal association: Causality analyses were carried out for all the commonly occurring ADRs and ECG chages using WHO-UMC scale. As per the WHO-UMC scale, the adverse events are categorized in to ‘certain’, ‘probable’, ‘possible’ and ‘unlikely’ denoting the strongest to weakest causal association respectively. In the absence of ‘dechallenge’ and ‘rechallenge’ there was no ‘certain’ or ‘probable’ causal relationship of the ADRs with bedaquiline. Majority of the recorded adverse reactions would fall under the ‘possible’ category (Table 3).

D. Mortality & SAE: There was no mortality during first three months of initiation of therapy. There was no other serious adverse event to withhold medication during this period.

Discussions:

The present observational study was targeted to detect the short term safety of bedaquiline in the MDR and XDR-TB patients over a period of initial 15 days from starting the therapy. Nausea, headache and arthralgia were commonly reported with no major change in laboratory

parameters. Mean QT interval was increased as a whole. High number of patients developed QT prolongation during first 14 days. Three distinct pattern of QT changes were noted where a subgroup of patients shown rise followed by fall in QTcF, another subgroup showing a fall of QTcF followed by rise and the third subgroup shown only rise in QTcF which were a commoner finding than previous two. Reduction of QTcF is a relatively new finding which needs to be investigated further.

Initial studies and reports including one on naïve TB patients found reported only occasional side effects with BDQ.[11,24,25] In contrast, the present study was on DR-TB patients and general side effects were often reported with nausea the commonest. Relatively higher incidence (in 83% patients) of treatment emergent adverse events (TEAE) was noted in another phase II study from Japan. However, other than nausea, many of these AEs were different from our present study.[26]

Alarmingly high incidences of QT change including QT prolongation as well as reduction in QT interval were observed in our study. QT prolongation beyond >500ms (QTcB or QTcF) is considered to increase the risk of torsades de pointes (TDP) by two to three folds and may lead to prolonged hospitalization and increase in all cause mortality.[27] Reports of QT prolongation were inconsistent in some of the previous BDQ studies and some did not notice any QT prolongation.[11,24–26] However, some other studies did notice QT prolongation following bedaquiline use. This includes a phase 2b study enrolling 160 MDR-TB patients where mean increase in QTcF of 15.4 miliseconds (ms) were noted following 24 weeks of bedaquiline containing anti-TB regimen with a maiden episode of QTcF >500 ms.[28] Consistent rise in QTcF above 500 ms from the 5th week of therapy was reported in an XDR patient on BDQ, delamanid and clofazimine.[29] A small number of drug withdrawals were reported (8 out of 1044 patients) in a larger survey (TBnet study) due to QT prolongation. One death was reported due to heart block from accidental gross overdosing of bedaquiline

during the continuation phase and was associated with QT prolongation.[30] A systematic review included the clinical trials, case reports and observational studies and found that despite use of BDQ in combination with other potential drugs like FQ, clofazimine, delamanid, pretomanid and azithromycin the increase in QT in most cases were < 20 ms. Out of total 1303 patients QT > 500ms were detected only in 42 patients. Many centers, though conducted monthly or weekly ECG to detect the QT changes, there were inconsistency in reporting QT and also in the frequency of ECG.[31] The reported incidences were much lower in these studies compared to our present study.

Many drugs can cause QT prolongation or TDP either alone or as a result of drug interaction.[27] The suggested most likely molecular mechanism for the acquired or drug induced long QT syndrome is a blockage of the inward rectifier potassium channel (IKr) which is also known as hERG channel. Due to a distinct molecular structure, the hERG channel remains susceptible to the actions of the drugs.[32–35] Genetic cause like mutation of the KCNH2 genes is considered to be associated with short QT.[36] The reason behind the very high number of cases of the prolonged QTcF is not clear in the present study. Possible reasons may be a) direct contribution of bedaquiline b) result of contribution of multiple background drugs like clofazimine to bedaquiline, c) phenotypic or genotypic variations of the patients d) closer observation with daily ECG evaluation. Whatever may be the cause; the findings of the present study may serve as an alert for possible serious implications on the patients' health in the long run.

Shortening of QT interval was not documented well in the previous clinical trials, large cohorts or case reports with bedaquiline and hence a novel finding of the present study. Such fall and also the subset of patients where QT interval had shown an initial fall followed by a rise was not associated with any major clinical symptom. The plasma electrolytes were within normal range during this period and the same ECG machine was used for recording the ECG

for all the patients. It is not known that whether such findings were missed earlier or did not occur. There is little explanation of such events and long term implications with our present knowledge. Possibilities of polymorphism of genes of hERG channel or other ion channels could not ruled out which were, however beyond the scope of the study.

The present study did not record efficacy of BDQ. Sample size and shorter follow up of ECG were some limitations of this study. However, the primary targets of the study namely a closer watch on the ECGs and detection of safety after drug exposure specifically for acute and bizarre AEs from the real world were achieved mostly. From the novel signals generated from this study, further studies should therefore be planned to explore the possible reasons and implications.

Conclusions:

We conclude that alarmingly high number of QT prolongation occurs in the MDR and XDR-TB patients receiving bedaquiline containing regimen during the first two weeks. Episodes of shortened QT without any short term clinical or laboratory abnormality is also possible in a subset of patients which has unknown implication in the long term. Intensive ECG monitoring and clinical follow up is therefore being recommended to detect QT changes receiving bedaquiline in combination with other anti TB drugs to avoid possible serious implications. Further studies including long duration studies, genetic studies and Pharmacovigilance studies are therefore recommended to explore the novel findings.

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Table 1a: Baseline demographic data of the enrolled DR-TB patients

		Number	%
Gender		32/ 17	65.3/ 34.7
Maietal status		35/ 14	71.4/ 28.6
*Age		38.63±1.63	
Family history of TB		0	
Smoking			
	No	18	36.73
	1	2	4.08
	2	5	10.2
	3	8	16.32
	4	10	20.4
	5	4	8.16
	6	2	4.08
Indication for bedaquiline			
	MDR-TB+ FQ resistant	44	89.8
	XDR-TB	5	10.2
Regimens			
	(6-12)CmEtoCsLzdZECfz +(6) Bdq	6	12.24
	(6-9)KmEtoCsZLzdCfz +(6)BDQ, followed by (18) EtoCsLzdCfz	43	87.76

* Value in mean ± standard error of mean (SE)

Table 1b: Baseline Laboratory parameters of the enrolled DR-TB patients

Parameter	Value (mean ± SE)
Haemoglobin (g%)	9.69± 0.30
TLC (/cmm)	8295.83± 239.33
N (/cmm)	66.67 ±0.62

E (/cmm)	2.94± 0.12
B (/cmm)	27.90± 0.59
L (/cmm)	2.33 ±0.11
M (/cmm)	26.10± 0.75
Serum Bilrubin- total (mg%)	0.80 ±0.01
ALT / SGPT (IU/L)	26.52± 0.47
AST /SGOT (IU/L)	24.79± 0.43
Alk. Phosphatase (IU/L)	144.96± 2.69
Total protein (g%)	6.73± 0.07
Albumin (g%)	3.81 ±0.05
Globulin (g%)	2.94 ±0.04
Urea (mg%)	13.48± 0.42
Creatinine (mg%)	0.86± 0.02
Serum Na^+ (mEq/L)	133.48± 0.42
Serum K^+ (mEq/L)	3.78± 0.04
Total cholesterol (mg%)	155.42± 1.55
Triglyceride (mg%)	107.85± 1.94
HDL (mg%)	39.38± 0.69
LDL (mg%)	81.71± 1.21
VLDL (mg%)	24.17± 0.64
Serum uric acid (mg%)	5.81± 0.08
Random Blood Sugar (mg/dL)	139.73± 4.03

Table 2a: Patient reported adverse events

Adverse Events	Sub-group 1 (n=49)
Nausea	33 (67.3)
Headache	30 (61.2)
Arthalgia	28 (57.1)
Anorexia	9 (18.4)
Diarhhoea	15 (30.6)
Chest pain	7(14.3)
Haemoptysis	2 (4.1)

* Nausea was reported most troublesome symptom (n=32)

Table 2b: Sub-groups and patient reported adverse events

Adverse Events	Sub-group 1 (n=8)	Sub-group 2(n=9)	Sub-group 3 (n=32)
Nausea	5 (62.5)	3 (33.3)	25 (78.1)
Headache	5(62.5)	6 (66.7)	19 (59.4)
Arthalgia	3 (37.5)	5 (55.6)	20 (62.5)
Anorexia	1 (12.5)	2 (22.2)	6 (18.75)
Diarrhoea	0	4 (44.4)	11 (34.4)
Chest pain	3 (37.5)	0	4 (12.5)
Haemoptysis	0	0	2 (6.2)

Table 3: Causality analysis* of the common adverse events

Adverse Event	Possible N(%)	Unlikely N(%)
QT prolongation	185 (66.5)	93 (33.5)
Tachycardia	9 (53)	8 (47)
Reported symptoms:		
Nausea	29 (88)	4 (12)
Headache	28 (93)	2 (7)
Joint pain	24 (86)	4 (14)
Anemia	4 (8)	45 (92)

* As per WHO-UMC causality Assessment scale

Figure legends:

Figure 1: Day-wise distribution of high QTcF values (QTcF >500ms)

Figure 2a: QTcF in Subgroup 1 during the first two weeks of initiation of BDQ (n=8).
Figure 2b: QTcF in Subgroup 2 during the first two weeks of initiation of BDQ (n=9).
Figure 2c: QTcF in Subgroup 3 during the first two weeks of initiation of BDQ (n=32).

Figure 3 : Comparison of Trends of QTcF during the first two weeks of initiation of BDQ.