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Promethazine use and QT prolongation risk during treatment with a shortened all-oral regimen for MDR/RR-TB

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Background: Shortened all-oral regimens for multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) combine multiple QTc prolonging agents, including bedaquiline and delamanid, which act partly through hERG potassium channel binding. Promethazine, a first-generation antihistamine used for nausea during TB therapy, shares this mechanism. Whether adjunctive promethazine further raises the risk of clinically relevant QTc prolongation in this setting is unclear.

Methods: We conducted secondary analyses from a prospective observational cohort study of patients ≥15 years in Lesotho who received a 9- to 12-month all-oral regimen (bedaquiline, linezolid, levofloxacin, clofazimine, delamanid) for pulmonary MDR/RR-TB. We modelled time-varying promethazine exposure using the Andersen-Gill formulation of Cox regression, with time-to-first grade ≥3 (>500 ms) QTc event as the outcome of interest. We conducted comparator analyses with time-varying exposure to metoclopramide, ondansetron, and episodes of nausea, dizziness, and vomiting.

Results: Among 247 participants (median age 41, 63.2% living with HIV), 62 (25.1%) received promethazine. Grade ≥3 QTc prolongation occurred in 10 (4.0%). Incident clinically significant QTc prolongation was higher during promethazine-exposed than unexposed periods (7.4 versus 1.3 per 10 000 person-days; HR 7.0, 95% CI: 1.4–35.3). No comparable elevation was seen in analyses of exposure to metoclopramide (HR 1.0, 95% CI: 0.3–3.6), ondansetron, or episodes of nausea, dizziness, or vomiting (HR 1.5, 95% CI: 0.3–6.9).

Conclusions: Promethazine use was associated with increased risk of clinically relevant QTc prolongation within a QTc-burdened all-oral MDR/RR-TB regimen. These findings provide preliminary evidence that clinicians may consider when selecting anti-emetics as part of MDR/RR-TB therapy with a shortened all-oral regimen and highlight the importance of evaluating adjunctive medications in DR-TB care.

Introduction

All-oral shortened regimens recommended by the World Health Organization for treatment of multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) contain multiple agents—such as bedaquiline, delamanid, clofazimine, and levo- or moxifloxacin—associated with QTc prolongation. In both clinical trials and subsequent prospective observational studies, regimens containing combinations of these agents have been shown to be generally safe and associated with low rates of clinically relevant events.[1–3] However, limited evidence exists regarding whether commonly used adjunctive medications with QTc prolonging potential, such as antiemetics, further increase QTc risk when added to MDR/RR-TB regimens, and whether the degree of added risk is different among agents of the same general class.

Promethazine is a first-generation H1-receptor antagonist that has been associated with QTc prolongation, thought to be mediated by direct hERG potassium channel binding.[4,5] This

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mechanism appears to be shared by bedaquiline, a cornerstone of all-oral shortened MDR/RR-TB regimens, by companion drug delamanid, and by their respective metabolites (e.g. M2, DM-6705).[6,7] Despite being an older medication with notable off-target effects, promethazine continues to be used for anti-emesis during TB therapy due to low cost and decades-long inclusion on national essential medications lists. Whether promethazine increases the risk of clinically relevant (>500 ms) QTc prolongation when co-administered with regimens containing other hERG antagonists remains unclear.

We conducted secondary analyses of data from a prospective observational cohort study evaluating a shortened, all-oral, five-drug regimen in Lesotho, where promethazine was commonly prescribed for nausea during TB therapy. Here, we evaluate whether promethazine exposure during treatment was associated with higher risk for new clinically relevant QTc prolongation.

Methods

Study population

Between September 2020 and October 2023, we enrolled patients ≥15 years with confirmed pulmonary MDR/RR-TB from national public sector referral hospitals within Lesotho's National Tuberculosis and Leprosy Program. Eligible, consenting participants received a standardized 9- to 12-month five-drug all-oral regimen consisting of bedaquiline, linezolid, levofloxacin, clofazimine, and delamanid. Outcomes and details regarding this study regimen have been reported.[8] In this analysis, we excluded participants with any grade of baseline QTc prolongation.

Outcome definition and assessment

The primary outcome was time to first clinically relevant QTc prolongation, defined as the first incident grade ≥3 (>500 ms) event occurring during treatment. Time-to-event was calculated as days from treatment initiation. Participants were monitored with EKG at baseline, 2 weeks, and monthly thereafter. Corrected QT intervals were calculated using Fridericia's formula. QTc prolongation events were reported using the Médecins Sans Frontières Severity Grading Scale.[9] Participants who experienced clinically relevant QTc prolongation contributed person-time until the date of the first event; those who did not have an event contributed person-time until the date of treatment completion, study withdrawal, or death.

Drug exposure

Promethazine exposure was identified from drug order records, and administration was ascertained by direct observation in both inpatient and outpatient settings. For patients managed as inpatients, all prescribed medications were administered by nursing staff. For patients managed as outpatients, all prescribed medications (DR-TB drugs and all adjunctive medications including promethazine) were administered under directly observed therapy (DOT) by an assigned treatment supporter.

All participants could contribute both exposed and unexposed person-time. Participants contributed exposed person-time during any period when an active promethazine prescription was recorded; multiple discrete exposure episodes per participant were permitted. Episodes included prescription start- and end-dates as exposed days. For the small number of prescriptions ($n=6$) without a recorded end-date, we imputed the median prescription duration across all episodes (14 days). Individuals stopped contributing person-time at the end of treatment or first occurrence of clinically relevant QTc prolongation, whichever came first.

Statistical analysis

We evaluated associations between promethazine exposure and incident QTc prolongation using Cox proportional hazards regression. Time-varying promethazine exposure was incorporated using the counting process (Andersen-Gill) formulation of the Cox model.[10] We estimated hazard ratios for developing new-onset grade ≥3 QTc prolongation during promethazine exposure versus non-exposure and used sandwich estimators to calculate standard errors.[11] We assessed the proportional hazards assumption using Schoenfeld residuals.

We repeated these analyses for exposure to two other common antiemetics, metoclopramide and ondansetron, used in the study setting. Because QTc prolongation associated with these other anti-emetics may occur through mechanisms other than direct hERG binding and inhibition (ex. sodium channel inhibition),[12–14] we hypothesized that exposure to these agents may have lower hazards for QTc prolongation, relative to promethazine. We used Cochran's Q test of heterogeneity to evaluate whether the magnitude of hazards differed between antiemetics. Given that nausea and vomiting may indicate a promethazine prescription and increase the risk of QTc prolongation (e.g. electrolyte derangement, secondary to emesis), we also repeated analyses for episodes of vomiting and of nausea, dizziness, or vomiting (time-varying). We conducted three sensitivity analyses: (1) using a shared frailty model, (2) adjusting for baseline QTc as a continuous variable in the Cox hazards model, and (3) excluding participants with prescription episodes with an unspecified end date.

All statistical analyses were conducted in STATA-19 (College Station, TX).

Research ethics

The Lesotho Ministry of Health and the Harvard Longwood Campus Institutional Review Board approved this study cohort. All participants provided written informed consent.

Results

Baseline characteristics

Of 255 enrolled participants, 8 had baseline QTc prolongation of any grade and were excluded from this analysis. Among 247 participants without baseline QTc prolongation, the median age was 41 years (IQR: 31–55), 73 (29.6%) were female, 156 (63.2%) were living with HIV, and 94 (38.2%) had baseline BMI <18.5. Median baseline QTc was 400 ms (IQR: 375–418). Sixty-two (25.1%) were prescribed promethazine sometime during treatment. Age did not differ between those who were (mean = 44) and were not (mean = 43.3) prescribed promethazine ($t=-0.3$, $P=0.8$). Median per-episode prescription was 14 days (IQR: 6–38); median prescription episodes per-person was 1 (IQR: 1–2, maximum: 5). The cohort accrued a total of 63 143 person-days of follow-up, of which 2690 (4.3%) were promethazine-exposed and 60 453 (95.7%) were unexposed (Table 1).

Grade ≥3 QTc prolongation events were observed in 10 of 247 participants (4.0%); median time-to-event was 208.5 days (IQR: 137–259 days) (Figure 1). Among those who developed clinically relevant QTc prolongation, five were never exposed to promethazine and five were exposed to promethazine sometime during TB therapy. Of the latter, two were actively taking promethazine at the time of the QTc prolongation event. Of these, one participant

Table 1. Time-varying univariable Cox proportional hazards models of incident QTc prolongation on exposures to promethazine, metoclopramide, ondansetron, and vomiting, nausea/vomiting/dizziness, STEM-TB Lesotho Cohort

	Exposure Status	Accrued At-Risk Person-Days	No. Incident QTc Events	Crude Rate (Events per 10 000 person-days)	Exposed versus Unexposed HR (95%CI)
Promethazine	Unexposed	60 453	8	1.3 (0.7–2.6)	7.0 (1.4–35.3)
	Exposed	2690	2	7.4 (1.9–29.7)	
Metoclopramide	Unexposed	35 238	6	1.7 (0.8–3.8)	1.0 (0.3–3.6)
	Exposed	27 905	4	1.4 (0.5–3.8)	
Ondansetron	Unexposed	61 621	10	1.6 (0.9–3.0)	–
	Exposed	1522	0	–	
Vomiting only	Unexposed	56 756	9	1.6 (0.8–3.0)	1.0 (0.1–7.4)
	Exposed	6387	1	1.6 (0.2–11.1)	
Nausea, vomiting, or dizziness	Unexposed	53 517	8	1.5 (0.7–3.0)	1.5 (0.3–6.9)
	Exposed	9626	2	2.1 (0.5–8.3)	

Exposed versus unexposed hazard ratios are from the counting process (Andersen-Gill) formulation of the Cox proportional hazards model. 95% confidence intervals are based on standard errors calculated from sandwich estimators, clustered by participant.

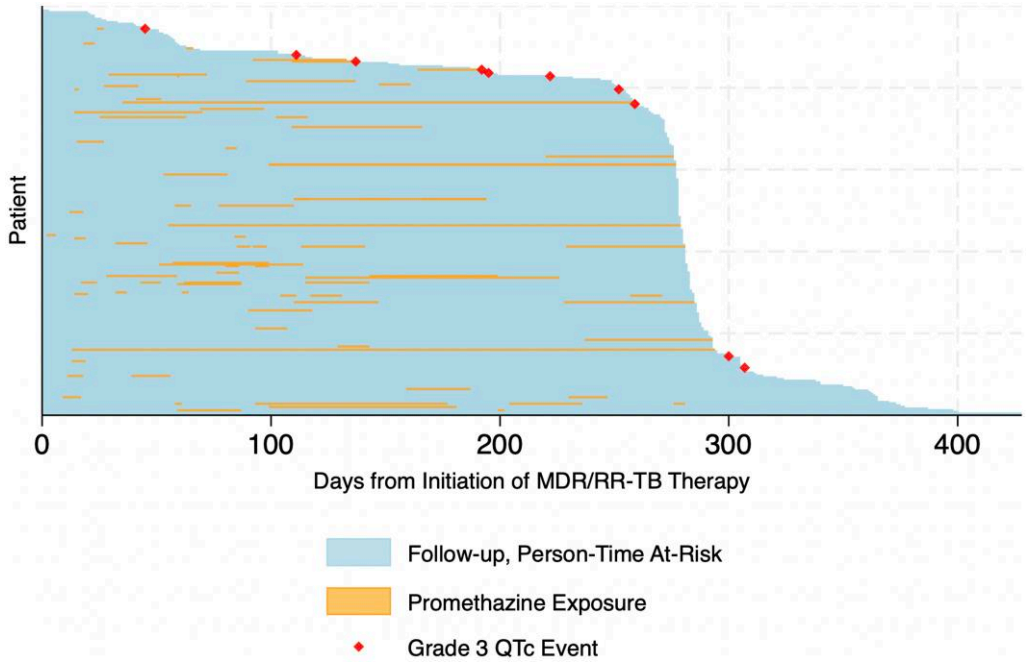


Figure 1. Swimmer plot of treatment duration, promethazine exposure, and incident QTc events during MDR/RR-TB therapy with a shortened all-oral regimen, STEM-TB Lesotho Cohort. Each individual horizontal line represents a single participant, with person-time at risk extending from the start of MDR/RR-TB therapy until the first of any of the following: a grade ≥3 QTc prolongation event, treatment completion, study withdrawal, treatment failure, or death. Filled red diamonds represent incident grade ≥3 QTc prolongation events. Participants ordered top to bottom by duration of total accrued person-time at-risk.

experienced a QTcF increase from 362 to 506 ms after initiation of promethazine, with subsequent reduction to 454 ms one month after promethazine was held. The second participant's QTcF increased from 450 to 503 ms after initiation of promethazine, but continued therapy on close monitoring and in one month was found to have a reduction to 472 ms. There were no cases of ECG- or telemetrically confirmed ventricular tachyarrhythmia within this cohort. Of the five participants with incident QTc prolongation but no promethazine prescriptions at any point during TB therapy, one died due to presumed out-of-hospital cardiac arrest two weeks following the detection of a grade-3 QTc event. Arrythmia in the setting of a recently prolonged QT interval was considered a possible cause of death but could not be ascertained.

The incidence of QTc prolongation was higher during promethazine-exposed periods than unexposed periods (7.4 versus 1.3 events per 10 000 person-days); promethazine exposure was associated with elevated hazards of QTc prolongation (HR: 7.0, 95% CI: 1.4–35.3) (Table 1). The proportional hazards assumption was not violated (Schoenfeld $P=0.92$). Similarly elevated hazards were observed in sensitivity analyses excluding the six participants with unspecified promethazine prescription end-dates (HR: 7.2, 95% CI: 1.4–36.0), adjusting for participant baseline QTc (aHR: 7.2, 95% CI: 1.5–34.3), or assessing promethazine exposure using a shared frailty model (HR: 8.4, 95% CI: 1.4–49.3).

No comparable elevation in hazard was observed with exposure (27 905 person-days) to metoclopramide (1.7 versus 1.4 events per 10 000 person-days; HR: 1.0, 95% CI: 0.3–3.6; Cochran's Q for comparison to promethazine: 3.4, $P=0.06$). No participants developed incident QTc prolongation during exposure to ondansetron (1522 person-days). We did not observe an increase in risk of clinically relevant QTc prolongation with episodes of vomiting alone (HR: 1.0, 95% CI: 0.1–7.4) or with exposure to of any episode of nausea, dizziness, or vomiting (9626 exposed person-days) (HR: 1.5, 95% CI: 0.3–6.9).

Discussion

Among individuals receiving a standardized all-oral shortened MDR/RR-TB regimen containing bedaquiline, delamanid, clofazimine, and levofloxacin—four agents with recognized QT prolonging potential—clinically relevant QTc prolongation was uncommon but associated with concurrent promethazine use. This association did not appear to be explained by confounding by indication; similar associations were not observed for comparator antiemetics (metoclopramide and ondansetron) or their indications (nausea, vomiting, dizziness).

This is among the first studies to examine the relationship between adjunctive medications and QTc risk for all-oral MDR/RR-TB regimens. One previous retrospective cohort evaluating bedaquiline-containing regimens identified exposure to azole antifungals as a risk for QTc prolongation during therapy.[15] QTc prolongation from adjunctive anti-emetic use during MDR-TB therapy has been discussed in-principle,[12] but there is limited empiric data evaluating the relative risk from exposure to different agents within this indication class. Although our findings should be interpreted with caution due to the small sample size, they raise the possibility that promethazine increases the risk of clinically relevant QTc prolongation in the context of an MDR/RR-TB regimen containing other QTc prolonging agents, with practical implications for symptomatic management during TB therapy. To reduce cardiac risk, clinicians may consider preferentially prescribing antiemetics other than promethazine.

Of note, metoclopramide and ondansetron also carry known QTc prolonging risk profiles but may induce prolongation through mechanisms other than direct hERG binding.[13,14,16] Our results are consistent with the idea that drugs with non-overlapping mechanisms may confer different levels of risk when used alongside a QTc-burdened MDR/RR-TB regimen and that risk-reducing antiemetic choices may exist. Further studies examining interactions between antiemetics and metabolites of QTc prolonging TB drugs, particularly at the interface of cardiac hERG channels, are needed to clarify the underlying pharmacodynamic mechanisms.

In the context of the Lesotho healthcare system, this study was conducted when initial management of nausea and vomiting typically involved use of metoclopramide. Promethazine was often selected as a secondary option during periodic metoclopramide stockouts. Ondansetron was not yet widely available. Our results emphasize the continued importance of strengthening health systems—including policy and infrastructure to improve the diversity of available adjunctive pharmaceuticals—alongside the scale-up of shortened all-oral regimens.

This study was characterized by a small number of incident QTc events, limiting multivariable adjustment and statistical precision. Residual confounding by unmeasured on-treatment factors cannot be excluded. Promethazine exposure was derived from prescription records rather than plasma drug concentrations. However, given its use in short-scheduled courses rather than long-term as-needed dosing, exposure misclassification is expected to be minimal.

This analysis provides preliminary evidence that warrants evaluation in larger cohorts. These findings underscore that optimizing DR-TB care involves not only selecting an effective TB regimen, but also evaluating adjunctive medications used in tandem. Reducing polypharmacy and selecting lower-risk options for symptom management may represent an opportunity to improve treatment safety.

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Study design: K.J.S., M.L.R., M.F.F., C.D.M., K.K.M, and L.M.
Analysis design: E.Q.L.S., M.F.F., and L.T.
Study implementation: S.M.,L.M., E.O., K.K.M., M.T., S.P., and L.O.
Data management: A.L., L.T., and K.K.M.
Statistical analyses: E.Q.L.S, M.F.F., and L.T.
Data interpretation: all authors.
First draft of the manuscript: E.Q.L.S and M.F.F.
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Disclaimer

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Data availability

To researchers with a methodologically sound proposal, pseudo-anonymized individual participant data that underlie the results reported in the text and tables of this article and a data dictionary may be made available upon request to the corresponding author, and execution of a data sharing agreement or alternate means that allow assurance that principles of Lesotho regulations will be met.

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