Eduvest – Journal of Universal Studies
Volume 5 Number 3, March, 2025
p- ISSN 2775-3735- e-ISSN 2775-3727

CHALLENGES OF MONITORING BLOOD LEVELS OF BEDAQUILINE IN DRUG-RESISTANT TUBERCULOSIS: A NARRATIVE REVIEW

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ABSTRACT

Bedaquiline, a second-line drug for drug-resistant tuberculosis (MDR-TB), is one of the latest generation drugs in the treatment of tuberculosis (TB). However, the challenge in determining the optimal dose and individual pharmacokinetic variability requires the implementation of Therapeutic Drug Monitoring (TDM). This article aims to evaluate the challenges of TDM bedaquiline through a narrative review of the current literature. Relevant articles were identified through computerized searches on PubMed and Google Scholar using a combination of keywords related to bedaquiline, pharmacokinetics, and TDM. Limited clinical data indicate a lack of standard exposure targets and reliable efficacy thresholds. Pharmacokinetic variability is influenced by factors such as age, weight, gender, genetics, comorbidities, and serum albumin. Technical challenges include the need for precise analytical methods and the accessibility of technology in clinical practice. The use of TDM for bedaquiline offers the potential to improve the efficacy of MDR-TB treatment, but more research is needed to address pharmacokinetic variability and develop standardized guidelines.

KEYWORDS *bedaquiline, tdm, pharmacokinetics, tb, mdr-tb*

INTRODUCTION

Tuberculosis (TB) is an infectious disease that can be treated and prevented, but it is also a disease that poses a threat to public health. TB ranks second as the second leading cause of death globally, after COVID-19, and causes twice as many deaths as HIV/AIDS (World Health Organization, 2023). Mycobacterium tuberculosis (Mtb) is the bacteria that causes tuberculosis. It is a pathogen that is very successful in infecting, especially the lungs, thus causing the classic pulmonary TB syndrome. In addition, these bacteria can affect other organs and tissues, including lymph nodes, brain, kidneys, and spine, in a condition known as extrapulmonary TB (Pai et al., 2016)

How to cite: Isra N et all (2025). Challenges of Monitoring Blood Levels of Bedaquiline in Drug-Resistant Tuberculosis: A Narrative Review. Journal Eduvest. 5(3), 3446-3459
E-ISSN: 2775-3727

Tuberculosis is a type of infectious disease prioritized by the WHO for drug research and development because patients with multidrug-resistant TB (MDR-TB) require complex and prolonged multi-drug treatment with expensive, highly toxic, and far less effective second-line drugs. The number of second-line drugs available to treat MDR-TB is very limited, and only 52% of patients are successfully treated globally (World Health Organization, 2017).

Bedaquiline is a diarylquinoline that eradicates M. tuberculosis by inhibiting the proton pump of the mycobacterial ATP synthase, primarily through binding to subunits encoded by the atpE gene (Sarathy et al., 2019). Bedaquiline is one of the newest anti-tuberculosis drugs, with guidelines for its use published by the WHO since 2013. However, there are still research gaps that need to be addressed, including pharmacokinetic studies as well as safety and effectiveness studies in specific populations. (World Health Organization, 2013)

Monitoring of therapeutic drug levels (*Therapeutic Drug Monitoring*/TDM) serves as an initial strategy for personalized treatment by allowing clinicians to tailor drug treatment according to the patient's individual needs. TDM aids in dose adjustment to achieve a therapeutically effective drug concentration and/or minimize the risk of side effects associated with drug levels (Eliasson et al., 2013). Use of TDM at the beginning of treatment to ensure adequate exposure to the drug during long treatment periods. This is essential to achieve optimal results and reduce the serious risks associated with treatment (Maranchick & Peloquin, 2024). The emergence of drug-resistant tuberculosis is played by poor adherence to long-term tuberculosis therapy, intermittent use of drugs, errors in prescribing, suboptimal quality of older generation tuberculosis drugs, and ineffective TB control measures (Esposito et al., 2015)

The main causes of the spread of resistant TB are a weak medical system, an increase in resistance patterns due to improper treatment, and transmission in the community and health facilities. Although patients carrying MDR and XDR strains pose a major challenge to treatment(Seung et al., 2015)

This study aims to conduct a narrative review of the literature that discusses the benefits and challenges of monitoring therapeutic drug levels (TDM), especially for the new drug bedaquiline in drug-resistant tuberculosis. To obtain a comprehensive understanding, we conducted a computerized search of relevant articles written in English. Relevant references were identified by searching PubMed and Google Scholar using various combinations of keywords such as "bedaquiline," "pharmacokinetics," "therapeutic drug monitoring," "tuberculosis," and "drug-resistant tuberculosis," either individually or in combination. In addition, we also manually browse the reference list of the original article to find additional relevant articles.

RESEARCH METHOD

This study utilized a narrative review approach to explore the challenges in monitoring blood levels of bedaquiline in patients with drug-resistant tuberculosis (MDR-TB). The method involved an extensive search and critical analysis of relevant scientific literature, without applying systematic review protocols such as PRISMA.

Relevant articles were identified through computerized database searches using PubMed and Google Scholar, employing various combinations of keywords including "bedaquiline", "pharmacokinetics", "therapeutic drug monitoring", "drug-resistant tuberculosis", and "MDR-TB". The search was limited to articles published in English and focused on studies addressing pharmacokinetic variability, therapeutic drug monitoring (TDM), dosage optimization, and analytical methods for bedaquiline.

In addition to database searches, a manual review of reference lists from selected primary studies was also conducted to identify other pertinent publications. Articles were included based on their relevance to the following topics:

a. Pharmacokinetic parameters and variability of bedaquiline
b. Clinical applications and limitations of TDM in MDR-TB treatment
c. Analytical techniques for measuring bedaquiline concentrations
d. Factors affecting drug exposure, such as age, weight, sex, genetic variation, and protein binding

The collected data were then synthesized descriptively to provide a comprehensive understanding of the current evidence and knowledge gaps regarding bedaquiline monitoring.

RESULTS AND DISCUSSION

Limitations of clinical data

In a double-blinded randomized study evaluating daily doses of bedaquiline over 14 days, it was found that higher doses (ranging from 100 mg to 400 mg) were associated with greater bactericidal activity, with a significant linear trend. However, the determination of the highest safe dose is still unclear and requires further evaluation (Diacon et al., 2013).

Activity against tuberculosis isolate has been documented from several references; However, the optimal dosage and exact exposure target are still uncertain. Therefore, a review of the pharmacokinetic and clinical pharmacodynamic literature related to drugs recommended for treating drug-resistant TB, particularly regarding bedaquiline, is needed to identify key areas for future research. To date, published studies are limited, but few have been identified to evaluate the pharmacokinetics and pharmacodynamics of these drugs. Exposure targets have been assessed and summarized for bedaquiline. Exposure-based targets (e.g., areas below the concentration-time curve/minimum inhibitory concentration) seem to be most commonly associated with prediction of drug efficacy (Wilby & Hussain, 2020).

Table 1. Pharmacokinetic/pharmacodynamic parameters of Bedaquiline

Article Author	Number of samples	Parameter	Influence
(Shao et al., 2023)	159	AUC0-24h/MIC	An $AUC_{0-24}h$/MIC ratio greater than 175.5 was associated with an increased likelihood of culture

		conversion after two months of treatment. An $AUC_{0-24}h$/MIC ratio exceeding 118.2 was associated with a higher probability of culture conversion after six months of treatment.
(Shao et al., 2023)	159 Cmax/MIC	The mean Cmax/MIC ratio of 41.1 (27.67-67.33) was associated with the conversion of sputum culture after the second month of treatment, and the mean Cmax/MIC ratio of 40.1 (20.47-66.82) was associated with the conversion of sputum culture after the sixth month of treatment.
(Bhatnagar et al., 2024)	Cmax	Delayed sputum conversion is observed in patients with drug concentrations lower than the target concentration (target Cmax 1-2 mcg/mL).

The efficacy threshold for bedaquiline, cited from various references, was set at 600 ng/mL. This target concentration was first determined in a mouse model and then applied in a phase II clinical trial, which showed that a dose of 400 mg/day for 2 weeks, followed by 200 mg three times a week for 6 weeks, resulted in a plasma concentration of BDQ that exceeded 600 ng/mL at the 2nd and 8th weeks of treatment. Continuing the regimen with a maintenance dose of 200 mg three times a week is proposed to prevent BDQ accumulation in plasma while maintaining concentrations above the target of 600 ng/mL (Perrineau et al., 2019).

Pharmacokinetic Variability

Pharmacokinetic variability is a broad topic and is influenced by patient, physiological, and pathological factors, which cause changes in drug absorption, distribution, metabolism, and excretion. This results in variability in drug concentrations at the site of effect after standard dose administration, which can cause one dose of the drug to be ineffective in one patient, but potentially toxic with unwanted side effects in other patients (Eusuf & Thomas, 2022).

Pharmacokinetic variability is considered one of the factors causing the failure of drug-resistant tuberculosis treatment (Bolhuis et al., 2016). Individual factors that affect pharmacokinetic variability (PK) are referred to as covariates, which explain part of the variability between individuals. Investigation of covariates allows for a clinical understanding of PK parameters and their relationship to the mechanism of action of drugs, as well as potential dose adjustments in patients based on covariate values (Bensalem & Ternant, 2020).

a. Age

Due to age-related changes in physiological function (kidneys and liver) as well as changes in blood flow, drug clearance can differ between children and the elderly (Burns et al., 2016).

Table 2. Effect of age on pharmacokinetic parameters of bedaquiline

Article Author	Number of samples	Parameter	Influence
(Hughes et al., 2022)	15	AUC	Children (6-<18 years) only 1/5 achieved the adult reference AUC (187 μg·h/mL).
(Svensson et al., 2016)	335	Cl	Increased age leads to a linear decrease in Cl bedaquiline and M2
(Alghamdi et al., 2021)	99	Cmin	The increase in age was correlated with the increase in Cmin (P = 0.0289).

b. Weight

Drug exposure is also affected by the patient's weight and ability to clear the drug through the liver and/or kidneys. Inadequate drug exposure has been shown to cause delayed treatment response, treatment failure, and drug resistance. In contrast, higher drug exposure is associated with faster clearance of tuberculosis. Therefore, drug exposure is an important factor in the effectiveness of treatment of tuberculosis patients, and fixed doses may not be appropriate for patients with higher body weight (Peloquin, 2017). According to the study (Krogstad et al., 2021), the intrinsic clearance value (CLint,u) for CYP3A decreased by 5% with each weight gain of 10% ($r^2 = 0.12$, $b = 0.558$, $p < 0.05$) (Krogstad et al., 2021).

Table 3. Effect of body weight on pharmacokinetic parameters of bedaquiline

Article Author	Number of samples	Parameter	Influence
(McLeay et al., 2014)	The total number of subjects is not listed.	Vc/F	No statistically significant relationship was found between continuous body size covariate and Vc/F.
(Svensson et al., 2016)	335	Vc	A linear relationship was observed between weight gain and the volume of bedaquiline distribution
(Alghamdi et al., 2021)	99	Cmin	For every 10 kg increase in body weight, Cmin bedaquiline

			decreased by 0.12 mg/L (P = 0.0011)
(Shao et al., 2023)	55	Vc	The volume of distribution changes proportionally following the change in weight.
(Shao et al., 2023)	55	Cl	The clearance rate increases proportionally by a power of 0.75 of body weight.

Gender

Sex differences in drug metabolism are believed to significantly affect pharmacokinetics (Flores-Pérez et al., 2023). There are differences in body composition between men and women. Women generally have higher fat mass, while men have greater muscle mass, and this difference decreases with age. As a result, if men and women receive the same dose of water-soluble drugs, the volume of distribution (Vd) will be higher in men due to greater muscle mass and total body water volume. In contrast, the Vd of fat-soluble drugs will be higher in women, who have a higher percentage of fat mass. Therefore, fat-soluble drugs may reach higher peak concentrations (Cmax) in women, increasing the risk of adverse drug reactions, especially in long-term therapy (Mauvais-Jarvis et al., 2021).

Table 4. Effect of sex on pharmacokinetic parameters of bedaquiline

Article Author	Number of samples	Parameter	Influence
(McLeay et al., 2014)	The total number of subjects is not listed.	Vc/F	Women showed a Vc/F which was 15.7% lower than men.
(Alghamdi et al., 2021)	99	Cmin	Men were found to have higher Cmin bedaquiline than women (0.79 mg/L versus 0.39 mg/L, P = 0.0001).
(Alghamdi et al., 2021)	99	AUC	Men were found to have a higher $AUC_{0–24}$ than women (33.0 mgh/L versus 21.3 mgh/L, P = 0.0203).

c. Protein binding

Bedaquiline exhibits high protein binding in plasma (>99.9%), which causes albumin to affect the pharmacokinetic disposition of bedaquiline(van Heeswijk et al., 2014). Albumin binds to endogenous ligands such as fatty acids, but also interacts with exogenous ligands such as drugs. The drug bond with albumin is reversible, and the albumin-drug complex acts as a reservoir for the drug, improving the biodistribution and bioavailability of the drug (Larsen et al., 2016). The effectiveness of the drug depends on several factors, including transportation and selective delivery to a specific target. Serum albumin is one of the most important

transporters of drugs. Therefore, the association of drugs with serum albumin can be a crucial factor affecting its pharmacology and pharmacodynamics (Encinas et al., 2013). Low serum albumin levels or concomitant use of drugs with high protein-binding capacity can increase over-the-counter drug concentrations, affecting therapy outcomes and the incidence of side effects (Umehara et al., 2023).

Table 5. Effect of protein on pharmacokinetic parameters of bedaquiline

Article Author	**Number of samples**	**Parameter**	**Influence**
(Svensson et al., 2016)	335	Vc	Higher levels of albumin are associated with a decrease in the volume of betaquiline distribution.
(Zou et al., 2022)	99	Cl/F	Bedaquiline clearance decreased by 30% when GGT levels doubled.

d. Genetic diversity.

Table 6. Genetic influence on the pharmacokinetic parameters of bedaquiline.

Article Author	Number of samples	Parameter	Influence
(McLeay et al., 2014)	Total number of subjects not listed	Cl/F	Black subjects showed a 52.0% higher CL/F compared to subjects from other races.
(Svensson et al., 2016)	335	Cl	Patients of the black race had significantly higher Cl bedaquiline and M2.
(Zou et al., 2022)	99	Cl/F	Bedaquiline clearance was found to be 1.4 L/hour lower in subjects with GG allele at SNP (single-nucleotide polymorphism) rs319952 compared to subjects with AG or AA alleles.

Availability of Technology and Resources

In order to accurately assess drug exposure in patients in clinical care, more precise and accurate TDM monitoring methods are needed, especially for samples with low concentrations. Currently, commonly used clinical TDM monitoring methods include High-Performance Liquid Chromatography (HPLC), Liquid Chromatography-Tandem Mass Spectrometry (LCMS/MS), Ultra-Performance Liquid Chromatography-Tandem Mass Spectrometry (UPLC-MS/MS), immunoassays, biosensor technology, electrochemical methods, capillary electrophoresis, and microbial testing (Fang et al., 2024).

The most reliable, highly sensitive, and high-quality tests are liquid chromatography combined with UV detectors, mass spectrometry, or fluorescence.

This technique is the main method used for TDM. Chromatography detection can separate the drug and metabolite to be analyzed from the detection matrix, by using selective detectors that increase specificity and sensitivity for monitoring (Fang et al., 2024).

Table 7. The method used for the analysis of bedaquiline in the blood

Article Author	Sample	Instrument	Sampling Points	Interval	Result
(Li et al., 2021)	Serum	HPLC-MS	Concentration of Trough (C trough) in Steady State	Every 2 weeks	The mean serum concentrations of bedaquiline were 0.586 ± 0.288 μg/ml during treatment and 0.205 ± 0.145 μg/ml at 16 weeks after discontinuation of bedaquiline.
(Shao et al., 2023)	Plasma	HPLC	Before dosing, as well as at 1, 2, 3, 4, 5, 6, 8, 12, 18, and 24 hours after administration.	In the second and fourth weeks after the administration of the first dose.	The lowest Cmin value during bedaquiline treatment was 0.08 mg/L (after 6 months of treatment) and the highest Cmin value was 1.74 mg/L (after 2 months of treatment).
(Gray et al., 2019)	Plasma	LC-MS/MS	At 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours after administration of the drug	After the drug level reaches a steady state.	Based on the graph presented from the results of the plasma

					examination study in 6 healthy subjects, it was observed that the average value of Cmin bedaquiline measured 24 hours after administration of the drug was below 1000 ng/mL.
(Zou et al., 2022)	Plasma	LC-MS/MS	Non-specific	Blood samples are taken during weeks 3 to 24 (as long as the patient receives a dose of 200 mg three times a week).	The measured cmin ranges from 0.176 to 2,815 mg/L, while the Cmax value ranges from 0.859 to 3,538 mg/L
(Svensson et al., 2016)	Blood (plasma or serum not mentioned).	LC-MS/MS	Sampling was carried out before the administration of the dose and at 1, 3, 5, 6, 8, 12, and 24 hours after the administration of the drug.	At the 2nd, 8th, 12th, and 24th weeks after the initial dose.	Based on a graph of monitoring the concentration of the drug in the blood during the 6-month treatment period, the level of bedaquiline in the blood remained stable between 500 ng/mL and

					1000 ng/mL after the fourth week.
(Alffenaar et al., 2015)	Serum	LC-MS/MS	After 4 months of therapy, sampling was performed at hours 0, 1, 2, 3, 4, 8, 12, and 24 after administration of bedaquiline	One sampling period is done after 4 months of therapy	Based on the blood drug concentration monitoring graph, the Cmin value of bedaquiline ranges from 500 ng/mL to 1000 ng/mL.

Supervision and Compliance

Poor adherence can negatively impact clinical outcomes, especially since most of these drugs are administered in standard doses that are not individually adjusted, although there is significant interpersonal variability that can lead to toxic or subtherapeutic concentrations of the drug. Undisclosed non-compliance, which affects the history of drug consumption, can lead to significant bias in the interpretation of drug concentrations and result in improper dosage adjustments (Cardoso et al., 2018).

Drug Interactions

Bedaquiline is metabolized by the CYP3A enzyme, which creates the potential for drug interactions when administered in conjunction with CYP3A inducers or inhibitors. Due to the possibility of decreased exposure to bedaquiline, concomitant administration with moderate or strong CYP3A4 inducers [such as efavirenz, etravirine, rifamycin including rifampicin, rifapentin, and rifabutin, carbamazepine, phenitoin, and St. John's wort (Hypericum perforatum)] should be avoided if used systemically. Similarly, due to the potential risk of side effects due to increased systemic exposure, concomitant administration with moderate or strong CYP3A4 inhibitors (such as ciprofloxacin, erythritisin, fluconazole, clarithromycin, ketoconazole, and ritonavir) for more than 14 consecutive days should also be avoided (van Heeswijk et al., 2014). The relative bioavailability of bedaquiline increases about 2 times when consumed with food compared to fasting conditions (McLeay et al., 2014).

CONCLUSION

Therapeutic Drug Monitoring (TDM) is an important tool to personalize bedaquiline therapy in MDR-TB patients. Despite the promising benefits, the implementation of TDM faces major challenges, including inter-individual pharmacokinetic variability, limited clinical data, and access to advanced analytics technologies. Further research is needed to identify optimal exposure targets,

address pharmacokinetic variability, and improve the accessibility and application of TDM in various clinical settings.

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