1. Introduction

Bedaquiline (BDQ), a new antimycobacterial novel drug was approved for the treatment of multidrug resistance tuberculosis (MDR-TB) by US Food and Drug Administration in 2012 [1]. MDR-TB is the type of infection which is caused by bacteria that are resistant to the potent first line anti-tubercular drugs isoniazid and rifampicin [2]. It is majorly caused by the transmission of multi resistant strains from one person to other person, by genetic factors [3] and by poor adherence to treatment [4]. Isoniazid resistance is observed because of katG (catalase peroxidase) and kasA(β-ketoacyl synthase) gene alterations and mutations in beta unit of ribonucleic acid (RNA)-polymerase results in rifampicin resistance [5]. The incidence of MDR-TB has increased and turned out to be a global threat. A total of approximately one hundred and thirty thousand incident multidrug resistant patients with TB emerge annually in India which includes approximately 79,000 patients with MDR-TB among notified pulmonary cases [7].

To overcome this multi-drug resistance-Bedaquiline, a diarylquinoline of antimycobacterial class [8] is prescribed along with other second line anti-tubercular drugs (ethionamide, kanamycin, cycloserine, linezolid, pyrazinamide) [9] for faster culture conversion, good efficacy and better patient outcome [10, 11]. Recommended dose of Bedaquiline is 400mg OD orally for 2 weeks followed by 200 mg thrice weekly for 22 weeks. After 22 weeks of Bedaquiline therapy, MDR-TB treatment should be continued as revised national tuberculosis control program (RNTCP) guidelines [12].

Bedaquiline binds to C subunit of an enzyme mycobacterial adenosine triphosphate (ATP) synthase (an enzyme necessary for the energy metabolism in *M. tuberculosis*) and inhibits its activity [13, 14, and 15]. The high selectivity index (>20 000) of the drug towards mycobacterium species less likely to produce toxicity in the host cells [16]. The unique mechanism of action & distinct target of the drug reduces the potential for cross-resistance with the existing anti-tuberculosis (TB) agents [17]. Bedaquiline acts on both dormant and replicating bacteria; this unique bactericidal activity differentiates it from other current anti-TB drugs [18].

Bedaquiline is well absorbed orally [19]. The volume of distribution of Bedaquiline is about 164 Liters [20]. Bedaquiline is 99.9% highly protein bound [21]. The administration of drug along with food increases its bioavailability [22]. Bedaquiline is eliminated primarily through feces [21].

Bedaquiline is metabolized by cytochrome (CYP) 3A4 enzyme majorly and other enzymes like CYP2C8, CYP2C19. Thus, when patients receive BDQ together with CYP3A4 inhibitors, BDQ metabolism is not blocked completely [23]. Administration of Bedaquiline along with potent CYP3A4 inducers should be avoided as it decreases therapeutic efficacy [24].Bedaquiline should not be prescribed with drugs that prolong QT-interval as it may result in additive QT prolongation [12, 25,].

The major adverse drug reactions observed during Bedaquiline treatment are QTc prolongation, arthralgia, headache, diarrhea, dizziness and nausea [26, 27].

Pharmacokinetic (PK) studies were performed in the healthy male volunteers and Pharmacokinetic profile of Bedaquiline was monitored. This study showed a linear and proportionate increase between Bedaquiline doses, maximum concentration (Cmax) and area under the curve (AUC) [28]. Phase I studies in 265 subjects have been conducted from 2005 to 2012 to evaluate pharmacokinetic characteristics, administration, drug-drug interactions, tolerability and safety of Bedaquiline. Current evidence of clinical efficacy of Bedaquiline is supported by data from phase II clinical trials, primarily phase IIb studies [29]. A study was conducted to evaluate the safety, efficacy, and pharmacokinetics of Bedaquiline in adult Japanese patients with MDR-TB. In this study, patients received Bedaquiline for 24 weeks or more (maximum 48 weeks) with an individualized background regimen (BR). Efficacy was assessed as the time to sputum culture conversion after the initiation of Bedaquiline treatment [30].

The pathophysiological alterations that occur in critically ill patient's shows impact on the absorption, distribution, metabolism and elimination patterns of a drug administered. During the diseased conditions the environment at the administration site and the physical properties of a drug differ from the healthy population which affect the PK parameters of the drug [31-37]. Till date, the pharmacokinetic properties of Bedaquiline in patients with MDR-TB infection have not been studied extensively in Indian scenario.

The present research aimed to investigate the pharmacokinetic profile of Bedaquiline in patients with MDR-TB under clinical settings. The impact of the patient's physiological & pathological conditions on PK of Bedaquiline also examined. This study serves as the evidence for the physicians to manage drug therapy for better patient outcomes in routine clinical practice.

2. Materials and Methods

The study was conducted from December 2018 to May 2019 in Government Chest and TB hospital, Hanamkonda, Warangal. The study protocol was approved by the Institutional HUMAN ethics committee (IHEC/CCPER/2019/009), Chaitanya College of Pharmacy education & Research, Warangal, Telangana, India. All patients included in this study gave written informed consent to participate in this pharmacokinetic study.

Patients suspected of MDR-TB, adults of age 20-50 years, receiving Bedaquiline as part of their treatment regimen served as inclusion criteria. Subjects were excluded with low hemoglobin count, coexisting medical illness like HIV, immunity disorders and other infectious diseases.

A total of 58 patients with diagnosed, smear-positive, MDR-TB were enrolled in this study that was on Bedaquiline regimen. Their standard treatment was according to RNTCP guidelines which comprised of Bedaquiline 400mg orally once daily for the first 2 weeks and 200mg three times a week for the following 22 weeks in combination with optimized background regimen.

For each MDR-TB suspect, baseline demographic, clinical & therapeutic data were collected. Patient's adherence to anti-tuberculosis drugs was monitored regularly. 2ml blood sample was collected at predose followed by at 1, 2, 3, 4, 5, 6, 8, 12, 24 hours first post-dose and at the 14 th day with similar time intervals. The collected samples were then centrifuged respectively at 3000rpm for 10 min. the obtained plasma was separated and stored at -26℃.

2.1 Chemicals and Reagents

Bedaquiline 100mg tablets were procured from Govt. TB and chest hospital, Hanamkonda, Warangal. Methanol (HPLC grade), Diammonium hydrogen ortho phosphate (Analytical grade), Acetonitrile (HPLC grade), Apremilast were procured from Chembros Private Limited, Hyderabad, India. Blank plasma was collected from Red Cross Society (Warangal, Telangana).

2.2 Chromatographic Conditions

The chromatrographic analysis was performed by high performance liquid chromatography (HPLC) equipped with ultra-violet (UV)-detector. The compounds of interest were separated by using Phenomenex C18 (250 mm× 4.6mm, 5µ) column. Mobile phase consisting of a mixture of 0.01M

diammonium hydrogen ortho phosphate buffer prepared at a pH of 4.5 (ortho-phosphoric acid - OPA) and methanol at a ratio of 10:90 v/v pumped at a flow rate of 1.5ml/min with a runtime of 6 min. The sample was injected through a fixed sample loop having a volume of 25 µl. The column temperature was maintained at 25˚C and the eluents were monitored at 250nm.Aprimalast was used as internal standard as it was similar to the structure of Bedaquiline. This method showed good accuracy and precision.

2.3 Preparation of quality control samples

25milligrams of standard Bedaquiline and internal standard were separately dissolved in the suitable diluent to get the stock solution having concentration of 1 mg/ml respectively. The concentrations ranging from 500 - 5000ng/ml were prepared by serial dilution method. In the same manner, spiked quality control (QC) samples were prepared by spiking plasma with known amount of drug to the calibration range. High quality control (HQC), medium quality control (MQC), low quality control (LQC) & lower limit of quantification (LLOQ) samples were used for further studies.

2.4 Sample Pretreatment

A simple protein precipitation method was followed. A mixture of acetonitrile & methanol (84:16 v/v) was used precipitating reagent for greater recoveries.

2.5 validations

The developed method was validated in accordance with FDA guidelines [39]. The linearity of the method was examined as the ratio of the peak area of the drug to that of the IS. This was performed in the concentration range of 500 - 5000 ng/mL. The correlation coefficient was found to be 0.985. The least square equation was used for the determination of test concentrations. The precision and accuracy of the method were evaluated for the HQC, MQC, LQC and LLOQ samples. The mean recovery of the drug was 93.4%. The LLOQ was found to be 500ng/ml. No endogenous peaks interfered with the analyte indicates the specificity of the method. The stability studies like freeze-thaw, short-term, long-term and bench-top stability of Drug and internal standard (IS) was investigated.

3. Results

From December 2018 to May 2019, a total of 58 patients with smear-positive, multidrug-resistant pulmonary tuberculosis administering Bedaquilline were included in this study (TABLE1). The study population was predominantly male and HIV-negative with a median age of 33 years (18 - 57).

The blood samples were collected from the first day of administration of the Bedaquiline and followed up to 14th day of the drug therapy. All the patients were under bedaquilline with background regimen under treatment. Patient consent along with the data was taken before blood sample was drawn. All patients were confirmed to have an organism resistant to both rifampin and isoniazid, as indicated by rapid screening tests, susceptibility tests, or both, and at least 85% of the patients showed mycobacterial susceptibility to each of the following drugs: capreomycin, kanamycin, ethionamide, and ofloxacin.

The drug dose prescribed to patients was 400mg once daily with 4 tablets of 100mg each. The pre dose samples were also collected from the subjects prior the treatment has been administered. The collected plasma samples were analyzed by high performance liquid chromatography equipped with UV- visible spectrophotometer using c18 column. The pharmacokinetic data was drawn by using software kinetica 2000, version 5.03. To show the applicability of the method in routine clinical practice, plasma samples from patients with MDR-TB were analyzed and the plasma concentration-time profile was drawn.

The mean value of the pharmacokinetic data was obtained for included subjects. The drug has shown the linear relationship with respect to the dose with rapid absorption showing mean maximum time (t_{max}) at 4 hours. The observed mean Cmax was 2523.08 ng/mL, $AUC_{(0-24)\ was}$ 21727.1 ng *hr/mL, area under the moment curce (AUMC) (0-24) was 222953.8 ng *hr^2/mL after the first oral dose of 400mg (figure 1). Whereas the half-life of the drug was found at 7.02 hrs. And mean residence time (MRT) was found to be 10.25 hrs. (TABLE 2). The data was even on 14^{th} day of therapy. The Cmax is shown to be 5937.1ng/mL reaching the maximum concentration at about 5 hours. While the AUC (0-24) was found to be 65780 ng *hr/mL (TABLE 3).

4. Discussion

In this present study a new, simple and selective method was developed and validated for the determination of Bedaquiline in the MDR-TB patient plasma. Bedaquiline is a newly approved drug by FDA in 2012.Till date there are no reported studies in Indian clinical settings which was basis for our study and BDQ is newly approved drug with minimum reported studies which was meant to be analyzed in clinical settings.

This study states the pharmacokinetic parameters of bedaquilline, the drug approved for MDR-TB in Indian clinical settings. The results depicts as mean Cmax values were within the expected ranges. Very few showed the low Cmax. Delayed absorption did not appear to be the primary reason. Albeit patients received the background regimen, it is unlikely that these medications reduced the drug absorption.

This study reported data for first and 14^{th} day in which subjects were on the treatment of 400mg OD with 100mg tablets each while the recommended dosage of Bedaquiline is 400 mg orally daily for 2 weeks [28]. In this study Bedaquiline was given to patients along with the background regimen of 5 second line anti-tubercular drugs kanamycin, ethionamide, pyrazinamide, cycloserine and linezolide as per RNTCP guidelines [27].

The interpretation of graph (FIGURE 1) after first oral dose depicts that there is an increase in plasma concentration after the oral administration represents the drug absorption phase. The drug reached its maximum concentration of 2523 ng/ml with the Tmax at 4 hrs. After reaching the peak plasma concentration the graph declined with reaching to its first half-life which is about 7.02 hours. The Tmax was found to be similar to the previously reported open-label, phase-2 study conducted in Japanese MDR-TB patients [23]. The observed value was consistent to previously reported pharmacokinetic drug interaction trial [32]. Area under the curve which was similar to the value reported open-label, randomized phase IIa trial [33].

The depiction of the FIGURE 2 which is the data on the 14^{th} day on which the patient is on his last day of 400mg dose the peak concentration has been reached after 5 hours. The change or increase in the concentration from the data represented on the first day can be seen. The change even in the AUC which is on 14^{th} day represents higher than the first post oral dose data. The data when compared with the interim analysis done in Japanese patients (23), there is the change for about

11, 710 ng *hr/mL less in the AUC in patients treated in clinical settings. The concentration is about 614.9 ng less in clinical settings. This represents the effect of clinical settings and the factors on the drug concentration, actions and their consequences. The factors that might affect the drug concentration may be non-adherence, missed dose, noncompliance to the requested data, misinformation about the drug dosage, no guidance while following the dosages, effect of other drugs co medication and etc.,

While compared to the study done by KazunariTsuyuguchi et al.,[31] the Cmax is 3990–8110ng/mL at week 2 and AUC24h ranged from 50,637 to 107,300 ng *h/mL with Tmax being 4.10 hrs, this study seems to be in the limits. The article written by Juan Carlos Palomino and Anandi Martin the Cmax of 400mg BDQ is 5500 ng/ml, and the AUC0–24 h was 64750 ng.h/ml, which seems to be less than that reported in this study. [38].

Patients were on the background therapy of second line anti-tb drugs along with the bedaquilline. Second line drugs didn't show any potential effects on CYP activity of Bedaquiline. Bedaquiline was well tolerated by the patients in this study. ECGS were monitored regularly in the patients for potential interactions while, slight QTc prolongation was observed which was in safety limits. No severe adverse effects were reported during the dosing interval which represents no change in the dosing or the dose of the drug.

This new and simple method can be further used in laboratories and daily clinical practice. During the optimization of the method as there are no HPLC-UV methods reported various attempts were made to prepare a suitable mobile phase and internal standard to obtain optimal separation for accurate results. In this present study no significant effect of pyrazinamide and ethionamide was observed on Bedaquiline as they had no remarkable CYP inhibition activities [30]. No interactions were found between kanamycin and Bedaquiline as kanamycin had low potential for drug drug interactions [21].Cycloserine had no effect on CYP activities and is metabolized by unknown pathways therefore no significant interaction was observed in this study [31]. Linezolid didn't show any significant effect on Bedaquiline as it is not an inducer or inhibitor of CYP enzymes [32].Therefore, these second line drugs didn't show any potential effects on CYP activity of Bedaquiline. Bedaquiline was well tolerated by the patients in this study. ECGS were monitored

regularly in the patients slight QTc prolongation was observed which was in safety limits. No severe adverse effects were reported during the dosing interval.

limitations of this study includes less sample size which might not be applicable to the whole population, further analysis with high sample size may show a greater change in pk parameters. Even though, the results should be not neglected. This study was not followed up till the end of the drug therapy (week 28) which doesn't give complete elimination parameters and the change in the peak plasma concentration. Since the patient is allowed to stay in clinical settings for a period of 14 days, which limited us to further analyses the drug till the end of therapy.

The advantage of this study is it is done in clinical settings which serve as the evidence for the physicians regarding the pharmacokinetic data and their change according to the environmental, physiological changes and managing drug therapy. The result of this study is useful in application and also for further investigation in Indian population. There are two ICP-LC/MS methods were only reported which involved liquid-liquid extraction and solid phase extraction which are expensive and time consuming [34, 35]. They were not made for pharmacokinetic study analysis. Another LC-MS method was reported which is unavailable for the laboratories and daily clinical practice [27]. Until now no HPLC-UV method has been reported in the literature for quantification of Bedaquiline in MDR-TB patient plasma. Therefore this method remains simple, very much useful selective and l for further research studies in laboratories and clinical practice.

5. Conclusion

In this analysis in clinical settings, there was a minimal change observed in the pharmacokinetic parameters of week 2 while compared to the trails done and various studies. This study supports the changes based in parameters and criteria in clinical settings for multi-drug regimen for at least 2 weeks, to treat Indian patients. Close monitoring in patients taking bedaquline might help to reduce the minimal changes occurred. There has been no interaction or any side effects neither seen in patients nor reported till week 2. Further study with higher subjects and extended therapy time period may serve the best results.

Ethical approval:

The study protocol was approved by the Institutional HUMAN ethics committee (IHEC/CCPER/2019/009), Chaitanya College of Pharmacy education & Research, Warangal, Telangana, India.

Human and animal rights:

No human/animal was used for studies that are base of this research.

Availability of data and materials

The data generated and analyzed during the current study are available from the corresponding author on reasonable request.

Funding

There is no funding for the current study.

Conflict of interest

The authors confirm that there are no potential conflicts or any financial contributions in the study.

Acknowledgements

Authors are thankful to the Chairman, Viswabharati Educational Society, Warangal, and Telangana, India for providing necessary facilities to carry out this work. We are also thankful to the technical and laboratory staff, government tuberculosis hospital, Warangal, India, for their clinical support. All authors read and approved the final version of the manuscript. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES:

1. Deoghare S. Bedaquiline: a new drug approved for treatment of multidrug-resistant tuberculosis. Indian J Pharmacol. 2013;45(5):536-537. doi:10.4103/0253-7613.117765
2. Ormerod LP. Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. Br Med Bull. 2005;73-74:17-24. Published 2005 Jun 14. doi:10.1093/bmb/ldh047
3. Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation; Russian Academy of Medical Science. The New Profile of Drug-Resistant Tuberculosis in Russia: A Global and Local Perspective. Washington (DC): National Academies Press (US); 2011.
4. Centers for Disease Control and Prevention. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis [published correction appears in MMWR Recomm Rep. 2013 Nov 15;62(45):906]. MMWR Recomm Rep. 2013;62(RR-09):1-12.
5. Ramaswamy S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in Mycobacterium tuberculosis: 1998 update. Tuber Lung Dis. 1998;79(1):3-29. doi:10.1054/tuld.1998.0002
6. Institute of Medicine (US). Facing the Reality of Drug-Resistant Tuberculosis in India: Challenges and Potential Solutions. Washington (DC): National Academies Press (US); 2012.
7. Kim DH, Kim HJ, Park SK, et al. Treatment outcomes and survival based on drug resistance patterns in multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010;182(1):113-119. doi:10.1164/rccm.200911-1656OC
8. Chahine EB, Karaoui LR, Mansour H. Bedaquiline: a novel diarylquinoline for multidrug-resistant tuberculosis. Ann Pharmacother. 2014;48(1):107-115. doi:10.1177/1060028013504087
9. Central TB Division. Guideline for PMDT in India 2017. https://tbcindia.gov.in/index1.php?lang=1&level=2&sublinkid=4780&lid=3306

10. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371(8):723-732. doi:10.1056/NEJMoa1313865
11. Pym AS, Diacon AH, Tang SJ, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J. 2016;47(2):564-574. doi:10.1183/13993003.00724-2015
12. U.S. Food and Drug Administration. SIRTURO Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf
13. Goel D. Bedaquiline: A novel drug to combat multiple drug-resistant tuberculosis. J Pharmacol Pharmacother. 2014;5(1):76-78. doi:10.4103/0976-500X.124435
14. Koul A, Dendouga N, Vergauwen K, et al. Diarylquinolines target subunit c of mycobacterial ATP synthase. Nat Chem Biol. 2007;3(6):323-324. doi:10.1038/nchembio884
15. Goulooze SC, Cohen AF, Rissmann R. Bedaquiline. Br J Clin Pharmacol. 2015;80(2):182-184. doi:10.1111/bcp.12613
16. Haagsma AC, Abdillahi-Ibrahim R, Wagner MJ, et al. Selectivity of TMC207 towards mycobacterial ATP synthase compared with that towards the eukaryotic homologue. Antimicrob Agents Chemother. 2009;53(3):1290-1292. doi:10.1128/AAC.01393-08
17. Huitric E, Verhasselt P, Andries K, Hoffner SE. In vitro antimycobacterial spectrum of a diarylquinoline ATP synthase inhibitor. Antimicrob Agents Chemother. 2007 Nov;51(11):4202-4. doi: 10.1128/AAC.00181-07. Epub 2007 Aug 20. PMID: 17709466; PMCID: PMC2151410.
18. Koul A, Vranckx L, Dendouga N, et al. Diarylquinolines are bactericidal for dormant mycobacteria as a result of disturbed ATP homeostasis. J Biol Chem. 2008;283(37):25273-25280. doi:10.1074/jbc.M803899200
19. Jyoti M. Benni. Bedaquiline: A Promising new agent for the treatment of MDR-TB. Int. J. Drug Dev.& Res., April-June 2013, 5(2): 24-28. https://www.ijddr.in/drug-development/bedaquiline-a-promising-new-agent-for-the-treatment-of-mdrtb.php?aid=6714.
20. DrugBank. Bedaquiline. https://go.drugbank.com/drugs/DB08903

21. Natap.org.Anti-infective drugs advisory committee meeting. Briefing Document. https://www.natap.org/2012/newsUpdates/20121128AIDACB103JANSSENBackgrounder.pdf.
22. Perrineau S, Lachâtre M, Lê MP, et al. Long-term plasma pharmacokinetics of bedaquiline for multidrug- and extensively drug-resistant tuberculosis. Int J Tuberc Lung Dis. 2019;23(1):99-104. doi:10.5588/ijtld.18.0042
23. McLeay SC, Vis P, van Heeswijk RP, Green B. Population pharmacokinetics of bedaquiline (TMC207), a novel antituberculosis drug. Antimicrob Agents Chemother. 2014;58(9):5315-5324. doi:10.1128/AAC.01418-13
24. Liu K, Li F, Lu J, et al. Bedaquiline metabolism: enzymes and novel metabolites. Drug Metab Dispos. 2014;42(5):863-866. doi:10.1124/dmd.113.056119
25. Nguyen TV, Cao TB, Akkerman OW, Tiberi S, Vu DH, Alffenaar JW. Bedaquiline as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis. Expert Rev Clin Pharmacol. 2016;9(8):1025-1037. doi:10.1080/17512433.2016.1200462
26. Guglielmetti L, Le Dû D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. Clin Infect Dis. 2015;60(2):188-194. doi:10.1093/cid/ciu786
27. Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. Eur Respir J. 2016;47(2):394-402. doi:10.1183/13993003.01891-2015
28. Matteelli A, Carvalho AC, Dooley KE, Kritski A. TMC207: the first compound of a new class of potent anti-tuberculosis drugs. Future Microbiol. 2010;5(6):849-858. doi:10.2217/fmb.10.50
29. van Heeswijk RP, Dannemann B, Hoetelmans RM. Bedaquiline: a review of human pharmacokinetics and drug-drug interactions. J Antimicrob Chemother. 2014;69(9):2310-2318. doi:10.1093/jac/dku171

30. Rustomjee R, Diacon AH, Allen J, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob Agents Chemother. 2008;52(8):2831-2835. doi:10.1128/AAC.01204-07
31. Tsuyuguchi K, Sasaki Y, Mitarai S, Kurosawa K, Saito Y, Koh T. Safety, efficacy, and pharmacokinetics of bedaquiline in Japanese patients with pulmonary multidrug-resistant tuberculosis: An interim analysis of an open-label, phase 2 study. Respir Investig. 2019;57(4):345-353. doi:10.1016/j.resinv.2019.01.001
32. Roberts DJ, Hall RI. Drug absorption, distribution, metabolism and excretion considerations in critically ill adults. Expert Opin Drug Metab Toxicol. 2013;9(9):1067-1084. doi:10.1517/17425255.2013.799137
33. Power BM, Forbes AM, van Heerden PV, Ilett KF. Pharmacokinetics of drugs used in critically ill adults. Clin Pharmacokinet. 1998;34(1):25-56. doi:10.2165/00003088-199834010-00002
34. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin. 2006;22(2):255-vi. doi:10.1016/j.ccc.2006.02.011
35. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. Chest. 2012;141(5):1327-1336. doi:10.1378/chest.11-1396
36. Clinical Pharmacokinetics Pharmacy Handbook, Second Edition . Pharmaceutical Services Programme. 2020. Available from: https://www.pharmacy.gov.my/v2/en/documents/clinical-pharmacokinetics-pharmacy-handbook-second-edition.html
37. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient--concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev. 2014;77:3-11. doi:10.1016/j.addr.2014.07.006

38. Palomino JC, Martin A. TMC207 becomes bedaquiline, a new anti-TB drug. Future Microbiol. 2013;8(9):1071-1080. doi:10.2217/fmb.13.85.

39. Food and Drug Administration. Guidance for Industry - Bioanalytical Method Validation May 2001. Available at http://www.fda.gov/downloads/Drugs/Guidance/ucm070107.pdf . United States Department of Health and Human Services Food and Drug Administration. 2001.