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THE UTILITY OF PHARMACOKINETIC STUDIES FOR THE EVALUATION OF EXPOSURE-RESPONSE RELATIONSHIPS FOR STANDARD DOSE ANTI-TUBERCULOSIS DRUGS

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Abstract

Tuberculosis (TB) is a major public health problem. Many countries still fall below the minimum World Health Organization (WHO) TB treatment target success rate. There is conflicting evidence about whether concentrations of anti-tuberculosis drugs given at standard doses have an effect on treatment outcomes. The current data correlating anti-TB drug concentrations and treatment outcome is limited. This article summarized the existing literature and their utility in evaluating the association between each anti-TB drug's concentrations using current target concentrations and treatment outcomes in patients with pulmonary tuberculosis receiving standard WHO-recommended dosing.

Keywords

anti-tuberculosis drugs; concentrations; treatment outcomes

INTRODUCTION

In 2015, 10.4 million people were diagnosed with tuberculosis (TB) worldwide and 1.5 million died. Only 8 out of the 30 high-burden countries have achieved the World Health Organization (WHO) minimum target TB treatment success rates of 90%.¹ Several factors may contribute to this low success rate including failure to achieve the optimal concentration

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of anti-TB drugs due to poor adherence, insufficient absorption, drug-drug interactions and other factors.^{2, 3}

Standard TB treatment includes 2 months of rifampicin, isoniazid, ethambutol and pyrazinamide followed by 4 months of rifampicin and isoniazid. Rifampicin and isoniazid both demonstrate concentration-dependent killing of *Mycobacterium tuberculosis*.^{4, 5} For ease of collection, the concentration at 2 hours (C_{2hr}) is frequently used to estimate the maximum drug concentration (C_{max}) during therapeutic drug monitoring (TDM). In some cases, the concentration at 6 hours is also collected to identify patients with delayed/poor absorption.^{6, 7} The Area under the concentration-time curve (AUC) which describes the drug exposure better, is expensive and tedious to perform in clinical practice. However, limited sampling strategies using appropriately timed blood draws (for example at 1, 2 and 6 hours post dose) can be used to predict the AUC.^{8, 9}

Reference ranges (targets) for the C_{max} of first line anti-TB drugs were derived primarily from phase I clinical trials in healthy volunteers; rifampicin: 8–24mg/L, isoniazid: 3–6mg/L, pyrazinamide: 20–60mg/L and ethambutol: 2–6mg/L.⁶ Several studies have highlighted the pharmacokinetic (PK) properties of first-line drugs in patients with TB, however, many patients have drug concentrations below the respective cut-offs.^{2, 10, 11} It is still unclear whether these low concentrations actually lead to a higher risk of unfavorable TB treatment outcomes and/or delay in sputum culture conversion to negative, specifically 2-month culture conversion.

This article summarizes the existing literature that reports the association between anti-TB drug concentrations and treatment outcomes in patients with pulmonary tuberculosis and receiving standard WHO-recommended dosing.

METHODS

Literature Search Strategy

We carried out a systematic review of studies among adults with TB in which pharmacokinetic data and TB treatment outcomes were reported and which evaluated the association between drug pharmacokinetics and outcomes (either TB treatment outcomes or sputum culture conversion) in patients on standard doses of first line anti-TB treatment. We searched English-language databases including PubMed/Medline, Embase and Cochrane reviews for publications up to 31st June 2016. The search strategy included the following Medical Subject Heading (MeSH) terms: “antituberculous drug” OR “isoniazid” OR “pyrazinamide” OR “rifampicin” AND “pharmacokinetics” OR “concentration” OR “kinetics” AND “treatment outcomes” OR “pharmacodynamics” OR “sputum conversion” OR “culture conversion”. We searched for abstracts from targeted conferences including Conference on Retroviruses and Opportunistic Infections (CROI), International AIDS Society (IAS), European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), the International Workshop on Pharmacology of Tuberculosis Drugs and the Union World Conference on Lung Health. We also searched referenced studies from publications.

Inclusion and Exclusion criteria

We included all retrospective and prospective observational studies as well as clinical trials in patients with pulmonary TB that met the following criteria: 1) Studies involving standard dose first-line anti-TB drugs: rifampicin, isoniazid, ethambutol and pyrazinamide with treatment provided daily according to current WHO guidelines 2) studies whose results include PK assessments of the anti-TB drugs 3) studies in which TB treatment outcomes were reported, 4) publications in English. We excluded: 1) studies involving children only 2) studies involving pregnant women only 3) studies that were categorized as case studies, commentaries, editorials and reviews 4) studies that did not explore the relationship between the PK parameters and treatment outcomes 5) studies that specifically enrolled patients with organ failure.

Data Extraction

Two researchers (CS and BC) extracted the data from the included studies and entered them into Excel 2013 (Microsoft Corporation; Redmond, WA, USA). Where discordance on studies to be included occurred, a third reviewer of (ML) was consulted and consensus achieved. The following data were extracted: author, year of publication, study characteristics (location, sample size, study design); population (sex, HIV status); PK parameters (C_{max} , AUC, concentration at 2hrs (C_{2h})); microbiologic outcomes (proportions of patients with sputum culture conversion at two months) and treatment outcomes (as defined by WHO).

RESULTS

We identified 3670 studies from our initial database search and search of referenced studies. From these, 18 articles were identified for full review after screening by title and abstracts (Figure 1). Eight articles were excluded following full review: 4 did not explore the relationship between anti-TB drug PK and treatment outcomes, 2 carried out dose adjustment before the sputum conversion was assessed, 1 had no outcome data, and 1 reported drug concentrations only in slow responders and not for the rest of the study population. In addition, dose adjustment was performed prior to assessment of treatment outcome. Dates of included studies ranged from 2007 to July 2016. Out of the 10 identified publications, 7 were prospective^{2, 12–17}, 2 retrospective^{18, 19}, and 1 case control study.²⁰ One study excluded participants who were HIV-infected²⁰, 1 study reported the proportion of patients on ART (18%)¹³ and 6 studies reported that anti-TB treatment was given under directly observed therapy (DOT).^{2, 12, 13, 15, 18, 20} Three studies defined the C_{max} as the highest of the measured time points,^{15, 18, 20} 4 studies used a single time point^{12, 14, 17} and 3 studies used non-compartmental analysis (NCA) to determine the PK parameters.^{2, 13, 16} Four studies carried out blood sampling after 8 weeks of TB treatment (Table 1).^{13, 17, 18, 20} For all studies low concentrations were defined as C_{max} or C_{2hr} values below the reference ranges for C_{max} previously defined.⁶

Rifampicin

Mah et al. found a trend towards increase in month 2 sputum culture positivity among patients with low rifampicin C_{max} (estimated from 2hr and 6hr blood draws) compared to

those with adequate concentrations, however this did not reach statistical significance (39% vs. 21%, $P=0.073$). This study was a retrospective study where serum drug concentrations were measured in patients with diabetes mellitus, HIV and those whom clinicians deemed to have poor clinical response to TB treatment.¹⁸ Prahl et al. found that a higher proportion of patients with a low C_{2hr} of both rifampicin and isoniazid experienced treatment failure compared to those with concentrations of at least one of the drugs within the reference range (5/13 versus 0/15, $P=0.013$). However, this study had a few limitations: the sample size was small ($N=62$), 9 patients received a fluoroquinolone in addition to the standard therapy and it included a group of patients who were undergoing TDM for various clinical reasons. There was however no difference in drug concentrations and the occurrence of failure between those who had TDM and those who did not.¹⁴

Van Crevel et al. found no association between rifampicin concentrations and time to sputum conversion. In this study, patient with rifampicin concentrations at $C_{2hr} < 4\text{mg/L}$ had a cure rate of 74% while those with $C_{2hr} > 4\text{mg/L}$ had a cure rate of 95%; however, the latter group had a high default rate and therefore this difference was not reported to be significant.¹⁷

Isoniazid

Mah et al. found a significant increase in month 2 sputum culture positivity among patients with a low C_{max} of isoniazid compared to those with adequate concentrations (42.5% vs. 18.3%, $P=0.0084$).¹⁸ Using 3 sampling time points (0hr, 2hr and 6hr), Sloan et al demonstrated that a low AUC of isoniazid was associated with a lower likelihood of month 2 sputum culture conversion ($P=0.045$) and a higher likelihood of failure or relapse ($P=0.035$).¹⁶ Burhan et al evaluated for the association between C_{2hr} of isoniazid and treatment outcome, however, no association was found. Although outcomes were generally good, Burhan demonstrated low concentrations of isoniazid especially among fast acetylators when compared with the slow acetylators (0.9 mg/liter versus 2.2 mg/liter, $P<0.001$).¹² In Prahl's study, patients with treatment failure had a significantly lower C_{2hr} of isoniazid than those who were cured ($P=0.004$).¹⁴ Park et al found no association between C_{2hr} of isoniazid and sputum conversion or treatment outcome, however, TDM with dose adjustment was carried out in 85% of the participants.¹⁹ Requena-Mendez et al found no association between the low isoniazid concentrations found in 30% of the study population and treatment outcomes despite deliberately including patients with diabetes mellitus and HIV, which are risk factors for poor outcomes.^{15, 21, 22}

Pyrazinamide

Burhan et al. evaluated the relationship between the C_{max} of pyrazinamide and month 2 sputum conversion. This study did not find an association when looking at month 2 sputum conversion alone however following a post hoc analysis including weeks 4, 8 and 24 sputum culture conversion as a composite outcome, patients with low pyrazinamide concentrations were less likely to have a negative cultures at either week 4, 8 or 24 sputum culture (Odds ratio (OR): 0.59; 95% Confidence Interval (CI): 0.37 to 0.93).¹² Chideya et al. found an association between low pyrazinamide C_{max} and treatment failure, these findings were more pronounced in HIV-infected patients with a CD4 cell count $< 200\text{cells}/\mu\text{l}$ ($P=0.01$).² On the other hand, Park et al. found no association between C_{2hr} of pyrazinamide and treatment

outcomes or sputum conversion.¹⁹ Sloan et al. and McIlleron et al. investigated the association between the AUC of pyrazinamide, month 2 sputum conversion and treatment outcomes and found no association.^{13, 16}

DISCUSSION

There is insufficient evidence to suggest that achieving current anti-TB drug targets correlates with a higher chance of favorable treatment outcomes or two-month sputum culture conversion in patients on the standard dose anti-TB treatment. Our main finding was the paucity of studies linking PK to TB treatment outcomes, despite the existence of PK target concentrations that are used commonly by TB programs around the world. We concluded that there is limited data to support these target concentrations. Some of the studies were retrospective or were designed to include patients that were at a high risk of unfavorable treatment outcomes. This clearly reflects on the quality of the studies and their ability to answer the question at hand. The small sample size of most of these studies limits their ability or statistical power to sufficiently evaluate the multiple factors that may affect outcomes. In addition, use of a single C_{2h} , which is not very representative of the typical drug exposure of an individual, may also affect the power to relate PK to treatment outcomes. The studies included applied highly variable blood sampling time points and analytical methods and therefore a meta-analysis of this type of heterogeneous information would be extremely difficult unless there is standardization of both laboratory and pharmacometric methodologies. Assessment of the proportion of patients who experienced sputum culture conversion also differed, for example use of different culture methods and variable definitions of culture conversion, in some instances more than one negative culture was required to ascertain culture conversion.

Population PK modeling which includes compartmental analysis is very useful in studies like these with sparse blood sampling and explains inter-individual PK variability by exploring several demographic or clinical factors where relationships between exposure and outcome are non-linear. However, very few studies were able to use this method.

That drug concentrations do not clearly appear to have an effect on outcome is somewhat counterintuitive. It is possible, though, that the cut-offs are poorly defined and are not 'targets'. Specifically, average concentrations are not necessarily optimal concentrations. Indeed, antimicrobial effect seems to be enhanced among patients receiving higher than standard-dose rifampicin in clinical trials, and the dosing of rifampicin has been called into question.^{23, 24}

Other pharmacodynamic (PD) markers have been described including the minimum inhibitory concentration (MIC) which takes into account the heterogeneity in the susceptibility of the mycobacteria isolates to the antimicrobial effect. Other authors have demonstrated that the C_{max}/MIC or AUC/MIC ratios may be more useful PK- PD markers for prediction of treatment outcomes.^{25, 26}

The validity of the commonly used reference ranges for first-line anti-TB drugs needs to be further investigated. Pasipanodya et al. used a CART analysis to develop new AUC and C_{max}

cut-offs that predict >91% of the outcomes.²⁷ These $C_{\max}$ cut-offs were higher than currently used cut-offs for isoniazid (8.8mg/L vs 3mg/L) and pyrazinamide (58.3mg/L vs 20 mg/Lf) but lower for rifampicin (6.6 mg/L vs 8 mg/L) and an association between $C_{\max}$ of pyrazinamide and 2 month sputum conversion was evident when using these new cut-offs. These new cut-offs need to be validated in other populations.

For TDM to be of value, the PK parameter that is more closely associated with TB treatment outcomes (AUC and $C_{\max}$) must be defined. Because the $C_{\max}$ and AUC are strongly correlated, either of these parameters may be useful and clinicians need to determine which one would be easier and more practical for clinical use during TDM. The 'target' for that PK parameter must be established, and the optimal sampling times for estimating the parameter must be determined. It is important to deliver doses that result in concentrations that maximize microbiologic activity, giving all patients, even hard-to treat patients, the best chance at cure. It is also essential to optimize dosing of a given drug to prevent emergence of resistance to companion drugs.²⁸ What exposures of first-line drugs are required to protect other drugs in the regimen? Since acquired drug resistance (DR) during treatment is relatively uncommon (and is often not identified because, in most settings, drug susceptibility testing is not performed pre-treatment), studying the relationship between PK and prevention of acquired DR is challenging.

In a meta-analysis by Pasipanodya et al., investigators found that pharmacokinetic variability of isoniazid, genetically mediated, has an important role in the development of acquired DR and TB treatment failure.²⁹ In *in vitro* testing on moxifloxacin, the exposures required to suppress the drug resistance were different from the exposures needed for maximal antimicrobial activity. This may apply to other anti-TB drugs.³⁰

This review demonstrates the limited number of adequately powered studies and the difference in the PK parameters used to evaluate the association between anti-TB drug concentrations and treatment outcomes in patients on the daily standard dose of the recommended WHO TB treatment regimen. Nevertheless, in reviewing the data to determine whether the current data supports the target concentrations, we high-light the gap in research on anti-TB drug pharmacology and its application in clinical practice (TDM). Larger studies, that do not deliberately include patients at risk of treatment failure need to be performed using the most suitable and practical pharmacological marker which can be applied in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
PRISMA flow diagram showing study inclusion

Table 1

Table demonstrating study characteristics and results.

Author	Year	Location	Design	Sample Size	Study drug	PK parameter	PK sampling occasion	PK Sampling time point(s)	Method for determination of PK parameter	Outcome measure	Correlation of drug concentration with outcome
Mah 2015 ¹²	2015	Canada	Retrospective	153 (134 for outcomes)	RIF, INH	C _{max}	8 weeks	1–2, 6 hr (INH) 2, 6 hr (RIF)	Highest of time points	Month 2 culture conversion	Yes (INH)
Chang 2008 ²³	2008	Hong Kong	Case control	36 cases 36 controls	RIF	C _{max}	8 weeks	2, 4 hr	Highest of time points	Month 2 culture conversion	No
Crevel R. 2002 ²⁴	2002	Indonesia	Prospective cohort	62	RIF	C _{2h}	4 and 8 weeks	2 hr	Single time point	Month 2 Culture conversion, cure, failure	No
Chideya 2009 ³	2009	Botswana	Prospective cohort	225	All	C _{max}	1 week	1, 2, 6 hr	NCA	Failure, death, cure	Yes (PZ)
Sloan 2014 ¹⁶	2014	Malawi	Prospective cohort	133	All	C _{max} , AUC(0–6h)	2 or 3 weeks	0, 2, 6 hr	NCA	Month 2 culture conversion, failure, death, cure and	Yes (INH)
Mclleron 2007 ¹⁷	2007	South Africa	Prospective cohort	142	All	AUC(0–8h)	8 weeks	0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hr	NCA	failure, death, cure relapse at 24 months	No
Burhan 2013 ¹⁴	2012	Indonesia	Prospective cohort	196	INH, RIF, PZ	C _{2h}	4 weeks	2 hr	Single time point	Month 2 culture conversion	No [*]
Prahl 2014 ¹³	2014	Denmark	Prospective cohort	32 active TB, 3 IPT	All	C _{2h}	After day 6	2 hr	Single time point	Failure, death, cure, relapse at 12 months	Yes (RIF and INH)
Requena-Mendez 2014 ²⁵	2014	Peru	Prospective cohort	107 (41 with outcomes)	INH	C _{max} , AUC(0–6h)	After 15 days	2, 6 hr	NCA	Failure, death, cure, relapse at 6 months	No
Park 2016 ¹⁵	2015	Korea	Retrospective	413	All	C _{2h}	After 1 week	2 hr	Single time point	Month 2 Culture conversion, cure, failure, relapse	No

Cmax: Maximum concentrations, AUC: Area under the concentration-time curve, RIF: Rifampicin, INH: Isoniazid, PZ: Pyrazinamide, NCA: Non-Compartmental analysis

* Post hoc analysis found patients with low pyrazinamide concentrations were at risk of either positive sputum at week 4/8/24/32