THERAPEUTIC DRUG MONITORING OF ANTI-TUBERCULAR DRUGS

DM SEMINAR

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OUTLINE

- Therapeutic drug monitoring

  -introduction

  -criteria
- Rifampicin
- Isoniazid
- Pyrazinamide and ethambutol
- Fluoroquinolones
- Second-line injectibles
- Other drugs
- Case scenario
- Summary

THERAPEUTIC DRUG MONITORING

- TDM is the clinical practice of measuring this drug concentration in blood or plasma, or in other biological fluids

Class	Drugs	Therapeutic range
Antiepileptics	Phenytoin	10-20 µg/mL
	Valproate	43-101 µg/mL
	Carbamazepine	4-11 µg/mL
	Phenobarbitone	12-30 µg/mL
	Lamotrigine	3-13 µg/mL
	Levetiracetam	5-41 µg/mL
	Oxcarbazepine	3-36 µg/mL
	Ethosuximide	39-99 µg/mL
Antimaniacs	Lithium	0.6-1mEq/L
Aminoglycosides	Amikacin	Peak: 20-35 µg/mL, Trough: 1-2 µg/mL
	Tobramycin	Peak: 4 to 8 µg/mL, Trough <10 µg/mL
	Gentamicin	Peak: 4 and 8 µg/mL, Trough <10 µg/mL
Cardiac glycosides	Digoxin	0.8-2 ng/mL
Phosphodiesterase inhibitors	Theophylline	10-20µg/mL
Calcineurin inhibitors	Cyclosporine	100-400 ng/mL
	Tacrolimus	7.0-20.0 ng/mL
mTOR inhibitors	Sirolimus	4-12 ng/mL
	Everolimus	3-8 ng/mL
Antimetabolites	Methotrexate	<1µmol/L

THERAPEUTIC DRUG MONITORING

- Interindividual variability
- There should be a clear relationship between drug plasma concentrations and response (which can either be therapeutic or undesirable, toxic response)
- The drug concentration range in which a drug is effective and tolerated well, should be known and narrow [therapeutic range]
- There should be no alternative, easier measurable indicator of treatment response available
- The duration of therapy must be long enough to draw a benefit from TDM

Magis-Escurra C et al, TDM in TB Pulmonary pharmacology & therapeutics. 2012 Feb 1;25(1):83-6.

INTERINDIVIDUAL VARIABILITY

Determinants of Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Pharmacokinetics in a Cohort of Tuberculosis Patients

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Evaluation of sources of pharmacokinetic variation can facilitate optimization of tuberculosis treatment regimens by identification of avoidable sources of variation and of risk factors for low or high drug concentrations in patients. Our objective was to describe the pharmacokinetics of rifampin, isoniazid, pyrazinamide, and ethambutol in a cohort of tuberculosis patients established on first-line treatment regimens and to evaluate the determinants of pharmacokinetic variation. Plasma concentration-time profiles were determined for each of the drugs in 142 patients with drug-sensitive pulmonary tuberculosis after 2 months of daily treatment in hospital. Pharmacokinetic measures were described by noncompartmental analysis. Multiple linear regression was used to evaluate the patient and the treatment factors associated with variation of the area under the concentration-time curve from 0 to 8 h. Several factors independently associated with variations in antituberculosis drug concentrations were identified: human immunodeficiency virus infection was associated with 39% and 27% reductions for rifampin and ethambutol, respectively; formulation factors were

- 142 patients
- Prospective PK study
- Drug sensitive TB
- Isoniazid
- Rifampicin
- Ethambutol
- Pyrazinamide
- Drug levels at 2 months

INTERINDIVIDUAL VARIABILITY

- Patients had been referred to the study - poor response to treatment, suspected nonadherence, debility, severe or complicated disease, and poor socioeconomic circumstances
- The daily ingestion of antituberculosis treatment was observed by the hospital staff
- The ATT drugs were administered under fasting conditions, and drug administration was monitored
- Blood samples were obtained immediately before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 h after drug ingestion
- Published HPLC methods with UV detection were used to determine the plasma concentrations of rifampin, isoniazid, and pyrazinamide; mass spectrometry method was used to measure the ethambutol levels in plasma

INTERINDIVIDUAL VARIABILITY

- Rifampin (mg/kg) - 10.9 [8.8–14.2], the multiple linear regression model described **36% of the variability** associated with $AUC_{0–8}$
- Isoniazid (mg/kg) - 6.5 [4.8–8.8], multivariate regression analysis explained **27% of the variability** associated with isoniazid $AUC_{0–8}$
- Pyrazinamide (mg/kg) - 35.7 [25.2–47.3], only two subjects out of 139 had significantly lower levels
- Ethambutol (mg/kg) - 24.5 [16.8–32.6], multivariate linear regression explained **31% of the variability** associated with $AUC_{0–8}$

PLASMA CONCENTRATION AND OUTCOMES - INH

Serum Levels of Antituberculosis Drugs and Their Effect on Tuberculosis Treatment Outcome

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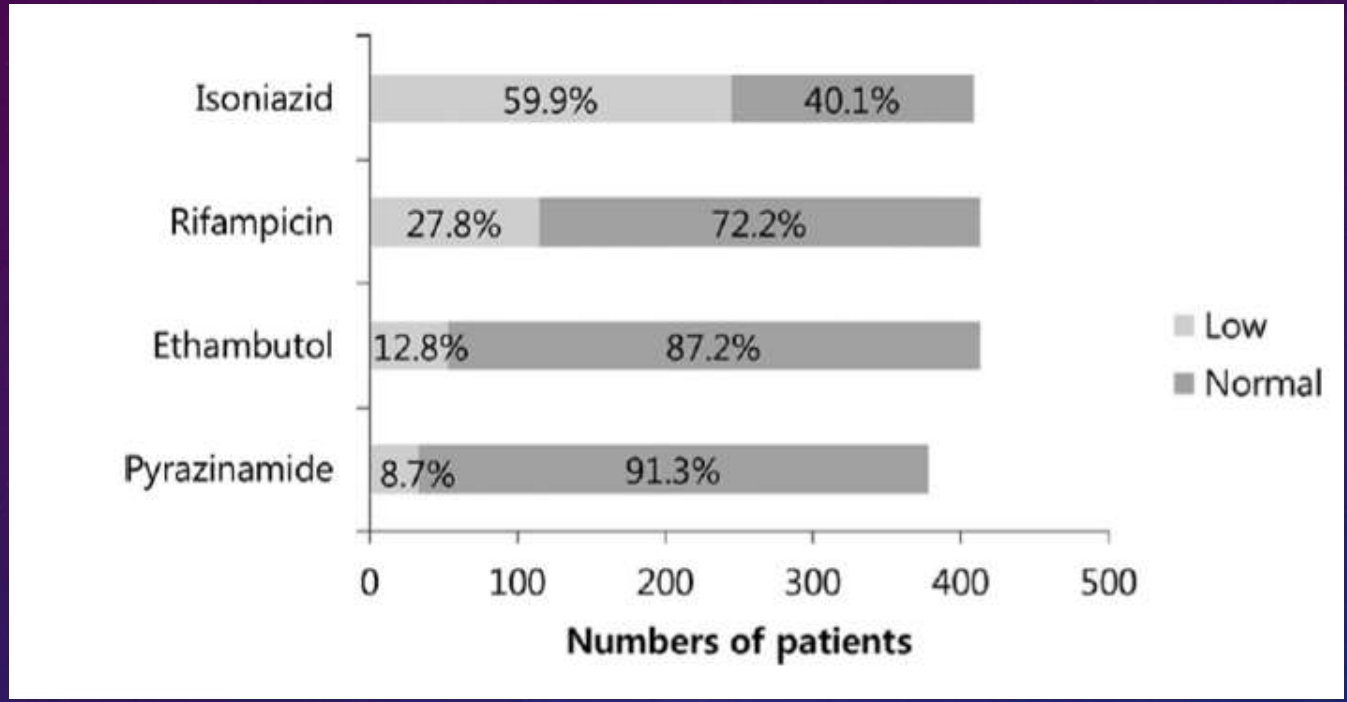
Therapeutic drug monitoring in tuberculosis remains controversial. We evaluated the relationship between antituberculosis drug levels in blood and clinical outcome. Serum concentrations of first-line antituberculosis drugs were measured in tuberculosis patients between March 2006 and April 2013. Venous blood was drawn 2 h after drug ingestion and was analyzed using high-performance liquid chromatography-tandem mass spectrometry. We retrospectively reviewed the data and determined the association of serum drug levels with clinical outcome. Among 413 patients, the prevalences of low serum concentrations of isoniazid (INH), rifampin (RMP), ethambutol (EMB), and pyrazinamide (PZA) were 59.9%, 27.8%, 12.8%, and 8.7%, respectively. The low INH group had a greater percentage of patients with a history of tuberculosis treatment (19.2% versus 11.0%; $P = 0.026$) and was more likely to present with drug-resistant strains (17.6% versus 8.8%; $P = 0.049$) than the normal INH group; however, low levels of INH, RMP, EMB, and PZA were not related to treatment outcome. Low INH level had a tendency to be associated with

Retrospective analysis
N=413
HPLC-TMS
Drug levels at 2 hours



- All were drug sensitive TB and none had HIV infection at the beginning of the study
- 40.4% of patients were fast acetylators [low INH levels]
- Increased recurrence was seen in patients with low INH group [13/17]
- Of these 13, 2, 2 had MDR-TB and 2 had INH-resistant TB
- 2 month culture positivity was associated with low INH levels
- Delayed culture positivity was not associated with low levels of other drugs

PLASMA CONCENTRATION AND OUTCOMES

Subtherapeutic Rifampicin Concentration Is Associated With Unfavorable Tuberculosis Treatment Outcomes

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Background. The relationships between first-line drug concentrations and clinically important outcomes among patients with tuberculosis (TB) remain poorly understood.

Methods. We enrolled a prospective cohort of patients with new pulmonary TB receiving thrice-weekly treatment in India. The maximum plasma concentration of each drug was determined at months 1 and 5 using blood samples drawn 2 hours postdose. Subtherapeutic cutoffs were: rifampicin <8 μg/mL, isoniazid <3 μg/mL, and pyrazinamide <20 μg/mL. Factors associated with lower log-transformed drug concentrations, unfavorable outcomes (composite of treatment failure, all-cause mortality, and recurrence), and individual outcomes were examined using Poisson regression models.

Results. Among 404 participants, rifampicin, isoniazid, and pyrazinamide concentrations were subtherapeutic in 85%, 29%, and 13%, respectively, at month 1 (with similar results for rifampicin and isoniazid at month 5). Rifampicin concentrations were lower with human immunodeficiency virus coinfection (median, 1.6 vs 4.6 μg/mL; $P = .015$). Unfavorable outcome was observed in 19%;

- N=404
- TDM at 1 month and 5 months
- Thrice weekly regimen
- Rifampicin 450 mg or 600 mg
- Isoniazid 600 mg
- Pyrazinamide 1500 mg
- Ethambutol 1200 mg
- Unfavorable outcome- seen in 19% [death, treatment failure, and recurrence]
- Low rifampicin concentration - UO

Serum Drug Concentrations Predictive of Pulmonary Tuberculosis Outcomes

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Background. Based on a hollow-fiber system model of tuberculosis, we hypothesize that microbiologic failure and acquired drug resistance are primarily driven by low drug concentrations that result from pharmacokinetic variability.

Methods. Clinical and pharmacokinetic data were prospectively collected from 142 tuberculosis patients in Western Cape, South Africa. Compartmental pharmacokinetic parameters of isoniazid, rifampin, and pyrazinamide were identified for each patient. Patients were then followed for up to 2 years. Classification and regression tree analysis was used to identify and rank clinical predictors of poor long-term outcome such as microbiologic failure or death, or relapse.

Results. Drug concentrations and pharmacokinetics varied widely between patients. Poor long-term outcomes were encountered in 35 (25%) patients. The 3 top predictors of poor long-term outcome, by rank of importance, were a pyrazinamide 24-hour area under the concentration–time curve (AUC) ≤ 363 mg·h/L, rifampin AUC ≤ 13 mg·h/L, and isoniazid AUC ≤ 52 mg·h/L. Poor outcomes were encountered in 32/78 patients with the AUC of at

- All patients [n=142] were hospitalized for 2 months
- Received daily therapy as inpatients under supervision
- 300 mg of isoniazid
- 20–35 mg/kg pyrazinamide
- 15 mg/kg ethambutol
- 600 mg of rifampicin if they weighed >50 kg or 450 mg if they weighed less
- All patients had confirmed drug-susceptible tuberculosis at the start of treatment

- After 2 months of treatment, sputum was sent for microscopy and liquid culture using the BACTEC 460 instrument
- Blood was drawn immediately before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours after a dose of drugs was given under fasting conditions
- Treatment failure was defined as inability to attain sputum smear conversion during the initial 6 months of treatment
- The secondary outcome was 2-month sputum culture conversion
- Of 142 patients, 15 (11%) did not convert their sputum cultures to negative after 2 months of treatment
- In total, 25% of 142 patients had poor long-term outcomes (19 relapsed, 15 died, and 2 had therapy failure)
- CART revealed that the 24-hour AUCs of pyrazinamide, rifampin and isoniazid were the most predictive of long-term outcomes among all factors
- The drug concentration thresholds predictive of this outcome were a 24-hour AUC of 363 mg·h/L for pyrazinamide, 13 mg·h/L for rifampin, and 52 mg·h/L for isoniazid

OTHER CRITERIA OF TDM

- There is no therapeutic range known of ATT drugs
- There is an alternate way to measure response to ATT- sputum conversion at 8 weeks or clinical response to ATT
- But these are delayed when recurrence or treatment failure have occurred
- So, TDM does have a role to play in cases where clinical failure of ATT is suspected

PK/PD DATA

- AUC over MIC for the first 24 hours is recognized as playing an important role in determining efficacy
- TDM is usually done on hollow fiber systems analyzed by artificial intelligence
- Animal models [mouse, rabbit, nonhuman primates] are a suitable alternative
- Drug levels are chosen to be 4-5 times higher than the MIC
- However, each patient has his/her duration of disease, host genetics and particular strain of *M. tuberculosis*
- In clinical scenario, TB is treated with a combination of drugs and hence individual drug MICs are not reflective of real-life picture

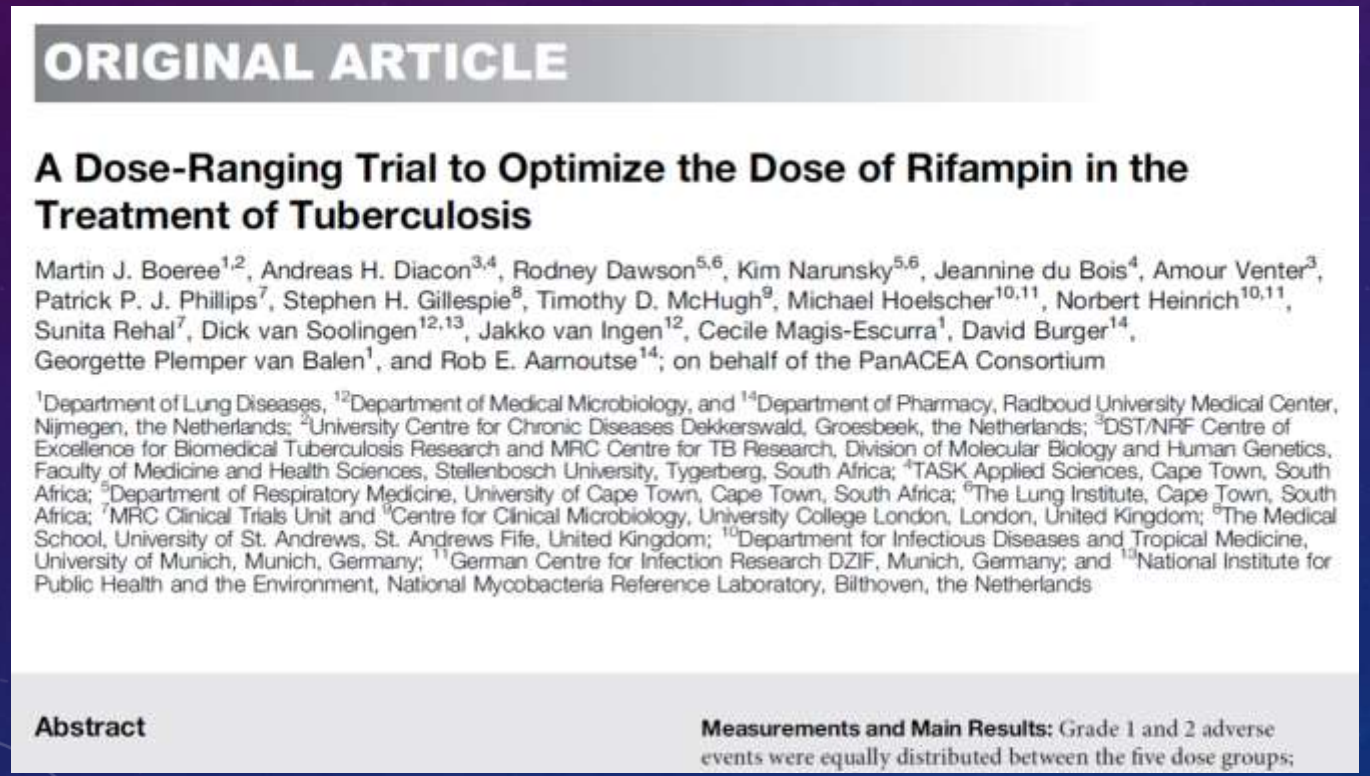
Falzon D et al. Pharmacology of ATT, Clinical Infectious Diseases. 2018 Nov 28;67(suppl_3):S365-7.

RIFAMPICIN

- A low AUC/MIC in first 24 hours is associated with delayed sputum conversion and poor outcomes
- So, increasing the dose of rifampicin based on PK/PD data is a reasonable option
- Rifampin at a dose of 10 mg/kg was introduced in 1971 based on pharmacokinetics, toxicity and cost considerations
- A trial in patients with pulmonary tuberculosis in Indonesia comparing 450 mg rifampin (10 mg/kg) with 600 mg (13 mg/kg) rifampin showed a **nonlinear**, more than proportional increase of pharmacokinetic exposure

EAST A. Controlled clinical trial of short-course regimens for treatment of PTB. Lancet. 1972:1079-85.
RuParwati I et al. PK and tolerability of a higher rifampin dose versus the standard dose in PTB. AAC. 2007 Jul;51(7):2546-51.

HIGH DOSE RIFAMPIN



ORIGINAL ARTICLE

A Dose-Ranging Trial to Optimize the Dose of Rifampin in the Treatment of Tuberculosis

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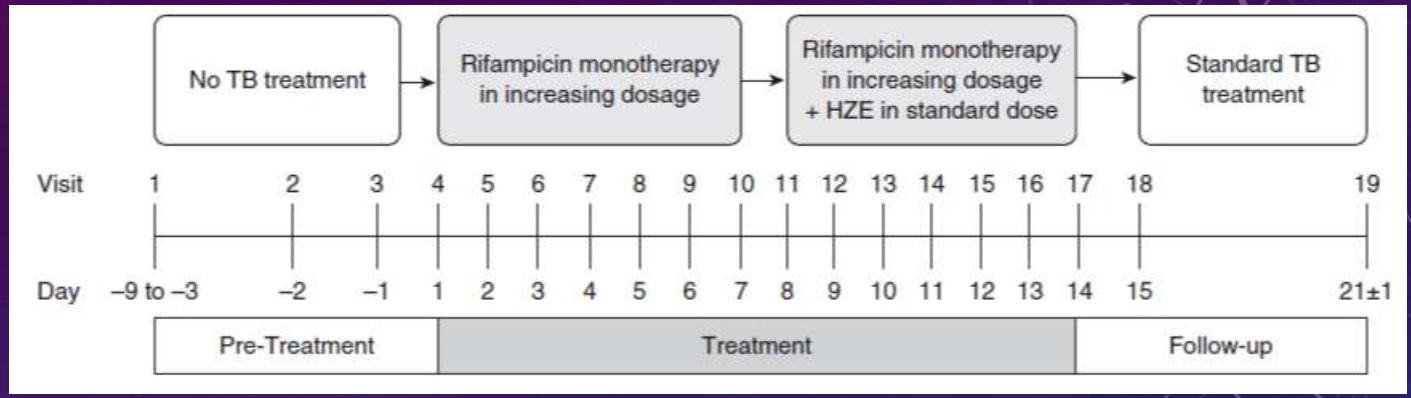
Abstract

Measurements and Main Results: Grade 1 and 2 adverse events were equally distributed between the five dose groups;

- Adults (18–65) with newly diagnosed, previously untreated, sputum smear positive uncomplicated pulmonary tuberculosis [n=68]
- HIV-positive subjects, a CD4 count >350 cells was mandatory

STUDY DESIGN



- The first eight patients were enrolled in a control cohort receiving rifampin 10 mg/kg
- Subsequently, patients were enrolled in consecutive intervention cohorts of 15 patients each
- The first cohort received rifampin at a dose of 20mg/kg
- The second cohort received 25, the third 30, and the last cohort received 35 mg/kg

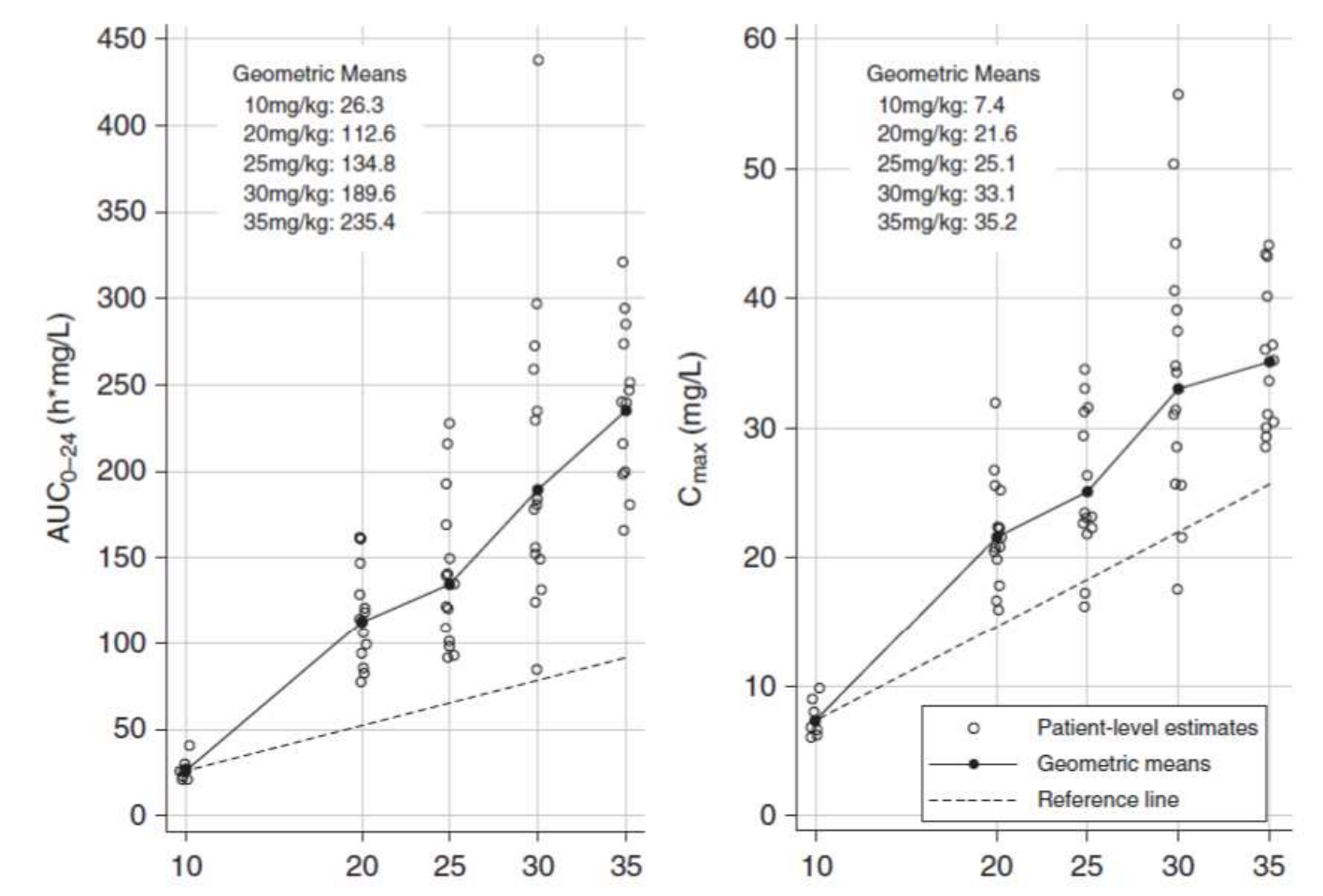
- Of note, the consecutive dose increases for rifampin were relatively small, considering the nonlinear PK of rifampin, which means that an increase in dose may result in an unpredictable, disproportionally larger increase in exposure

- The primary objective of this study was to assess the maximum tolerated dose, which is defined as the dose below that producing unacceptable but reversible toxicity

- Blood samples were taken on Days 7 and 14 with a standardized meal for a full pharmacokinetics curve
- Spot sputum samples were collected before enrollment, at Day 19, and after 12 weeks

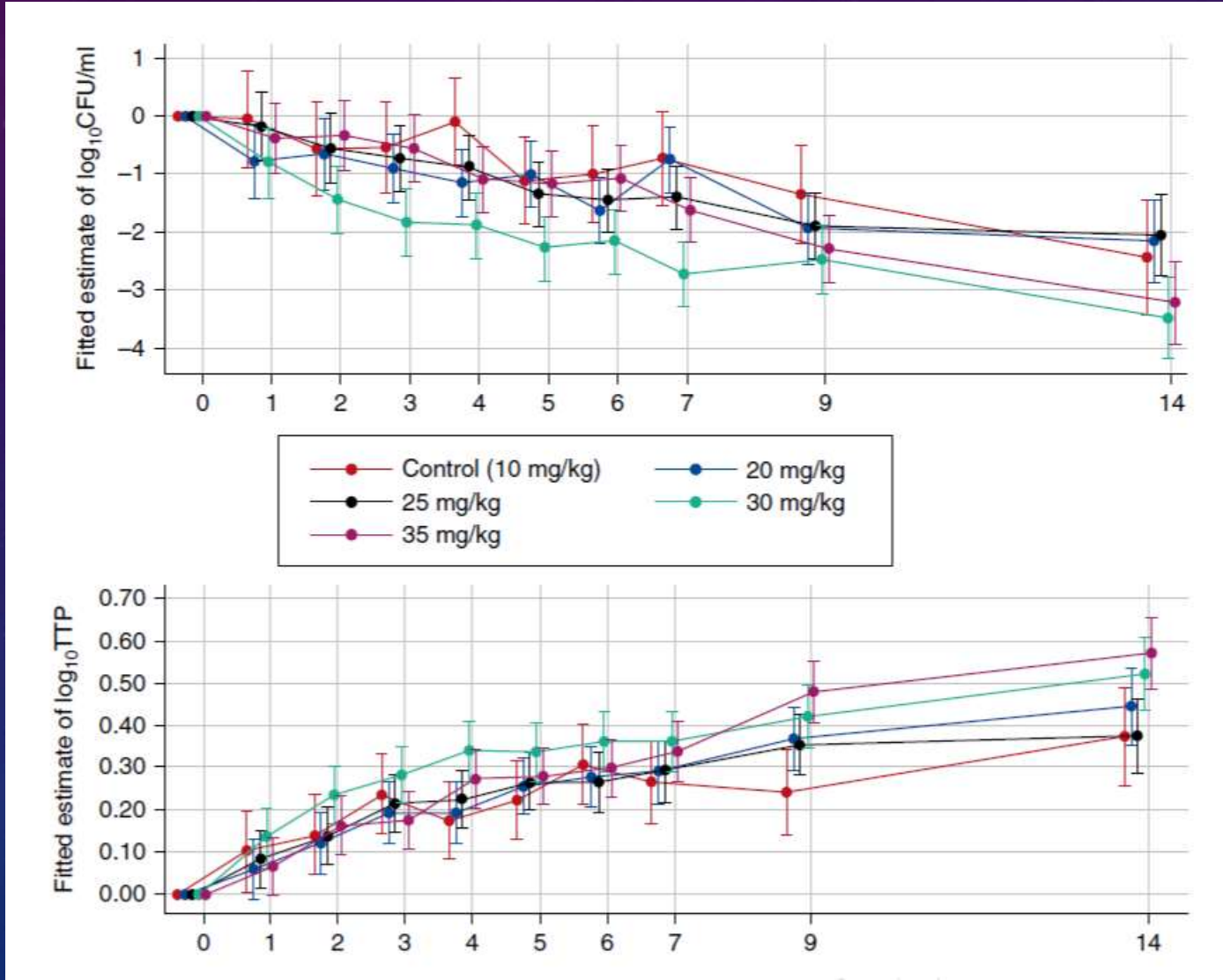
RESULTS-PK

Group	AUC_{0-24h} (h · mg/L)	C_{max} (mg/L)*
10 mg/kg (control)	26.3 (21.3–40.9)	7.4 (6.1–9.9)
20 mg/kg	113 (77.5–162)	21.6 (16.0–31.9)
25 mg/kg	135 (91.5–228)	25.1 (16.3–34.6)
30 mg/kg	190 (84.7–436)	33.1 (17.6–55.8)
35 mg/kg	235 (166–321)	35.2 (28.6 –44.2)

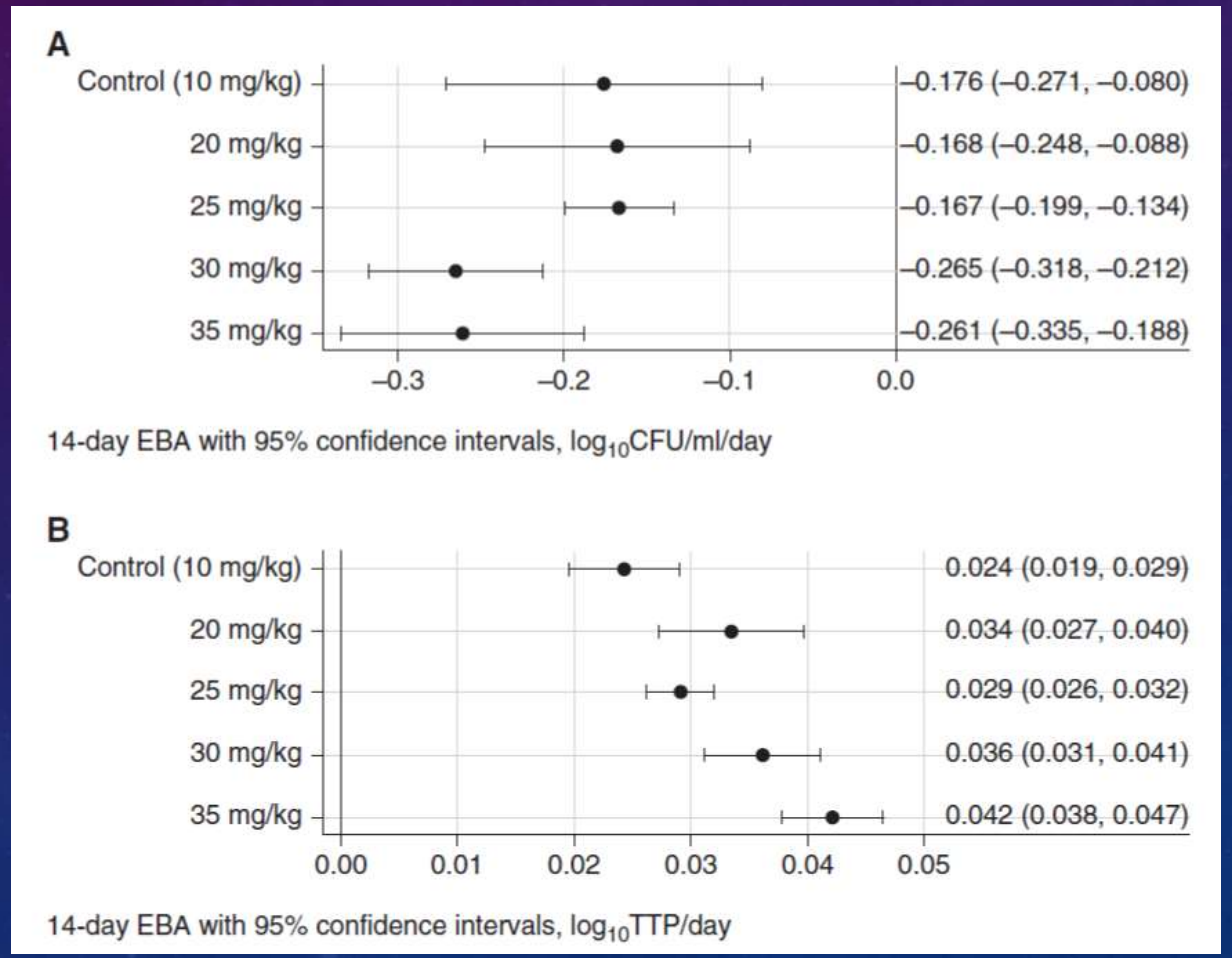


- Non-linear, disproportional increase
- No ceiling in rifampin AUC0–24 or flattening of the relationship between dose administered and AUC0–24 achieved was observed

RESULTS-ANTIMYCOBACTERIAL ACTIVITY



RESULTS-ANTIMYCOBACTERIAL ACTIVITY



RESULTS-SAFETY ANALYSIS

- There were a total of 163 adverse events: 128 grade 1, 30 grade 2, and five grade 3 adverse events
- No grade 4 and 5 adverse events occurred
- A total of 53 adverse events were unrelated to rifampin, 102 were “possibly” related, and eight were assessed to be “definitely” related to rifampin
- The most common adverse events related to monotherapy with rifampin were abdominal pain, vomiting, headache, and pruritus

Group	Total	Grade 1		Grade 2		Grade 3*	
		Possibly Related	Related	Possibly Related	Related	Possibly Related	Related
10 mg/kg RIF (control)	7	0	0	0	0	0	0
20 mg/kg RIF	39	21	1	4	0	2	0
25 mg/kg RIF	24	11	2	2	0	0	0
30 mg/kg RIF	39	21	3	4	0	1	0
35 mg/kg RIF	54	27	2	9	0	0	0
Total	163	80	8	19	0	3	0

RESEARCH ARTICLE

High-dose rifampicin in tuberculosis: Experiences from a Dutch tuberculosis centre

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Abstract

Background

Recent evidence suggests that higher rifampicin doses may improve tuberculosis (TB) treatment outcome.

Retrospective analysis of 87 patients on high dose rifampicin from Jan 2008 to May 2018
High dose was used because- CNS TB [n=26], low drug concentration [n=57] and extensive PTB [n=5]

TDM

- relapse TB
- delayed culture conversion (culture positive beyond two months of treatment)
- delayed clinical response
- HIV coinfection
- Diabetes Mellitus
- suspicion of gastrointestinal malabsorption
- severe weight loss or cachexia (BMI < 18.5 kg/m2)
- history of alcohol or drug abuse
- renal or hepatic failure
- important drug interactions

	Group 1	Group 2	
	(*n* = 26)	(*n* = 57)	
Initial dose and pharmacokinetic parameters		**Initial dose 450 mg**	**Initial dose 600 mg**
		n = 5	*n* = 52
Rifampicin dose (mg/kg)		11.4 (9.6–14.5)	17.7 (7.8–30.0)
C_{max}*		2.8 (0.2–6.6)[5]	5.3 (1.5–13.6)[43]
AUC_{0-24}*		26.5 (20.1–35.0)[2]	27.7 (8.8–65.7)[27]
Adjusted dose and pharmacokinetic parameters			
Rifampicin 900mg	*n* = 4	*n* = 3	*n* = 21
Rifampicin dose (mg/kg)	15.1 (13.1–17.3)	24.9 (21.4–29.0)	15.2 (7.8–20.9)
C_{max}*	18.6[1]	15.6 (12.9–18.7)[3]	11.6 (6.5–22.1)[13]
AUC_{0-24}*	105.0[1]	104.0 [1]	58.4 (42.0–119.4)[8]
Rifampicin 1200mg	*n* = 18	*n* = 2	*n* = 28
Rifampicin dose (mg/kg)	18.0 (12.6–27.4)	22.9 (19.2–26.7)	18.6 (12.5–27.7)
C_{max}*	19.3 (13.0–37.3)[8]	19.1[1]	16.8 (8.7–29.7)[13]
AUC_{0-24}*	139.5 (103.0–250.0)[7]	79.0[1]	85.7 (47.0–150.0)[6]
Rifampicin 1500mg	*n* = 1		*n* = 1
Rifampicin dose (mg/kg)	29.4		30.0
Rifampicin 1800mg	*n* = 3		*n* = 1
Rifampicin dose (mg/kg)	30.2 (28.3–32.0)		28.6
C_{max}			17.5
AUC_{0-24}			117.0
Rifampicin 2400mg			*n* = 1
Rifampicin dose (mg/kg)			26.3
C_{max}			37.8
AUC_{0-24}			236

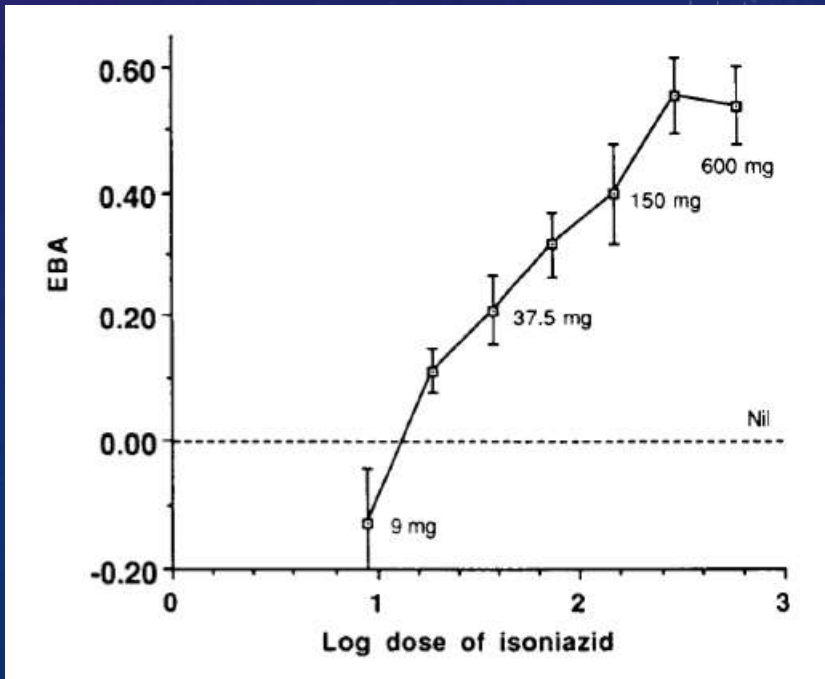
Severe illness low drug levels

SAFETY AND TOLERABILITY OF HIGH-DOSE RIFAMPICIN

- In terms of safety or tolerability, no difference was observed between 20 or 30 mg/kg
- Drug induced liver injury developed in four patients (4.5%) (ALT range 243–899 U/L and AST range 242–1482 U/L (severity grade 3–4)
- In two patients, isoniazid-related hepatitis was proven with an isoniazid re-challenge
- Re-introduction of high-dose rifampicin, was successful in all four patients
- One patient with liver cirrhosis (Child Pugh class C) with bilirubin levels > 5 times the upper limit of normal before start of treatment, tolerated high-dose rifampicin (21 mg/kg) well
- In the first 12 days of treatment his bilirubin levels further increased from 4.97 mg/dL to 6.2 mg/dL and then slowly decreased to 2.4 mg/dL over 4 months [AUTO-INDUCTION]

ISONIAZID

- Normal INH dose is 4-6 mg/kg and higher dose is 10-15 mg/kg
- The two most important factors in deciding the dose of INH are *InhA* and *KatG* mutation and NAT2 mutation status
- EBA [early bactericidal activity] studies in dose-ranging INH in drug susceptible TB shows clear dose-response relationship and indicating **saturation of the effect at doses** more than 300 mg per day
- Toxicity is expected more than bactericidal effect



Peloquin CA et al .Population PK of H,R,Z. Antimicrobial agents and chemotherapy. 1997 Dec;41(12):2670-9.

A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis

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SUMMARY

SETTING: Tertiary care hospital in Kanpur, India.

BACKGROUND: The need for a standardised treatment protocol for multidrug-resistant tuberculosis (MDR-TB) in resource-limited countries is being increasingly recognised.

OBJECTIVE: To assess the effectiveness of high-dose isoniazid (INH) (16–18 mg/kg) adjuvant to second-line therapy in documented cases of MDR-TB.

DESIGN: The present study is a double blind, randomised controlled trial with three treatment arms, high-dose INH, normal-dose INH and placebo, in addition to second-line drugs. Primary outcomes of the study were time to sputum culture conversion and proportion with

RESULTS: After adjustment for potential confounders, subjects who received high-dose INH became sputum-negative 2.38 times (95%CI 1.45–3.91, $P = 0.001$) more rapidly than those who did not receive it, and had a 2.37 times (95%CI 1.46–3.84, $P < 0.001$) higher likelihood of being sputum-negative at 6 months. These subjects showed significantly better radiological improvement without an increased risk of INH toxicity.

CONCLUSION: In low-resource scenarios where a standardised therapeutic protocol is used for MDR-TB, the protocol can be significantly improved by including high-dose INH as an adjuvant.

KEY WORDS: randomised controlled trial; multidrug-

Addition of high dose INH to treatment regimen increased the likelihood of being sputum negative at 6 months

PYRAZINAMIDE

- Preclinical and clinical evidence (based on culture conversion data) suggests that the current dose in standard use is not optimized (20-30mg/kg/d)
- The PK/PD parameter linked to sterilizing effect is AUC/MIC ratio
- Monte Carlo simulations indicate that at the current standard dose of pyrazinamide only about 57% of patients achieve optimal AUC/MIC
- Doubling the dose has been shown to have a higher sterilizing effect in animal models
- Optimal outcomes were associated with a serum AUC >363 mg·h/L
- However, any further consideration of increasing the pyrazinamide dose needs to be considered considering increasing liver toxicity
- There is very little interindividual variation

Ramachandran G et al. Subtherapeutic rifampicin and TB outcomes Clinical Infectious Diseases. 2020 Mar 17;70(7):1463-70.
Magis-Escurra C et al, TDM in TB Pulmonary pharmacology & therapeutics. 2012 Feb 1;25(1):83-6

ETHAMBUTOL

- There is no data to correlating ethambutol serum concentrations and treatment outcome
- There is no role for routine serum concentration monitoring
- Circumstances in which serum concentration monitoring may be useful to guide dosing include kidney insufficiency, suspected malabsorption, or therapeutic failure.
- Target peak (2 hours post dose) concentrations after daily doses of 15 to 25 mg/kg are between 2 and 6 micrograms/mL
- Since absorption may be delayed or impaired in some patients, a second sample (6 hours after dosing) is recommended

Mota L et al. TDM of ATT The International Journal of Tuberculosis and Lung Disease. 2016 Jun 1;20(6):819-26.

FLUOROQUINOLONES

- There have been no dose-ranging studies to provide guidance on optimization of dose
- Increased doses of fluoroquinolone carry safety concerns, namely prolonged QT-interval (moxifloxacin) and dysglycaemia (gatifloxacin)
- Since data on exposure-response and exposure-safety are lacking, it is not clear how benefit/risk ratio might be impacted by replacing one medicine with another
- PK/PD data is available for moxifloxacin based on HFIM and murine models

BMJ Open

Prospective evaluation of improving fluoroquinolone exposure using centralised therapeutic drug monitoring (TDM) in patients with tuberculosis (PERFECT): a study protocol of a prospective multicentre cohort study

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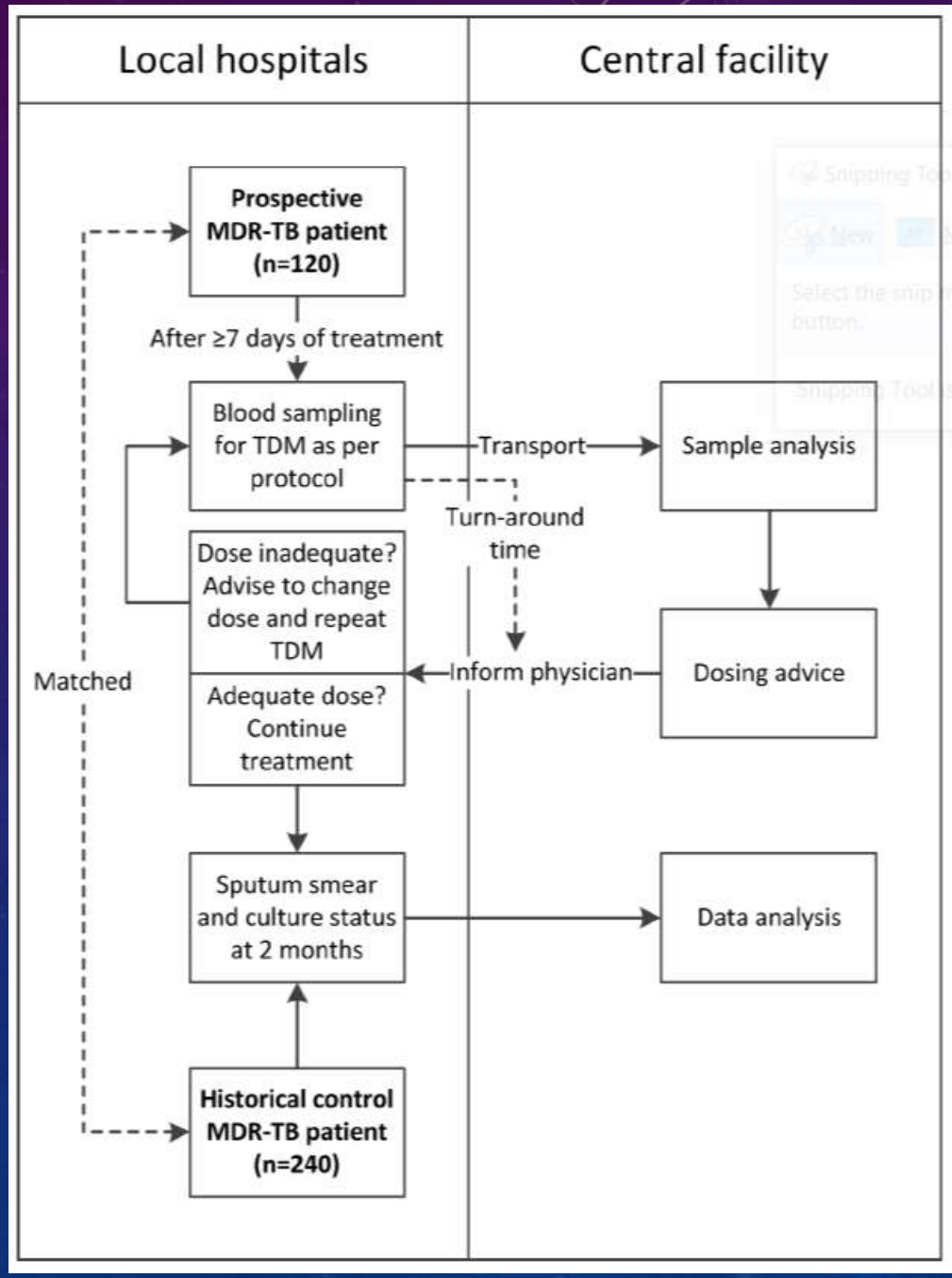
To cite: van den Elsen SHJ, Sturkenboom MGG,

PERFECT STUDY-PLAN

- N=120 (60 with moxifloxacin and 60 with levofloxacin)
- compared with 240 matched historical controls (120 with moxifloxacin and 120 with levofloxacin)
- The first sample collection - just before drug intake (t=0) and the other at 5 hours after drug intake (t=5)
- liquid chromatography-mass spectrometry
- Dosing is optimized based on $AUC_{0–24}$/MIC [>150 for levofloxacin and >100 for moxifloxacin]or $AUC_{0–24}$



SECOND-LINE INJECTIBLES

- Dose-ranging studies of amikacin (15mg/kg/day) showed that it has no early bactericidal activity
- In vitro studies show that amikacin is weakly bactericidal, and that kanamycin is bacteriostatic
- Evidence from the HFIM indicates that C_{max}/MIC is the best PK/PD index and a Cmax/MIC ratio of 10 (in lung tissue) has been proposed as a target from HFIM system
- The penetration of aminoglycosides into the lung tissue is known to vary and is not well defined.
- This has an important bearing on the correlation between the measurable plasma levels and those that can be achieved in the lungs as the target organ (conversion of the C_{max}/MIC ratio)
- C_{min}/MIC is the best indicator of toxicity

Donald P et al. The EBA of amikacin in PTB. The International Journal of TB and Lung Disease. 2001 Jun 1;5(6):533-8
Sanders Jr WE et al, Activity of amikacin against mycobacteria in vitro and in murine tuberculosis. Tubercle. 1982 Sep 1;63(3):201-8
Srivastava S et al. Amikacin optimal exposure targets in the HFIM of TB. Antimicrobial agents and chemotherapy. 2016 Oct 1;60(10):5922-7

TDM OF AMIKACIN

- Injectable agents carry several serious safety concerns, ototoxicity [which appears to be dependent on cumulative dose/exposure], nephrotoxicity [which is associated with trough levels]
- Ototoxicity seems to be related to penetration into deep compartments from which the half-life of disappearance is extremely slow and not necessarily correlated with measurable plasma levels
- Cmax is estimated from post infusion peak blood level
- Target level Cmax: 40 to 50 mg/L
- Trough (30 minutes pre-dose): <2 mg/L

Srivastava S et al. Amikacin optimal exposure targets in the HFIM of TB. Antimicrobial agents and chemotherapy. 2016 Oct 1;60(10):5922-7

Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Amikacin Dosing for MDR Tuberculosis: A Systematic Review to Establish or Revise the Current Recommended Dose for Tuberculosis Treatment

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Background. Amikacin has been used for over 40 years in multidrug resistant tuberculosis (MDR-TB), but there is still debate on the right dose. The aim of this review was to search relevant pharmacokinetic (PK) and pharmacodynamic (PD) literature for the optimal dose and dosing frequency of amikacin in MDR-TB regimens trying to optimize efficacy while minimizing toxicity.

Methods. A systematic review on the value of amikacin as second-line drug in the treatment of MDR-TB was performed.

Results. Five articles were identified with data on PK, hollow-fiber system model for TB and or early bactericidal activity of amikacin. Despite the long period in which amikacin has been available for the treatment of MDR-TB, very little PK data is available. This highlights the need for more research.

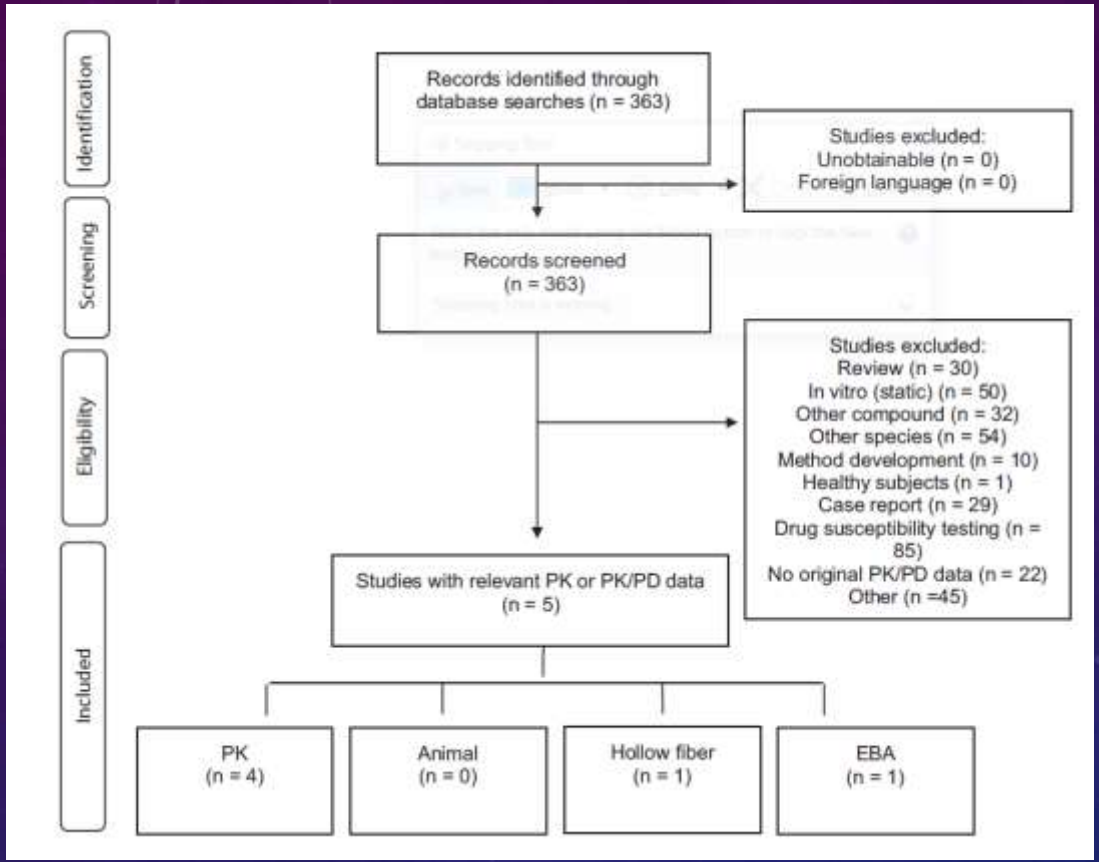
Conclusions. Maximum concentration (C_{max}) of amikacin related to MIC proved to be the most important PK/PD index for efficacy. The target C_{max}/MIC ratio should be 10 at site of infection. Cumulative area under the concentration-time curve (AUC) corresponding with cumulative days of treatment was associated with an increased risk of toxicity.

Keywords. pharmacokinetics/pharmacodynamics; optimal dose; Monte Carlo simulation; probability of target attainment.

Multidrug-resistant (MDR) tuberculosis is defined as simultaneous resistance to rifampicin and isoniazid, the cornerstones of the treatment of drug-susceptible tuberculosis. This necessitates the use of expensive and toxic second-line treatment regimens. The World Health Organization (WHO) has recategorized the

the recommended dosages for the treatment of MDR tuberculosis with regimens that contain amikacin. Here, our aim was to search relevant pharmacokinetic/pharmacodynamic (PK/PD) literature for the optimal dose and dosing frequency of amikacin in MDR tuberculosis regimens, trying to optimize efficacy while

4 PK/PD Studies
1 HFIM study
1 EBA study



Study	Sampling	N	Dose	Peak Concentration (mg/L) Median (Range)	0–24 Hour Area Under the Concentration-Time Curve (mg*h/L) Median (Range)
Donald et al [3]	$C_{max,\ IM}$	12	5 mg/kg IM	13.5 ± 2.7[b]	…
		13	10 mg/kg IM	26.7 ± 5.5[b]	…
		15	15 mg/kg IM	39.2 ± 9.0[b]	…
Peloquin et al [4][a]	$C_{max,\ IV}$	11	15 mg/kg IV	46 (26–54)	…
		11	25 mg/kg IV	79 (54–98)	…
Modongo et al [5]	$C_{max,\ IM}$	17	17.4 (13.7–19.2) mg/kg IM	49.4 (22.0–65.6)	557 (242–989)
		11	17.0 (11.1–19.2) mg/kg IM	49.4 (25.9–77.0)	600 (446–767)
Van Altena et al [6]	C_{peak}	39	6.5 mg/kg IV	29.3 (11.0–72.5)	113 (49–232)

- **Hollow-fiber System Model Studies**
- The amikacin MIC against the M. tuberculosis strain was 0.5 mg/L
- The PK/PD index linked to M. tuberculosis kill was the peak concentration Cmax/MIC ratio, closely followed by the AUC_{0-24}/MIC ratio
- EC_{90} (concentration mediating 90% of maximal kill [Emax]), was a C_{max}/MIC ratio of 10.1 (95% confidence interval [CI], 7.76 to 12.5) at the site of infection
- This translates into a serum C_{max}/MIC ratio of 75
- An AUC_{0-24}/MIC ratio of 103 (95% CI, 77.7 to 128) also reached EC_{90}
- **Early Bactericidal Activity Studies**
- The study concluded that the EBA did not differ significantly after administration of amikacin at doses of 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg or 25 mg/kg

TOXICITY

Reduced Chance of Hearing Loss Associated with Therapeutic Drug Monitoring of Aminoglycosides in the Treatment of Multidrug-Resistant Tuberculosis

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- 80 Patients with MDR-TB, retrospective analysis
- Aminoglycosides-15 mg/kg with a max dose of 1 g/day
- PK/PD parameters targeting Cmax/MIC ratio of <20
- maintains efficacy while preventing toxicity
- TDM was done once in 3 weeks
- Dose was escalated or reduced accordingly
- **REGIMENS**
- **Daily**
- **5 times a week**
- **3 times a week**
- cumulative AUC was well below this threshold of 87,232 mg/liter·h·day, which could explain the relatively low incidence of ototoxicity

THIONAMIDES

- Ethionamide and prothionamide are derivatives of isonicotinic acid
- PK/PD studies have shown MIC to be two times of that of isoniazid
- There are no studies to show TDM is helpful in dosing of thionamides

Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis, WHO 2016

CYCLOSERINE AND TERIZIDONE

- PK/PD data for cycloserine are extremely sparse and based on outdated bioanalytical methods
- No results from HFIM studies have been published
- there have not been preclinical or clinical studies performed to identify a correct PK/PD target
- Inter-person variability in PK of cycloserine is not clear

Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis, WHO 2016

LINEZOLID

- Linezolid activity in TB EBA trials was modest at best and it may only have modest bactericidal activity against dividing TB bacilli
- In vitro data suggest that its efficacy is driven by C_{min}/MIC and AUC/MIC
- An AUC/MIC with a target of 100 based on exposure of 600mg twice daily and MIC of 2mg/L
- The MIC of 2 is non-species related
- No RCTs are available with regards to linezolid in TB patients

Dietze R et al. Early and extended early bactericidal activity of linezolid in pulmonary tuberculosis. AJRCCM. 2008 Dec 1;178(11):1180-5.

Linezolid Dose That Maximizes Sterilizing Effect While Minimizing Toxicity and Resistance Emergence for Tuberculosis

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ABSTRACT Linezolid has an excellent sterilizing effect in tuberculosis patients but high adverse event rates. The dose that would maximize efficacy and minimize toxicity is unknown. We performed linezolid dose-effect and dose-scheduling studies in the hollow fiber system model of tuberculosis (HFS-TB) for sterilizing effect. HFS-TB units were treated with several doses to mimic human-like linezolid intrapulmonary

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- Linezolid dose-effect and dose-scheduling study
- HFIS model
- PK/PD studies were done for 2 months
- Optimal microbial kill was achieved at an $AUC_{0–24}$/MIC ratio of 119
- Optimum sterilizing effect using Monte-carlo simulations
- Clinical doses of 300 and 600 mg/day (or double the dose every other day) achieved this target in 87% and 99% of 10,000 patients
- The susceptibility breakpoint identified was 2 mg/liter

TOXICITY

- The major concern limiting the increase of dose, frequency or duration of use is toxicity
- Serious neuropathies (e.g., peripheral and optic neuropathies), myelosuppression, and hyperlactatemia [inhibition of mitochondrial protein synthesis]
- Bone marrow toxicities appear to be concentration driven, while neuropathy is cumulative dose/AUC driven
- Duration of use in MDR-TB regimens is usually much longer than the maximal period of use recommended non-TB indications (28 days)
- Linezolid is retained in the regimen for as long as the individual patient can tolerate it
- Rifampicin may reduce linezolid concentrations

Nagiec EE et al. Oxazolidinones inhibit proliferation via inhibition of mitochondrial protein synthesis. ASM. 2005 Sep;49(9):3896-902.
Lee M, et al. . Linezolid for treatment of chronic extensively drug-resistant tuberculosis. NEJM. 2012 Oct 18;367(16):1508-18

CLOFAZIMINE

- Clofazimine is highly lipophilic and its concentration in tissues is higher than in blood and serum
- PK/PD studies are not available for clofazimine in TB patients
- Dosing is extrapolated from leprosy patients
- TDM is not proposed to be useful for clofazimine
- QTc prolongation is an adverse event beyond doses of 100 mg per day
- So additive toxicity with bedaquiline, delamanid and fluoroquinolones is exepcted

Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis, WHO 2016

BEDAQUILINE

- The high protein binding (>99.9%) and extensive tissue distribution of bedaquiline makes direct comparison between plasma exposure and MIC difficult
- The PK/PD relationship has been evaluated by comparing time to sputum culture conversion for exposure quartiles, but no significant relationship could be detected
- TDM has not been proven to be useful for bedaquiline

Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis, WHO 2016

CASE SCENARIO

- Mr. A, 20 years of age, developed fever for 1 month [April-May 2019] and evaluation revealed axillary lymphadenopathy with necrosis on CECT chest and abdomen.
- Empiric ATT for 6 months [July 2019 to Dec 2019], complete resolution of fever and weight gain was documented
- 8 months later, he had fever and weight loss, and evaluation revealed axillary lymphadenopathy and lymph node biopsy revealed caseous necrosis and Mtb gene xpert was positive, rifampicin resistance-absent
- He was started on ATT in October 2020
- At the end of 6 months, he did not have complete resolution of symptoms and x ray revealed left LZ consolidation
- ATT was further continued for 2 months

CASE SCENARIO

- ATT was continued as his symptoms were persistent and he developed dyspnea on exertion
- His sputum was repeated and was positive for AFB smear
- Mtb gene xpert – positive, rifampicin resistance- absent
- MGIT- Growth of *Mycobacterium tuberculosis*
- LPA- Rifampicin and isoniazid- sensitive
- Till now he had received 12 months of ATT

WHY DRUGS DO NOT WORK

- Diagnosis is wrong
- Drug is of subpar quality
- Compliance
- Absorption or metabolism issue
- Dosing is wrong

CASE SCENARIO

- Isoniazid 3.5 hour level = 0.10 ug/ml [SUBTHERAPEUTIC]
- Rifampicin 3.5 hour level = 0.03 ug/ml [SUBTHERAPEUTIC]
- Dose of both the drugs were increased
- INH – 10 mg/kg
- Rifampicin- 20 mg/kg
- This dose was continued for another 4 weeks
- Repeat TDM was done and the report is as follows

Time [Hours]	Isoniazid [mg/L]	Rifampicin [mg/L]	Pyrazinamide [mg/L]
0	0.129	0.052	0
2	0.401	0.903	0.968
4	1.33	0.215	25.263
6	2.196	5.213	46.499
8	0.831	3.596	22.299
24	0.129	0.052	0
AUC [mg.h/L]	16.61 [>13]	45.51 [>52]	346.751 [>363]

Interpretation-

1] All the drugs have their peak at 6 hours, reflecting delayed absorption or rapid metabolism/excretion

2] AUC- Isoniazid is adequate, rest both are not [reflecting rapid metabolism/excretion or suboptimal dosing]

Final impression – RAPID METABOLISM/EXCRETION for rifampicin and pyrazinamide and delayed absorption peak of isoniazid

PERSONALIZED REGIMEN

- Isoniazid [10 mg/kg]
- Avoid rifampicin and pyrazinamide enterally, IV rifampicin can bypass the first-pass effect [drug levels must be repeated after 15 days of starting IV therapy to avoid auto-induction effect of rifampicin]
- Ethambutol
- Fluoroquinolones
- Amikacin/streptomycin
- Addition of either linezolid/clofazimine
- Duration of therapy can be decided based on clinical response

SUMMARY

- Poor response to tuberculosis treatment despite adherence and fully drug-susceptible TB strain
- Severe gastrointestinal abnormalities: severe gastroparesis, short bowel syndrome, chronic diarrhoea with malabsorption
- Drug–drug interactions
- Impaired renal clearance: renal insufficiency, peritoneal dialysis, critically ill patients on continuous renal replacement
- HIV infection
- Diabetes mellitus
- Treatment using second-line drugs MDR-TB

Nahid P et al. Official ATS/CDC and prevention IDSA clinical practice guidelines: treatment of DS-TB. Clinical infectious diseases. 2016 Oct 1;63(7):e147-95.

SUMMARY

Drug	TDM
Rifampicin	Useful, can increase the dose up to 32mg/kg if tolerated
Isoniazid	Saturation beyond doses of 300 mg/day
Pyrazinamide	Increases in doses beyond 30 mg/kg would do more harm than benefit
Ethambutol	TDM data is very scarce to comment
Fluoroquinolones	TDM data is very scarce to comment
Amikacin	TDM is useful to reduce toxicity
Thionamides/Cycloserine/Terizidone	TDM data is very scarce to comment
Clofazimine/Bedaquiline	TDM is not useful
Delamanid	PK/PD data has not been explored
Linezolid	TDM can help minimize toxicity

IS TDM EXPENSIVE ?

- TDM is considered a costly affair
- The only other alternative is to wait, watch and hope for the best, which is not really a strategy
- Clinically, patient remains infectious for longer, has his treatment prolonged for longer [leads to adverse events] and provides a niche for emergence of drug resistant bacilli
- Economically, longer duration of treatment imply more expenditure
- So, is TDM expensive - yes- think again [especially when our goal has changed to focus on elimination]

THANK YOU…