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General information

Badge policy
All registered delegates will receive an identity badge upon registration. Please wear it at all times to ensure admission to the meeting.

Certificate of attendance
A certificate of attendance can be picked up from the registration desk on Monday 9 September.

Conference materials
The presentations will be posted on www.eme-medicaleducation.com shortly after the workshop.

Evaluation form
Your feedback is very valuable to us and enables us to further improve this workshop. An evaluation form will be distributed after the PM break. Please complete this form and return it at the registration desk.

Language
The official language of the workshop is English.

Location of the different activities
- Plenary session: Cottonwood Ballroom A (level 2)
- Coffee breaks, lunch & posters: Cottonwood Ballroom B (level 2)

Oral presenters
The presentations should be handed in at least 30 minutes before the start of the presentation, at the tech table in the plenary session room.

Poster presenters
Poster presenters are requested to stand near their poster during the poster sessions. Please hang your poster as early as possible. Posters must be removed at the end of the meeting.

Registration desk
The registration desk is located in the foyer of the Cottonwood Ballroom (level 2). It opens on Monday 9 September at 07.45 AM and will remain open during all meeting hours. The conference organizers can be addressed for all questions concerning the logistics of the meeting.

Workshop dinner
A workshop dinner is scheduled for Monday evening 9 September (on pre-registration only).
## Program Monday 9 September

### Session 1 Pharmacokinetics & pharmacodynamics of approved TB drugs

**Chairs:** G. Davies & E. Nuermberger

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<td>Invited lecture: Innovative trial designs to evaluate new treatment combinations for TB</td>
<td>P. Phillips</td>
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<tr>
<td>09:15h</td>
<td>Clinical significance of 2-hour plasma concentrations of first-line tuberculosis drugs</td>
<td>J. Prahl_1</td>
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<td>09:30h</td>
<td>Pharmacokinetics of rifabutin during Atazanavir / ritonavir co-administration in HIV-infected TB patients in India</td>
<td>G. Ramachandran_2</td>
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<td>09:45h</td>
<td>Associations between rifampicin and moxifloxacin plasma and CSF concentrations and mortality during intensified treatment of tuberculous (TB) meningitis</td>
<td>L. te Brake_3</td>
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<td>10:00h</td>
<td>Population pharmacokinetics and limited sampling strategy for first-line tuberculosis drugs and moxifloxacin</td>
<td>R. Aarnoutse_4</td>
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<td>10:15h</td>
<td>Discussion</td>
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<td>10:30h</td>
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### Session 2 Pharmacokinetics & pharmacodynamics of new TB drugs

**Chairs:** K. Mdluli & R. Aarnoutse

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<td>S. Mallikaarjun</td>
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<td>11:30h</td>
<td>Second Line TB Drugs in Comination with a Novel Drug Candidate SQ109</td>
<td>L. Ferstenberg_5</td>
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<td>Population PK/PD analysis of the mycobactericidal activity of sutezolid (PNU-100480) and its major metabolite in ex vivo whole blood cultures (WBA) of patients with pulmonary tuberculosis</td>
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<td>12:00h</td>
<td>Phase I Trial of the Safety and PK of the Investigational Anti-TB Drug PA-824 Co-Administered with Lopinavir/ritonavir or Rifampin: ACTG Study A5306</td>
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<td>12:15h</td>
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<td>12:30h</td>
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<td>13:15h</td>
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### Session 3 Population pharmacokinetics & pharmacokinetic-pharmacodynamic modeling

**Chairs:** C. Peloquin & K. Mdluli

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<td>Invited lecture: Key Clinical Pharmacology Aspects of TB Drug Development</td>
<td>D. Chilukuri</td>
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<tr>
<td>14:15h</td>
<td>Population pharmacokinetics of thrice weekly rifampin in Indian children</td>
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<td>14:30h</td>
<td>Pharmacokinetic Modeling and Limited Sampling Strategies for Therapeutic Drug Monitoring of Rifampicin in Patients with Tuberculosis</td>
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<tr>
<td>14:45h</td>
<td>A Model Predicting Penetration of Rifampicin From Plasma to Epithelial Lining Fluid and Alveolar Cells</td>
<td>O. Clewe_10</td>
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<tr>
<td>15:00h</td>
<td>PKPD analysis of rifapentine in patients during intensive phase treatment for tuberculosis from Tuberculosis Trial Consortium Studies 29 and 29X</td>
<td>R. Savic_11</td>
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15:15h Population pharmacokinetics of levofloxacin in children treated for multidrug resistant tuberculosis  
C. Peloquin_12

15:30h Discussion

15:45h Coffee break

15:45h Guided poster session
Moderators: E. Nuermberger & R. Aarnoutse

**Session 4 Drug development and optimization: approaches & tools**

**Chairs:** E. Nuermberger & C. Peloquin

16:15h Invited lecture: Potential interactions between ARV and investigational TB regimens (implications for phase II/III clinical trials)  
K. Dooley

16:45h Quantification of Rifapentine Concentrations in Dried Blood Spot Samples Using Liquid Chromatographic-Tandem Mass Spectrometric Analysis  
T. Parsons_13

17:00h Multivariate adaptive regression splines analysis of the effect of drug concentration and MIC on sterilizing activity in patients on multidrug therapy  
E. Chigutsa_14

17:15h Innovative PK/PD approaches to optimize tuberculosis meningitis treatment in children: Use of modeling to design confirmatory pediatric clinical trial  
R. Savic_15

17:30h A dynamic integrated drug, Mtb and host archetype for testing novel treatment interventions  
J. Fors_16

17:45h Discussion

18:00h Adjournment
Invited Speakers
Innovative trial designs to evaluate new treatment combinations for TB

Patrick Phillips, PhD
MRC Clinical Trials Unit at UCL, United Kingdom

Patrick Phillips, PhD, is a Senior Statistician at the Medical Research Council Clinical Trials Unit in London, United Kingdom.

Since 2005 he was been the statistician for several completed and ongoing phase II and III trials evaluating new treatment regimens for both drug-sensitive and drug-resistant TB. During this time he completed his PhD on the evaluation of culture results as prognostic and surrogate endpoints for TB treatment trials and continues to be involved in methodological research in the design and analysis of clinical trials with a particular focus on adaptive trial designs.

Update on Delamanid

Suresh Mallikaarjun, PhD, FCP
Otsuka Pharmaceutical Development and Commercialization, USA

Suresh Mallikaarjun, PhD, FCP, obtained his B.Pharm degree from the University of Bombay in 1978. He subsequently joined the M.Pharm program at the Government College of Pharmacy, Bangalore in 1980, following which he obtained a PhD from Virginia Commonwealth University, Richmond, Virginia, USA in the area of Pharmacokinetics.

In 1988 he joined the Food and Drug Administration as a Pharmacokinetic Reviewer responsible for reviewing clinical pharmacology applications from various clinical divisions. In 1993 he joined Procter and Gamble Pharmaceuticals in Cincinnati, Ohio as a Senior Scientist in the Clinical Pharmacology and Pharmacokinetics department where he was responsible for the development of the first approved treatment for H. pylori. Subsequently in 1996, he joined Otsuka America Pharmaceuticals as a Senior Pharmacokineticist in the Clinical Pharmacology department. Within Otsuka, he assumed positions of increasing responsibility and is currently a Senior Director in Clinical Pharmacology in the Otsuka Novel Products group, OPDC in Rockville, Maryland.

He has been involved in the development of numerous therapies in several therapeutic areas, i.e. central nervous system, cardiovascular, respiratory, anti-infective and oncology. He has given several invited lectures on early drug development and has in-depth experience in the utilization of clinical pharmacology in all stages of drug development. He is a diplomate of the American Board of Clinical Pharmacology and is a Fellow of the American Association of Clinical Pharmacology.
Key Clinical Pharmacology Aspects of TB Drug Development

Dakshina Chilukuri, PhD
FDA, USA

**Dakshina Chilukuri, PhD,** is a clinical pharmacology reviewer at the FDA. Prior to his joining the FDA, he was employed by Globomax LLC (now ICON USA) and Genzyme Corporation. Dr. Chilukuri received his Ph.D. degree in Pharmaceutical Sciences from the Medical University of South Carolina, Charleston.

Dr. Chilukuri has been involved with the drug development of anti-infective agents, including TB drugs for the past 12 years. At the FDA, he is responsible for the review of clinical pharmacology information submitted in INDs and NDAs. Dr. Chilukuri has written several reviews for various anti-infective agents including several pediatric applications. He has delivered presentations at Advisory Committee meetings and several other scientific and regulatory meetings. At the FDA, he has worked on the draft TB Guidance and is currently involved in revising the BA/BE guidance and has been a member of the BCS Technical Committee. He has co-edited a book entitled “Pharmaceutical Product Development : IVIVC”.

Potential interactions between ARV and investigational TB regimens (implications for phase II/III clinical trials)

Kelly Dooley, MD, PhD
Johns Hopkins University, USA

**Kelly Dooley, MD, PhD,** is an Assistant Professor of Medicine, Pharmacology & Molecular Sciences at Johns Hopkins University.

She completed fellowships in Infectious Diseases and Clinical Pharmacology and a doctoral degree at the Johns Hopkins Bloomberg School of Public Health. Dr. Dooley is an investigator with the Tuberculosis Trials Consortium and the AIDS Clinical Trials Group. She also maintains an HIV clinical practice.

Her research interests include the pharmacokinetics and pharmacodynamics of experimental TB regimens; optimization of existing drugs for the treatment of drug-sensitive and drug-resistant TB; and co-treatment of HIV and TB.
6th International Workshop on Clinical Pharmacology of Tuberculosis Drugs

Abstracts
Abstract: 1

PK/PD of approved TB drugs

Clinical significance of 2-hour plasma concentrations of first-line tuberculosis drugs

J. Prahl¹, I.S. Johansen², N. Frimodt-Møller³, A.B. Andersen⁴

¹Statens Serum Institut, Int. Ref. Laboratory of Mycobacteriology, Copenhagen, Denmark; ²Copenhagen University Hospital Hvidovre, Department of Infectious Diseases, Copenhagen, Denmark; ³Copenhagen University Hospital Hvidovre, Department of Clinical Microbiology, Copenhagen, Denmark; ⁴Copenhagen University Hospital Rigshospitalet, Department of Infectious Diseases, Copenhagen, Denmark

Introduction: Low plasma concentrations of first-line tuberculosis (TB) drugs (isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA)) have frequently been reported, but the clinical significance remains to be determined. The aims of this study were to assess the prevalence of, investigate possible risk factors for and consequences of low plasma concentrations in TB patients.

Material & Methods: One 2-hour blood sample was collected from 32 patients with active TB and 3 patients receiving prophylactic treatment at different time points in treatment. Plasma concentrations were determined using LC-Tandem Mass Spectrometry. Target ranges were obtained from the literature. Clinical charts were reviewed for baseline characteristics and clinical status at 2, 4 and 6 months after initiation of treatment.

Results: Plasma concentrations below lower limit of RIF were observed in 19/33 (58%), of INH in 25/35 (71%), of EMB in 13/28 (46%), of PZA in 3/29 (10%) and of both INH and RIF in 15/33 (45%), respectively. Plasma concentrations of INH were correlated inversely with CRP at baseline (p=0.007) and at time of sampling (p<0.001), and positively with treatment time (p=0.014, adjusted for CRP at baseline). Plasma concentrations of RIF were significantly lower among patients with low hemoglobin at baseline (p=0.003). During 1 year follow up of 28 patients treatment failure (TF) occurred in 5 patients (3 died, 2 relapsed). Using the median 2-hour plasma concentration to divide the patients into two groups, TF was observed more frequently in patients with below median values of RIF (p=0.044), of INH (p=0.041) and of both drugs (p=0.005). Using target ranges from the literature TF was observed more frequently in patients with both RIF and INH below the suggested 'Benchmark values' (p=0.013).

Conclusions: 2-hour plasma concentrations of RIF and INH below lower recommended limit were frequently observed in 32 closely supervised TB patients in Denmark. The association of plasma concentrations of INH and RIF with respectively CRP and hemoglobin at baseline may be interpreted as an association with disease severity. Low values of RIF and INH are associated with an increased risk of TF.

No conflict of interest
Abstract: 2

PK/PD of approved TB drugs

Pharmacokinetics of rifabutin during Atazanavir / ritonavir co-administration in HIV-infected TB patients in India

G. Ramachandran¹, P.K. Bhavani², A.K. Hemanth Kumar¹, R. Srinivasan³, K. Raja⁴, V. Sudha⁵, S. Venkatesh⁵, C. Chandrasekaran⁶, S. Soumya⁷

¹Tuberculosis Research Center, Biochemistry & Clinical Pharmacology, Chennai, India; ²Tuberculosis Research Center, Clinical Research, Chennai, India; ³Tuberculosis Research Center, Statistics, Chennai, India; ⁴Government Hospital of Thoracic Medicine, Clinic, Chennai, India; ⁵Tuberculosis Research Centre, Biochemistry & Clinical Pharmacology, Chennai, India; ⁶Government Hospital of Thoracic Medicine, Superintendent, Chennai, India; ⁷Tuberculosis Research Centre, Director, Chennai, India

Background: Currently a rifampicin-based regimen is recommended for treatment of HIV related TB. However Rifampicin (RMP) lowers serum levels of PIs and NNRTIs by inducing the activity of CYP3A4. Rifabutin (RBT) is as effective against TB as RMP, has less inducing effect on CYP enzymes and is the preferred rifamycin with PI-based ART. Furthermore, ritonavir (RTV), being a CYP3A4 inhibitor increases serum concentrations and potentially, the toxicity of RBT. The Revised National TB Control Programme in India recommends RBT 150mg thrice-weekly (along with other anti-TB drugs) during RTV co-administration, though pharmacokinetic data to support this dose is lacking.

Objective: To study the pharmacokinetics of RBT at 150mg thrice-weekly dose during atazanavir/RTV co-administration in HIV-infected TB patients

Methods: Sixteen adult HIV-infected TB patients attending the Government Hospital of Thoracic Medicine, Chennai, were included. These patients were being treated with an atazanavir/ritonavir-containing ART regimen and a short-course thrice-weekly ATT regimen containing RBT 150mg thrice-weekly. Serial blood draws at pre-dosing and at 1, 2, 4, 6, 8, 12 and 24 hours after drug administration were done. Plasma RBT was estimated by HPLC. The target peak concentration range was taken as 0.3 – 0.8 µg/ml.

Results: Peak RBT concentrations were below the lower limit of therapeutic range in seven patients, while there were no patients with peak concentrations above the upper therapeutic limit. Taking 0.06µg/ml as the minimal inhibitory concentration (MIC) of RBT against M. tuberculosis, 10 patients had their trough concentration < MIC, trough levels being undetectable in five patients. Significant correlations were observed between CD4 cell counts and peak concentration (p=0.044), trough concentration (p=0.002) and exposure (p=0.028). Multiple regression analysis showed sex and CD4 cell counts to significantly influence RBT peak concentrations, the p values being 0.008 and 0.024 respectively.

Conclusions: Sub-therapeutic RBT peak concentrations and trough concentrations below the MIC in a high proportion of patients is a matter of concern, and suggestive of inadequate dosing. Prospective studies in different settings are required to arrive at the proper therapeutic dose of RBT to be used during RTV co-administration, in order to achieve therapeutic success.

No conflict of interest
Abstract: 3

Late Breaker

Associations between rifampicin and moxifloxacin plasma and CSF concentrations and mortality during intensified treatment of tuberculous (TB) meningitis

te Brake, L. 1,*, Dian, S. 2*, Ruesen, C. 1, Ganiem, A.R. 2, van Crevel, R. 1, Ruslami, R. 2, Aarnoutse, R. 1

*Shared first authorship

1Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, 2. Faculty of Medicine, Universitas Padjadjaran / Hasan Sadikin Hospital, Bandung, Indonesia

Background. Meningitis is the most severe form of tuberculosis (TB). Previously we described that intensified antibiotic treatment with a higher dose of rifampicin i.v. resulted in lower mortality at 6 months (35% versus 65%) whereas concurrent administration of moxifloxacin did not seem to add survival benefit (Lancet Infect Dis 2013;13;27-35). For the current analysis we evaluated the relevance of rifampicin and moxifloxacin plasma and cerebrospinal fluid (CSF) concentrations as an intermediary link between dose and response.

Materials and methods. In an open-label, phase 2 trial with a factorial design in Indonesia, patients aged >14 years with TB meningitis were randomly assigned to receive rifampicin standard dose administered orally (450 mg, about 10 mg/kg) or high dose rifampicin (600 mg, about 13 mg/kg) intravenously, combined with either oral moxifloxacin 400 mg, moxifloxacin 800 mg or ethambutol 750 mg once daily and other drugs (isoniazid, pyrazinamide, adjunctive corticosteroids). After 14 days of treatment all patients continued with standard treatment for TB. PK sampling was performed once in every patient during the first 3 days of treatment. Plasma AUC_{0-6}, AUC_{0-24} (moxifloxacin only), Cmax and CSF Cmax were assessed for rifampicin and moxifloxacin. Log-transformed measures of exposure were compared between patients who survived and those who had died after 2 weeks, 1 month, 2 months and 6 months after start of treatment, using the independent-samples T-test. Logistic regression analysis was performed to relate AUC and Cmax values to mortality at the same time points. A Receiver Operating Characteristic-curve was constructed to determine the rifampicin plasma concentration cut-off value that would predict mortality with optimal sensitivity and specificity.

Results. Compared to patients who died at 2 weeks, surviving patients had significantly higher rifampicin plasma AUC_{0-6}, Cmax and CSF Cmax (p=0.018; 0.036; 0.031). Similar results were found for 1 month mortality and 2 month mortality. Among those who survived and those who had died after 2 weeks of treatment, the geometric mean AUC_{0-6}, plasma Cmax and CSF Cmax for rifampicin were 51.3 vs 26.6 mg.h/L, 13.3 vs 7.2 mg/L and 0.4 vs 0.2 mg/L, respectively. An increase of one IQR in rifampicin plasma AUC_{0-6}, Cmax and CSF Cmax was associated with a lower odds of dying at 2 months of treatment (IQ-OR 0.46, CI 0.21-0.98; 0.38, CI 0.16-0.92; 0.22, CI 0.05-0.97), while adjusting for the effect of HIV status and Glasgow coma scale at baseline. A rifampicin Cmax threshold plasma concentration of 14 mg/L predicted survival with 65% sensitivity and 78% specificity. There was no statistically significant difference in AUC or Cmax of moxifloxacin between patients who had survived or died at any time after start of treatment. The IQ-OR for moxifloxacin was not different from 1.0 at any time point either.

Conclusions. The survival benefit associated with administration of a higher dose of rifampicin administered i.v. for TB meningitis is mediated by a higher exposure to rifampicin in plasma and CSF. Average exposures in those who survived and the derived threshold can be used to develop pharmacokinetically optimized dosing regimens for rifampicin in TB meningitis.

No conflict of interest
Abstract: 4

Therapeutic Drug Monitoring

Population pharmacokinetics and limited sampling strategy for first-line tuberculosis drugs and moxifloxacin


1Radboud University Medical Centre, Nijmegen and University Centre for Chronic Diseases Dekkerswald, Groesbeek, The Netherlands; 2 Radboud University Medical Centre, Nijmegen, The Netherlands; 3University Medical Centre Groningen, Groningen, The Netherlands; 4University Medical Centre Groningen, Tuberculosis Centre Beatrixoord, Haren, The Netherlands

Background: Therapeutic drug monitoring (TDM) of first-line TB drugs currently focuses on peak plasma concentrations (Cmax) of these drugs, yet evolving data suggest that the total exposure (AUC0-24) is more relevant to the efficacy of these drugs, as well as for moxifloxacin which is being evaluated as a potential first-line TB drug. The objectives of this study were to describe population pharmacokinetic (PK) data especially concerning AUC0-24 for first-line TB drugs and moxifloxacin in adults, as well as to develop limited sampling strategies to estimate AUC0-24 values of these drugs conveniently.

Materials and methods: PK sampling based on 11 sampling points (T=0, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0 and 24.0 h post dose) was performed in consecutively recruited hospitalized TB patients from two TB referral centers in The Netherlands. PK curves were recorded after intake of TB drugs on an empty stomach after at least two weeks in the intensive phase of TB treatment. Drug concentrations were assessed with validated HPLC methods and pharmacokinetic parameters were assessed with non-compartmental pharmacokinetic methods. Best subset selection multiple linear regression was performed to derive limited sampling equations predictive of the AUC0-24 of individual TB drugs, and for simultaneous prediction of the AUC0-24 of isoniazid, rifampicin, pyrazinamide, ethambutol and moxifloxacin. To maintain clinical applicability, all models were constrained to include three samples at the most, collected within 6h after drug administration. To assess the predictive performances of the models, residuals for each patient were calculated based on models fitted to a dataset where that patient was omitted (jackknife analysis).

Results: 41 patients were included in the study, 78% was male, their median age was 42 years, and various races and ethnicities were included. Median doses of isoniazid (n=14), rifampicin (n=34), pyrazinamide (n=19), ethambutol (n=19) and moxifloxacin (n=12) were 4.5; 9.3; 28.7; 20.3 and 7.0 mg/kg. Geometric mean AUC0-24 values for isoniazid, rifampicin, pyrazinamide, ethambutol and moxifloxacin were 15.2, 41.1, 380, 25.5 and 33.6 h*mg/L respectively. Limited sampling at two or three fixed sampling points allowed for an accurate and precise estimation of the AUC0-24 values of all drugs separately and simultaneously, as reflected in median percentage prediction error (MPPE) and median absolute percentage prediction error (MAPE) values <15%. Sampling at 1, 4 and 6 h best predicted the AUC0-24 of all drugs together. Sampling at 2, 4 and 6 h post dose, as can be applied to ‘catch’ the peak plasma concentrations, also enabled a good prediction of AUC0-24 for all drugs.

Conclusions: In the absence of clinically validated target values for AUC0-24, the derived population (average) values for AUC0-24 from this population could be used as reference values in TDM, similar to the current use of ‘normal’ Cmax values of TB drugs. Limited sampling of AUC0-24 of TB drugs is feasible and allows for TDM at a larger scale.
Abstract: 5

Drug interactions

Second Line TB Drugs in Combination with a Novel Drug Candidate SQ109

L. Ferstenberg1, M. Protopopova2, B. Nikonenko2, A. Are2, L. Einck2, C. Nacy2

1Sequella Inc., Clinical Development, Rockville MD, USA; 2Sequella Inc., Product Development, Rockville MD, USA

Background: As new agents are added to combination drug regimens to treat drug sensitive (DS) and drug resistant (DR) tuberculosis (TB), the pharmacokinetics and pharmacodynamics of drug interactions are essential to ensure that individual drugs within the regimen do not interfere with efficacy or create unexpected toxicity for any other drug in the combination. SQ109 is a novel antibiotic with high potency against Mycobacterium tuberculosis (Mtb) and low potential for resistance. The compound is currently in clinical trials of both DS and DR TB where it is being combined with an array of agents. In preparation for clinical use, experiments were done to characterize the pharmacokinetics and pharmacodynamics of drug interactions between SQ109 and both first line and second line drugs.

Materials and Methods: Pharmacokinetics: Female C57BL/6 mice received SQ109 25 mg/kg; AMK 150 mg/kg; MOX 100 mg/kg, KAN 150 mg/kg; ETA 75 mg/kg; CS 150 mg/kg, PAS 750 mg/kg. Single drug controls were administered PO or SC, and two-drug combinations of SQ109 and each of the above drugs were delivered as a single administration by the same routes. Plasma samples were analyzed for drug concentrations at 15, 30 min, 1, 2, 4, 6, 10 and 24 hours by LC/MS/MS.

Efficacy: Effectiveness of each two-drug combination was evaluated in a standard mouse model of chronic TB. Female C57BL/6 mice were inoculated with 0.2 ml suspensions of 10^5 CFU Mtb H37Rv in PBS with 0.05% Tween-80. Drug treatment was initiated 3-weeks after inoculation. At defined times, spleens and lungs were extracted, homogenized, diluted and plated for CFU counts 15-18 days later. Drugs included SQ109 formulated in 5% e/w(v/v) dosed at 25 mg/kg (PO); PZA formulated in SWI dosed at 150 mg/kg (PO); EMB in SWI dosed at 100 mg/kg (PO), MOX in SWI dosed at 100 mg/kg (PO); ETA in SWI dosed at 75 mg/kg (PO); and AMK in SWI dosed at 150 mg/kg (SC). Drugs were sequentially administered to mice once daily.

Results: Pharmacokinetic profiles of SQ109 and MOX are not affected by co-administration. ETA and SQ109 co-administered results in a 50% increase in AUC of SQ109 and a 2-fold decrease in AUC of ETA. In the presence of CS and KAN, exposure to SQ109 is decreased by 2-fold. Co-administration of SQ109 and PAS results in a 50% increase in AUC of SQ109. Efficacy: SQ109 had no antagonistic interactions with any of the five drugs studied. Combinations of SQ109 with MOX, ETA and PZA were the most efficacious. All three drug combinations (MOX, ETA and PZA) had better efficacy with the addition of SQ109 than the drugs given alone. No additive effect of SQ109 plus EMB was observed.

Conclusions:
Clinical trials using multiple drugs for the treatment of tuberculosis can be more safely and effectively planned if data are available regarding drug interactions.

Acknowledgements: SQ109 PK study was carried out at Cerep (Redmond, WA).

Conflict of interest: Financial relationship(s): Employed by Sequella, Inc as Medical Director
Abstract: 6

PK/PD modeling

Population PK/PD analysis of the mycobactericidal activity of sutezolid (PNU-100480) and its major metabolite in ex vivo whole blood cultures (WBA) of patients with pulmonary tuberculosis

T. Zhu1, G. Nucci1, S. Friedrich2, A. Diacon2, R. Wallis1

1Pfizer, Groton, CT, USA ; 2Stellenbosch University, Cape Town, South Africa

Background: Sutezolid (PNU-100480) is an oxazolidinone antimicrobial being developed for treatment of tuberculosis. An active sulfoxide metabolite (PNU-101603), which reaches concentrations in plasma several times those of the parent, has been reported to drive killing of extracellular M. tuberculosis by sutezolid in hollow fiber culture. However, the relative contributions of parent and metabolite against intracellular M. tuberculosis are not fully understood.

Methods: The present study examined the relationship of plasma concentrations of sutezolid and its metabolite to intracellular mycobactericidal activity in corresponding ex vivo whole blood cultures (WBA) of TB patients enrolled in study B1171003, using a population PK-PD model. The relationship between drug concentration and bactericidal activity was described using competitive 4-parameter sigmoid curves, based on the results of prior in vitro studies.

Results: A total of 690 PK and 345 WBA determinations from 50 subjects were analyzed. The median U-480/U-603 concentration ratio in these plasma specimens was 1:7.1, with a range of from 1:1 to 1:28. The model was solved iteratively to determine parameters that best predicted observed results. The main finding was that the concentration of the metabolite required for a half-maximal effect against intracellular M. tuberculosis was 17-fold greater than that for the parent (90% CI, 9.9 to 53). As a result, the parent accounted for 82% and 86% of the total or cumulative daily activity when sutezolid was administered at 1200 mg QD and 600 mg BID, respectively (fig 1).

Conclusions: Killing of intracellular M. tuberculosis by orally administered sutezolid is mainly due to activity of the parent compound. Sutezolid and its metabolite appear to exert their main effects against different mycobacterial subpopulations.

Conflict of interest: Financial relationship(s): Employed by Pfizer
Abstract: 7

**Drug interactions**

**Phase I Trial of the Safety and PK of the Investigational Anti-TB Drug PA-824 Co-Administered with Lopinavir/ritonavir or Rifampin: ACTG Study A5306**

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**Background:** The investigational nitroimidazole PA-824 is being developed for the treatment of tuberculosis (TB). It is partially metabolized by cytochrome P450 (CYP) 3A, which is induced by rifampin and can be either induced or inhibited by lopinavir/ritonavir (LPV/r). It is unknown whether co-administering these drugs alters PA-824 pharmacokinetics (PK).

**Methods:** This phase I, open-label, multicenter trial characterized potential interactions between steady-state PA-824 and efavirenz (Arm 1), LPV/r (Arm 2), and rifampin (Arm 3) in healthy, HIV-uninfected volunteers. Preliminary results from Arms 2 and 3 are presented herein. Subjects in Arm 2 were randomized to Sequence 1 (PA-824 200 mg once daily for 7 days, then a 2-week washout period, then LPV/r 400/100 mg twice daily for 14 days, then LPV/r + PA-824 together for 7 days) or Sequence 2 (LPV/r, then LPV/r + PA-824, washout, then PA-824 alone). In Arm 3, participants received PA-824 for 7 days, then rifampin 600 mg for 7 days, then PA-824 + rifampin together for 7 days. Intensive plasma PK sampling was performed at the end of each dosing period with PA-824 concentrations determined using LC-MS/MS. PK parameters were estimated in SAS using noncompartmental methods. Drug interactions were evaluated using geometric mean ratios (GMRs) and 90% confidence intervals (CI). Preliminary results are presented here.

**Results:** Of 18 subjects enrolled in Arm 2, median age was 30 years, median weight was 88.7 kg, 33% were African American, and 44% were female. Comparing PA-824 + LPV/r versus PA-824 alone from 16 PK-evaluable subjects, the GMR for maximum concentration (C$_{max}$) was 0.87 (90% CI 0.75-1.0), for 24-hour area under the time-concentration curve (AUC$_{0-24h}$) was 0.83 (90% CI 0.71-0.98), and for trough concentration (C$_{min}$) was 0.78 (90% CI 0.66-0.93). Of 16 subjects enrolled in Arm 3, median age was 27 years, median weight was 72.4 kg, 38% were African American, and 38% were female. Comparing PA-824 + rifampin versus PA-824 alone from 16 PK-evaluable subjects, the GMR for C$_{max}$, AUC$_{0-24h}$, and C$_{min}$ were 0.47 (90% CI 0.39-0.56), 0.34 (90% CI 0.27-0.42), and 0.15 (90% CI 0.11-0.21), respectively. Two subjects in Arm 2 were discontinued from the study prematurely because of errors in self-administered LPV/r dosing. One subject in Arm 2 had a grade 3 aspartate aminotransferase value after starting a vigorous exercise regimen. One subject in Arm 3 had an asymptomatic grade 3 neutropenia on the final day of study drug administration.

**Conclusions:** In this Phase I study, PA-824 was well-tolerated when given together with LPV/r or rifampin. Concomitant administration of PA-824 with LPV/r resulted in modest reductions in PA-824 concentrations, while co-administration with rifampin reduced PA-824 AUC$_{0-24h}$ by about 66%. These data support the use of PA-824 together with LPV/r among patients with TB and HIV co-infection without dose adjustment. The clinical importance of reductions in PA-824 exposures when PA-824 is given with rifampin is unknown but should be considered in evaluations of combinations including these two drugs for drug-sensitive TB.

*No conflict of interest*
Abstract: 8

TB treatment in Special Populations

Population pharmacokinetics of thrice weekly rifampin in Indian children

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Background: In our recent study of rifampin pharmacokinetics (PK) in Indian children with tuberculosis, children aged <3 years had significantly lower RMP concentrations than older children, and 90% of all children had sub-therapeutic RMP maximum concentrations (Cmax <8 μg/ml). To elucidate the reasons for underexposure in young children, we investigated the developmental pharmacokinetics of rifampin in Indian children using a population pharmacokinetic modeling approach.

Methods: The database included PK data from 84 Indian children without HIV who received standard anti-tuberculosis treatment three times a week during the intensive phase of therapy. Intensive PK sampling was performed after at least 3 weeks of treatment. Model development was done using a non-linear mixed effects approach in NONMEM 7. The developmental changes in rifampin clearance in young children were investigated as well as the effect of covariates, including weight, age, sex and dose.

Results: The database included 374 concentration-time measurements from 84 children. A one-compartment model with allometrically scaled parameters described the data well. Apparent oral clearance per kilogram of body weight was significantly higher in younger children compared to the older ones. This relationship was described by a maturation function, where clearance for the 2 year old child was estimated to be 0.6 L/h/kg, decreasing to the fully matured value of 0.24 L/h/kg by age of 12 years (half-life of 1.4 years). This relationship indicates higher metabolic activity in very young children requiring more than a 2 fold higher dose per kilogram of body weight in very young children compared to the older ones in order to reach same exposure. The between-subject variability in clearance was 45%. Sex or dose was not found to influence rifampin pharmacokinetics.

Conclusions: Our population pharmacokinetic model of thrice weekly rifampin in Indian children shows that clearance in younger children is higher compared to older children but decreases with age; therefore younger children require higher dosages per kilogram of body weight to reach the equivalent adult exposure. This increase in clearance per kilogram of body weight is higher than that anticipated from allometry alone. Population PK models of rifampin in children from other parts of the world (South Africa, Malawi) reported that allometry was sufficient to describe maturation of rifampin clearance. This suggests that there may be ethnicity–related differences in rifampin developmental pharmacokinetics. A large meta-analysis using rifampin data from children from different parts of the world is warranted to fully elucidate developmental PK in different ethnic groups.

No conflict of interest
Abstract: 9

PK/PD modeling

Pharmacokinetic Modeling and Limited Sampling Strategies for Therapeutic Drug Monitoring of Rifampicin in Patients with Tuberculosis

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Introduction: Rifampicin is, together with isoniazid, the backbone of the current first-line treatment of tuberculosis. The area under the concentration-time curve from 0 to 24 hours (AUC_{0-24h}) to MIC ratio is the best predictive pharmacokinetic-pharmacodynamic parameter for efficacy. Increased breakpoints for susceptibility of the first-line tuberculosis agents have been suggested. The critical concentration is the lowest concentration of drug that inhibits ≥ 95% of wild type strains of bacilli. For rifampicin, this critical concentration has recently been lowered from 1.0 mg/L to 0.0625 mg/L. Furthermore, inter and intraindividual changes in PK have been suggested as an important cause of therapy failure or emergence of drug resistance. As obtaining a full concentration-time curve of rifampicin for AUC calculation and Therapeutic Drug Monitoring is not feasible in clinical practice, the objective of this study is to develop a limited sampling procedure based on population pharmacokinetics.

Materials & Methods: 55 Patients received rifampicin orally once daily as part of their anti-tuberculosis treatment. Rifampicin plasma concentrations were measured either by a validated LC-MS/MS or HPLC-UV method. A one-compartment pharmacokinetic population model with first-order absorption and with lag time was developed using rifampicin doses and observed rifampicin plasma concentrations. The population pharmacokinetic model was validated using an iterative two-stage Bayesian procedure and was cross validated by developing models based on n=5. Limited sampling strategies were calculated using Monte Carlo simulation (n=1000). Correlation between the estimated AUC_{0-24h} and the calculated AUC_{0-24h} was evaluated by Bland-Altman analysis and calculating the Spearman correlation coefficient.

Results: Pharmacokinetic modeling was done using 55 concentration-time curves with a median AUC_{0-24h} of 38.7 (IQR, 22.7) mg*h/L. Pharmacokinetic analysis resulted in a population pharmacokinetic model with the following parameters: metabolic clearance CL_m 15.5 ± 8.0 L/h/1.85m^2, volume of distribution Vd 0.71 ± 0.28 L/kg corrected lean body mass (LBM), absorption constant ka 1.14 ± 1.0 /h, and lag-time in the absorption phase T_{lag} 0.89 ± 0.57 h. Based on literature, renally cleared fraction was fixed at 0.14 and bioavailability was fixed at 1. Median values of the 11 submodels developed for cross validation were CL_m 15.34 (IQR, 0.70) L/h/1.85 m^2, Vd 0.708 (IQR, 0.02) L/kg LBM, ka 1.153 (IQR, 0.03) /h, and T_{lag} 0.875 (IQR, 0.07) h. Hence, these were not statistically different from the developed model. Limited sampling using concentrations at 1, 3, and 8 h post dosing with r^2 0.96, root mean squared error 12.6%, and prediction bias – 0.4% was considered clinically suitable. Estimated AUC_{0-24h} using the pharmacokinetic model and limited sampling strategy was highly correlated to the calculated AUC_{0-24h} (Spearman correlation coefficient, 0.95 (p<0.01)).

Conclusions: This study shows that rifampicin AUC_{0-24h} in patients with tuberculosis can be predicted with acceptable accuracy and precision using the developed population pharmacokinetic model with limited sampling at t=1, 3, and 8 h.

No conflict of interest
Abstract: 10

PK/PD modeling

A Model Predicting Penetration of Rifampicin From Plasma to Epithelial Lining Fluid and Alveolar Cells

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Introduction: In a non-tuberculosis infected population describe rifampicin’s autoinduced plasma concentrations and predict the concentration ratios between epithelial lining fluid, alveolar cells and plasma. Based on model simulations evaluate study design aspects in relation to optimized BAL sampling.

Methods: Data from a previously published study were used in this population analysis. In short the study compromised forty adult subjects without tuberculosis which received rifampicin at 600 mg orally once daily for five days. Rifampicin concentrations were measured in plasma, and rifampicin concentrations in epithelial lining fluid and alveolar cells were recovered by bronchoalveolar lavage. The data analysis was performed with a nonlinear mixed-effects approach as implemented in the software NONMEM, version 7.2 (ICON Development Solutions). The model building process was performed in a stepwise fashion, starting from a previously published rifampicin pharmacokinetic enzyme turn-over model. Rifampicin’s autoinduction was described with an enzyme turn-over-model, where rifampicin’s plasma concentration increase the enzyme production rate which in turn increases the enzyme pool in a non-linear fashion by means of an E_MAX-model. The epithelial lining fluid and alveolar cell drug penetration were described using effect compartments, where the penetration coefficients between plasma and epithelial lining fluid (P_elf) and plasma and alveolar cells (P_ac) were estimated. The time rate constants k_elf and k_ac were fixed to a value mimicking an almost instantaneous transfer of drug from plasma to epithelial lining fluid or alveolar cell due to the sparse sampling design. In order to evaluate study design aspects in relation to optimized bronchoalveolar lavage sampling for epithelial lining fluid and alveolar cells drug quantification, the final model was used to simulate different scenarios.

Results: The final rifampicin plasma model was a one compartment model with transit absorption compartments and an enzyme turn-over model describing rifampicin’s autoinduction. Parameters related to the absorption and enzyme turnover was fixed to previously published values. Oral clearance and volume of distribution were estimated to 4.8 L/h and 50 L respectively. The data supported inclusion of inter individual variability on oral clearance (69%). At four hours post dose the rifampicin penetration coefficients for epithelial lining fluid and alveolar cells were estimated to 0.27 and 1.17 respectively. This resulted in a mean epithelial lining fluid to plasma ratio of 1.36 and a mean alveolar cell to plasma ratio of 5.81 when compensating for the free fraction (0.2) of rifampicin concentration in plasma.

Conclusions: The final model propose a way to describe the often sparse data originating from the use of bronchoalveolar lavage, where only one or a few samples are possible to withdraw from each subject. The model characterizes rifampicin’s plasma pharmacokinetic properties including auto-induction as well as the penetration of drug from plasma to epithelial lining fluid and alveolar cells.

No conflict of interest
Abstract: 11

PK/PD of new TB drugs

PKPD analysis of rifapentine in patients during intensive phase treatment for tuberculosis from Tuberculosis Trial Consortium Studies 29 and 29X


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Background: Higher doses of rifamycins demonstrate promising preclinical activity to shorten duration of tuberculosis (TB) treatment. In this pharmacokinetic-pharmacodynamic study, a component of two Phase 2B clinical trials, we (i) characterized population pharmacokinetics of rifapentine, (ii) identified covariates to explain variability in rifapentine pharmacokinetics-pharmacodynamics, (iii) established rifapentine exposure-response relationships, and (iv) modeled rifapentine regimens most likely to shorten treatment duration.

Methods: In a preliminary analysis, 476 patients with sputum smear-positive pulmonary TB were evaluated from Tuberculosis Trial Consortium randomized, double-blind clinical trials. In Study 29, rifapentine at 10 mg/kg was compared to rifampin at 10 mg/kg daily as part of multidrug intensive phase therapy (IPT) for 8-weeks. In Study 29X, rifapentine at 10, 15, or 20 mg/kg or rifampin at 10 mg/kg daily was taken as part of IPT. In Study 29X, rifapentine was taken with food. After >2 weeks of treatment, intensive or sparse pharmacokinetic sampling was performed. Sputum samples during IPT were collected every 2 weeks. Pharmacokinetic-pharmacodynamic analyses were performed using non-linear mixed effects modeling. Rifapentine and its desacetyl metabolite pharmacokinetics were initially modeled, followed by covariate analyses of pharmacokinetic parameters. A parametric time-to-event approach was used to model four efficacy endpoints. Comparative efficacy of rifapentine versus rifampin was modeled as a function of regimen, dose or exposure.

Results: Rifapentine and metabolite pharmacokinetics were best described with a one compartment model. Rifapentine bioavailability decreased with greater rifapentine doses (median decreases of 11%, 12% and 20% for 600, 900 and 1200 mg respectively compared to the 450 mg dose). The increase in exposure was less than dose proportional; median exposures were of 321, 472 and 578 mcg*h/L for 600, 900 and 1200 mg doses. With this cohort of adult patients, rifapentine clearance did not significantly increase with weight. Rifapentine exposure needed to reach half maximal effect (AUC50) was 295 mcg*h/ml. With rifampin, time to sputum culture conversion to negative on solid media was estimated to be a median of 38 days by the Weibull hazard function, and it was estimated that 95% of patients would have negative sputum cultures on solid media by 81 days of treatment. With rifapentine 1200 mg daily with food, time to sputum culture conversion to negative on solid media was estimated to be a median of 26 days, and 57 days were needed for 95% of the modeled TB cohort to develop negative sputum cultures on solid media. Lung cavitation increased AUC50 3-fold.
Conclusions: Rifapentine exposure increased with higher doses, but was less than dose proportional. Rifapentine clearance was not weight dependent for adults in this study, and provides a rationale for flat versus mg/kg dosing. Rifapentine decreases time to sputum culture conversion compared to rifampin and the efficacy of rifapentine is exposure dependent. For culture conversion, patients with cavities require higher rifapentine doses or longer treatment compared to patients without cavities. Model simulations suggest that the maximal shortening to stable sputum culture conversion can be achieved in most patients with a 1200 mg daily dose of rifapentine administered with food.

No conflict of interest
Abstract: 12

PK/PD modeling

Population pharmacokinetics of levofloxacin in children treated for multidrug resistant tuberculosis

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Introduction: Levofloxacin, a fluoroquinolone, has bactericidal activity against Mycobacterium tuberculosis. Population pharmacokinetics (PK) of levofloxacin has not been studied previously in children treated for, or exposed to, TB. During two simultaneous outbreaks of TB in the Federated States of Micronesia (FSM) and Republic of Marshall Islands (RMI), PK studies were performed by the Centers for Disease Control and Prevention. We characterize levofloxacin population PK in 50 children studied during these MDRTB outbreaks.

Methods: In Chuuk (FSM), 33 children (age 1-14 years) were administered levofloxacin (5-20 mg/kg/day) as an oral gel for the treatment of MDR-TB or presumed MDR latent TB infection (LTBI). In Majuro (RMI), during another outbreak, 17 children (1-15 years) were treated with levofloxacin (11-16 mg/kg/day) as an oral gel for LTBI. Following 6 weeks of treatment or longer, plasma samples were taken in all 50 children after 1, 2, and 6 hours. In Majuro, we added a 0-hour time point. Samples were stored at -70°C before being shipped on dry ice to University of Florida for analysis using a validated HPLC method with fluorescence detection.

A population PK analysis was performed with NONMEM, version 7.2. The first-order conditional estimation method with interaction algorithm was used for all models. NONMEM execution and run management was performed using Pirana, while prediction-corrected visual predictive checks (pcVPC) and a bootstrap analysis (n=1,000 simulations) was performed using Perl-speaks-NONMEM (PsN). For the bootstrap analysis, the 2.5th and 97.5th percentile were calculated based on the samples generated. Goodness of fit and pcVPCs were generated using the R (version 2.15.2) packages lattice and Xpose. Addition of covariates (age, gender, weight, height, and breakfast status) was tested using generalized additive modeling implemented in the Xpose package. One- and two-compartment PK models and several error models were tested. A fixed exponent allometric model was applied to both CL/F and V/F using a 70 kg standardized weight. Simulations were performed in NONMEM to evaluate target attainment; (fAUC/MIC)>100 was evaluated as a target. A total of 1,000 simulations were performed for varying dosing regimens (5, 10, 15, and 20 mg/kg) and target attainment was calculated for various potential MIC values.

Results: We chose one-compartment body model. The population parameter estimates for the absorption rate constant(Ka), and the standardized clearance (CL/F) and volume of distribution (V/F) were 2.69 hours⁻¹, 11.61 liters/hour, and 88.39 liters, respectively. Inter-individual variability estimates in Ka,CL/F, and V/F were 82.5%, 33.2%, and 24.5%, respectively. Only weight resulted in statistically significant improvements in the data fit. For the exposure target fAUC/MIC ≥ 100, for the lowest assumed MIC (0.25 μg/mL), a dose of 10 mg/kg resulted in a highly likelihood of target attainment; while for an MIC of 0.5 μg/mL, a dose of 20 mg/kg was needed. Poor target attainment rates were obtained with higher MIC values.

Conclusions: Levofloxacin may be an effective treatment option for children with MDR-TB or presumed MDR LTBI. Further clinical research is needed to evaluate appropriate targets for PK/PD indices that can be used to optimize drug dosing.

No conflict of interest
Abstract: 13

Therapeutic Drug Monitoring

Quantification of Rifapentine Concentrations in Dried Blood Spot Samples Using Liquid Chromatographic-Tandem Mass Spectrometric Analysis

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Background: Rifapentine (RPT) is a rifamycin antibiotic with potent activity against Mycobacterium tuberculosis. In a recent clinical trial among patients with drug-sensitive pulmonary TB, substitution of RPT (10-20 mg/kg daily) for rifampin reduced time to sputum culture conversion. Further, RPT plus isoniazid once weekly for a total of 12 doses was recently recommended for treatment of latent TB infection. Planning is underway for a RPT dose-finding trial in young children and an international Phase 3 trial of RPT for TB disease.

There are established methods for measuring RPT and its metabolite, desacetyl-rifapentine (des-RPT), in plasma using liquid chromatographic-tandem mass spectrometry (LC-MS/MS). Use of standard pharmacokinetic (PK) sampling for PK/PD analyses in trials, though, can be limited by the need for adequate sample volume, rapid processing by laboratory technicians, and shipping of potentially hazardous materials to analytical laboratories. We describe here the development, validation, and application of LC-MS/MS methods for the quantification of RPT and des-RPT in Dried Blood Spots (DBS).

Materials & Methods: Plasma and DBS samples were obtained from subjects in TBTC Study 29B, a phase I dose escalation study of RPT. Intensive plasma PK sampling was performed after the 1st and 14th daily doses (5-20 mg/kg) of RPT. A paired venous whole blood DBS sample was collected on a Whatman 903® card at one time point at each PK visit. For bioanalysis, 20 µL plasma or a 6 mm diameter DBS punch was used. Isotopically-labeled rifampin was the internal standard, and ascorbic acid was added to prevent drug oxidation. Analytes were quantitated using a UPLC system (Waters) attached to an API 5500 triple quadrupole mass spectrometer (SCIEX). The assay was validated according to FDA Guidance for Industry, Bioanalytical Method Validation.

Results: The analytical measuring ranges for both RPT and des-RPT were 50-80,000 ng/ml. Quadratic regression analysis yielded average \( r^2 \) values of \( \geq 0.996 \) for both analytes over the analytical range. Quality control samples containing RPT and des-RPT yielded precisions within 9.5% and 10.3% and accuracies ranging from -8.2% to 9.7% and -9.6% to 6.8%, respectively. RPT and des-RPT collected on DBS filter cards were stable for 48 h unprotected from light at room temperature and for 11 weeks in desiccant at room temperature protected from light. Neither RPT nor des-RPT was stable at temperatures \( \geq 40^\circ \text{C} \). Method concordance for paired plasma and DBS samples (n=43) was determined after correcting for participant hematocrit. The application of this correction factor resulted in good correlation between plasma and DBS RPT (\( y = 0.951x + 883; r^2 = 0.941 \)) and des-RPT (\( y = 0.865x + 100; r^2 = 0.983 \)).

Conclusions: Concentrations of RPT and its metabolite may be accurately determined from DBS after normalization to participant-specific hematocrit to account for the dilutional effects of red blood cells. The advantages of low blood volume and simplicity of processing, storage, and shipping make DBS an attractive option for RPT PK evaluations, especially in international or pediatric trials.

No conflict of interest
Abstract: 14

**PK/PD of approved TB drugs**

**Multivariate adaptive regression splines analysis of the effect of drug concentration and MIC on sterilizing activity in patients on multidrug therapy**

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**Background:** Whilst hollow fiber models have identified relationships between drug concentration and effect on *Mycobacterium tuberculosis*, clinical data is limited. The objective was to characterise the sterilizing activity of antituberculosis drug concentrations in patients on a standard first-line regimen. Identification of the drug exposures predictive of cure would then enable evaluation of the adequacy of current doses.

**Materials and Methods:** Fifty-four patients received standard first-line drug combination therapy for pulmonary tuberculosis, and had both drug concentrations measured and *Mycobacterium tuberculosis* isolates available for minimum inhibitory concentration (MIC) identification. Baseline and weekly sputum specimens were collected for 8 weeks. A time-to-event model based on days to positivity in the mycobacterial growth indicator tube system was used to estimate the β-slope, a measure of sterilizing activity. Compartmental pharmacokinetic parameters of rifampin, isoniazid, ethambutol and pyrazinamide were identified for each patient. Multivariate adaptive regression splines analyses were used to identify both-linear and non-linear relationships between potential predictors and β-slope. Predictor variables included HIV status, lung cavitation, 24-hour area-under-the-curve (AUC), the peak concentration (C_max), AUC/MIC, C_max/MIC and time that concentration persisted above MIC.

**Results:** Predictors of sterilizing activity were serum rifampin AUC and C_max, pyrazinamide AUC/MIC ratio, ethambutol C_max/MIC ratio and isoniazid C_max. A minimum rifampin C_max of 8.2 mg/L coupled with a pyrazinamide AUC/MIC ratio >11.3 were found to be predictive of sterilizing activity and sputum conversion. Isoniazid C_max was negatively correlated with sterilizing activity, in a concentration-dependent fashion, suggesting dose-dependent antagonism. For current pyrazinamide doses, the highest MIC that allows a reasonable probability of attaining an AUC/MIC ratio >11.3 is 25 mg/L. For both rifampin and pyrazinamide, higher doses than those currently in use are required, with smaller patients needing even higher doses per unit bodyweight than heavier patients.

**Conclusions:** Sterilizing activity is concentration and MIC dependent and these predictors interact in a non-linear fashion. The pyrazinamide AUC/MIC>11.3, translates to epithelial lining fluid AUC/MIC ratio of 201, virtually the same as identified in the hollow fiber. Since the speed of the sterilizing effect is concentration-dependent, faster time to cure could be achieved with increased drug doses and replacing isoniazid.

*No conflict of interest*
**Abstract: 15**

TB treatment in Special Populations

Innovative PK/PD approaches to optimize tuberculosis meningitis treatment in children: Use of modeling to design confirmatory pediatric clinical trial

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**Background:** In a Phase 2 factorial trial of 60 adults evaluating standard-dose oral rifampin (450mg daily) versus higher-dose IV rifampin (600 mg) with or without moxifloxacin for tuberculosis meningitis (TBM) in Indonesia, use of high-dose IV rifampin for 2 weeks was associated with a 58% reduction in 6-month mortality from 65% to 35%. Fluoroquinolones may also improve adult TBM treatment outcomes, and levofloxacin appears safe among children with latent or active MDR-TB. Only one therapeutic clinical trial has evaluated regimens for TBM in children. Here, we use modeling to design a clinical trial of TBM treatment in children.

Our aims were to (i) estimate pediatric rifampin doses needed to reach target exposures associated with reduction in mortality in adults, (ii) estimate levofloxacin doses in children needed to match target exposures in the adults (iii) power the study for efficacy using a model-based approach.

**Methods:** To understand developmental pharmacokinetics of rifampin and levofloxacin, we compiled a database including 1051 plasma rifampin samples from 151 children and 128 plasma levofloxacin samples from 23 children. 229 plasma and 59 CSF rifampin samples were compiled from the adult trial. Three models were developed: i) population pharmacokinetic model of rifampin in children, ii) population pharmacokinetic model of levofloxacin in children, (iii) population pharmacokinetic model of orally and intravenously administered rifampin in plasma and CSF in adults. Main goals with model I and II were to elucidate developmental pharmacokinetics of R and L in children. The main goals with model III were to quantify the pharmacokinetics of R in CSF, to estimate target plasma and CSF rifampin exposure associated with reduced mortality and to quantify main pharmacokinetic differences between IV and oral rifampin. Model-based Clinical Trial Simulations were performed to assess power of the designed study assuming a graded longitudinal primary outcome (death, grade of neurologic disability). For this purpose, we implemented in silico proportional odds model (graded outcome model) with efficacy estimates derived from the adult trial with corrections for differences in pediatric treatment response. All model-based analyses were done using a non-linear mixed effects approach.

**Results:** Rifampin bioavailability in the integrated adult plasma–CSF rifampin model was estimated to be 60%. Fraction of rifampin in CSF was steady over time (ratio to plasma 8.2%). This model was used to estimate target exposure from an adult receiving 600 mg of intravenous R. Rifampin model in children was then used to estimate intravenous doses needed in children needed to match target AUCss (105 mcg*h/L). Literature exposure of fluoroquinolones associated with improved outcome in TBM was used to determine target levofloxacin exposures, and the population PK levofloxacin model was used to estimate optimized pediatric doses. Clinical trial simulations demonstrated increased power with the planned study design by using model-based analysis of graded outcome versus conventional approaches.
Conclusions: The planned clinical trial of TBM was designed based on model-based analysis. Significant amount of modeling was done a priori to integrate all available knowledge in order to ensure maximal success of planned clinical trial of TBM in children.

No conflict of interest
Abstract: 16

PK/PD modeling

A dynamic integrated drug, Mtb and host archetype for testing novel treatment interventions

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Background: Most in-vitro experiments and in-silico simulations of TB drug effectiveness are based on monotherapy. However, standard treatment for TB usually involves lengthy therapy comprising of up to four different drugs taken over 6 months. Previous PK/PD models for TB have focused on short-term drug effects during the initial 2 to 10 days of treatment rather than overall therapy outcome. Shorter-duration therapy would mean less need for high patient adherence, and reduced risk of bacterial resistance.

Methods: A novel dynamic integrated drug, Mtb and host archetype including rifampin, isoniazid, and pyrazinamide was developed and aligned with existing clinical data. Cell-mediated immune system response to acute pulmonary TB infection - involving multiple types of lymphocytes, cytokines, and macrophages, with interaction between lung and lymph tissue was also included. Bacterial resistance was modeled as multiple distinct strains, each separately influenced by individual drugs in the test regimen at their respective previously reported mutation rates. Bacterial exchange between intra- and extracellular space was also permitted in the model. The host-bug-drug framework was implemented as a population-based simulation for 5,000 patients over 500 days, including within- and between-patient variability in PK. Additional host and Mtb parameters incorporated in the model were based on literature values from numerous earlier TB PK/PD studies, and were surveyed at the point estimate with 20% coefficient of variance.

Results: Relative effectiveness of competing TB therapies was determined by change in intra-cellular and extra-cellular bacterial load. Treatment regimen variables (drug combination, dose, schedule, duration), and therapy initiation relative to time of infection were tested. Results strongly suggest that intracellular bacterial growth inhibition and killing is central to therapeutic outcome, illustrated by: i) Treatment duration is predominantly driven by the net kill rate of intracellular bacteria, ii) exchange of bacteria between intra- and extracellular compartments, bursting, creates a bacterial reservoir effectively reducing the effect of drugs, which only act extracellularly, such as isoniazid, iii) a novel cycling high-low dose every-other-day rifampin regimen, may reduce overall treatment duration by 35-40 percent. The benefit of increased dose and of alternating high/low dose is thought to primarily stem from substantially elevated bacterial kill rates by rifampin believed to occur at higher concentration levels evident when sufficient transit time is allowed for rifampin to accumulate intra-cellularly, iv) quantification of patient TB therapy effect based on extracellular bacterial count, alone such as sputum smear test, may underestimate remaining intracellular bacteria, which later may lead to renewed acute infection, and v) complete bacterial clearance may take 60 days or more beyond when extracellular bacteria is fully eliminated. Additional notable findings were, a) higher doses of rifampin, may lead to as much as 40-60 percent shorter therapy duration, and b) as expected, the timing for therapy intervention since initial TB infection has significant influence on total treatment time.

Conclusions: The proposed novel dynamic integrated drug, Mtb and host archetype provides a basis for further analysis of therapy alternatives. The established system can also support extended multi-drug therapy comparative studies of different bacterial resistance patterns.

No conflict of interest
Abstract: 18

PK/PD of approved TB drugs

Isoniazid/acetylisoniazid urine concentrations as a marker of adherence to isoniazid preventive therapy in HIV-infected children

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Introduction: International guidelines recommend the use of isoniazid preventive therapy as a means to reduce the incidence of tuberculosis in populations at risk for developing the disease. The Arkansas colorimetric method monitors adherence by detection of isoniazid/degradation products in urine. However, the test is limited by a drop in sensitivity with increasing time post isoniazid dose. Moreover, the Arkansas test results have not been evaluated against objective measurements of isoniazid and acetylisoniazid concentrations. This study evaluates the Arkansas urine test using high performance liquid chromatography tandem mass spectrometry measurements of urine isoniazid and acetylisoniazid.

Method: We collected urine samples 4, 24, 48 and 72 hours after isoniazid or placebo doses (dose, 8 – 12 mg/kg) in 41 HIV-infected children, aged 15 years and below, receiving daily or thrice weekly isoniazid preventive therapy. Urine samples were blindly tested and the proportion of positives as determined by the Arkansas test and high performance liquid chromatography tandem mass spectrometry, respectively, were compared.

Results: A total of 31 children (median age 7.7 years; interquartile range 6.6 – 9.5 years) on isoniazid were studied. The Arkansas test was positive in 29/31 (94%), and isoniazid/acetylisoniazid concentrations were obtained using mass spectrometry in 30/31, of 4-hour samples. At 24, 48 and 72 hours only 78/94%, 23/69% and 0/33%, respectively, were Arkansas test/mass spectrometry positive.

Conclusion: The Arkansas test reliably predicted isoniazid ingestion at a clinic visit 4 hours after the morning dose, but did not perform well at 24 hours.

No conflict of interest
Abstract: 19

PK/PD of approved TB drugs

Associations between salivary, protein-unbound and total plasma concentrations of rifampicin

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Background. Plasma is the traditional biological sample for PK studies and Therapeutic Drug Monitoring (TDM) of the pivotal anti-tuberculosis (TB) drug rifampicin. Saliva may be an attractive alternative matrix, also considering that it may reflect protein-unbound, active plasma concentrations. The objectives of this study were (1) to compare the PK of rifampicin in saliva and plasma and (2) to assess whether saliva could be an alternative matrix for PK studies and TDM with this drug.

Materials and methods. A descriptive PK study was performed among 15 adult Tanzanian TB patients who were in the intensive phase of TB treatment. Time-matched samples of stimulated saliva (obtained with a Salivette\textsuperscript{®} device containing citric acid) and plasma were collected at predose and at 1, 2, 3, 4, 6, 8, 10 and 24 hours after intake of rifampicin. Salivary, total (protein-unbound plus bound) and unbound plasma concentrations of rifampicin were measured with validated HPLC methods. Salivary and plasma PK parameters were assessed. Ratios of salivary to (total and unbound) plasma concentrations were calculated for loose concentrations. Based on loose concentrations, salivary to plasma conversion factors and regression equations were assessed. The predictive performance of these estimations was based on datasets in which one out of the 15 patients was omitted, followed by use of the conversion factors or regression equations to estimate the (total and unbound) plasma concentrations of the 15th patient (jackknife method).

Results. The geometric mean AUC\textsubscript{0-24h} of rifampicin in saliva (3.1 h\textsuperscript{*}mg/L) was slightly but significantly lower than the protein-unbound AUC\textsubscript{0-24h} in plasma (5.3 h\textsuperscript{*}mg/L) and these were much lower than the plasma AUC\textsubscript{0-24h} based on total concentrations (32.7 h\textsuperscript{*}mg/L). Corresponding geometric mean C\textsubscript{max} values were 0.64, 1.0 and 6.8 mg/L. Average (geometric mean) ratios of loose salivary versus total or unbound plasma concentrations were 0.099 and 0.614 and these ratios were not dependent on time post dose or associated rifampicin plasma concentrations (repeated measures ANOVA). The prediction of total and unbound plasma concentrations based on salivary concentrations of rifampicin resulted in median percentage prediction errors (MPPE) of 13.4% and 6.0% and median absolute percentage prediction errors (MAPE) of 35.7% and 23.0%, respectively, which means that these predictions were sufficiently accurate (<15%) yet imprecise (>15%). Regression equations had similar predictive performance.

Conclusions. AUC\textsubscript{0-24h} and C\textsubscript{max} of rifampicin in saliva were much lower than those in plasma based on total plasma concentrations. The AUC\textsubscript{0-24h} of rifampicin in saliva was significantly lower than the protein-unbound plasma AUC\textsubscript{0-24h}. It is not possible to predict total or protein-unbound plasma concentrations from salivary concentrations, due to inadequate precision associated with this prediction.

Document not received
Abstract: 20

PK/PD of approved TB drugs

Moxifloxacin population pharmacokinetics and model-based comparison of efficacy between moxifloxacin and ofloxacin in African patients


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Introduction: Fluoroquinolones play an important role in the treatment of multi-drug resistant tuberculosis (MDR-TB) including resistance to both rifampin and isoniazid. Fluoroquinolones differ from each other in their activity against Mycobacterium tuberculosis (M.tb) and their pharmacokinetics in humans. The efficacy of fluoroquinolones has been related to the ratio of area under unbound concentration-time curve (fAUC0-24)/minimum inhibitory concentration (MIC), i.e. the fAUC0-24/MIC. The in vitro bactericidal activity of moxifloxacin against M.tb is superior to that of ofloxacin, but ofloxacin is still widely used to treat MDR-TB because of its affordability and availability. We compared the efficacy of moxifloxacin and ofloxacin for the treatment of MDR-TB against pre-defined pharmacodynamic targets using modeling and simulation.

Materials and methods: The steady-state population pharmacokinetics of moxifloxacin was described in 241 tuberculosis patients in Southern Africa. Monte Carlo simulations were applied to obtain the fAUC0-24 after daily doses of 400 mg or 800 mg moxifloxacin, and 800 mg ofloxacin. For a specific MIC, the probability of target attainment (PTA) was defined as the likelihood of achieving a fAUC0-24/MIC ratios ≥53 and ≥100, respectively. The MIC distributions of ofloxacin and moxifloxacin were determined by the BACTEC MGIT 960 system in 197 drug resistant M.tb clinical isolates. The PTAs were used to calculate the cumulative fraction of response (CFR) for each M.tb strain, target CFR ≥90%.

Results: For a target fAUC0-24/MIC ratio ≥53, the CFRs in multidrug-resistant (MDR) strains were 98% and 84% for moxifloxacin and ofloxacin, respectively. The respective drugs achieved 86% and 51% CFR in MDR isolates with additional resistance to an injectable drug. Using a more stringent target (fAUC0-24/MIC ≥100), the respective CFR achieved for moxifloxacin and ofloxacin were 88% and 43% for MDR strains. However for daily moxifloxacin doses of 800 mg, the CFR increased to 98% for the more stringent target.

Conclusions: Our results predict that moxifloxacin is more efficacious than ofloxacin in the treatment of MDR-TB. Further studies are however required to determine the optimal pharmacodynamic target for moxifloxacin in a multidrug regimen and to clarify safety issues when it is administered at higher doses.

No conflict of interest
Abstract: 21

Therapeutic Drug Monitoring

Moxifloxacin exposure changes over time during tuberculosis treatment

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Background: Moxifloxacin (MFX) has high in vivo and in vitro bactericidal effects against Mycobacterium tuberculosis (MTB) and therefore fulfils an important role in case of resistance or intolerance against first line anti-TB agents. Furthermore, it is now being evaluated to become part of a new drug-susceptible TB regimen. Individualised dosing seems to be needed in selected patients (i.e. rifampicin (RIF) co medication; MIC ≥ 0.25 mg/L) to achieve treatment success by means of an adequate exposure. We earlier observed high between-patient pharmacokinetic (PK) variability for MFX. As disease severity, inflammatory and nutritional status of an individual TB patient changes over time during treatment, we studied if MFX exposure changes over time from onset of active TB treatment or start of MFX.

Material and methods: We retrospectively reviewed medical charts along with pharmacokinetic data of patients (aged > 18 yrs) receiving 400 mg MFX orally once daily as part of their TB regimen between January 1st 2006 and January 1st 2013 at the Tuberculosis Centre Beatrixoord (Groningen, The Netherlands), who were subjected at least once to therapeutic drug monitoring (TDM) of MFX. Pharmacokinetic sampling was performed after at least 5 days of treatment (steady-state). Plasma concentrations of MFX were determined using a LC-MS/MS method. MFX exposure was predicted using our validated population pharmacokinetic model. Time period between first initiation of TDM and start of active TB regimen as well as start of MFX treatment was collected. As RIF may influence MFX exposure, concomitant treatment of RIF during MFX TDM was scored as well. A simple linear regression was used to evaluate any contribution of these factors to the area under the concentration-time curve (AUC).

Results: 47 patients were at least once subjected to TDM. At 400 mg a mean AUC\(_{0-24h}\) of 24.2 (range: 9.9 – 51.2) mg*h/L was observed after 36 (range: 5 – 155) days of MFX treatment in accordance with -29 - 153 days after initiation of an active TB regimen. This observed exposure is considerably lower compared to the published AUC in healthy volunteers (i.e. 33.9 ± 1.22 mg*h/L). 28/46 patients were concomitantly treated with RIF. Simple linear regression showed a significant (p<0.05) contribution of both RIF co-treatment (approx. -8 mg*h/L for RIF) and time to start of an active TB regimen or start of MFX treatment (0.1 mg*h/L per day) to MFX AUC at initiation (approx. 23 mg*h/L). Ten patients were subjected more than once to TDM during treatment due to among others MFX dose escalation. Disproportional increase (i.e. >15% of expected due to any dose-escalation) was observed at least once in 5/10 patients over a mean active treatment interval of 98 days. These five patients were not concomitantly treated with RIF.

Conclusions: This study showed that exposure changes over time during TB treatment. Patients with low exposure at start of treatment may run the risk of treatment failure. However, more research is needed to show the impact of this low exposure but also to detect clinical and inflammatory markers reflecting disease severity, and MFX exposure during TB treatment.

No conflict of interest
Abstract: 22

Treatment of MDR-TB and XDR-TB

Co-trimoxazole 960 mg is a suitable dose for future studies in MDR-TB

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Background: Tuberculosis (TB) treatment has increasingly become complicated because of co-infection with HIV and the emergence of Mycobacterium tuberculosis strains resistant against current antituberculosis drugs, causing multidrug-resistant (MDR) TB. In a small cohort study, co-trimoxazole (SXT) showed favorable drug exposure, a low MIC of M. tuberculosis isolates and only limited toxicity. Drug susceptibility testing of M. tuberculosis to SXT showed promising results in isolates from normal sensitive TB, HIV-TB and MDR-TB patients. The aim of this study was to determine if the potential target \( \frac{fAUC}{MIC} \) ratio of 25 is met using commonly tolerated dosages of SXT.

Materials & Methods: AUC and MIC values from our retrospective study in MDR TB patients combined with MIC’s from drug-susceptible TB cases and HIV-TB patients were used to determine AUC/MIC ratios. AUC were determined according to the log-linear trapezoidal rule with a standard non-compartmental PK method using the KINFIT module of MW/Pharm 3.60 (Mediware, Groningen, The Netherlands). The susceptibility of M. tuberculosis strains collected from MDR-TB, normal sensitive TB and HIV-TB patients was determined according to the Absolute Concentration Method. Percentage of unbound concentration of SXT was estimated to be 35%.

Results: After receiving 480 mg of SXT, the geometric means of \( fAUC0-24/MIC \) ratio’s did not exceed 25 in normal sensitive TB, MDR TB and HIV-TB patients and were 16.6 (Inter Quartile Range (IRQ), 12.9-27.7), 16.9 (IRQ, 12.2-44) and 11.9 (IRQ, 9.2-19.8), respectively. The geometric means of \( fAUC0-24/MIC \) ratios exceeded 25 following receiving dose of 960 mg for SXT in normal sensitive TB and MDR-TB patients and were 33.3 (IRQ, 25.8-55.4) and 33.9 (IRQ, 24.3-87.9), respectively. A dose of 1440 mg of SXT achieved the assumed target ratio in normal sensitive TB, MDR TB and HIV-TB patients and were 49.9 (IRQ, 38.6-83.1), 50.8 (IRQ, 36.5-131.9) and 35.7 (IRQ, 27.6-59.3), respectively. If we considered MIC of SXT to be 0.25, the geometric means of \( fAUC0-24/MIC \) of SMX exceeded 25 after receiving three doses of SXT (480, 960, 1440) mg and were 33.3 (IRQ, 27.1-55.4), 66.5 (IRQ, 54.1-110.7) and 99.8 (IRQ, 81.2-166.1), respectively.

Conclusion: 960 mg of SXT is a suitable dose for further exploration in a hollow fiber infection model and in a prospective study to evaluate efficacy of this drug in the treatment of MDR-TB.

No conflict of interest
Abstract: 23

TB treatment in Special Populations

Administering second-line antituberculous medications to children with multidrug-resistant tuberculosis: a qualitative study

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Introduction: There are more than 65,000 children living with multidrug-resistant tuberculosis (MDR-TB) in the world today, and, while children have excellent outcomes from MDR-TB therapy, fewer than 1% are diagnosed and treated for their disease. Even when a child is started on a regimen containing second-line drugs to treat MDR-TB, there are significant barriers to completing successful therapy and achieving cure. There are limited data on the pharmacokinetics of most second-line TB drugs in children. Furthermore, almost none of these drugs is available in a child-friendly formulation. This paper presents data from a small qualitative study on administration of second-line drugs to children under program conditions from five countries. We sought to describe the challenges of administering these medications in the absence of pediatric formulations.

Materials & Methods: Open-ended interviews were conducted with nurses and physicians from National TB Programs in Peru, South Africa, Georgia, Romania and Bangladesh. Questions focused on challenges of administering second-line drugs to children. Detailed interview notes were kept and analyzed for theme and content according to standard anthropologic techniques.

Results: We completed interviews with five nurses and four physicians (N=9). All were staff members at referral hospitals for MDR-TB. Participants identified four major themes concerning administration of second-line drugs to children. These were: (1) difficulties figuring out the correct dosage of medications (6/9; 66.7%); (2) difficulties preparing the medications (9/9; 100%), including pill burden (9/9; 100%), cutting the tablets (6/9; 66.7%), and mixing the tablets for administration (8/9; 88.9%); (3) difficulties getting the medications into the child (7/9; 77.8%); and (4) children vomiting after ingesting the medicines (5/9; 55.6%). All participants reported spending at least 10% of their time dedicated to problems with administering second-line medications to children.

Conclusions: Trained health professionals reported significant problems administering second-line antituberculous drugs to children. As a result, all of them spent a large portion of their time attempting to overcome these administration difficulties, placing a great burden on understaffed medical teams. There is an urgent need to provide products that can be dosed and administered more easily without compromising efficacy and safety. Ideally, this child-friendly regimen is in a dispersible solid form, facilitates dosing across different weight groups, and does not require injections. Without pediatric formulations for drug-resistant TB treatment, children will continue to die needlessly of this treatable infection, and the target of zero TB deaths, new infections and suffering will remain elusive.

No conflict of interest
Abstract: 24

PK/PD modeling

Clinical Pharmacokinetics of Pyrazinamide in Patients with Tuberculosis

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Introduction: The treatment of active tuberculosis (TB) requires multiple drugs and a treatment duration of at least 6 months. The standard regimen for drug-susceptible TB consists of rifampin, isoniazid, pyrazinamide (PZA), and ethambutol. Of these four TB drugs, PZA is the only one known to be bactericidal against TB organisms in acidic environments. The use of PZA during the first two months of TB treatment allows for the shortening of treatment from nine to six months. Recent evidence suggests that PZA activity is dose dependent and that maximum concentration (Cmax) values > 35 ug/ml are associated with better efficacy. Higher doses than those currently recommended in the U.S.A. (25 mg/kg) might be needed to achieve this Cmax target. The goal of this study was to determine the proportion of patients with a Cmax > 35 ug/ml and to estimate the pharmacokinetics (PK) of PZA among patients enrolled in Tuberculosis Trial Consortium (TBTC) trials 27 and 28.

Methods: The data are from PK sub-studies of TBTC Studies 27 and 28. In both studies, PZA was dosed at approximately 25 mg/kg daily, rounded to the nearest 500 mg. Seventy-two patients participated in the sub-studies. Blood was collected pre-dose then 1, 2, 6, 8, 12 and 24 hours post dose. Blood PK sampling was performed after the fourth or fifth dose of PZA, administered under directly observed therapy. Noncompartmental analysis (NCA) was performed with WinNonlin Professional Version 4.0. Population PK analysis was analyzed using nonlinear mixed effect modeling software, Monolix version 3.2.

Results: NCA: The median dose received in the two studies was 1500 mg. The median (interquartile range) for Cmax and time to maximum concentration (Tmax) were 29.77 (9.16) ug/ml and 1 (1) hour respectively. Only 18 patients (25%) had Cmax >35 ug/ml and females in general had a higher Cmax compared to men. Population PK Analysis: A one-compartment model with first order absorption and linear elimination best described PZA PK. Residual variability was described using a combined error model. The median population estimates for total body clearance (Cl/F) and volume of distribution (V/F) were 4.42 L/hr and 47 L respectively. Inter-individual variability (%CV) for V/F and Cl/F were 10 and 23%, respectively. Significant covariates influencing PZA’s PK were body weight and sex. The slope effects of weight and sex on V/F were 0.2 and 0.76, respectively, and of weight on Cl/F, 0.58. Women had a lower V/F compared to men, and both Cl/F and V/F increased with body weight.

Conclusions: Higher doses of PZA than those currently used in the U.S. and globally for TB will be required to achieve the proposed Cmax target of 35 ug/ml. Sex and weight both significantly affected PZA pharmacokinetics, and patients with higher mg/kg doses were more likely to achieve target concentrations, suggesting that weight-based dosing for this drug is appropriate. The next step is to simulate different dosing regimens based on the final model to help guide the dosing of PZA.

No conflict of interest
Abstract: 25

PK/PD modeling

PK/PD with Monte Carlo simulation of isoniazid in tuberculosis patients


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Introduction: Low plasma concentrations of the tuberculosis (TB) drug isoniazid (INH) has frequently been reported in TB patients, but the therapeutic relationship between INH concentrations and treatment response has not yet been defined in human studies. An animal study has suggested that INH drug activity is concentration dependent, that AUC24/MIC best describes the bactericidal effect of INH and that an AUC24/MIC ratio of 500 h is required for optimal efficacy of INH. The present study reports the results of a Monte Carlo simulation based PK/PD analysis of INH in TB patients receiving standard TB treatment of INH, rifampicin, ethambutol and pyrazinamide once daily.

Material and Methods: Twenty consecutive male HIV negative patients with pulmonary TB (age 23 to 67 years) were studied one week after start of standard TB treatment. INH was administered orally in a dose of 300 mg to fasting patients. Venous blood samples were drawn 0, 30, 60, 90, 120, 150, 180, 240 and 360 min after ingestion. Plasma was separated by centrifugation and quantification of INH in plasma was processed by liquid chromatography tandem mass spectrometry (inter-assay CV 15%). We applied a fixed MIC value of 0.05 mg/L as determined in the above mentioned animal study. PK/PD analysis was performed by Monte Carlo population modeling in order to determine probability of target attainment (PTA) for AUC24/MIC of 500 h.

Results: One patient was left out of the analysis due to an aberrant plasma INH concentration curve. For the remaining 19 patients, the mean weight was 64.9 kg (range 51.9 – 83.5 kg) resulting in a mean INH dose of 4.7 mg/kg (range 3.6 - 5.8). Mean Cmax was 3.5 mg/L (range 1.4 - 8.1 mg/L) and mean T½ was 3½ h. Mean AUC24/MIC was 229 h for MIC = 0.05 mg/L. Monte Carlo simulation for a population of 10,000 patients revealed a PTA of only 1.4% for a target AUC24/MIC ratio of 500 h, and 15% for a target of 300 h. Even at MIC = 0.018 mg/L PTA was only 50% for a target AUC24/MIC ratio of 500 h.

Conclusion: INH standard dose of 300 mg is not sufficient to reach the suggested AUC24/MIC target of 500 h in our patient population. Further analysis based on clinical effect parameters after 2 and 6 months treatment will be pursued.

No conflict of interest
Abstract: 26

PK/PD modeling

Limited sampling strategies for Therapeutic Drug Monitoring of amikacin and kanamycin in patients with multidrug-resistant Tuberculosis

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Introduction: Amikacin and kanamycin are considered important and effective drugs in the treatment against multidrug (MDR) and extensively drug resistant (XDR) tuberculosis (TB). Unfortunately, the incidence of ototoxicity and nephrotoxicity is high. Ototoxicity incidence rates up to 37% have been reported. Since ototoxicity is not reversible adequate precautions need to be taken. Toxicity is related with pharmacokinetic parameters, such as the area under the concentration-time curve (AUC) and the maximal serum concentration (Cmax). The Cmax is commonly accepted to predict the efficacy of aminoglycosides, yet there is evidence that the AUC0-24h could also be used as efficacy predicting parameter. A population pharmacokinetic model may help to reduce the incidence of side effects whilst maintaining efficacy by calculating the Cmax and AUC0-24h. Furthermore, a limited sampling model can reduce the number of samples needed to predict the pharmacokinetic profile. In this study, we aim to develop a population pharmacokinetic model and a limited sampling model useful in daily practice to optimize pharmacotherapy.

Materials & Methods: MDR-TB patients that have received amikacin or kanamycin as part of their treatment with one or more full plasma drug concentration-time curves were evaluated. Amikacin and kanamycin plasma concentrations were analyzed using the Axsym immunoassay or an LC-MS/MS method. A population pharmacokinetic model was developed using MW\Pharm 3.60 (Mediware, The Netherlands) with all amikacin curves at 400 mg and this model was subsequently cross validated using the n-1 method. The predictive value of this model was calculated for other dosages of amikacin and for kanamycin. Furthermore, a limited sampling model was developed based on our population model.

Results: Thirteen patients receiving amikacin and three patients receiving kanamycin were included in this study. Mean observed AUC0-24h was 87.35 (± 24.09) mg*h/L for amikacin and 72.35 (range 65.5 – 76.4) mg*h/L for kanamycin. The mean clearance was 5.60 (± 2.55) L/h, mean distribution volume 0.19 (± 0.08) L/kg and the mean half time was 1.89 (± 0.573) h. The pharmacokinetic model was developed with all patients using 400 mg amikacin and validated with a root mean square error (RMSE) of 3.78%. Observed Cmax values were underestimated by an average of 13.07% with a RMSE of 7.90% (n = 7). With this model, the AUC0-24h of other dosages of amikacin was predicted with a RMSE of 5.76%. The AUC0-24h of kanamycin was calculated with a RMSE of 3.56%. A limited sampling model was developed based on two samples obtained at 2 and 7 hours after administration with a R2 of 0.92 and a bias and RMSE of 0.1% and 4.5%, respectively.

Conclusions: We developed a robust population model suitable for predicting the AUC0-24h and Cmax of amikacin and kanamycin. With an estimation of these two parameters, both toxicity and efficacy can be optimized. This model can be used as a daily routine in guiding the dosing of amikacin and kanamycin.

No conflict of interest
Abstract: 27

PK/PD modeling

Population Pharmacokinetic and Pharmacogenetic Analysis of Rifampicin in Healthy Adults

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Background: Rifampicin exhibits pharmacokinetic variability which can contribute to variable clinical response. The aim of this study was to develop a population pharmacokinetic model and investigate the impact of genetic variations and demographic variables on rifampicin pharmacokinetics among healthy adults at steady state.

Materials & Methods: 34 subjects (age: 22–56 years; weight: 46–86 kg) were recruited for this clinical trial. Subjects were randomised to either rifampicin (600 mg) or rifampicin (600 mg) co-administered with isoniazid (300 mg) daily for 14 days. After 14 days of washout period, the subjects were switched over to rifampicin (600 mg)/isoniazid (300 mg) or rifampicin (600 mg) daily for 14 days. Concentrations of rifampicin were measured at 0, 1, 2, 4, 6, 8, 10, 12, 18 and 24 hours postdose. Rifampicin plasma concentrations (n = 534) were quantified using a validated LC-MS/MS assay. Subjects were genotyped for 12 single nucleotide polymorphisms (SNPs), including CYP3A4, SLCO1B1 and ABCB1. A one compartmental pharmacokinetic model with first-order absorption and elimination kinetics was developed using nonlinear mixed-effects modeling in NONMEM. Variability in the shape of the absorption curve was described using a flexible transit compartment model, in which a delay in the onset of absorption and a gradually changing absorption rate were modelled as the passage of drug through a chain of hypothetical compartments, ultimately reaching the absorption compartment.

Results: In the final model, apparent oral clearance (CL/F) was 10 L.h⁻¹, while the volume of distribution (V/F) was estimated to be 31.8 L. Rifampicin relative bioavailability was 58% higher (95% confidence interval, [27–89%]) in expressers for CYP3A4 (rs4646437). Other investigated covariates, such as co-administration with isoniazid, SLCO1B1 genes and bodyweight, did not substantially explain interindividual variability. Interindividual variability was estimated to be 27.1, 26.4 and 33.1% for CL/F, mean transit time (MTT) and bioavailability (F), respectively. Intercasual variability was estimated for CL/F (13%), MTT (138%) and F (19.9%).

Conclusions: The model identified CYP3A4 (rs4646437) as a significant predictor of rifampicin plasma exposure in healthy subjects after chronic exposure. As such, this factor should be considered in the evaluation of optimal dosing approaches for rifampicin.

No conflict of interest
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PK/PD modeling

Impact of antiretroviral drugs lopinavir/ritonavir and nevirapine on bedaquiline pharmacokinetics

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Background: Bedaquiline (BDQ) was recently approved by the FDA for treatment of multidrug resistant tuberculosis. The label (United States Product Insert) allows concomitant treatment with antiretroviral drugs nevirapine (NVP) and ritonavir-boosted lopinavir (LPV/r) but warns that clinical data in HIV/MDR-TB co-infected patients on the combined use are not available. NVP is an inducer and LPV/r is an inhibitor of the cytochrome (CYP) P450 isoenzyme 3A4, the enzyme primarily responsible for the metabolism of BDQ and its main metabolite M2. The objective of this work was to obtain model-based estimates of the impact of NVP and LPV/r on the PK of BDQ and M2.

Materials & Methods: BDQ and M2 plasma concentrations from interaction studies with NVP (study C117) and LPV/r (study C110) were utilized. Each study included 16 individuals, and PK samples were collected over 14 days after each BDQ dose. C117 was a single-sequence study including two BDQ doses; NVP administration started four weeks before the second dose. The interaction effect was assumed to start after two weeks of NVP. C110 was a randomized crossover study where two doses of BDQ were given four weeks apart; LPV/r was started 10 days before one of the doses. The interaction effect was assumed to occur during the days of LPV/r dosing. Non-linear mixed effects modeling was performed in NONMEM 7.2 with FOCE-I. All trials were conducted in accordance with Good Clinical Practice standards and local ethical legislation.

Results: The population PK model was found to fit the data well. NVP was not found to increase BDQ clearance (CL) but increased M2 CL to 117% (relative standard error, RSE, 10%) of normal (BDQ administered alone). LPV/r was found to decrease BDQ CL and M2 CL to 35% (RSE 9.2%) and 58% (RSE 8.4%) of normal. The inter-individual variability in the decrease was 35% (RSE 17%) and 12% (RSE 73%), respectively, and not significantly correlated to individual CL. Bioavailability of BDQ was not found to be altered by NVP or LPV/r.

Conclusions: NVP has minimal impact on BDQ PK. With LPV/r, significant inhibitory effects on BDQ and M2 CL were identified. The clinical relevance is uncertain since the relationships between BDQ and M2 exposure and response and potential toxicity are not well known. BDQ must be used with caution when co-administered with LPV/r and appropriate clinical monitoring for BDQ-related adverse reactions is recommended.

No conflict of interest
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Late Breaker

Product Development Research Resources: U.S. National Institute of Allergy and Infectious Diseases

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The Division of Microbiology and Infectious Diseases (DMID) of the National Institutes of Allergy and Infectious Disease (NIAID)/National Institutes of Health (NIH) is committed to finding new ways to better understand, diagnose, treat, and prevent infectious diseases, including those of global health importance, such as tuberculosis (TB). NIAID plays an important role in facilitating the development of drugs, vaccines and diagnostics particularly for infectious disease with limited pharmaceutical company participation.

This presentation focuses on the preclinical and clinical resources available through DMID (http://www.niaid.nih.gov/labsandresources/resources/dmid/Pages/default.aspx) that may be of interest to researchers engaged in development of TB drugs, vaccines and diagnostics. These services are not intended to be the sole source of development; rather the services are offered to fill gaps and provide critical information necessary to move a product forward, thus lowering the risk inherent in product development. While NIAID/DMID’s preclinical services for researchers are comprehensive, this presentation focusses on activities that are relevant for development of drugs, vaccines and diagnostics for infectious diseases in general. Services include preclinical IND-enabling and non-clinical development services such as drug and vaccine formulation, chemical synthesis, regulatory consultation, product profiles, GMP manufacturing, metabolism testing, GLP toxicology/pharmacology. Clinical resources include Phase 1 evaluations of candidate interventions.

Services specific for early preclinical development of TB drugs, vaccine and diagnostics, including in vitro assessment for antimicrobial activity, in vivo animal testing services, and research reagents are also available

Resources are without charge to U.S. and international investigators in academia, not-for-profit organizations, industry and government through an application process. The approval process is transparent and begins with an informal exploration of the request between the DMID Program Officer and the Requestor. Multiple levels of proposal review and evaluation are conducted and are based on standard criteria. Services are contingent upon availability of required preliminary data, and agreements ensure confidentiality and protect intellectual property rights.