Evaluation of dried blood spot sampling for pharmacokinetic research and therapeutic drug monitoring of anti-tuberculosis drugs in children

Martial, Lisa C.; Kerkhoff, Jordy; Martinez, Nilza; Rodriguez, Mabel; Coronel, Rosarito; Molinas, Gladys; Roman, Myriam; Gomez, Roscio; Aguirre, Sarita; Jongedijk, Erwin

Published in:
International journal of antimicrobial agents

DOI:
10.1016/j.ijantimicag.2018.04.020

Publication date:
2018

International Journal of Antimicrobial Agents 52 (2018) 109–113

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Evaluation of dried blood spot sampling for pharmacokinetic research and therapeutic drug monitoring of anti-tuberculosis drugs in children

Lisa C. Martial[a], Jordy Kerkhoff[b], Nilza Martinez[c], Mabel Rodríguez[c], Rosarito Coronel[c], Gladys Molinas[c], Myriam Roman[c,d], Roscio Gomez[c,d], Sarita Aguirre[d], Erwin Jongedijk[e], Justine Huisman[e], Daan J. Touw[e], Domingo Pérez[c], Gilberto Chaparro[c], Felipe Gonzalez[c], Rob E. Aarnoutse[a], Jan-Willem Alffenaar[e], Cecile Magis-Escurra[b,*]

[a] Radboud University Medical Center, Radboud Institute for Health Sciences, Department of Pharmacy, Nijmegen, The Netherlands
[b] Radboud University Medical Center-Dekkerswald, Department of Pulmonary Diseases, Groesbeek, The Netherlands
[c] Instituto Nacional de Enfermedades Respiratorias y del Ambiente, Asunción, Paraguay
[d] Programa Nacional de Lucha contra la Tuberculosis, Asunción, Paraguay
[e] University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 21 December 2017
Accepted 29 April 2018

Keywords:
Tuberculosis
Pharmacokinetics
Dried blood spot
Anti-tuberculosis drugs
Therapeutic drug monitoring
Children

ABSTRACT

Background: Dried blood spot (DBS) sampling for pharmacokinetic (PK) studies and therapeutic drug monitoring have unique advantages over venous sampling. This study aimed to evaluate a DBS method for first-line anti-tuberculosis drugs in children, and DBS sampling to assess PK parameters.
Methods: Paraguayan children were treated according to the revised paediatric dosing scheme of the World Health Organization. A PK curve was performed both with DBS sampling and conventional venous sampling for rifampicin, pyrazinamide and ethambutol. Passing–Bablok regression, Bland–Altman plots and predictive performance evaluation were used to assess agreement between DBS and plasma concentrations. The percentages of patients attaining population PK values for C_{max} and AUC_{0-24h} were calculated.
Results: After use of a conversion factor, Passing–Bablok regression showed no significant proportional or systematic bias between DBS and plasma concentrations. Bland–Altman plots showed that 95% of the ratios of the DBS predicted:observed plasma concentrations lay between 0.6 and 1.4 for rifampicin, 0.5 and 1.6 for pyrazinamide and -0.4 and 2.8 for ethambutol. DBS measurements showed acceptable predictive performance for rifampicin and pyrazinamide, but not for ethambutol. Assessment of C_{max} target attainment was 62.5% for isoniazid, 25% for rifampicin, 100% for pyrazinamide and 75% for ethambutol.
Conclusion: For rifampicin and pyrazinamide, the DBS method was accurate in predicting plasma concentrations, and was used successfully for PK parameter assessment. However, predicting ethambutol plasma concentrations with DBS measurement was associated with too much imprecision. Despite higher dosing, only 25% of the population reached average target adult rifampicin exposures.

1. Introduction

With an annual incidence exceeding nine million, tuberculosis (TB) is one of the leading public health problems worldwide. In children, the total estimated incidence of TB in 2015 was ca. 1 million. Various factors are known to affect TB treatment outcome, including adherence to TB drugs, comorbidity and drug resistance. In addition, variability in the pharmacokinetics (PK) of first-line TB drugs is a major determinant of treatment outcome [1]. From adult studies, it is known that low plasma concentrations of TB drugs are related to treatment failure and to acquired TB drug resistance [2–6]. Few data are available on the PK of first-line TB drugs in children [7–10]. To reach the same drug concentrations as in adults, children require higher doses of TB drugs on a mg/kg basis [11,12]. Therefore, the World Health Organization (WHO) increased the recommended dose of first-line anti-TB drugs in children in 2010. In addition to this revision, a new fixed-dose combination has been developed with a rifampicin:isoniazide ratio of 3:2, suiting the new dosing regimen. Despite these efforts, recent

* Corresponding author. Address: Radboud University Medical Center-Dekkerswald, Department of Pulmonary diseases, Nijmeegsebaan 91, 6561 KE Groesbeek, The Netherlands.
E-mail address: Cecile.magis-escurra@RadboudUMC.nl (C. Magis-Escurra).

https://doi.org/10.1016/j.ijantimicag.2018.04.020
0924-8579/

studies have suggested that this revised dose is not sufficient to reach appropriate plasma concentrations of rifampicin and ethambutol in children [7–9].

Therapeutic drug monitoring (TDM) may be a helpful tool to further optimize and individualize TB treatment [4,13–15]. TDM can be defined as the measurement of plasma or blood concentrations to adapt dosages to achieve predefined targets that are associated with maximal efficacy while minimizing toxicity. Conventionally, TB drugs are measured in plasma or serum obtained by venous sampling. In high-incidence countries, frequently with poor resources, TDM is very difficult to implement due to economic and logistic challenges.

Dried blood spot (DBS) sampling may offer an alternative to conventional sampling as it only requires a few drops of blood, easily obtained with a finger prick. These drops are applied to filter paper and kept dry until analysis, and drug concentrations usually remain stable under these circumstances. DBS sampling may facilitate the implementation of TDM of anti-TB drugs in limited-resource countries and in remote areas [16].

To the authors' knowledge, no paediatric PK studies have been performed to date to examine DBS techniques to evaluate plasma concentrations of anti-TB drugs. Moreover, no studies have used the recommended rifampicin:isoniazide dosing ratio of 3:2. Therefore, this study aimed to evaluate a DBS sampling method for rifampicin, pyrazinamide and ethambutol, and describe the PK of all first-line anti-TB drugs using limited sampling in children. No DBS method was available to measure isoniazid, as isoniazid binds to DBS filter paper causing variable extraction recoveries.

2. Materials and methods

2.1. Patients and setting

This study was undertaken at the hospital 'Instituto Nacional de Enfermedades Respiratorias y del Ambiente' in Asunción, Paraguay. From June 2015 to February 2016, both hospitalized and ambulatory patients were asked to participate in the study. Informed consent was obtained from all parents and from children aged ≥12 years. Treatment-naive children (aged 1–15 years) with pulmonary or extrapulmonary TB, who started treatment with a fixed-dose combination of first-line anti-TB drugs, were eligible for inclusion. There were no exclusion criteria. A sample size of 10–20 patients was chosen for this study in order to obtain at least 40 paired DBS and plasma samples. The study protocol was approved by the Ethics Committee of Laboratory Central De Salud Pública, Asunción (No: 58/180615).

2.2. Drug doses and study procedures

In the absence of a paediatric formulation in Paraguay, all patients were treated with the adult fixed-dose combination tablets of rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg and ethambutol 275 mg from Svizera Europe B.V. (see WHO list of prequalified medicinal products). The dosage scheme for these tablets followed the Paraguayan national TB guideline which has adopted the revised WHO dosing scheme for children: rifampicin 15 mg/kg (range 10–20 mg/kg), isoniazid 10 mg/kg (range 10–15 mg/kg), pyrazinamide 35 mg/kg (range 20–40 mg/kg) and ethambutol 20 mg/kg (range 15–25 mg/kg).

Basic demographics were collected and comedication was recorded. Biochemical parameters were determined at baseline and on the PK sampling day, and included haematocrit, serum creatinine and liver enzymes. PK sampling was performed just prior to observed TB drug intake [predose sample (t=0 h)] and 2, 4 and 8 h after administration after reaching steady-state conditions on day 7–10 of treatment. Patients had to remain fasted from 4 h prior to the TB drug intake until the last sample was taken. At each time point, both a venous sample and a DBS fingerprick sample were taken. The DBS sampling procedure was as described previously [17]. Venous blood samples (3.5 mL EDTA) were centrifuged directly after sampling, and the plasma was stored in a liquid nitrogen container until transport to University Medical Center Groningen, The Netherlands.

2.3. Sample analysis

Plasma samples were measured based on previously published assays [19,20]. DBS samples were measured using an assay validated for accuracy, precision, linearity, matrix effect, haematocrit effect, spot volume and stability upon storage. Details on the DBS assay of rifampicin have been published previously [18]. The DBS assays for pyrazinamide and ethambutol were linear over the range (2–65 mg/L for pyrazinamide, 0.2–6.5 mg/L for ethambutol), with accuracy and precision <10% (dependent on concentration).

2.4. Assessment of agreement between DBS sampling and conventional sampling

The assessment of agreement between the plasma concentrations and the predicted plasma concentrations from DBS sampling was assessed using Passing–Bablok regression, Bland–Altman plots and quantification of the predictive performance (see Text File 1, online supplementary material).

2.5. Pharmacokinetic analysis

The following PK parameters were assessed: area under the concentration–time curve (AUC) during the sampling interval (AUC_{0-8h}), AUC during the dosing interval (AUC_{0-24h}), apparent clearance (CL/F), apparent volume of distribution (Vd/F), maximal concentration (C_{max}) and half-life ($t_{1/2}$). In addition, the proportions of patients attaining adult population values for C_{max} and AUC values were computed [13]. Detailed information is provided in Text File 2 (see online supplementary material).

2.6. Pain score

Pain was assessed after DBS fingerprick sampling by a parent (and children if ≥12 years) with a facial pain score based on Tse et al. [20]. In this six-point scale, 1 represents 'no pain' and 6 represents the worst imaginable pain. In addition, photographs taken during the DBS sampling procedure were scored by three independent observers and translated into a facial score.

3. Results

3.1. Demographic information

From June 2015 to February 2016, a total of 15 parents and/or patients gave informed consent. From those patients, 15 completed the PK sampling day, of whom 11 had samples evaluable for PK parameter determination (all samples were missing in one patient, three other patients had at least one missing sample). Baseline demographic information is shown in Table 1. Thirty-six percent of the children were female, their median age was 1.5 years (range 0.5–15 years) and their median weight was 11 kg (range 6–53 kg). None of the patients had comorbidities.

3.2. Assessment of agreement between methods

In total, 60 DBS samples and 50 plasma samples were available, of which 47 samples matched in time. From these 47 matched

Table 1
Baseline demographic information. Continuous variables are given as median (range).

Demographics	Value
Number of patients (*n*)	14[a]
Sex, % female	36
Age (years)	1.5 (0.5–15)
Body weight (kg)	10.6 (5.5–53)
Height (cm)	74 (50–162)
Ethnicity: mixed/indigenous	5/9
Type of TB	
Pulmonary (*n*) (%)	13 (87%)
Extrapulmonary (*n*) (%)	2 (15%)[b]
HIV co-infection (*n*) (%)	0 (0%)
Dose information	
Rifampicin (mg/kg)	14 (8–27)
Isoniazid (mg/kg)	7 (4–14)
Pyrazinamide (mg/kg)	38 (22–72)
Ethambutol (mg/kg)	26 (15–49)
Biochemical parameters	
Creatinine (mg/dL)	0.45 (0.10–0.80) (*n*=8)
Liver enzymes	
ALT (U/L)	19 (12–79) (*n*=8)
AST (U/L)	21 (10–110) (*n*=10)
AF (U/L)	311 (94–905) (*n*=8)
GGT (U/L)	12 (7–102) (*n*=5)
Haemoglobin (g/dL)	10.7 (6.2–12.7) (*n*=13)
Haematocrit (%)	34 (19–39) (*n*=12)

TB, tuberculosis; HIV, human immunodeficiency virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AF, alkaline phosphatase; GGT, gamma-glutamyl transferase.
[a] Demographic information was lost from one patient.
[b] Information missing from one subject.

pairs, 33 rifampicin, 39 pyrazinamide and 35 ethambutol pairs were above the lower limit of quantification. A conversion factor using the inverse geometric mean of the DBS:plasma concentration ratio resulted in better agreement between both methods. The ratio was 0.75 for rifampicin, 0.81 for pyrazinamide and 0.51 for ethambutol. After application of the conversion factor, Passing–Bablok regression analysis showed no significant proportional or systematic bias between DBS and plasma concentrations for each of the compounds (Fig. 1 and Fig. S1, see online supplementary material), as the slope was not significantly different from '1', indicating no proportional error, and the intercept was not significantly different from '0', indicating no systematic bias. Bland–Altman plots showed that 95% of the ratios of the predicted:observed plasma concentrations lay between 0.6 and 1.4 for rifampicin, 0.5 and 1.6 for pyrazinamide, and 0.4 and 2.8 for ethambutol (Fig. 1 and Fig. S2, see online supplementary material). In addition, for rifampicin, pyrazinamide and ethambutol, 76%, 77% and 20% of the samples lay between 0.80 and 1.20 of the predicted:observed ratio, respectively. No trend in variation over concentration range was observed from the Bland–Altman plots (Fig. 1). Ethambutol had the lowest agreement between predicted and observed plasma concentrations (Fig. 1). The bias and precision in the predictive performance given by the median percentage prediction error and median absolute percentage prediction error were 1.8% and 16% for rifampicin, 1.6% and 9.7% for pyrazinamide, and -2.3% and 47% for ethambutol, respectively. Using the actual haematocrit levels did not improve this agreement.

3.3. Pharmacokinetic parameters

The median treatment period on the PK sampling day was 18 days (range 11–62 days). Given the good predictive performance for rifampicin and pyrazinamide, PK parameters were calculated by plasma concentrations as well as by DBS predicted plasma concentrations for these drugs. However, plasma concentrations alone were used for ethambutol (Table 2).

Attainment of reference exposures based on plasma measurements was particularly low for rifampicin: 25% for C_{max} (≥8 mg/L) and 38% for AUC (target 30.8 mg*h/L). Sixty-three percent of patients reached the isoniazid C_{max} target (3 mg/L) and 57% reached the AUC target (11.4 mg*h/L). All patients attained the pyrazinamide C_{max} (20 mg/L) and AUC (285 mg*h/L) targets. The ethambutol C_{max} target (2 mg/L) was achieved in 75% of patients and the AUC target (17.6 mg*h/L) was reached in 29% of patients.

3.4. Pain score and feasibility

The median pain score as indicated/evaluated by the independent observers using the facial pain score was 5 (range 2–6) (*n*=13). One patient was sedated, and no pain score was assessed for this patient.

4. Discussion

To the authors' knowledge, this is the first evaluation of a DBS sampling method for three first-line anti-TB drugs in children (i.e. rifampicin, pyrazinamide and ethambutol).

Various DBS assays of anti-TB drugs in adults have been described in the literature. The present assay was based on an assay of rifampicin and clarithromycin and their metabolites [16]. When taking into account drug-specific conversion factors, DBS concentrations could predict the rifampicin and pyrazinamide plasma concentrations with bias and precision of <16%. Imprecision may be considered high, however, which implies that a single DBS measurement may only discriminate between low, intermediate and high concentrations. For rifampicin, the use of a conversion factor decreased the proportional bias, as illustrated by improvement of the Passing–Bablok regression (slope increased from 0.75 to 0.99).

Table 2
Pharmacokinetic parameters of all tuberculosis drugs as measured by plasma or dried blood spot (DBS) concentrations, given as geometric mean (range).

Parameter	Isoniazid (*n*=8) in plasma	Rifampicin (*n*=8) in plasma	Rifampicin (*n*=11) in DBS	Pyrazinamide (*n*=8) in plasma	Pyrazinamide (*n*=11) in DBS	Ethambutol (*n*=8) in plasma
C_{max}	3.1 (1.4–6.4)	5.1 (2.3–9.2)	5.5 (1.9–13.4)	42.5 (29.7–63.3)	40.1 (23.6–70.6)	2.3 (1.1–3.7)
AUC_{0-8h}	11.0 (4.9–23.1)[a]	19.7 (8.4–37.8)	24.2 (9.2–53.6)	214 (168–282)[a]	218 (133–444)[d]	9.6 (5.9–14.0)[a]
AUC_{0-24h}	12.7 (5.4–26.7)	21.4 (8.9–50.0)	24.6 (9.7–57.6)[b]	395 (310–509)[c]	519 (329–874)[c]	14.5 (7.4–23.3)[a]
CL (L/h/kg)	0.50 (0.19–1.32)[a]	0.6 (0.2–1.6)	0.53 (0.25–1.5)	0.10 (0.07–0.14)[a]	0.1 (0.05–0.31)[d]	1.6 (1.0–2.5)[a]
Vd (L/kg)	1.7 (0.7–3.7)[a]	1.6 (0.9–3.9)	1.3 (0.65–2.9)	0.8 (0.6–1.2)[a]	0.8 (0.5–1.8)[d]	12.6 (7.2–27.1)[a]
$T_{1/2}$ (h)	2.3 (1.9–3.4)	1.8 (1.1–3.3)	1.7 (0.8–4.6)	6.0 (4.9–9.2)[a]	5.8 (3.9–12.4)[b]	4.8 (2.2–8.6)

C_{max}, maximal concentration; AUC, area under the concentration–time curve; $T_{1/2}$, half-life; CL, clearance; Vd, volume of distribution.
[a] *n*=7
[b] *n*=10.
[c] *n*=4.
[d] *n*=9

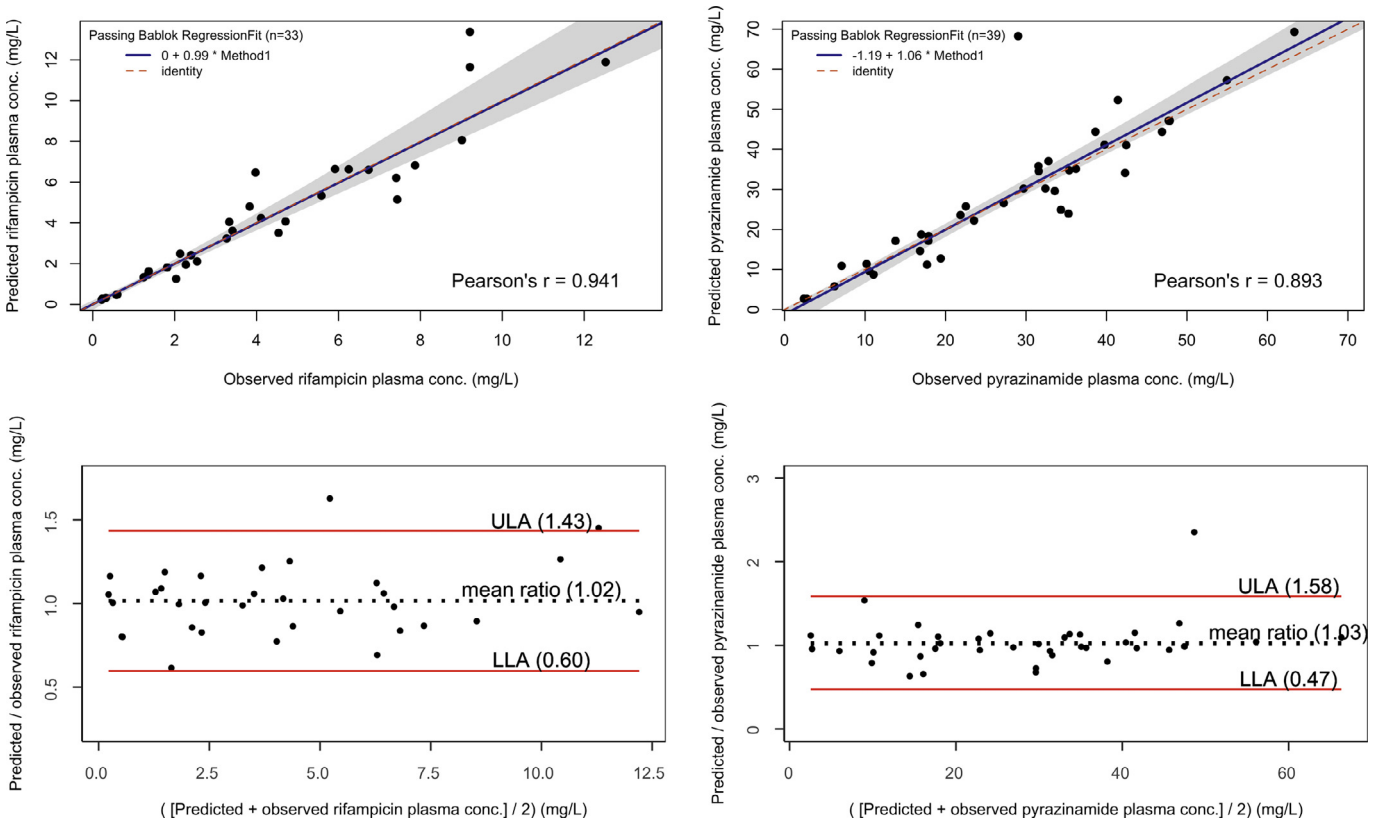

Fig. 1. Top left: Passing–Bablok regression of rifampicin. Intercept 0.003871 [95% confidence interval (CI) -0.2606–0.1961], no significant systemic error; slope 0.9938 (95% CI 0.9007–1.193), no significant proportional error. Top right: Passing–Bablok regression of pyrazinamide. Intercept 1.193 (95% CI -5.027–0.5064), no significant systemic error; slope 1.057 (95% CI 0.9773–1.186), no significant proportional error. Bottom left: Bland–Altman plot of rifampicin. Ratio of the predicted and observed rifampicin plasma concentrations plotted against the average of the predicted and observed plasma concentrations. Level of agreement: 95% of pairs lay between 0.6 and 1.4, and 76% of pairs lay between 0.80 and 1.20. Bottom right: Bland–Altman plot of pyrazinamide. Ratio of the predicted and observed pyrazinamide plasma concentrations plotted against the average of the predicted and observed plasma concentrations. Level of agreement: 95% of pairs lay between 0.5 and 1.6, and 77% of pairs lay between 0.80 and 1.20.

Such a conversion factor was not used in the authors' previous study in adults [17]. Despite the observed haematocrit effect for rifampicin during method development [17], correction for haematocrit did not further improve the agreement or the predictive performance in this study. Comparison between the authors' previous results in adults and the current findings in children is difficult, considering that PK differences between adults and children may have an impact on the peripheral distribution of the TB drugs, and the sample size was limited in both studies. Unfortunately, DBS sampling appeared to be unsuitable for ethambutol concentration measurement. Although the bias to predict plasma concentrations was well below 15%, the precision was not acceptable (47%).

From a few small studies, it is known that children require higher mg/kg body weight doses of TB drugs to attain pharmacokinetic targets [11,12]. Based on this observation, and the knowledge that low plasma concentrations are associated with worse outcome in adults, WHO recently recommended a new dosing regimen for children, with a 3:2 ratio of rifampicin:isoniazid in tablets (instead of 2:1). Evaluations of this dose of rifampicin suggest that even higher doses are required [7–9].

This study used adult fixed-dose combinations with rifampicin:isoniazid 2:1 ratios, and the number of tablets was adjusted to reach the recommended rifampicin dose per kg body weight, as only this formulation is available in Paraguay. The median rifampicin dose was 14 mg/kg body weight [WHO recommended dose 15 mg/kg (range 10–20 mg/kg)], while the median isoniazid dose was 7 mg/kg [recommended dose 10 mg/kg (range 10–15 mg/kg)]. Only 25% and 29% of children reached the rifampicin target C_{max} and the AUC was reached in 38% of the children. The currently available adult formulation fixed-dose tablets in Paraguay do not facilitate changing to the WHO-recommended dosing regimens. Based on current knowledge on the importance of rifampicin in TB treatment outcome results in adults, investigation of a higher paediatric dosage of this TB drug is needed, with the final aim being to shorten treatment duration.

This study has a few limitations. First, the sample size for evaluation of DBS sampling was relatively small. Second, the applied conversion factors may only be valid for this specific paediatric Paraguayan population. Third, PK was described in a relatively limited group of patients (n=8–11).

5. Conclusions

This study found that the DBS method for rifampicin and pyrazinamide was accurate but less precise, and was able to assess PK characteristics in this group of Paraguayan children. In future paediatric research with rifampicin and pyrazinamide, it will be feasible to include DBS-based PK, or even apply TDM on an individual basis, in order to optimize treatment.

Acknowledgements

The authors would like to thank all participating patients and their parents, and also the nursing department and medical staff from Instituto Nacional de Enfermedades Respiratorias y del Ambiente (INERAM) and the national TB programme.

Funding: This research was funded by the Department of Clinical Pharmacy and Pharmacology, University Medical Center

Groningen and the non-profit organization Stichting Suppletiefonds Sonnevanck.

Competing interests: None declared.

Ethical approval: The study protocol was approved by the Ethics Committee of Laboratory Central De Salud Pública, Asunción (No. 58/180615).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.04.020.

References

[1] Pasipanodya JG, McIlleron H, Burger A, Wash PA, Smith P, Gumbo T. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. J Infect Dis 2013;208:1464–73.
[2] Srivastava S, Pasipanodya JG, Meek C, Leff R, Gumbo T. Multidrug-resistant tuberculosis not due to noncompliance but to between-patient pharmacokinetic variability. J Infect Dis 2011;204:1951–9.
[3] Chideya S, Winston CA, Peloquin CA, Bradford WZ, Hopewell PC, Wells CD, et al. Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from Botswana. Clin Infect Dis 2009;48:1685–94.
[4] Magis-Escurra C, van den Boogaard J, Ijdema D, Boeree M, Aarnoutse R. Therapeutic drug monitoring in the treatment of tuberculosis patients. Pulm Pharmacol Ther 2012;25:83–6.
[5] Mehta JB, Shantaveerapa H, Byrd RP Jr, Morton SE, Fountain F, Roy TM. Utility of rifampin blood levels in the treatment and follow-up of active pulmonary tuberculosis in patients who were slow to respond to routine directly observed therapy. Chest 2001;120:1520–4.
[6] Pasipanodya JG, Gumbo T. A new evolutionary and pharmacokinetic–pharmacodynamic scenario for rapid emergence of resistance to single and multiple anti-tuberculosis drugs. Curr Opin Pharmacol 2011;11:457–63.
[7] Bekker A, Schaaf HS, Draper HR, van der Laan L, Murray S, Wiesner L, et al. Pharmacokinetics of rifampin, isoniazid, pyrazinamide, and ethambutol in infants dosed according to revised WHO-recommended treatment guidelines. Antimicrob Agents Chemother 2016;60:2171–9.
[8] Hiruy H, Rogers Z, Mbowane C, Adamson J, Ngotho L, Karim F, et al. Subtherapeutic concentrations of first-line anti-TB drugs in South African children treated according to current guidelines: the PHATISA study. J Antimicrob Chemother 2015;70:1115–23.
[9] Kwara A, Enimil A, Gillani FS, Yang H, Sarfo AM, Dompreh A, et al. Pharmacokinetics of first-line antituberculosis drugs using WHO revised dosage in children with tuberculosis with and without HIV coinfection. J Pediatric Infect Dis Soc. 2016 Dec;5(4) 2016;5(4):356–65.
[10] Thee S, Seddon JA, Donald PR, Seifart HI, Werely CJ, Hesseling AC, et al. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations. Antimicrob Agents Chemother 2011;55:5560–7.
[11] Schaaf HS, Parkin DP, Seifart HI, Werely CJ, Hesseling PB, van Helden PD, et al. Isoniazid pharmacokinetics in children treated for respiratory tuberculosis. Arch Dis Child 2005;90:614–18.
[12] Thee S, Detjen A, Wahn U, Magdorf K. Rifampicin serum levels in childhood tuberculosis. Int J Tuberc Lung Dis 2009;13:1106–11.
[13] Magis-Escurra C, Later-Nijland HM, Alffenaar JW, Broeders J, Burger DM, van Crevel R, et al. Population pharmacokinetics and limited sampling strategy for first-line tuberculosis drugs and moxifloxacin. Int J Antimicrob Agents 2014;44:229–34.
[14] Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. Drugs 2014;74:1061.
[15] Zuur MA, Bolhuis MS, Anthony R, den Hertog A, van der Laan T, Wilffert B, et al. Current status and opportunities for therapeutic drug monitoring in the treatment of tuberculosis. Exp Opin Drug Metab Toxicol 2016;12:509–21.
[16] Alffenaar JW. Dried blood spot analysis combined with limited sampling models can advance therapeutic drug monitoring of tuberculosis drugs. J Infect Dis 2012;205:1765–6 author reply 6.
[17] Vu DH, Koster RA, Bolhuis MS, Greijdanus B, Altena RV, Nguyen DH, et al. Simultaneous determination of rifampicin, clarithromycin and their metabolites in dried blood spots using LC-MS/MS. Talanta 2014:2931–9.
[18] Vu DH, Alffenaar JW, Edelbroek PM, Brouwers JR, Uges DR. Dried blood spots: a new tool for tuberculosis treatment optimization. Curr Pharm Des 2011;17:2931–9.
[19] Sturkenboom MGG, van der Lijke H, Jongedijk EM, Kok WT, Greijdanus B, Uges DRA, et al. Quantification of isoniazid, pyrazinamide and ethambutol in serum using liquid chromatography-tandem mass spectrometry. J Appl Bioanal 2015;1:89–98.
[20] Tsze DS, von Baeyer CL, Bulloch B, Dayan PS. Validation of self-report pain scales in children. Pediatrics 2013;132:e971–9.