J Antimicrob Chemother 2016; **71**: 703–710
doi:10.1093/jac/dkv394 Advance Access publication 11 December 2015

Journal of Antimicrobial Chemotherapy

Impact of food on the pharmacokinetics of first-line anti-TB drugs in treatment-naive TB patients: a randomized cross-over trial

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Received 28 August 2015; returned 1 October 2015; revised 7 October 2015; accepted 22 October 2015

Objectives: Concomitant food intake influences pharmacokinetics of first-line anti-TB drugs in healthy volunteers. However, in treatment-naive TB patients who are starting with drug treatment, data on the influence of food intake on the pharmacokinetics are absent. This study aimed to quantify the influence of food on the pharmacokinetics of isoniazid, rifampicin, ethambutol and pyrazinamide in TB patients starting anti-TB treatment.

Methods: A prospective randomized cross-over pharmacokinetic study was conducted in treatment-naive adults with drug-susceptible TB. They received isoniazid, rifampicin and ethambutol intravenously and oral pyrazinamide on day 1, followed by oral administration of these drugs under fasted and fed conditions on two consecutive days. Primary outcome was the bioavailability while fasting and with concomitant food intake. This study was registered with clinicaltrials.gov identifier NCT02121314.

Results: Twenty subjects completed the study protocol. Absolute bioavailability in the fasted state and the fed state was 93% and 78% for isoniazid, 87% and 71% for rifampicin and 87% and 82% for ethambutol. Food decreased absolute bioavailability of isoniazid and rifampicin by 15% and 16%, respectively. Pyrazinamide AUC_{0-24} was comparable for the fasted state (481 mg·h/L) and the fed state (468 mg·h/L). Food lowered the maximum concentrations of isoniazid, rifampicin and pyrazinamide by 42%, 22% and 10%, respectively. Time to maximum concentration was delayed for isoniazid, rifampicin and pyrazinamide. The pharmacokinetics of ethambutol were unaffected by food.

Conclusions: Food decreased absolute bioavailability and maximum concentration of isoniazid and rifampicin, but not of ethambutol or pyrazinamide, in treatment-naive TB patients. In patients prone to low drug exposure, this may further compromise treatment efficacy and increase the risk of acquired drug resistance.

Introduction

TB is the infectious disease with the second-highest morbidity and mortality by a single pathogen around the world. In 2013, an estimated 9.0 million people became TB infected and 1.5 million people died because of TB.[1] First-line treatment of TB consists of isoniazid, rifampicin, pyrazinamide and ethambutol during the first 2 months, continuing with isoniazid and rifampicin for another 4 months.[2,3] Reported treatment success rates range from 60% to 87% depending on co-morbidity.[4,5] Conceivably, filling the gaps of our knowledge of pharmacokinetics and pharmacodynamics may help to improve TB treatment, thereby preventing the emergence of drug-resistant organisms.

Effective pharmacokinetic parameters for TB drugs are AUC and maximum concentration of drugs in the blood (C_{max}). Higher AUC values are associated with increased efficacy, while low C_{max} has been associated with emergence of drug resistance.[6] During the first 2 weeks of treatment, when TB patients are seriously ill, they often suffer from gastrointestinal reactions such as abdominal pain, nausea and vomiting. Concomitant intake of food has been recommended,[2,3] but it has an ambivalent impact on drug therapy. Food makes patients less vulnerable

to nausea and vomiting, possibly resulting in a decrease in refusal of medication. However, exposure to isoniazid and rifampicin in healthy volunteers has been shown to be reduced by dosing with meals.[7–10]

A meta-analysis by Lin *et al*.[11] showed that both AUC and C_{max} of isoniazid were decreased by food. C_{max}, but not AUC, of rifampicin and ethambutol were decreased by food. Pyrazinamide absorption was not influenced by food. However, the majority of these data were obtained in healthy volunteers[11] and not in TB patients.[12,13] One study in TB patients after 2 weeks of treatment showed that a high-carbohydrate diet decreased AUC_{0-8} and C_{max} of isoniazid.[12] Recently, it was shown that food reduced the C_{max} and AUC_{0-10} of all first-line anti-TB drugs in TB patients after a minimum of 4 days of treatment.[14] The pharmacokinetics of first-line drugs in treatment-naive patients may be different from those of TB patients who are on anti-TB therapy for some time because of differences in severity of disease, malnutrition and hypoalbuminaemia.[15,16] Furthermore, in treatment-naive patients, the number of bacilli is high, and when the drug exposure is inadequate, the risk of acquired drug resistance is higher.[6] To prevent nausea, vomiting and possible treatment failure in patients, it is important to quantify the impact of food on drug exposure of the first-line anti-TB drugs in TB patients starting their treatment. Therefore, the goal of this study was to investigate the absolute bioavailability of isoniazid, rifampicin, ethambutol and pyrazinamide in treatment-naive TB patients under fasting conditions and with food on the first 3 days of treatment.

Patients and methods

Study design and population

This was a prospective randomized cross-over pharmacokinetic study. The study protocol followed the guidelines of the Helsinki Declaration of 2008 and was approved by the institutional review board at Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia (KE/FK/626/EC) and the National Agency of Food and Drug Control, Indonesia (PN.01.06.1.31.11.12.7158). Written informed consent was obtained from each subject before the study. This study was registered with clinicaltrials.gov identifier NCT02121314.

We considered the comparison between fasted and fed to be a type of bioequivalence study. The EMA guideline on bioequivalence states that ≥12 subjects should be used for a bioequivalence study.[17] Therefore, it was thought that 20 patients should be sufficient to detect the influence of food on the bioavailability of anti-TB drugs.

Newly diagnosed, treatment-naive TB patients ≥18 years old were eligible for inclusion. Subjects were recruited from the governmental chest clinics in Yogyakarta and Sardjito General Hospital, Yogyakarta, Indonesia. Exclusion criteria were active unstable liver disease, history of kidney disease or use of antacids that could not be discontinued during the study. The subjects agreed to refrain from the use of non-prescription drugs and alcohol during the entire study period.

The study was performed on the first 3 days of anti-TB treatment, so there was no washout period and patients did not reach steady-state of any of the four drugs (Figure 1). To determine absolute bioavailability, all subjects started on day 1 with intravenous treatment of isoniazid, rifampicin and ethambutol. Pyrazinamide is not available as an injection and was therefore administered orally on day 1 (Table S1, available as Supplementary data at *JAC* Online). All subjects fasted overnight for the 3 days of the study. For the fasted treatment, they continued to fast until 2 h after drug dosing. For the fed treatment, they consumed a high-carbohydrate breakfast containing 600 Kcal 0.5 h before dosing. Primary endpoints were absolute bioavailability (F) and AUC from time of administration to 24 h after (AUC_{0-24}). Secondary endpoints were C_{max} and its corresponding time (T_{max}).

Subjects were dosed according to their pre-study weights and the WHO guidelines, i.e. 5 mg/kg isoniazid, 10 mg/kg rifampicin, 15 mg/kg ethambutol and 25 mg/kg pyrazinamide.[2] On day 1, intravenous drugs were administered using isoniazid 100 mg/mL injection (Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, The Netherlands, license number 108964F), Rifadin 600 mg injection (Sanofi Aventis, Gouda, The Netherlands) and EMB-Fatol 1000 mg injection (Riemser Arzneimittel AG, Greifswald-Insel Riems, Germany). Isoniazid was given as a short infusion of 30 min. Rifampicin and ethambutol were infused in 2 h. Pyrazinamide was administered as a 500 mg tablet orally (PT; Indofarma, Bekasi, Indonesia).

Participants were randomly assigned following simple randomization procedures to one of the two treatment groups (fasted day 2 and fed day 3, or fed day 2 and fasted day 3; Figure 1). Allocation concealment was performed with sequentially numbered, sealed and stapled envelopes. These envelopes contained information about the treatment group, which was put inside randomly by a nurse in Sardjito Hospital who was not involved in the trial. The envelopes were kept in a safe, locked cabinet in each recruitment place. The allocation sequence was concealed from the doctors enrolling and assessing participants. After the patient had given written informed consent, the patient's name and code was written on the envelope. Corresponding envelopes were opened just before the time of intervention by the researcher (A. M. I. S.).

On days 2 and 3, a fixed drug combination containing 75 mg of isoniazid, 150 mg of rifampicin, 400 mg of ethambutol and 275 mg of pyrazinamide (PT; Indofarma) was administered orally.

Pharmacokinetic analysis

Serial blood samples were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 h after dosing. Samples were centrifuged and stored at −80°C until they were analysed. Plasma samples were analysed by LC-MS/MS, as previously described (a short description is available as Supplementary data at *JAC* Online).[18–20] The technicians who analysed the samples were blinded to group assignment.

C_{max} and T_{max} were derived from the plasma concentration data. The AUC_{0-24} was calculated using the log-linear trapezoidal rule in MW\Pharm (version 3.60, Mediware, Groningen, The Netherlands). Concentrations at timepoint 0 of days 2 and 3 also served as C_{24} of days 1 and 2. C_{24} of day 3 was calculated using the formula $C_{24}=C_{max}\times e^{-\beta\times(24-Tmax)}$, in which β is the first order elimination rate constant. Plasma concentrations below the quantification lower limit were treated as zeros. Absolute bioavailability (F) was normalized for dosage and calculated as $(AUC_{0-24,\ fasted\ or\ fed}/AUC_{0-24,\ intravenously})\times(dose_{intravenously}/dose_{orally})$.

Patients with a calculated half-life of isoniazid of ≤2 h were considered fast acetylators; otherwise, they were considered slow acetylators.[7]

Statistical analysis

For the patient characteristics, mean ± standard deviation (SD) values are reported. C_{max}, AUC_{0-24} and F were logarithmically transformed to calculate geometric mean (and range). Differences between fasted and fed treatments were tested using the Wilcoxon signed rank test. Statistical analysis was performed using IBM SPSS Statistics 22 (IBM, Armonk, NY, USA). Two-sided *P* values ≤0.05 were considered significant.

Results

From November 2012 to March 2013, 20 subjects were included in the study. One patient vomited shortly after ingestion of the medication on both the fed and fasted day. This patient was excluded

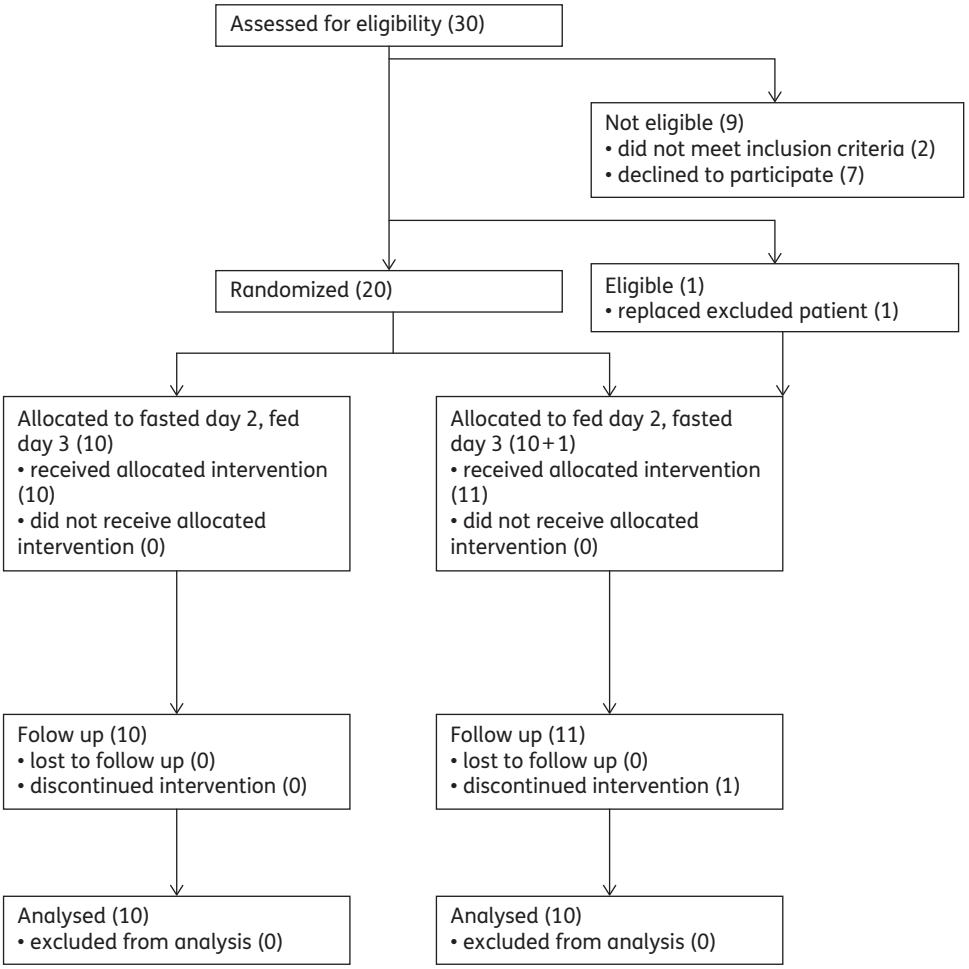

Figure 1. Study design. Numbers of patients are in parentheses.

from the study and replaced by inclusion of another subject (Figure 1). Patient characteristics are presented in Table 1. The mean BMI was 17.4 ± 2.6 kg/m^2, showing that a large proportion of the study population (70%) was underweight (i.e. BMI <18.5 kg/m^2).[21,22] Fifteen subjects were fast acetylators for isoniazid. Two patients also suffered from type II diabetes mellitus and two others were co-infected with HIV.

Dosing information of the subjects is presented in Table S2. Because it was possible to achieve a more exact dose with the injection, there is a statistically significant difference between intravenous (median 15.0 mg/kg) and oral (19.6 mg/kg, $P<0.001$) dosing of ethambutol. It was assumed that this difference in dosing had no influence on the bioavailability itself, and a linear correction was performed.[23,24]

In Table 2 and Figure 2, the pharmacokinetic data of the first-line anti-TB drugs after intravenous administration and after oral administration in both the fasted state and the fed state are presented. From one patient, data of timepoints 0.5, 1, 1.5 and 2 h of the intravenous administration of rifampicin and ethambutol were omitted from the analysis, as these samples were drawn from the arm in which the infusion was given.

The high-carbohydrate meal had significant effects on C_{max} and T_{max} of all drugs apart from ethambutol. The decrease of C_{max} in the fed state compared with that in the fasted state was 1.9 mg/L (42%) for isoniazid, 2.4 mg/L (22%) for rifampicin and 4.4 mg/L (10%) for pyrazinamide. T_{max} was significantly delayed for these three drugs. The time to T_{max} for isoniazid almost doubled; T_{max} in the fasted state was 1.3 h and T_{max} in the fed state was 2.5 h. For rifampicin, T_{max} was 2.3 h in the fasted state and 3.6 h in the fed state. T_{max} of pyrazinamide was 1.5 h in the fasted state and 2.8 h in the fed state. The time delays for all three drugs were similar: 1.2, 1.3 and 1.3 h, respectively. Absolute bioavailability in the fasted state and the fed state was 93% and 78% for isoniazid, 87% and 71% for rifampicin and 87% and 82% for ethambutol (Table 2 and Figure 3). The decreases of 15% and 16% in absolute bioavailability of isoniazid and rifampicin, respectively, were statistically significant. Because of the absence of an intravenous injection, we were unable to determine the absolute bioavailability of pyrazinamide. No significant decrease in AUC_{0-24} for pyrazinamide was observed. Finally, none of the pharmacokinetic parameters of ethambutol were affected by concomitant food intake.

Discussion

To the best of our knowledge, this is the first randomized crossover trial in which the influence of food on the absolute

bioavailability and pharmacokinetics of all first-line anti-TB drugs has been investigated quantitatively in treatment-naive TB patients. The high-carbohydrate meal influenced all pharmacokinetic parameters of isoniazid and rifampicin but not those of ethambutol or pyrazinamide.

Table 1. Patient characteristics $N=20$

Characteristic	
Male/female, *n*/*n* (%/%)	12/8 (60/40)
Age (years), mean (SD)	40.5 (19.6)
Bodyweight (kg), mean (SD)	42.9 (6.4)
BMI (kg/m^2), mean (SD)	17.4 (2.6)
Underweight, *n* (%)[a]	14 (70)
Acetylator fast/slow, *n*/*n* (%/%)[b]	15/5 (75/25)
Ethnicity, *n* (%)	
Javanese	17 (85)
Sudanese	2 (10)
Madura	1 (5)
Co-morbidity, *n* (%)	4 (20)
HIV positive	2 (10)
diabetes, type II	2 (10)
Co-medication, *n* (%)[c]	8 (40)

[a]Underweight is defined as BMI <18.5 kg/m^2.
[b]Patients with a calculated half-life of isoniazid ≤2 h were considered fast acetylators; otherwise, they were considered slow acetylators.
[c]Co-medication: acetaminophen (1); acetaminophen/acetylcysteine (2); acetaminophen/acetylcysteine and salbutamol (1); metformin (1); metformin, insulin and simvastatin (1); methylprednisolone (1) and nystatin (1).

The absolute bioavailability of isoniazid, rifampicin and ethambutol has been reported to be 91% ± 10%, 93% and 75%–80%, respectively.[23,25–28] In the fasted state, our data are in line with these earlier findings. Data on absolute bioavailability in the fed state have not been published before, as far as we know. Food decreased the absolute bioavailability of isoniazid and rifampicin by <20% and may therefore be considered not to be clinically relevant according to regulatory guidelines.[17] However, this conclusion may be too conservative. A further reduction of drug exposure in patients prone to low drug exposure may actually increase the risk of poor treatment outcome.[6,29]

For isoniazid and rifampicin, the differences in C_{max} between the fasted state and the fed state do not meet the criteria for bioequivalence.[17] These lowered maximum concentrations may further increase the risk of acquired drug resistance.

Our study is different from other pharmacokinetics studies in TB patients, as we included treatment-naive patients at the start of their treatment. Other trials on the influence of food on the pharmacokinetics of anti-TB drugs were in steady-state: after ≥4 days of treatment[14] or after ≥2 weeks.[12] The latter study did not investigate ethambutol, and neither trial provided data on the absolute bioavailability of isoniazid, rifampicin or ethambutol, as they did not compare their treatments with the gold standard, intravenous treatment. This difference in time of treatment made it difficult to compare our data with those of the earlier studies.[12,14] The differences in AUC_{0-24} of rifampicin can be explained by the fact that auto-induction by

Table 2. Pharmacokinetic data of first-line anti-TB drugs after administration intravenously and orally under fasted and fed conditions

Drug	Intravenously	Orally, fasted	Orally, fed	P^a
Isoniazid				
T_{max} (h), median (IQR)	0.67 (0.58–0.93)	1.28 (0.48–1.52)	2.48 (1.62–3.13)	0.001
C_{max} (mg/L), geometric mean (range)	6.2 (3.4–14.1)	4.5 (2.0–7.5)	2.6 (1.2–5.9)	0.001
AUC_{0-24} (mg·h/L), geometric mean (range)	16.3 (7.8–35.5)	15.6 (7.5–33.0)	13.1 (5.5–36.8)	0.014
F (%), geometric mean (range)	100	92.7 (43.3–172)	77.8 (28.3–192)	0.014
Rifampicin				
T_{max} (h), median (IQR)	1.83 (1.00–2.25)[b]	2.28 (1.50–2.50)	3.60 (2.48–5.02)	<0.001
C_{max} (mg/L), geometric mean (range)	12.3 (7.5–17.3)[b]	10.7 (7.1–15.1)	8.3 (4.1–13.3)	0.002
AUC_{0-24} (mg·h/L), geometric mean (range)	79.6 (36.9–162)	71.8 (36.0–129)	58.2 (29.0–115)	<0.001
F (%), geometric mean (range)	100	87.1 (58.8–131)	70.9 (36.3–110)	<0.001
Ethambutol				
T_{max} (h), median (IQR)	1.25 (1.00–1.55)[b]	3.00 (2.18–3.13)	3.00 (2.52–4.12)	0.136
C_{max} (mg/L), geometric mean (range)	5.3 (2.6–10.4)[b]	2.8 (0.6–6.3)	2.5 (0.8–3.7)	0.126
AUC_{0-24} (mg·h/L), geometric mean (range)	14.4 (8.1–26.8)	15.7 (7.0–24.9)	14.8 (7.3–33.5)	0.681
F (%), geometric mean (range)	100	86.6 (27.4–155)	81.5 (29.5–146)	0.681
Pyrazinamide[c]				
T_{max} (h), median (IQR)		1.50 (1.02–1.98)	2.78 (2.00–4.00)	<0.001
C_{max} (mg/L), geometric mean (range)		44.0 (32.4–66.3)	39.6 (27.6–56.4)	0.001
AUC_{0-24} (mg·h/L), geometric mean (range)		481 (290–668)	468 (278–688)	0.263

[a]Related-samples Wilcoxon signed rank test was used to compare 'orally, fasted' and 'orally, fed' treatments.
[b]C_{max} and T_{max} of rifampicin and ethambutol were unavailable for one patient ($N=19$).
[c]Pyrazinamide is not available as an injectable drug.

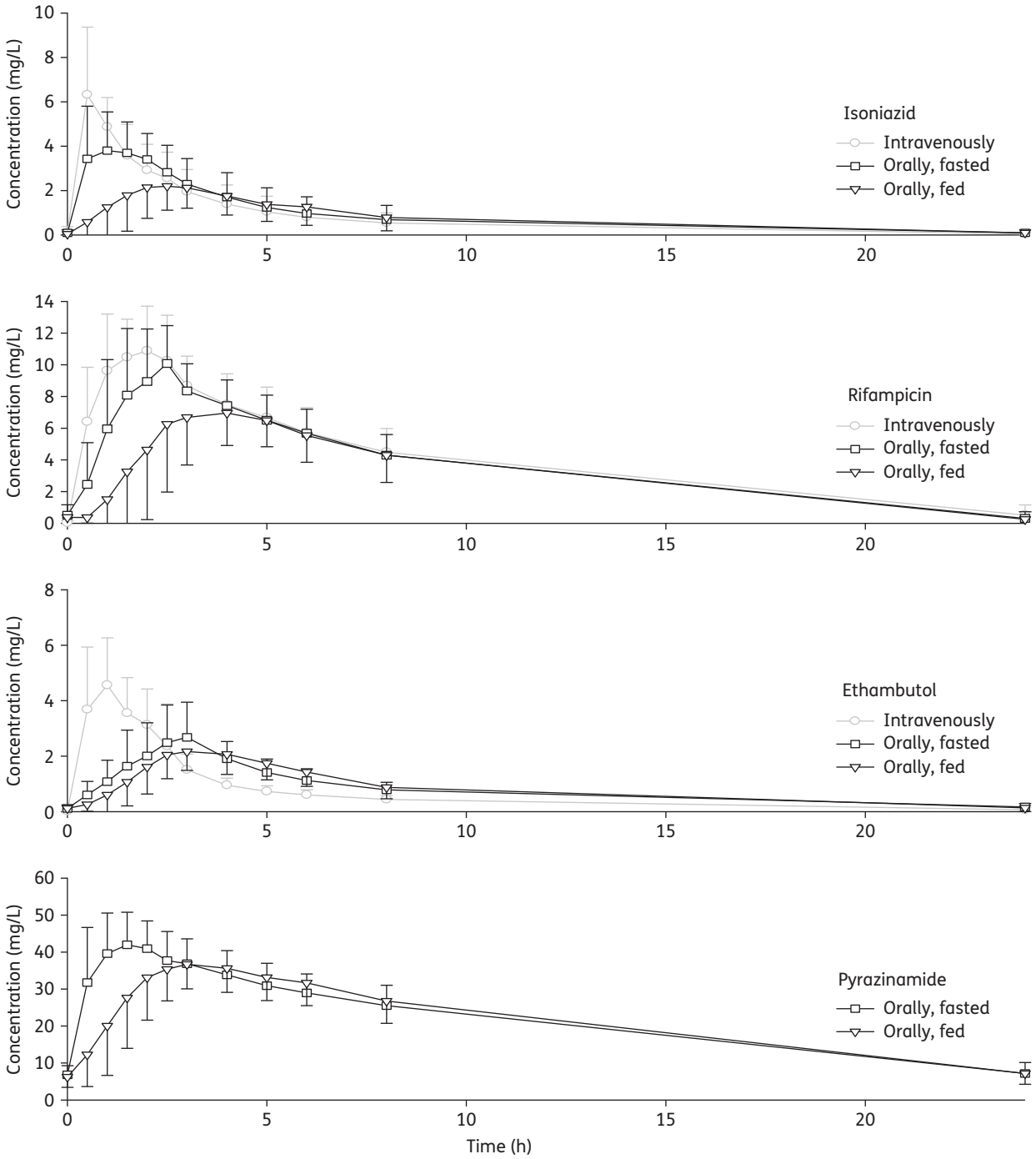

Figure 2. Time-concentration curves (mean and SD) of first-line anti-TB drugs.

rifampicin is not maximized until 20–40 days of treatment and our study was performed in the first 3 days of treatment.[27,30]

As for many TB patients who start drug treatment, the subjects in this study were actually really ill. The mean BMI of the subjects was 17.4 ± 2.6 kg/m^2, and the majority of subjects were underweight. Most (79%) of these low-BMI subjects showed low albumin levels, indicating that subjects were malnourished. Malnourished people may be underdosed, as a low BMI approximates to fat mass but also to low weight and fat-free mass.[31] A poor nutritional status in addition to inflammation might affect the intestinal mucosa, reducing drug absorption. It might delay gastric emptying, alter the gastric pH and change bio-distribution of the drugs.[15] On the other hand, low serum albumin might be beneficial for rifampicin, as the drug is highly protein bound, resulting in a higher free fraction of the drug.[15]

There are several limitations to this study. Free drug concentrations were not measured. This measure would have been more informative, as perhaps high free fractions of relatively low total

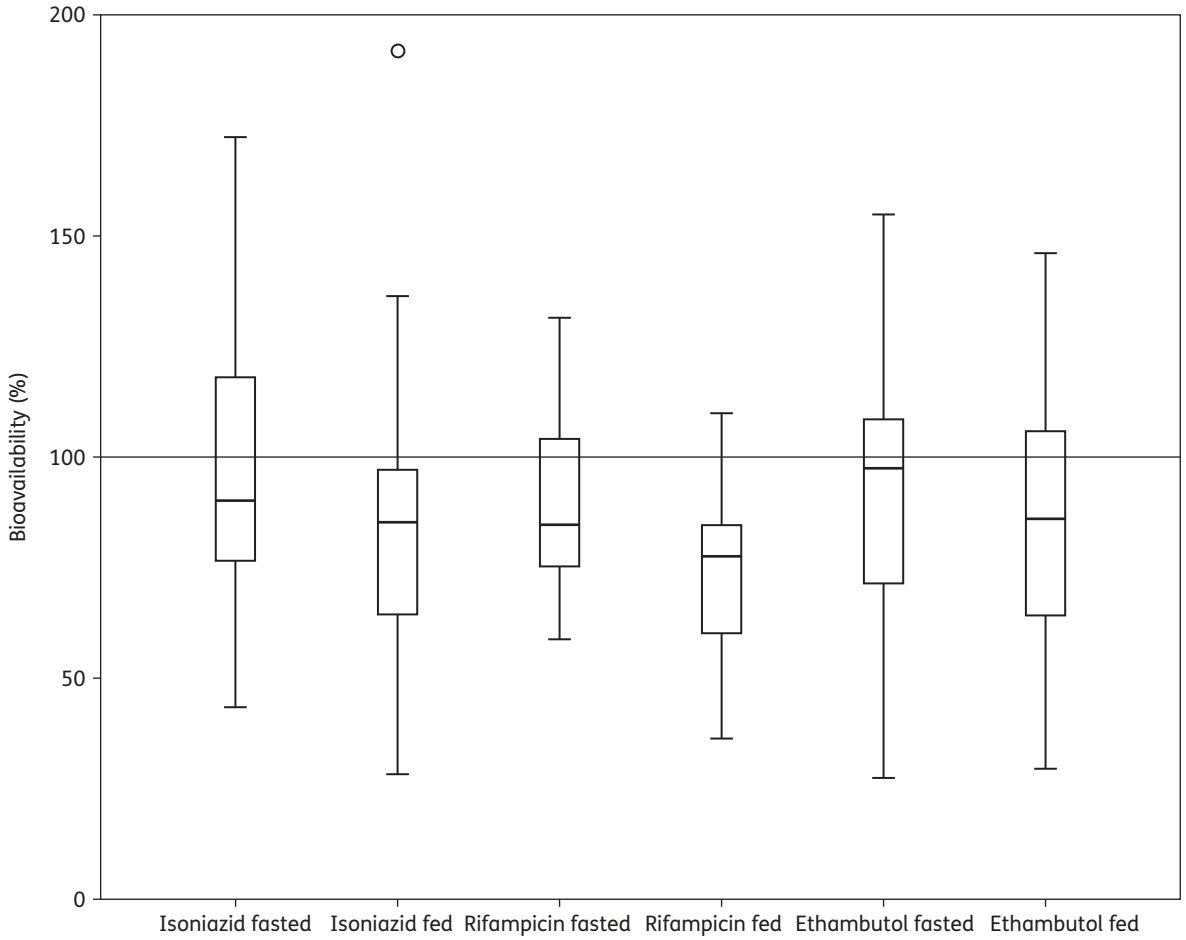

Figure 3. Median bioavailability of isoniazid, rifampicin and ethambutol under fasted and fed conditions.

Table 3. Number of patients with exposure lower than reference values

Drug	Intravenously	Orally, fasted	Orally, fed
Isoniazid, *n*/*N*			
patients with C_{max} ≤8.8 mg/L	16/20	20/20	20/20
patients with AUC_{0-24} ≤52 mg·h/L	20/20	20/20	20/20
Rifampicin, *n*/*N*			
patients with C_{max} ≤6.6 mg/L	0/19[a]	0/20	4/20
patients with AUC_{0-24} ≤13 mg·h/L	0/20	0/20	0/20
Pyrazinamide, *n*/*N*[b]			
patients with C_{max} ≤58.3 mg/L		19/20	20/20
patients with AUC_{0-24} ≤363 mg·h/L		2/20	4/20

[a]C_{max} of rifampicin was unavailable for one patient (N=19).
[b]Pyrazinamide is not available as an injectable drug.

concentrations could still have resulted in a favourable drug exposure.[15] Actual pharmacokinetic/pharmacodynamic ratios could not be calculated, because only breakpoints were available and not actual MICs. Because of the absence of an intravenous formulation of pyrazinamide, we were unable to determine the absolute bioavailability of pyrazinamide.

Recently, poor treatment outcome has been linked with low TB drug exposure, and it was shown that risk of treatment failure was almost 9-fold higher in patients with low drug exposure based on AUC compared with patients with higher drug exposure.[6] Sufficient drug exposure in the first days of treatment is important to reduce bacterial load rapidly.[32,33] Pasipanodya *et al*.[6] showed that to

achieve a favourable outcome, in order of importance, AUC_{0-24} of pyrazinamide, rifampicin and isoniazid should be >363, >13 and >52 mg·h/L, respectively. Pyrazinamide AUC_{0-24} was sufficiently high in the majority of patients with respect to long-term outcome. Eighteen (90%) and 16 (80%) patients in the fasted and fed groups, respectively, showed sufficiently high AUC_{0-24} (Table 3). The observed AUC_{0-24} of rifampicin was sufficient in all patients, regardless of fasted or fed state. It is, however, striking to see that none of the AUC_{0-24} values of isoniazid met this target to predict a favourable long-term outcome.

It was also shown that low C_{max} preceded acquired drug resistance.[6] Therefore, there is a need to safeguard adequate C_{max}/MIC ratios. Only in one patient in the fasted state was the C_{max} of pyrazinamide sufficiently high to prevent acquired drug resistance (Table 3).[6] The majority of patients had sufficient C_{max} of rifampicin. For isoniazid, again none of the patients, whether fasted or fed, achieved a C_{max} that was high enough.

The magnitude of these pharmacokinetic findings underlines the importance of the evaluation of drug exposure in relation to the drug susceptibility of the pathogen.[34] Because actual MIC values were unknown, it remains difficult to understand the impact of the observed differences in AUC_{0-24} and C_{max} between the fasted state and the fed state for each individual patient.

This study has shown that food decreases absolute bioavailability and C_{max} of isoniazid and rifampicin. More than the difference between the fed state and the fasted state, the very large ranges that were shown for AUC_{0-24} and absolute bioavailability worried us. Between the highest and lowest values within a group, a factor of 2.2, for fasted rifampicin, to 6.8, for fed isoniazid, was observed. Therefore, the effect of food intake contributed only partly to the large inter- and intra-individual pharmacokinetic variability.[35]

Inter-individual variability caused by comorbidities such as HIV and diabetes mellitus or pharmacogenetics of N-acetyltransferase 2 (NAT2), intra-individual variability such as the auto-inducing activity of rifampicin and variability of MICs all have their impact on the pharmacokinetic/pharmacodynamic ratio. In spite of that, we emphasize that further reduction of drug exposure due to concomitant food in patients prone to low drug exposure may increase the risk of poor treatment outcome.[6,29]

Optimizing drug exposure of first-line drugs by means of therapeutic drug monitoring including helpful tools such as optimal sampling strategies[36,37] and dried blood spot analysis[38] or higher dosing of rifampicin[39,40] have recently been the subject of investigation. Compared with the introduction of new compounds for first-line treatment of TB in an effort to shorten drug therapy,[41–44] the optimization of the current treatment may not be inferior. With higher doses of rifampicin and therapeutic drug monitoring to safeguard drug exposure and shortened treatment may be pursued.

Taking into account all these initiatives, we propose a randomized controlled trial including drug exposure and actual MIC values for TB strains in comparison with standard care. Long-term follow-up should be performed to fully understand the true impact of the optimization of current first-line treatment.

In conclusion, this study showed that food intake decreased absolute bioavailability, AUC_{0-24} and C_{max} of isoniazid and rifampicin in treatment-naive TB patients starting with anti-TB treatment. C_{max} of pyrazinamide was decreased by a high-carbohydrate meal, but AUC_{0-24} was not. The pharmacokinetics of ethambutol were unaffected by food intake. Absolute bioavailability in the fed state met the criteria for bioequivalence. Nevertheless, the decreased drug exposure in fed patients may place them at greater risk for poor treatment outcome or acquired drug resistance.

Acknowledgements

Our high appreciation is addressed to the patients for their participation in this study and to the staff at the governmental chest clinic/Balai Pengobatan Penyakit Paru-paru (BP4) Yogyakarta and Sardjito General Hospital for their cooperation. The technicians of the lab of the Department of Clinical Pharmacy and Pharmacology (University Medical Center Groningen) are greatly acknowledged for the analysis of plasma samples.

Funding

This work was supported by the Directorate of General Higher Education (DGHE) of Indonesia.

Transparency declarations

None to declare.

Author contributions

Concept and design: J.-W. C. A., M. G. G. S., A. M. I. S., Y. S. and T. S. v. d. W. Performance and analysis of the study: A. M. I. S., M. G. G. S., Y. W. S., S. and Y. S. Data interpretation: M. G. G. S., A. M. I. S., J.-W. C. A., Y. S. and T. S. v. d. W. Drafting the manuscript for important intellectual content: M. G. G. S., A. M. I. S., J.-W. C. A., Y. S., Y. W. S., S., J. G. W. K. and T. S. v. d. W.

Supplementary data

Supplementary data, including Tables S1 and S2, are available at *JAC* Online (http://jac.oxfordjournals.org/).

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