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IMPACT OF FOOD ON THE PHARMACOKINETICS OF FIRST-LINE ANTI-TB DRUGS IN TREATMENT-NAÏVE TB PATIENTS: A RANDOMIZED CROSS-OVER TRIAL

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ABSTRACT

Background

Concomitant food influences pharmacokinetics of first-line anti-tuberculosis drugs in healthy volunteers. However, in treatment-naïve TB patients who are starting with drug treatment, data on the influence of food intake on the pharmacokinetics are absent.

Objectives

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 crossover pharmacokinetic study was conducted in treatment-naïve adults with drug-susceptible TB. They received isoniazid, rifampicin and ethambutol intravenously and oral pyrazinamide on day one, followed by oral administration of these drugs in fasted and fed condition on the two consecutive days. Primary outcome was the bioavailability while fasting and with concomitant food (NCT02121314).

Results

Twenty subjects completed the study protocol. Absolute bioavailability in fasted and fed state for isoniazid was 93% and 78%, for rifampicin 87% and 71% and for ethambutol 87% and 82%. Food decreased absolute bioavailability of both isoniazid and rifampicin by 15% and 16%. Pyrazinamide AUC_{0-24h} was comparable for fasted (481 mg*h/L) and fed state (468 mg*h/L). The maximum concentration of isoniazid, rifampicin and pyrazinamide was lowered by food by 44%, 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-naïve TB patients. In patients prone to low drug exposure, this may further compromise treatment efficacy and increase risk of acquired drug resistance.

INTRODUCTION

Tuberculosis is the infectious disease with the second highest morbidity and mortality by one single pathogen around the world. In 2013 an estimated 9.0 million people became TB-infected and 1.5 million people died due to TB.¹ First-line treatment of TB consists of isoniazid, rifampicin, pyrazinamide and ethambutol during the first two months, continuing with isoniazid and rifampicin for another four months.^{2,3} Reported treatment success rates range from 60 to 87% depending on comorbidity.^{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 two 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 has an ambivalent impact on drug therapy. Food makes patients less vulnerable to nausea and vomiting, possibly resulting in a decrease of 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. showed that both AUC and C_{max} of isoniazid were decreased by food.¹¹ C_{max} of rifampicin and ethambutol were decreased by food. Pyrazinamide absorption was not influenced by food. However, the majority of these data was obtained in healthy volunteers¹¹ and not in TB patients.^{12,13} One study in TB patients after two weeks of treatment showed that a high carbohydrate diet decreased AUC_{0-8h} and C_{max} of isoniazid.¹² Recently, it was shown that food reduced C_{max} and AUC_{0-10h} of all first-line anti-TB drugs in TB patients at least after four days of treatment.¹⁴ Pharmacokinetics of first-line drugs in treatment-naïve patients may be different from TB patients who are on anti-TB therapy for some time because of differences in severity of disease, malnutrition and hypoalbuminemia.^{15,16} Furthermore, in treatment-naïve 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 patients from nausea, vomiting and possible treatment failure, 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 absolute bioavailability of isoniazid, rifampicin, ethambutol and pyrazinamide in treatment-naïve TB patients under fasting conditions and with food on the first three days of treatment.

PATIENTS AND METHODS

Study Design and Population

This was a prospective randomized crossover 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 at least 12 subject 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.

Newly diagnosed, treatment-naïve TB patients aged at least 18 years 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 which 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 three 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 1). All subjects fasted overnight for the three study days. For the fasted treatment, they continued to fast until 2h after drug dosing. For

Table 1. Study design

	Fasted day 2, fed day 3	Fed day 2, fasted day 3
day 1		
t = 0h	isoniazid 5 mg/kg iv rifampicin 10 mg/kg iv ethambutol 15 mg/kg iv pyrazinamide 25 mg/kg orally ^a	
blood sampling	0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8h after dosing	
day 2		
t = - 0.50h	-	high-carbohydrate meal
t = 0h	FDC orally	FDC orally
t = 2h	high-carbohydrate meal	-
blood sampling	0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8h after dosing	
day 3		
t = - 0.50h	high-carbohydrate meal	-
t = 0h	FDC orally	FDC orally
t = 2h	-	high-carbohydrate meal
blood sampling	0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8h after dosing	

iv, intravenously, FDC, fixed drug combination containing 75/ 150/ 400/ 275 mg of isoniazid, rifampicin, ethambutol and pyrazinamide.

^aPyrazinamide is unavailable as injectable drug.

the fed treatment, they consumed a high-carbohydrate breakfast containing 600 Kcal 0.5h before dosing. Primary endpoints were absolute bioavailability (F) and AUC from time of administration to 24h after (AUC_{0-24h}). Secondary endpoints were C_{max} and its corresponding time (T_{max}).

Subjects were dosed on their pre-study weights according to the WHO guidelines, i.e. 5mg/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, UMCG, 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 minutes. Rifampicin and ethambutol were infused in 2 hours. Pyrazinamide was administered as 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 (AMS).

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

Pharmacokinetic analysis

Serial blood samples were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8h after dosing. Samples were centrifuged and stored at -80 °C until they were analyzed. Plasma samples were analyzed by LC-MS/MS, as previously described.¹⁸⁻²⁰ The technicians who analyzed the samples were blinded to group assignment.

C_{max} and T_{max} were derived from the plasma concentration data. The AUC_{0-24h} was calculated using the log-linear trapezoidal rule in MW\Pharm (version 3.60, Mediware, Groningen, The Netherlands). Concentrations at time points 0 of day 2 and 3 also served as C_{24} of days 1 and 2. C_{24} of day 3 was calculated using the formula $C_{24} = C_{max} * e^{-\beta * (24 - T_{max})}$ 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 $(AUC_{0-24h, \text{fasted or fed}} / AUC_{0-24h, \text{intravenously}}) * (Dose_{\text{intravenously}} / Dose_{\text{orally}})$.

Patients with calculated half-life of isoniazid \leq 2h were considered fast acetylators, otherwise they were considered slow acetylators.⁷

Statistical analysis

For the patient characteristics, means are reported \pm standard deviation (SD). C_{max} , AUC_{0-24h} 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 Corp., 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 from the study and replaced by inclusion of another subject (Figure 1). Patient characteristics are presented in Table 2. The mean body mass index (BMI) was 17.4 ± 2.56 kg/m² showing that a large proportion of the study population (70%) was underweight (i.e. BMI < 18.5 kg/m²).^{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 3. Due to the fact that it was possible to dose more exactly with the injection, there is a statistically significant difference in 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 linear correction was performed.^{23,24}

Table 2. Patient characteristics

Characteristic	Subjects (n=20)
Sex male/female (%)	12/8 (60/40)
Age, years mean (SD)	40.5 (19.6)
Bodyweight, kg mean (SD)	42.9 (6.4)
Body mass index, kg/m ² mean (SD)	17.4 (2.6)
Underweight, n (%) ^a	14 (70)
Acetylator fast/slow (%) ^b	15/5 (75/25)
Ethnicity	
Javanese, n (%)	17 (85)
Sudanese, n (%)	2 (10)
Madura, n (%)	1 (5)
Comorbidity, n (%)	4 (20)
HIV positive, n (%)	2 (10)
Diabetes, type II, n (%)	2 (10)
Comedication, n (%) ^c	8 (40)

^aUnderweight is defined as BMI < 18.5 kg/m². ^bPatients with calculated half-life of isoniazid ≤ 2 h were considered fast acetylators, otherwise they were considered slow acetylators. ^cComedication: acetaminophen (1), acetaminophen/ acetylcysteine (2), acetaminophen / acetylcysteine and salbutamol (1), metformine (1), metformine, insulin and simvastatin (1), methylprednisolone (1), nystatin (1).

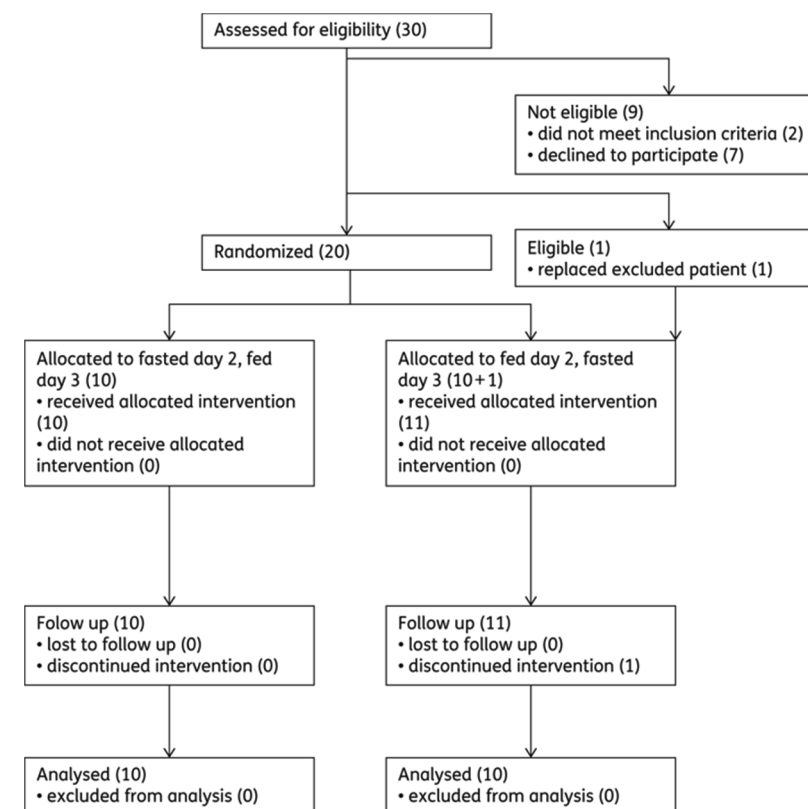


Figure 1. Study design.

*Number of patients in parentheses

In Table 4 and Figure 2, the pharmacokinetic data of the first-line anti-TB drugs after intravenous administration and after oral administration in both fasting and fed state are presented. From one patient, data of time points 0.5, 1, 1.5 and 2h of the intravenous administration of rifampicin and ethambutol were omitted from the analysis, as these samples were drawn from the same arm as infusion was given.

T_{max} , time of maximum concentration in h, is presented as median (interquartile range (IQR)), C_{max} , maximum concentration in mg/L, AUC_{0-24h} , area under time-concentration curve 0-24h in mg*h/L, and F, absolute bioavailability in %, are presented as geometric mean (range).

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 fasting state was 1.3h and T_{max} in fed state was 2.5h. For rifampicin, T_{max} was 2.3h in fasted and 3.6h in fed state. T_{max} of pyrazinamide was 1.5h in

Table 3. Dosing information

Drug	Intravenously day 1	Orally day 2-3	P ^a
Isoniazid			
dose, mg/kg	5.0 (5.0-5.0)	5.4 (4.2-6.0)	0.234
dose, mg	208 (150-275)	225 (150-300)	0.136
Rifampicin			
dose, mg/kg	10.0 (9.9-10.0)	10.7 (8.3-12.0)	0.141
dose, mg	415 (300-550)	450 (300-600)	0.234
Ethambutol			
dose, mg/kg	15.0 (15.0-15.3)	19.6 (15.3-22.0)	<0.001
dose, mg	623 (450-825)	825 (550-1100)	<0.001
Pyrazinamide	Orally ^b		
dose, mg/kg	25.5 (22.7-29.8)	28.6 (22.2-32.0)	0.040
dose, mg	1000 (750-1500)	1200 (800-1600)	0.046

Data are presented as median (range).

^a Related Samples Wilcoxon Signed Rank Test was used to compare intravenous and oral dosing. ^b Pyrazinamide is unavailable as injectable drug.

Table 4. Pharmacokinetic data of first-line anti-TB drugs after intravenous administration and orally in fasted and fed condition.

Drug	Intravenously	Orally, fasted	Orally, fed	P ^a
Isoniazid				
T _{max} median (IQR, h)	0.67 (0.58-0.93)	1.28 (0.48-1.52)	2.48 (1.62-3.13)	0.001
C _{max} geometric mean (range, mg/L)	6.2 (3.4-14.1)	4.5 (2.0-7.5)	2.6 (1.2-5.9)	0.001
AUC _{0-24h} geometric mean (range, mg [*] h/L)	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} median (IQR, h)	1.83 (1.00-2.25) ^b	2.28 (1.50-2.50)	3.60 (2.48-5.02)	< 0.001
C _{max} geometric mean (range, mg/L)	12.3 (7.5-17.3) ^b	10.7 (7.1-15.1)	8.3 (4.1-13.3)	0.002
AUC _{0-24h} geometric mean (range, mg [*] h/L)	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} median (IQR, h)	1.25 (1.00-1.55) ^b	3.00 (2.18-3.13)	3.00 (2.52-4.12)	0.136
C _{max} geometric mean (range, mg/L)	5.3 (2.6-10.4) ^b	2.8 (0.6-6.3)	2.5 (0.8-3.7)	0.126
AUC _{0-24h} geometric mean (range, mg [*] h/L)	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} median (IQR, h)		1.50 (1.02-1.98)	2.78 (2.00-4.00)	< 0.001
C _{max} geometric mean (range, mg/L)		44.0 (32.4-66.3)	39.6 (27.6-56.4)	0.001
AUC _{0-24h} geometric mean (range, mg [*] h/L)		481 (290-668)	468 (278-688)	0.263

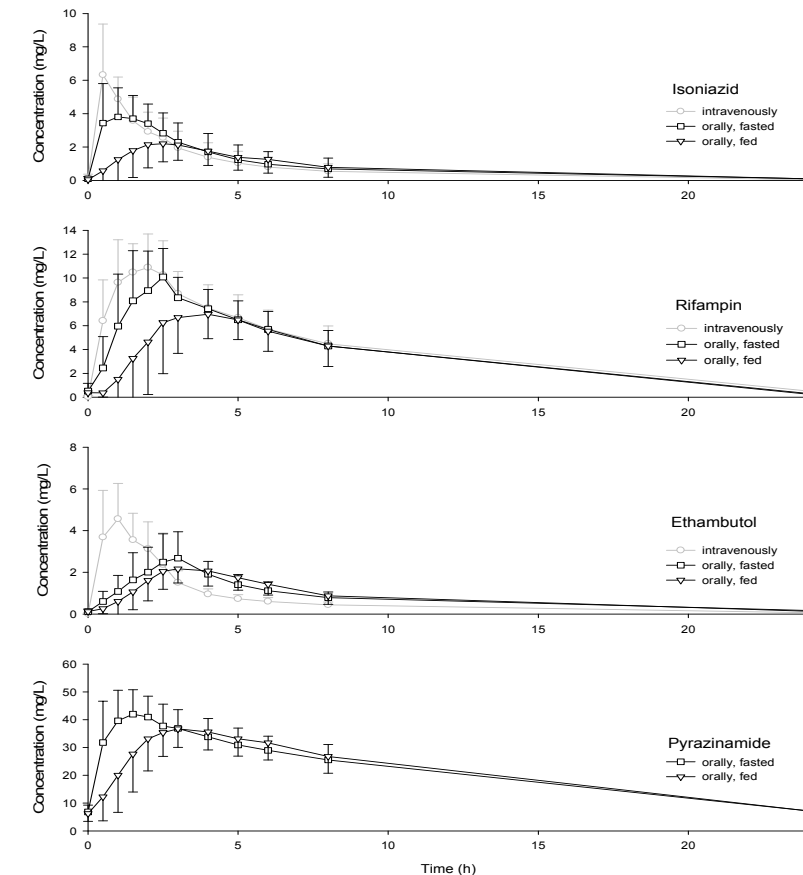
^a Related Samples Wilcoxon Signed Rank Test was used to compare orally, fasted and orally, fed treatment. ^b C_{max} and T_{max} of rifampicin and ethambutol were unavailable for one patient (n=19). ^c Pyrazinamide is not available as injectable drug.

fasted and 2.8h in fed state. The time delays for all three drugs were similar, 1.2h, 1.3h and 1.3h respectively.

Absolute bioavailability in fasted and fed state for isoniazid was 93% and 78%, for rifampicin 87% and 71% and for ethambutol 87% and 82% (Table 4 and Figure 3). The 15% and 16% decrease in absolute bioavailability of isoniazid and rifampicin, respectively, were statistically significant. Due to the absence of an intravenous injection, we were unable to determine the absolute bioavailability of pyrazinamide. No significant decrease in AUC_{0-24h} 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

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

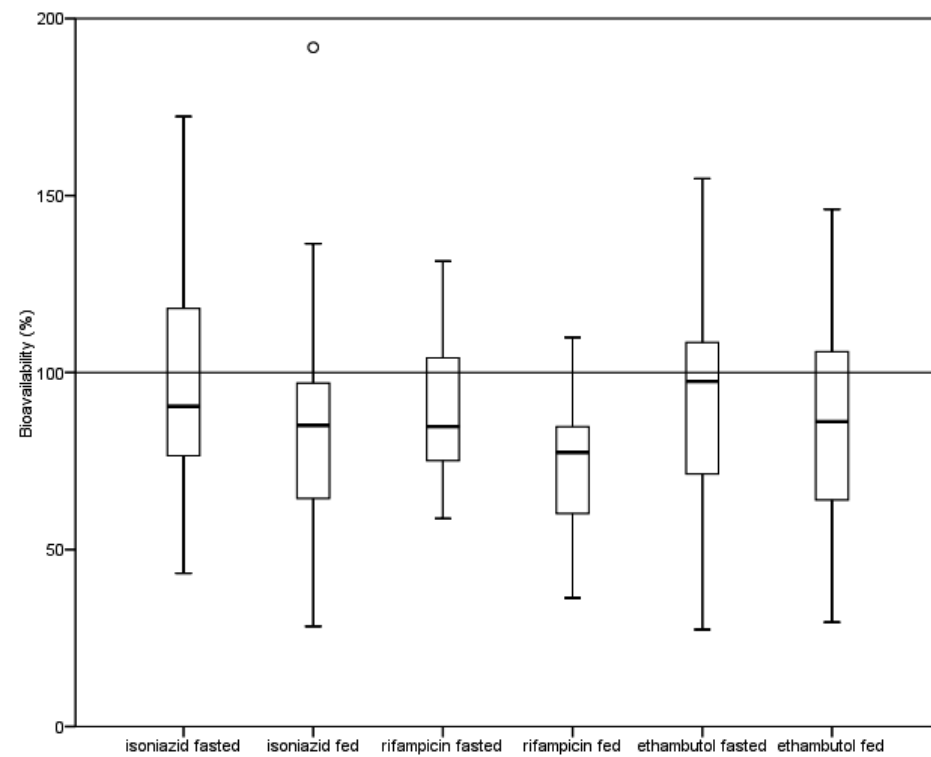


Figure 3. Median bioavailability of isoniazid, rifampicin and ethambutol in fasted and fed condition.

Table 5. Number of patients with exposure lower than reference values.

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

C_{max} , maximum concentration in mg/L and AUC_{0-24h} , area under time-concentration curve 0-24h in mg*h/L.

^a C_{max} of rifampicin was unavailable for one patient (n=19). ^bPyrazinamide is not available as injectable drug.

has been investigated quantitatively in treatment-naïve TB patients. The high-carbohydrate meal influenced all pharmacokinetic parameters of isoniazid and rifampicin but not of ethambutol or pyrazinamide.

The absolute bioavailability of isoniazid, rifampicin and ethambutol has been reported to be $91 \pm 10\%$, 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 fed state have not been published before as far as we know. Food decreased absolute bioavailability of isoniazid and rifampicin by less than 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 fasted and fed state do not meet the criteria for bioequivalence.¹⁷ This may further increase the risk of acquired drug resistance.

Our study is different from other pharmacokinetics studies in TB patients as we included treatment-naïve patients at the start of their treatment. Other trials on the influence of food on pharmacokinetics of anti-TB drugs were in steady state: after at least 4 days of treatment,¹⁴ or at least two weeks.¹² The latter 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_{0-24h} of rifampicin can be explained by the fact that auto-induction of rifampicin is not maximized until 20-40 days of treatment and our study was performed in the first three days of treatment.^{27,30}

As for many TB patients who start with drug treatment, the subjects in this study were actually really ill. The mean BMI of the subjects was $17.4 (\pm 2.56)$ kg/m² 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 The 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 would have been more informative as perhaps high free fractions of relative low total 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. Due to 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 on treatment failure was almost nine fold higher in patients with low drug exposure based on AUC compared to 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. showed that to achieve a favourable outcome, in order of importance, AUC_{0-24h} of pyrazinamide, rifampicin and isoniazid should be over 363, 13 and 52 mg*h/L respectively.⁶ Pyrazinamide AUC_{0-24h} 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 group showed sufficiently high AUC_{0-24h} (Table 5). Observed AUC_{0-24h} of rifampicin were sufficient in all patients, regardless of fasted or fed state. It is however striking to see that none of the AUC_{0-24h} of isoniazid met this target to predict a favourable long-term outcome.

Low C_{max}/MIC ratios was also shown to precede acquired drug-resistance,⁶ and therefore, there is a need to keep C_{max}/MIC ratios adequate. Only in one patient in the fasted state, was the C_{max} of pyrazinamide was sufficiently high to prevent acquired drug resistance (Table 5).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_{0-24h} and C_{max} between fasted and 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 and fasted state, the very large ranges that were shown for AUC_{0-24h} and absolute bioavailability worried us. Between the highest and lowest value within a group, a factor 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 like 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 worried us, 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 (TDM) including helpful tools like optimal sampling strategies^{36,37} and dried blood spot analysis³⁸ or higher dosing of rifampicin^{39,40} have recently been 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 optimization of the current treatment may not be inferior. With higher doses of rifampicin and TDM to safeguard drug exposure, shortened treatment may be pursued.

Taken into account all these initiatives, we propose a randomized controlled trial including drug exposure, actual MIC values of 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.

CONCLUSION

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

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