The pharmacokinetics of enteral antituberculosis drugs in patients requiring intensive care

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Background. There is a paucity of data on the pharmacokinetics of fixed-dose combination enteral antituberculosis treatment in critically ill patients.

Objectives. To establish the pharmacokinetic profile of a fixed-dose combination of rifampicin, isoniazid, pyrazinamide and ethambutol given according to weight via a nasogastric tube to patients admitted to an intensive care unit (ICU).

Methods. We conducted a prospective, observational study on 10 patients (mean age 32 years, 6 male) admitted to an ICU and treated for tuberculosis (TB). Serum concentrations of the drugs were determined at eight predetermined intervals over 24 hours by means of high-performance liquid chromatography.

Results. The therapeutic maximum plasma concentration (C_{max}) for rifampicin at time to peak concentration was achieved in only 4 patients, whereas 2 did not achieve therapeutic C_{max} for isoniazid. No patient reached sub-therapeutic C_{max} for pyrazinamide (6 were within and 4 above therapeutic range). Three patients reached sub-therapeutic C_{max} for ethambutol, and 6 patients were within and 1 above the therapeutic range. Patients with a sub-therapeutic rifampicin level had a higher mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score ($p=0.03$) and a lower estimated glomerular filtration rate (GFR) ($p=0.03$).

Conclusions. A fixed-dose combination tablet, crushed and mixed with water, given according to weight via a nasogastric tube to patients with TB admitted to an ICU resulted in sub-therapeutic rifampicin plasma concentrations in the majority of patients, whereas the other drugs had a more favourable pharmacokinetic profile. Patients with a sub-therapeutic rifampicin concentration had a higher APACHE II score and a lower estimated GFR, which may contribute to suboptimal outcomes in critically ill patients. Studies in other settings have reported similar proportions of patients with 'sub-therapeutic' rifampicin concentrations.

The global increase in the incidence of tuberculosis (TB), especially in conjunction with the HIV pandemic, has resulted in an increased number of hospital admissions due to TB.[1] Previous studies have shown that approximately 1.5% of hospitalised adults with active TB develop respiratory failure requiring admission to an intensive care unit (ICU).[2,3] Mortality among these patients can be as high as 65%.[4]

A myriad of factors may influence pharmacokinetics in patients admitted to the ICU. Drug absorption is generally decreased. Tarling and co-workers found sub-therapeutic plasma levels of enterally administered paracetamol, and showed that gastric emptying time varied significantly between patients.[5] Patients in the ICU often have increased vascular permeability secondary to cytokine release, as well as hypo-albuminaemia, which alter the volume of distribution.[6] Furthermore, drug metabolism and excretion may be profoundly affected by hepatic and renal dysfunction.[6]

There are also certain factors specific to patients with TB in the ICU that may influence pharmacokinetics, the chief of which is that patients are fed continuously. Drugs are therefore not administered on an empty stomach, as is recommended for some anti-TB drugs to achieve optimal absorption.[7] Interestingly, evidence suggests that the functional absorptive area of the intestines of patients with tuberculosis is also decreased when compared with healthy volunteers, which in turn results in decreased absorption.[8]

There are currently no published studies on absorption rates and pharmacokinetic patterns of anti-TB drugs in patients requiring intensive care. The aim of this pilot study was therefore to assess whether therapeutic plasma drug concentrations are achieved following nasogastric administration of first-line fixed-dose combination standard anti-TB treatment in critically ill patients.

Methods

Study design and patient selection

All adult patients (≥18 years) admitted between April 2010 and June 2011 to the Medical ICU of Tygerberg Academic Hospital (TBAH), Western Cape, South Africa, and treated for pulmonary tuberculosis for at least 7 days were candidates for this prospective observational study, provided a nasogastric tube was *in situ* on the day of enrolment. Exclusion criteria included the use of concomitant intravenous (IV) TB treatment, an estimated glomerular filtration rate (GFR) of <50 ml/min, evidence of hepatic dysfunction (alanine transaminase (ALT) or aspartate transaminase (AST) >3 times the upper limit of normal), bowel surgery in the preceding 7 days, and pregnancy. TBAH is a 1 200-bed tertiary hospital, one of two academic referral centres in the Cape Town area, and renders a service to a population of approximately 1.5 million. In 2010 the incidence of pulmonary TB in this population was 981 cases per 100 000.[9] The Health Research Ethics Committee of Stellenbosch University approved the study. Written informed consent was obtained by proxy on enrolment.

Clinical parameters and general special investigations

Apart from general demographic information, the number of days on treatment and the presence of co-morbid illnesses and/or sepsis were actively sought.[10] Acute Physiology and Chronic Health Evaluation (APACHE) II scores,[11] the presence of bowel sounds and co-administration of sedatives and inotropic agents were documented on enrolment. As per standard procedure in the unit, 4-hourly gastric aspirates were performed on patients receiving enteral feeds (to measure residual volume). Serum creatinine, bilirubin, ALT and AST were measured, and the GFR calculated according to the Cockcroft and Gault estimation.[12]

Administration of antituberculosis medication

All patients received Rimstar 4-FDC (Sandoz, Kempton Park, South Africa), which is a combination of rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg and ethambutol 275 mg. The ideal body weight for each patient was calculated according to the Devine formula,[13] and patients were given 2 tablets for weight <37 kg, 3 for weight 38 - 54 kg, 4 for weight 55 - 70 kg and 5 for weight >70 kg. The tablets were crushed and given with 20 ml tap water via a nasogatric tube.

Plasma drug concentration sampling and analysis

Plasma rifampicin, isoniazid and pyrazinamide concentrations were measured before and 0.5, 1.25, 2.25, 3.5, 5.0, 12 and 24 hours after drug administration. Blood was collected into 10 ml ethylenediaminetetra-acetic acid (EDTA)-containing blood sampling tubes, embedded into crushed ice immediately and transported to the bio-analytical laboratory within 1 hour.

Rifampicin concentrations were measured by means of precipitation of plasma proteins with a mixture of acetonitrile and methanol. Quantification was performed by a high-performance liquid chromatography (HPLC) method in conjunction with triple quadrupole mass spectrometry (MS/MS) detection (quantification range 1 - 15 µg/ml). Isoniazid levels were assessed by the precipitation of plasma proteins with 10% trichloroacetic acid (TCA) solution, followed by derivatisation with 1% cinnamaldehyde and ultraviolet (UV) detection at 340 nm (quantification range 1 - 25 µg/ml). In the case of pyrazinamide, precipitation of plasma proteins was achieved with 10% TCA solution; 30 µl of the supernatant was injected into the HPLC with UV detection at 269 nm (quantification range 10 - 150 µg/ml). Ethambutol levels were measured by means of precipitation of plasma proteins with acetonitrile at a ratio of plasma/organic solvent of 1:3. Quantification was performed by an HPLC method in conjunction with MS/MS (quantification range 1 - 15 µg/ml). The acetylator status of patients for the metabolism of isoniazid was determined by means of phenotyping, and patients were categorised as slow, intermediate or fast acetylators according to accepted criteria.[14-17]

Pre-dose concentration, maximum plasma concentration (C_{max}), time to peak concentration (t_{max}) and area under the curve for 24 hours (AUC_{0-24h}) were documented, and concentrations compared with data from healthy volunteers in the literature.[7]

Statistical aspects

Descriptive statistics and Fisher's exact tests (where indicated) were performed on dichotomous categorical variables, and *t*-tests on continuous data. Unless stated otherwise, data are displayed as means and standard deviations (SDs).

Results

Patients

Over a 1-year period 35 patients admitted to the medical ICU were screened, and the first 10 patients (32 (SD 12) years, 6 male) who fulfilled the criteria entered into the study. Of these, 1 patient died in the ICU. The mean ICU admission duration was 19.9 days (range 6 - 33 days), and the mean APACHE II score was 21 (SD 6). Indications for ICU admission included respiratory failure (*n*=8), life-threatening haemoptysis (*n*=1) and a drug overdose (*n*=1). At the time of blood sampling, all patients required ventilatory support, either invasive (*n*=9) or non-invasive (*n*=1). Only 1 patient had feeding interrupted at the time of inclusion and 9 received enteral feeding. None of the study patients had large residual volumes at 4 hours after feeds (mean volume 2.22 ml), which suggested that gastric emptying was adequate.

Measured plasma concentrations

Therapeutic C_{max} for rifampicin at t_{max} was achieved in only 4 patients (Table 1). Only 2 patients did not achieve therapeutic C_{max} for isoniazid, and 5 patients had C_{max} levels above the therapeutic range. No patient reached sub-therapeutic C_{max} for pyrazinamide, 6 patients falling within and 4 above the therapeutic range. Three patients reached sub-therapeutic C_{max} for ethambutol, and 6 patients were within and 1 above the therapeutic range. The acetylator status was slow and indeterminate in the 2 cases in which sub-therapeutic isoniazid concentrations were measured (Table 1). The plasma concentrations over time (AUC_{0-24h}) for the various drugs are given in Figs 1 - 4.

Patients with sub-therapeutic rifampicin plasma levels had a significantly higher APACHE II score and a lower estimated GFR than patients with therapeutic levels (Table 2). The low patient numbers precluded similar comparison with the other drugs.

Discussion

To the best of our knowledge, this is the first study to investigate the pharmacokinetic profile of a fixed-dose combination of rifampicin, isoniazid, pyrazinamide and ethambutol given according to weight via a nasogastric tube to patients with TB admitted to the ICU. In this pilot study we found sub-therapeutic rifampicin levels in more than half of all cases. The other drug components, pyrazinamide in particular, had more favourable pharmacokinetic profiles. Patients with a sub-therapeutic plasma rifampicin level had a significantly higher APACHE II score and lower estimated GFR when compared with patients with therapeutic concentrations, but similar gastric emptying.

Rifampicin and isoniazid remain the cornerstone drugs in the treatment of tuberculosis and combination treatment is essential to reduce drug resistance.[18] Of the four first-line drugs, only rifampicin is available as an IV injection in much of the developing world. The pharmacokinetic profile of anti-TB drugs has been extensively investigated outside the intensive care environment. It has been shown that there is a dose-dependent relationship with clinical outcomes in respect of rifampicin.[19] Furthermore, McIlleron and co-workers demonstrated a wide variation in plasma concentrations of rifampicin, with almost 70% of the study group at the lower end (<8 µg/l) and 22% at the very low end (<4 µg/l) of the therapeutic range.[20] Kimerling et al. reported very similar findings, 64% of subjects having levels below 8 µg/l for rifampicin.[21] In a cohort of patients, the majority of whom were HIV-infected, Chideya et al.

Table 1. Therapeutic concentrations (C_{max}, µg/ml) achieved and acetylator type (N=10)

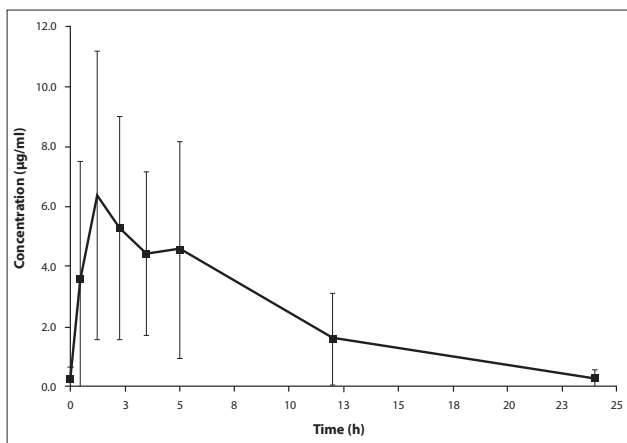|	Drug levels achieved			
	Rifampicin	Isoniazid	Pyrazinamide	Ethambutol
Therapeutic range	8 - 24	3 - 6 (A)	20 - 50	2 - 6
Patient				
1	1.2	2.4 (S)	29.4	2.1
2	7.3	3.9 (F)	40.4	3.9
3	6.1	4.4 (F)	51.0	5.0
4	2.8	6.2 (I)	69.2	6.0
5	9.6	9.0 (S)	118.3	1.5
6	11.7	8.7 (I)	75.4	9.0
7	14.1	9.7 (I)	65.2	3.0
8	5.6	3.5 (I)	36.8	1.3
9	9.6	8.8 (I)	48.0	2.0
10	3.5	1.4 (X)	30.2	1.0

A = acetylator type: S = slow; I = intermediate; F = fast; X = indeterminate.

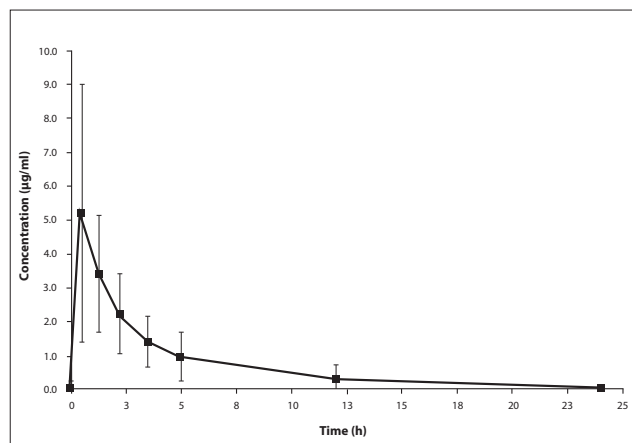Fig. 1. Rifampicin plasma concentration over time (0 - 24 hours, mean (SD), N=10). C_{max}=6.37µg/ml, t_{max}=1.25 h, $AUC_{(0-24)}$=60.70 µg x h/ml.

Fig. 2. Isoniazid plasma concentration over time (0 - 24 hours, mean (SD), N=10). C_{max}=5.20 µg/ml, t_{max}=0.5 h, $AUC_{(0-24)}$=19.97 µg x h/ml.
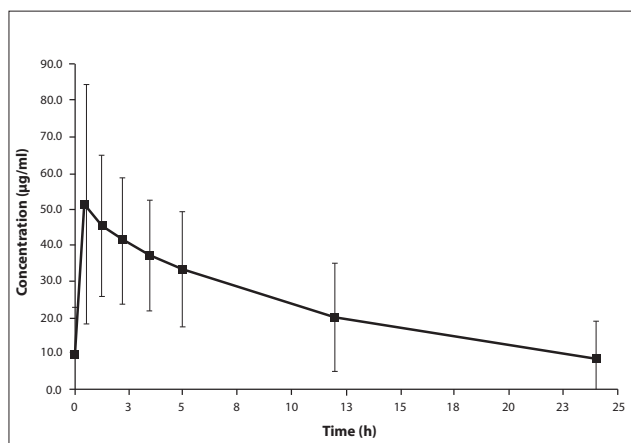
Fig. 3. Pyrazinamide concentration over time (0 - 24 hours, mean (SD), N=10). C_{max}=51.2 μg/ml, t_{max}=0.5 h, $AUC_{(0-24)}$=475.23 μg x h/ml.
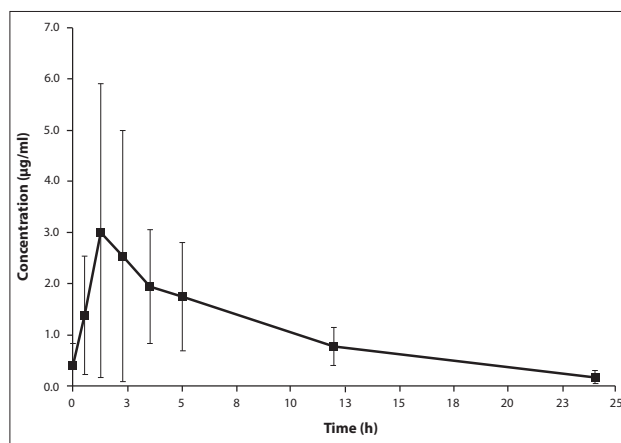

Fig. 4. Ethambutol concentration over time (0 - 24 hours, mean (SD), N=10). C_{max}=3.02 μg/ml, t_{max}=1.25 h, $AUC_{(0-24)}$=26.18 μg x h/ml.

Table 2. Patients with therapeutic rifampicin plasma concentrations v. patients with sub-therapeutic concentrations

	Therapeutic	Sub-therapeutic	*p*-value
No. of patients	4	6	NA
Days in ICU*, mean (SD)	15.5 (10.2)	12.0 (9.4)	0.59
Days on treatment, mean (SD)	25.8 (24.3)	37.8 (69.7)	0.79
APACHE II score, mean (SD)	16.6 (1.7)	25.2 (6.1)	0.03
Serum albumin (g/l), mean (SD)	25.3 (2.2)	25.7 (4.2)	0.86
Serum ALT (U/l), mean (SD)	49.0 (55.6)	51.2 (30.5)	0.93
Estimated GFR (ml/min/1.73 m²), mean (SD)	180.0 (73.5)	102.3 (11.9)	0.03
Inotropic support, *n*	0	1	NA
IV sedation, *n*	4	2	NA
Continuous feeding, *n*	5	4	NA
Nil by mouth, *n*	1	0	NA
Gastric residual volume (ml)†, mean (SD)	14.0 (10.7)	11.5 (11.2)	0.73

ICU = intensive care unit; SD = standard deviation; APACHE II = Acute Physiology and Chronic Health Evaluation II; ALT = alanine transaminases; GFR = glomerular filtration rate; IV = intravenous; NA = not applicable.
*At time of sampling.
†Mean 4-hourly aspirate.

found that 84% of patients had levels below 8 μg/l.[22] These data are comparable to our findings.

Several mechanisms, which are not necessarily specific to the critically ill patient, may contribute to sub-therapeutic plasma concentrations of rifampicin. Previous studies demonstrated that there is a decrease in functional absorptive area of the intestines in patients with TB.[8,23] This is especially true in patients with multidrug-resistant TB.[23] It has been demonstrated that intestinal paracellular absorption in patients with active pulmonary TB is markedly decreased, but that this is unlikely to contribute significantly to lower plasma levels, as it represents less than 5% of the total absorptive area of the small intestine.[24] The patients in our study group were given rifampicin in a combination tablet either on an empty stomach with the addition of an antacid (sucralfate) or while given continuous feeds. It has been shown that antacids do not influence peak drug levels of rifampicin, but a high-fat meal can reduce C_{max} by 36% and nearly double t_{max}.[25] The 4-hour nasogastric aspirates are a surrogate marker of gastric emptying, and higher volumes aspirated suggest slower gastric emptying.[26] Of note is the fact that we found no significant correlation between a higher volume of 4-hourly nasogastric aspirates and sub-therapeutic rifampicin levels. Data from Ruslami and co-workers previously suggested that the concentrations of rifampicin in ambulant patients receiving rifampicin orally were somewhat higher than those in patients who received drugs (at a similar dose) via a nasogastric tube, suggesting that adsorption of rifampicin to plastics, and potentially to nasogastric tubing, play a role.[27]

The association of a lower plasma rifampicin concentration with a lower estimated GFR may very well be spurious, as only approximately 15% of rifampicin is renally excreted, and theoretically a lower GFR should result in higher plasma concentrations.[19] The small sample size and the fact that patients with an estimated GFR of <50 ml/min were excluded confounds this apparent association, as a lower GFR may very well be an indicator of general disease severity.

The sub-therapeutic plasma concentrations observed in our study strongly support the weight of evidence that use of IV rather than oral rifampicin in the critically ill TB patient should become routine practice, given the drug's apparent safety in higher doses.[27,28] Interestingly, in a very recent study, a 33% higher dose of IV rifampicin (600 mg v. 450 mg), led to a three times higher geometric mean area under the time-concentration curve up to 6

hours after the dose and, importantly, to maximum plasma and cerebrospinal fluid concentrations.[28]

The pharmacokinetic profile of isoniazid varies greatly from patient to patient on the basis of acetylator status, as the drug is cleared mostly by acetylation.[4] Slow acetylators obtain higher plasma levels and better therapeutic responses. Interestingly, we found little correlation between acetylator status and plasma levels – in fact, one of the 2 patients with sub-therapeutic isoniazid levels was a slow acetylator.

We observed a mortality rate well below published figures.[4] Although the small sample size complicates meaningful comparison with previous studies, it remains likely that this observation was merely a selection bias, as we only included patients with preserved renal and liver function.

Our study has certain limitations. Our sample size was small and many factors may have influenced the pharmacokinetics, including extremes of weight and days on treatment.[29] The lack of a control group may also be viewed as a limitation of our study. We used historical pharmacokinetic data in our analysis, as it was deemed impractical and unethical to subject 10 healthy volunteers to 7 days of TB treatment, a nasogastric feeding tube and 24 hours of pharmacokinetic sampling.

In conclusion, we found that a fixed-dose combination tablet (Rimstar 4-FDC; Sandoz) given according to weight via a nasogastric tube to patients admitted to the ICU resulted in sub-therapeutic rifampicin plasma concentrations in the majority of patients, whereas the other components had a more favourable pharmacokinetic profile. Patients with sub-therapeutic rifampicin concentrations had a higher APACHE II score and a lower estimated GFR. If confirmed in a larger study, our findings strongly support the use of IV rifampicin in addition to anti-TB drugs given by nasogastric tube in the critically ill TB patient.

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