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Short Communication

Pharmacokinetics of pyrazinamide during the initial phase of tuberculous meningitis treatment

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ABSTRACT

Tuberculous meningitis (TBM) is the most severe manifestation of tuberculosis. Pyrazinamide (PZA) is a pivotal antituberculous drug, but its dose has not been optimised for TBM. The aims of this study were to describe the pharmacokinetics of PZA during TBM treatment, to identify predictors of PZA exposure and to assess relationships between PZA dose and exposures in plasma and CSF. Plasma PZA pharmacokinetic data were assessed on Days 2 and 10 of treatment in 52 adult TBM patients. A CSF-to-plasma concentration ratio was determined on Day 2. Predictors of plasma PZA exposure, correlation between plasma and CSF exposures, and prediction of CSF concentrations based on dose and plasma exposure were evaluated. The geometric mean plasma PZA exposure (AUC_{0-24}) and peak concentration (C_{max}) on Day 2 were 709 h·mg/L and 59 mg/L following a median dose of 33.3 mg/kg/day; AUC_{0-24} on Day 10 (523 h·mg/L) was lower ($P < 0.001$). Dose and BMI correlated with AUC_{0-24} and C_{max}. The CSF concentration at 3–6 h was 42 mg/L and the CSF-to-plasma ratio was 90%. AUC_{0-24}, C_{max} and CSF concentration were highly correlated. CSF concentration could be predicted based on dose and various plasma exposure measures with <5% bias and <21% imprecision. Exposure to PZA decreases during the first days of TBM treatment, possibly due to the evolving inductive effect of rifampicin. PZA penetrates well in CSF. The association between PZA dose and exposures in plasma and CSF provides a rationale to study higher PZA doses for TBM.

1. Introduction

Tuberculosis (TB) is the leading infectious cause of death worldwide, and Indonesia has the third highest TB case load in the world [1]. Tuberculous meningitis (TBM) occurs in approximately 1% of TB cases but is disproportionally important as it is the most severe manifestation of TB, leading to death or permanent disability in >30% of those affected [2,3].

Treatment of drug-susceptible TBM is based on the treatment regimen for pulmonary TB, which includes an intensive phase of 2 months with rifampicin (RIF), isoniazid, pyrazinamide (PZA) and ethambutol, followed by a continuation phase for up to 10 months with RIF and isoniazid [2]. However, RIF and ethambutol do not cross the blood–brain barrier or blood–cerebrospinal fluid (CSF) barrier easily [2,4], and doses for none of the first-line anti-TB drugs, including PZA, have been optimised for TBM. Therefore, it is essential to determine the optimal treatment regimen for this devastating disease.

PZA is a pivotal first-line anti-TB drug, showing little or no bactericidal activity during the first 2 days of treatment [5] and a strong sterilising effect that enabled shortening of the pulmonary TB treatment duration from 9 months to 6 months [6]. Most studies on TBM treatment have not compared treatment regimens with and without PZA [7], apart from one small non-randomised study in children showing that a PZA-containing regimen is more efficacious than longer treatment regimens without PZA [8]. Nevertheless, PZA is used worldwide as a standard first-line anti-TB drug in TBM [2].

In vitro, animal and clinical studies have shown that a higher dose of PZA could be more efficacious than a standard dose of

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25–30 mg/kg in pulmonary TB [9–11]. Using higher doses of PZA could also be a potential strategy for optimising TBM treatment. Considering that doses of PZA result in exposures which subsequently determine the effects of PZA, it is important to have a good understanding of the pharmacokinetics of PZA and the interrelationships of dose and exposures in plasma and CSF in patients with TBM. Limited data are available, especially in the Indonesian population, on the pharmacokinetics of PZA during TBM treatment [4].

The aims of this study were (i) to describe the pharmacokinetics of PZA during the critical initial phase of TBM treatment in Indonesian TBM patients, (ii) to identify predictors of PZA exposure in plasma and CSF and (iii) to assess the relationships between PZA dose and exposures in plasma and CSF.

2. Materials and methods

2.1. Study design and patient population

This was a descriptive pharmacokinetic (PK) study focusing on PZA performed among patients with TBM who were included in a clinical trial. In this phase II clinical trial, 60 suspected TBM patients were randomised into three groups receiving different daily doses of RIF (450, 900 or 1350 mg) in addition to standard doses of other anti-TB drugs, including 1500 mg PZA, according to Indonesian national guidelines. This study was approved by the Ethical Review Board of the Faculty of Medicine of Universitas Padjadjaran (Bandung, Indonesia). Written informed consent to participate in the trial was obtained from all patients or from their relatives if the patient could not provide informed consent. In the latter case, patients who regained the capacity to consider participation were consulted and the study was continued after obtaining informed consent. Detailed methods of the main study have been reported previously (ClinicalTrials.gov NCT02169882) [3].

2.2. Pharmacokinetic sampling and bioanalysis

PK samples were taken twice, on Day 2 ± 1 and Day 10 ± 1 of treatment. Blood samples were taken in fasting condition just before and at 1, 2, 4, 8 and 12 h after administration of anti-TB medication. In addition, one CSF sample was taken 3–9 h after drug administration on Day 2 ± 1. Total PZA concentrations in plasma and CSF were analysed using validated ultra performance liquid chromatography (UPLC) methods. Accuracy for PZA standard samples was 99.8–104.8% for plasma and 85.6–95.5% for CSF depending on the concentration level. The intraday and interday coefficients of variation were <4.9% and <6.6% over the 0.2–60 mg/L concentration range for plasma and CSF, respectively.

2.3. Pharmacokinetic data analysis

PK parameters for PZA were assessed with non-compartmental PK methods using Phoenix WinNonlin v.7.0 (Certara USA Inc., Princeton, NJ) as described previously [3]. The CSF-to-plasma concentration ratio was determined based on PZA CSF concentration and calculated corresponding plasma PZA concentration at the time of CSF sampling. These PZA concentrations were calculated based on the nearest plasma concentrations before and after the time the CSF sample was taken, assuming first-order pharmacokinetics in the decay of PZA.

2.4. Statistical analysis

PK parameters were described using the geometric mean and range, apart from time to peak concentration (T_{max}) and CSF-to-plasma ratio which were described using the median (range) and arithmetic mean (range), respectively. PK parameters of PZA on Days 2 and 10 were compared using a paired samples t-test on log-transformed PK parameters; T_{max} values were compared using the Wilcoxon signed-rank test. Univariate analyses were performed to assess the effect of patient sex, age, body mass index (BMI), PZA dose (in mg/kg), human immunodeficiency virus (HIV) status, use of a nasogastric tube, and RIF 24-h area under the concentration–time curve (AUC_{0-24}) on PZA plasma exposure measures on Day 2. Predictors of PZA exposure ($P < 0.1$) were to be included in a multiple linear regression analysis.

Plasma AUC_{0-24}, peak plasma concentration (C_{max}) and CSF concentration were correlated with each other using rank correlation. Linear regression formulae were used to predict CSF concentrations based on PZA dose (in mg/kg), plasma AUC_{0-24}, plasma C_{max} and plasma concentration calculated at the time of CSF sampling using the jackknife method for resampling. Bias was assessed using the median percentage prediction error (MPPE) and imprecision was assessed by the median absolute percentage prediction error (MAPE), where both should be <15–20% [12].

All statistical analysis were performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY). A P-value of <0.05 was considered statistically significant in all analyses.

3. Results

3.1. Patients

PK samples for PZA on Day 2 were available for 52 patients and a CSF sample was available for 51 patients. PK samples for PZA on Day 10 were available for 36 patients. Approximately one-half of the patients were male and the median age was 30 years. The vast majority of patients (91%) had British Medical Research Council (BMRC) disease grade 2, 7.5% were HIV-positive and approximately 60% had a nasogastric tube on Day 2 of treatment. The median PZA daily dose was 33.3 mg/kg (range 19.2–44.5 mg/kg).

3.2. Pharmacokinetics of pyrazinamide

The geometric mean AUC_{0-24} and C_{max} values for PZA on Day 2 were 709 h·mg/L and 59 mg/L, respectively (Table 1). The AUC_{0-24} on Day 10 (523 h·mg/L) was significantly lower than that on Day 2 ($P < 0.001$) (Fig. 1A; Table 1). CSF samples were taken on average 4.2 h (range 3–6 h) after drug administration. The mean CSF concentration on Day 2 was 42 mg/L and the mean CSF-to-plasma ratio was 90% (range 55–115%). Individual CSF concentrations and calculated plasma concentrations at the time of CSF sampling are shown in Fig. 1B.

Univariate analysis showed that only PZA dose ($r_s = 0.530$, $P < 0.001$) and BMI ($r_s = -0.434$, $P = 0.001$) were significantly correlated with PZA AUC_{0-24} and C_{max} on Day 2, and no multivariate analysis was performed. PZA AUC_{0-24}, C_{max} and CSF concentration were all highly correlated with each other ($r_s \geq 0.80$, $P < 0.001$). The PZA dose, plasma AUC_{0-24}, C_{max} and plasma concentration at the time of CSF sampling all predicted CSF concentration with a MPPE of –4.4%, 1.5%, 1.0% and –2.7% and a MAPE of 20.6%, 12.0%, 16.9% and 9.9%, respectively.

4. Discussion

This study provides important data on the pharmacokinetics of PZA in adult Indonesian patients with TBM. The mean AUC_{0-24} (709 h·mg/L) and C_{max} (59 mg/L) during the first days of TBM treatment following a median dose of 33.3 mg/kg were relatively high compared with reference data ($AUC_{0-24} = 473$ h·mg/L and $C_{max} = 44$ mg/L) in an Indonesian population using the same dose, although these reference data were recorded at steady-state [13].

Table 1
Pharmacokinetic (PK) parameters of pyrazinamide after a daily dose of 1500 mg in tuberculous meningitis patients[a]

PK parameter	Day 2 ($n=52$)	Day 10 ($n=36$)	P-value[b]
AUC_{0-24} (h·mg/L)	709 (355–1906)	523 (275–1047)	<0.001
C_{max} (mg/L)	59 (37–126)	57 (33–83)	0.532
T_{max} (h)	1.2 (0.9–8.0)	1.4 (1.0–8.0)	0.725[c]
CL/F (L/h)	2.1 (1.3–4.3)	2.9 (1.4–5.5)	<0.001
V_d/F (L)	31 (16–54)	27 (20–36)	<0.001
$t_{1/2}$ (h)	10.1 (5.9–24.6)	6.5 (4.2–17–8)	<0.001
CSF concentration (mg/L) ($n=51$)	42 (17–112)	N/A	N/A
CSF-to-plasma ratio (%) ($n=51$)	90 (55–115)	N/A	N/A

AUC_{0-24}, area under the concentration–time curve from 0–24 h; C_{max}, peak plasma concentration; T_{max}, time to C_{max}; CL/F, apparent total clearance; V_d/F, apparent volume of distribution; $t_{1/2}$, elimination half-life; CSF, cerebrospinal fluid; N/A, not available.

[a] PK parameters are presented as geometric mean (range), except for T_{max} and CSF-to-plasma ratio that are shown as median (range) and arithmetic mean (range), respectively.

[b] Paired samples t-test on log-transformed data of 36 patients for whom PK data were available both on Day 2 and Day 10.

[c] Wilcoxon signed-rank test between Day 2 and Day 10.

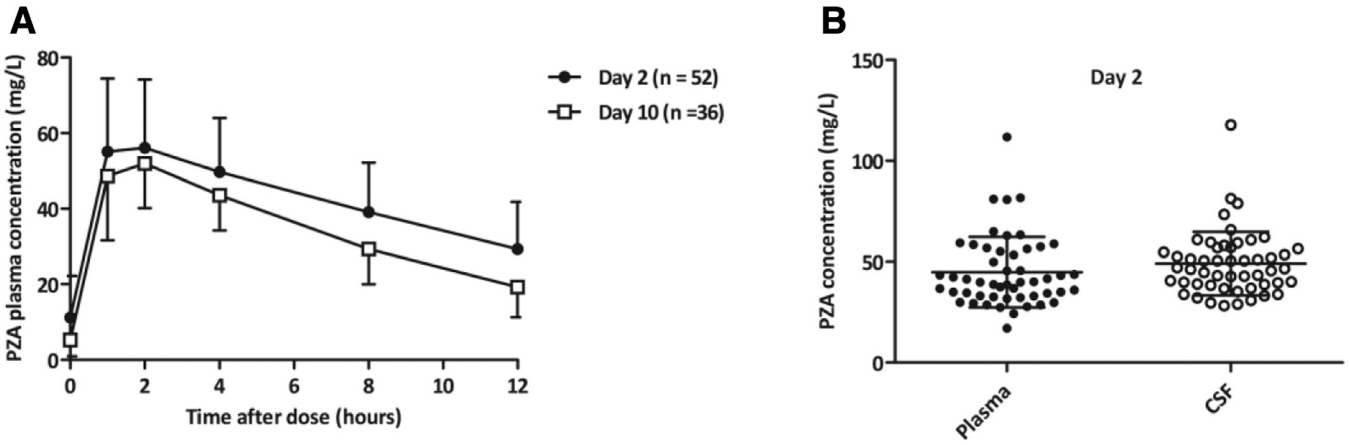

Fig. 1. Pharmacokinetic profiles of pyrazinamide (PZA) after a daily dose of 1500 mg in tuberculous meningitis patients: (A) plasma concentration versus time curves of PZA on Day 2 and Day 10 of treatment (mean ± standard deviation); and (B) individual plasma concentrations calculated at the time of cerebrospinal fluid (CSF) sampling and measured CSF concentrations ($n=51$) of PZA on Day 2 of treatment. Bars represent the mean ± standard deviation.

This is in agreement with our observation that the PZA AUC_{0-24} on Day 2 was significantly higher than that on Day 10, whilst no significant difference in C_{max} was observed (Table 1). The higher exposure during the first days of treatment is remarkable since steady-state is not yet reached and thus an increase rather than a decrease in exposure would be expected. A similar finding was observed previously in a study among pulmonary TB patients; PZA exposure decreased after >2 weeks of treatment compared with <2 weeks [14]. PZA is metabolised both by bacterial pyrazinamidase and host-mediated metabolism and is also converted by xanthine oxidase [15]. A likely explanation for the decrease in exposure to PZA is that RIF, a potent inducer of metabolic enzymes and transporters, influences the metabolism of PZA considering that induction by RIF takes time and develops in 1–2 weeks [16]. The exact mechanism of this possible interaction is currently unknown.

Adequate exposure to PZA in the CSF and brain is essential for the treatment of TBM. The mean CSF concentration (42 mg/L) was within the reference range for the C_{max} of PZA in plasma (20–60 mg/L) [17]. The high mean CSF-to-plasma ratio of 90% also shows that PZA penetrates the CSF well, which is in agreement with previous studies [4].

In this study, a correlation was found between PZA dose administered and plasma exposure achieved. Furthermore, high correlation was found between PZA plasma AUC_{0-24} and C_{max} on the one hand and PZA CSF concentration on the other. CSF concentration could be predicted based on PZA dose and various measures of exposure to PZA in plasma. This implies that higher doses of PZA, leading to higher exposure in plasma, will in turn result in higher CSF exposure, and it should be investigated whether this results in improved outcome. It is important to take into account that this should be balanced against a possible increased risk of hepatotoxicity and neurotoxicity [18,19].

A limitation of this study was that only one CSF sample was taken in a short time interval, whereas the CSF-to-plasma ratio could vary over the dosing interval. Ideally, a CSF-to-plasma ratio is determined for total exposure (AUC_{0-24}), which requires multiple CSF samples [20]. Also, total PZA plasma concentrations were measured, whereas unbound concentrations are ideally measured for determining CSF-to-plasma ratios [18], but this is not relevant for PZA which has only 1% protein binding in plasma [21].

In conclusion, exposure to PZA was high during the first days of TBM treatment and was significantly lower around Day 10, possibly due to an interaction with RIF. PZA penetrates well into the CSF, and an association between dose and exposures in plasma and CSF was observed. This provides a rationale for follow-up research into the pharmacokinetics, efficacy and safety of higher doses of PZA for TBM as well as the interrelationships of these.

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Declaration of Competing Interest

None declared.

Ethical approval

This study was approved by the Ethical Review Board of the Faculty of Medicine of Universitas Padjadjaran (Bandung, Indonesia).

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