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Pharmacokinetics and safety/tolerability of higher oral and intravenous doses of rifampicin in adult tuberculous meningitis patients

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ABSTRACT

High-dose intravenous (i.v.) rifampicin improved the outcome of tuberculous meningitis (TBM) in a previous study. Unfortunately, i.v. rifampicin is not available in many high-endemic settings. This study examined exposures to and safety of higher oral rifampicin doses compared with i.v. rifampicin. Thirty adult Indonesian TBM patients were randomised to rifampicin 750 mg (ca. 17 mg/kg) orally, 900 mg (ca. 20 mg/kg) orally or 600 mg (ca. 13 mg/kg, as used previously) i.v. over 1.5 h for 14 days, combined with other TB drugs. The pharmacokinetics of rifampicin was assessed in the critical phase of TBM treatment (≤3 days after treatment initiation) and at ≥9 days. In the first days of treatment, the geometric mean (range) plasma AUC_{0-24} values following rifampicin 750 mg orally, 900 mg orally and 600 mg i.v. were 131.4 (38.1–275.1), 164.8 (66.9–291.2) and 145.7 (77.7–430.2) mg·h/L, respectively; C_{max} values were 14.3 (6.1–22.2), 16.2 (5.7–28.3) and 24.7 (13.9–37.8) mg/L. CSF concentrations correlated with plasma exposures. After ≥9 days, AUC_{0-24} values had decreased to 100.1, 101.2 and 94.9 mg·h/L. Transient grade 3 ALT increases (8/30 patients) and one grade 4 ALT increase occurred, not related to rifampicin exposure. Higher oral rifampicin doses resulted in approximately similar plasma AUC_{0-24} but lower plasma C_{max} values compared with 600 mg i.v. over 1.5 h. Exposures to rifampicin varied substantially and decreased due to autoinduction. Liver function disturbances occurred in this severely ill population. Future studies should examine even higher rifampicin doses in TBM treatment.

1. Introduction

Meningitis is the most severe form of tuberculosis (TB). Up to 50% of patients with tuberculous meningitis (TBM) die, mostly within the first 2 weeks after presentation of the disease, and the remainder often ends up with neurological sequelae [1,2]. Treatment of TBM follows the model of short-course chemotherapy in pulmonary TB patients, with intensive and continuation phases of treatment, and uses the same TB drugs and dosing guidelines. However, the site of infection in TBM is hard to reach for many drugs because they have to penetrate through the blood–brain and blood–cerebrospinal fluid (CSF) barriers [3]. In fact, rifampicin as a pivotal antituberculous drug shows only limited penetration into the CSF [4].

We hypothesised that a higher dose of rifampicin could increase exposure to rifampicin in the CSF and brain tissue, leading to a better outcome for TBM patients. In this respect, we also considered accumulating evidence suggesting that the current dose of rifampicin is at the lower end of the dose–response curve [5–8]. In a previous clinical trial we therefore used a 33% higher dose of rifampicin [600 mg instead of 450 mg (10 mg/kg in Indonesian patients)] and administered this intravenously (rather than orally) for 2 weeks, which led to a three-fold higher drug exposure in plasma and CSF owing to the higher dose, the intravenous (i.v.) administration and the non-linear pharmacokinetics of rifampicin [9]. The 6-month mortality was decreased in the higher-dose group compared with the standard-dose group (35% vs. 65%; adjusted hazard ratio = 0.42, 95% confidence interval 0.20–0.91; $P = 0.03$), and high-dose rifampicin was safe and well tolerated [9].

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Unfortunately, the i.v. formulation of rifampicin is not widely available, especially in low- or middle-income countries. In addition, its cost is relatively high, and i.v. treatment beyond 2 weeks of in-hospital treatment is complex from a logistical viewpoint. The current explorative study therefore aimed to assess exposures to higher oral doses of rifampicin (750 mg and 900 mg orally, ca. 17 mg/kg and 20 mg/kg in Indonesian patients) and to compare these with exposures following 600 mg (ca. 13 mg/kg) i.v. in TBM patients as well as to assess the safety and tolerability of these regimens.

2. Materials and methods

2.1. Subjects

This study was conducted at the Department of Neurology of Hasan Sadikin Hospital (Bandung, Indonesia). Enrolled subjects were adults (age ≥17 years) with clinically suspected untreated TBM.

Initial screening included standard physical examination, chest radiography, and CSF and blood examinations. Neuroradiology is not a routine screening for TBM in Indonesia. Microbiological testing included microscopy for acid-fast bacilli (Ziehl–Neelsen stain), cryptococci [India ink stain, in human immunodeficiency virus (HIV)-infected patients] and bacterial pathogens in the CSF; culture for *Mycobacterium tuberculosis* and bacterial pathogens in the CSF; cryptococcal antigen testing; and *M. tuberculosis* drug resistance testing with proportional methods. All patients with definite, probable or possible TBM, as determined by a scoring system [10], were eligible for inclusion in the study.

Subjects were excluded if they had been treated for TB for ≥3 days before admission, had alanine aminotransferase (ALT) more than five times the upper limit of normal, had a positive urine pregnancy test, had a history of hypersensitivity to rifampicin, failure to do a diagnostic lumbar puncture, or evidence of bacterial or cryptococcal meningitis. HIV status was assessed after inclusion with consent from the patient or their representative.

The neurological status of the TBM subjects was classified according to a modification of the British Medical Research Council (BMRC) grading system [11].

The Independent Ethics Committee of the Faculty of Medicine of Universitas Padjadjaran (Bandung, Indonesia) approved the study, and informed consent was obtained from all subjects or from their representatives if the subjects were incapacitated.

2.2. Study design

This was an explorative, open-label, randomised, three-arm, two-period pharmacokinetic (PK) and safety/tolerability study. Thirty subjects were randomised to three groups of subjects who received fixed daily doses of rifampicin 750 mg (ca. 17 mg/kg) orally, 900 mg (ca. 20 mg/kg) orally or 600 mg (ca. 13 mg/kg) i.v. for 14 days, in addition to isoniazid 300 mg, pyrazinamide 1500 mg and ethambutol 750 mg daily. After 14 days, the subjects were treated with a standard TB regimen according to the Indonesian National TB programme. During the 14-day period of in-hospital treatment, two PK assessments took place, and safety and tolerability were assessed.

The dose of 750 mg (ca. 17 mg/kg) was estimated to provide similar total exposures in plasma compared with 600 mg i.v. based on available data on the pharmacokinetics of orally administered rifampicin in Indonesian patients [12], the bioavailability of rifampicin in Indonesian patients [13] and the non-linear increase in exposure with dose [12,14], but uncertainties in this respect were related to previous exposures assessed during the initial days of TBM treatment and not at steady-state [9]; for that reason, a second dose of 900 mg (ca. 20 mg/kg) was also selected for evaluation.

2.3. Drug administration

All oral TB drugs were manufactured by PT Kimia Farma (Jakarta, Indonesia) and were formulated in separate tablets. Bioequivalence of the rifampicin tablets and an international reference standard were established previously [15]. All tablets were taken once daily on an empty stomach and under directly observed treatment. For unconscious subjects, drugs were dissolved in 30 mL of plain water in a closed syringe and were delivered through a nasogastric tube. The tube was flushed two times with 10 mL of water.

For i.v. use, 600 mg of rifampicin (Rifadin®; Sanofi-Aventis, Gouda, The Netherlands) was dissolved in 10 mL of distilled water and was further diluted in 250 mL of normal saline 0.9%, which was then administered over 1.5 h.

All subjects were also given adjunctive dexamethasone i.v. for the first 6–8 weeks, starting with 0.3 mg/kg for grade 1 and 0.4 mg/kg for grade 2 or 3 TBM with dose reductions described formerly as standard treatment [11].

2.4. Pharmacokinetic assessments

The first PK assessment was done within the first 3 days of drug administration, as in our previous study, considering that these first days of treatment are pivotal for treatment success [9]. Serial venous blood samples were collected just before and at 1, 2, 4, 8 and 12 h after administration of the oral dose or the start of i.v. administration. A second PK assessment took place ≥9 days after treatment initiation, when steady-state for the TB drugs can be expected. A CSF sample was taken on the same days as the blood samples, between 3 h and 6 h after drug administration. Subjects had an overnight fast from 23:00 h on the day preceding PK assessments until 2 h after administration of the study drug. Blood samples were centrifuged at 3000 rpm for 15 min and plasma was separated and stored at –80 °C within 30 min after sampling.

2.5. Bioanalysis and pharmacokinetic analysis

Analysis of rifampicin concentrations in plasma and CSF was performed at the Pharmacokinetic Laboratory of the Faculty of Medicine of Universitas Padjadjaran using a validated ultraperformance liquid chromatography (UPLC) method. Accuracy was between 95.1% and 102.4% for plasma samples and between 94.5% and 100.7% for CSF samples, depending on the concentration level. The intraday and interday coefficients of variation were <4.2% over the 0.26–30 mg/L concentration range for rifampicin in plasma and <3.4% over the 0.25–30 mg/L range in CSF.

PK parameters for rifampicin in plasma were assessed using standard non-compartmental methods in Phoenix WinNonlin v.6.3 (Certara USA Inc., Princeton, NJ) as described previously [12,13].

2.6. Safety/tolerability

Possible drug-related adverse events were monitored daily during administration of the higher doses of rifampicin for 2 weeks. Full blood count and ALT examination were performed twice weekly. Because of the severity of TBM with many effects occurring in severely ill TBM patients and based on experience with high-dose rifampicin in our previous study [9], liver function disturbance and hypersensitivity were predefined as adverse events that were possibly or probably related to the higher dose of rifampicin. All other adverse events (e.g. new neurological signs) were not incorporated in the assessment of safety and tolerability. Classification of adverse events was based on the US National Institutes of Health Common Terminology Criteria for Adverse Events v.4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm; accessed 25 July 2016). Predetermined toxicity management