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Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis

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ABSTRACT

Recent data suggest that intensified antimicrobial treatment may improve the outcome of tuberculous meningitis (TBM). Considering that drug exposure is the intermediate link between dose and effect, we examined the concentration–response relationship for rifampicin and moxifloxacin in TBM patients. In an open-label, phase 2 clinical trial performed in Indonesia (ClinicalTrials.gov NCT01158755), 60 TBM patients were randomised to receive standard-dose (450 mg oral) or high-dose rifampicin (600 mg intravenous) plus either oral moxifloxacin (400 mg or 800 mg) or ethambutol (750 mg). After 14 days, all patients continued with standard tuberculosis treatment. Pharmacokinetic sampling was performed once in every patient during the first three critical days. Differences in exposure between patients who died or survived were tested with independent samples *t*-tests. The relationship between drug exposure and mortality was examined using Cox regression. Compared with patients who died during the 2 weeks of intensified treatment, surviving patients had significantly higher rifampicin plasma $AUC_{0-6\,h}$, plasma C_{max} and CSF $C_{highest}$. Additionally, patients had a 32–43% lower relative likelihood of dying with an interquartile range increase in rifampicin exposure. Moxifloxacin exposure did not show a clear relationship with survival. From exposure–response curves, a rifampicin plasma $AUC_{0-6\,h}$ of ~70 mg·h/L ($AUC_{0-24\,h}$ of ~116 mg h/L) and a C_{max} of ~22 mg/L were deduced as minimum target values for treatment. A strong concentration–effect relationship was found, with higher rifampicin exposure leading to better TBM survival. The current treatment dose of rifampicin is suboptimal; higher doses of rifampicin should be evaluated.

1. Introduction

Tuberculous meningitis (TBM), the most severe manifestation of *Mycobacterium tuberculosis* infection, results in death or neurological disability in up to 50% of affected patients [1,2]. Treatment of TBM patients follows the model for short-course chemotherapy in pulmonary tuberculosis (TB) patients, comprising an intensive and a continuation phase of treatment [3,4]. In addition, the same anti-TB drugs and dosing guidelines are applied, even though it is known that penetration of some first-line antituberculous drugs, especially rifampicin, into cerebrospinal fluid (CSF) is limited [5].

One way to improve the outcome of TBM may be to intensify antimicrobial treatment. We have recently examined this in a phase 2 clinical trial among TBM patients in Indonesia [6]. Intensified treatment consisted of a 30% higher dose of intravenous (i.v.) rifampicin plus standard-dose or high-dose moxifloxacin administered orally, combined with oral isoniazid and pyrazinamide during the first 2 weeks. The higher dose of rifampicin was safe and led to a three-fold higher drug exposure in plasma and CSF. In addition, high-dose i.v. rifampicin was associated with a strong reduction in 6-month mortality compared with standard-dose oral treatment [35% vs. 65%; adjusted hazard ratio = 0.42, 95% confidence interval (CI) 0.20–0.91], although the study was not powered to detect

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differences in outcome. Moxifloxacin was not associated with a survival benefit.

Previously, mortality and resolution of coma were related to the dose of rifampicin and moxifloxacin, but not to individual concentrations of these drugs. However, administration of the studied rifampicin and moxifloxacin doses resulted in large interindividual variability in exposures both in plasma and CSF [6]. Accumulating data suggest that exposure to TB drugs is relevant for outcome in pulmonary TB [7–12]. Considering that concentrations of TB drugs are the intermediate link between the doses administered and their eventual effects, the current analysis examined the relationship between rifampicin and moxifloxacin (plasma and CSF) concentrations and mortality and resolution of coma in TBM patients. The results of this analysis may reveal exposure thresholds predictive of good treatment response in TBM. Such exposure thresholds help in the assessment of the optimal oral (rather than i.v.) dose of TB drugs needed to treat TBM and aid in the design of pharmacokinetically-optimised dosing regimens for TBM in other populations (e.g. children).

2. Methods

2.1. Study design

The study evaluated an open-label, randomised, phase 2 clinical trial with a factorial design performed at Hasan Sadikin Hospital (Bandung, Indonesia) [6]. All patients >14 years with definite, probable or possible TBM were eligible for the study. Exclusion criteria were failure to perform a diagnostic lumbar puncture or evidence of bacterial or cryptococcal meningitis. Other exclusion criteria were treatment for TB for >7 days before admission, a history of TBM, pregnancy, lactation, a known contraindication to moxifloxacin, alanine aminotransferase activity more than five times the upper limit of normal, known hypersensitivity or intolerance to rifampicin or moxifloxacin, rapid clinical deterioration during the screening process, and no informed consent. Written informed consent for participation in the trial and rapid human immunodeficiency virus (HIV) testing was obtained from patients or from close relatives of patients who were unconscious.

Patients were randomised to receive a regimen with standard-dose (450 mg once daily; ca. 10 mg/kg in Indonesian TB patients, orally) or high-dose rifampicin (600 mg once daily; ca. 13 mg/kg, i.v.), plus either standard-dose moxifloxacin (400 mg), high-dose moxifloxacin (800 mg) or oral ethambutol (750 mg) [6]. All patients were given oral isoniazid (300 mg/day), pyrazinamide (1500 mg/day) and pyridoxine (50 mg/day). After 14 days, all patients continued taking the standard TB regimen, consisting of oral isoniazid 300 mg/day, rifampicin 450 mg/day, pyrazinamide 1500 mg/day and ethambutol 750 mg/day for 2 months, with subsequent rifampicin 450 mg/day and isoniazid 300 mg/day for 4 months in accordance with the Indonesian National Tuberculosis Program. All participants were given adjunctive corticosteroid treatment for the first 6–8 weeks according to international guidelines [13]. Patients were followed up until 6 months after the start of treatment. The study was approved by the Ethical Review Board of Hasan Sadikin Hospital/Medical Faculty of Universitas Padjadjaran. For specifics on randomisation and masking, treatment and follow-up, we refer to our previously published work [6].

2.2. Pharmacokinetic assessment

Pharmacokinetic sampling was performed in the first 3 days of drug administration as these days were considered to be critical for outcome. Serial blood sampling was done just before and at 1, 2, 4, 6 and 24 h after dosing. Two CSF samples were taken, one on the same day as the blood samples (at 3–6 h after dosing) and one on the next day (at 6–9 h after dosing). Total (protein-bound plus unbound) plasma and CSF rifampicin and moxifloxacin concentrations were assessed at Radboud University Medical Center (Nijmegen, The Netherlands) using validated high-performance liquid chromatography (HPLC) assays. For rifampicin, accuracy for standard concentrations was between 99.8% and 100.4% depending on the concentration. The intra-assay and inter-assay coefficients of variation were <4% for a concentration of 0.26–30 mg/L. The lower limit of quantification (LLOQ) was 0.26 mg/L. For moxifloxacin, accuracy was >95% at all standard concentrations. Intra-assay and inter-assay coefficients were 1.4–5.4% and 0.2–3.9%, respectively. The LLOQ was 0.03 mg/L. Parameters for rifampicin and moxifloxacin in plasma were assessed non-compartmentally using WinNonlin Professional v.5.0 (Pharsight Corp., Mountain View, CA) as previously described [6]. The highest plasma concentration was defined as C_{max}, with the corresponding time as T_{max}. The area under the plasma concentration–time curve up to 6 h and up to 24 h after dosing ($AUC_{0-6\,h}$ and $AUC_{0-24\,h}$, respectively) were calculated with the log-linear trapezoidal rule. $C_{highest}$ in the CSF represents the highest concentration measured in the intervals of 3–6 h and 6–9 h after dosing.

2.3. Statistical analysis

2.3.1. Descriptive statistics

First, patient characteristics, pharmacokinetic (PK) data and mortality data were presented descriptively for all patients included, irrespective of their study group. Correlation analyses using Spearman's rank were performed between measures of rifampicin and moxifloxacin exposure: AUC in plasma versus C_{max} in plasma; C_{max} in plasma versus $C_{highest}$ in CSF; and AUC in plasma versus $C_{highest}$ in CSF. In addition, rifampicin and moxifloxacin $C_{highest}$ CSF/C_{max} plasma ratios were plotted against plasma C_{max}.

2.3.2. Categorising data by exposure

Tertiles were formed based on the rifampicin and moxifloxacin exposure parameters (plasma AUC, plasma C_{max} and CSF $C_{highest}$), which were designated groups with 'low', 'standard' or 'high' exposure. Tertiles were chosen because with more than three groups the number of patients per group becomes too small. The use of tertiles also enabled us to check the presence of a U-shaped exposure–response relationship as reported by Thwaites et al. [14]. Continuous characteristics or treatment outcomes per group were compared using one-way analysis of variance (ANOVA) with post-hoc Tukey's test. Dichotomous measures were examined using Pearson's χ^2 tests.

2.3.3. Comparing exposure per outcome value

Differences in exposure measures between patients who died and patients who survived, and between those with and without resolution of coma [Glasgow Coma Scale (GCS) score of 15] were tested with independent samples *t*-tests on the logarithmically transformed values of plasma AUC, plasma C_{max} and CSF $C_{highest}$.

2.3.4. Correlating exposure with outcome

Relationships between rifampicin and moxifloxacin exposure and the time-to-event outcome mortality were examined using Cox regression. Hazard ratios were assessed for an interquartile range (IQR) increase (IQ-HRs) in exposure, i.e. an increase in exposure from the 25th percentile to the 75th percentile, an approach previously used by Burhan et al. [15]. Relationships between exposure measures and the dichotomous outcome 'clearance of coma' were examined using logistic regression. Multivariate analyses were conducted by means of ENTER all independent variables, including the exposure measures (plasma AUC, plasma C_{max} and CSF $C_{highest}$),