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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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