AAC Journals.ASM.org

Exposure to Total and Protein-Unbound Rifampin Is Not Affected by Malnutrition in Indonesian Tuberculosis Patients

L. H. M. te Brake,[a,b] R. Ruslami,[c] H. Later-Nijland,[a] F. Mooren,[a] M. Teulen,[a] L. Apriani,[d] J. B. Koenderink,[b] F. G. Russel,[b] D. M. Burger,[a] B. Alisjahbana,[d] F. Wieringa,[e] R. van Crevel,[f] R. E. Aarnoutse[a]

Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands[a]; Department of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, The Netherlands[b]; Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Padjadjaran/Hasan Sadikin Hospital, Bandung, Indonesia[c]; Health Research Unit, Faculty of Medicine, Universitas Padjadjaran/Hasan Sadikin Hospital, Bandung, Indonesia[d]; Institut de Recherche pour le Developpement, UMR Nutripass IRD-UM2-UM1, Montpellier, France[e]; Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands[f]

Nutritional status may have a profound impact on the pharmacokinetics of drugs, yet only few data are available for tuberculosis (TB) drugs. As malnutrition occurs frequently among TB patients, we assessed the effect of malnutrition on the steady-state pharmacokinetics of total and protein-unbound rifampin during the intensive phase of TB treatment. In a descriptive pharmacokinetic study in Bandung, Indonesia, patients received a fixed standard rifampin dose of 450 mg once daily during the intensive phase of TB treatment. A full pharmacokinetic curve for rifampin was recorded, and total and unbound concentrations of rifampin were analyzed in all samples. Rifampin pharmacokinetic parameters were compared between severely malnourished (BMI of <16.0 kg/m^2), malnourished (BMI of <18.5 kg/m^2), and well-nourished (BMI of ≥18.5 kg/m^2) individuals. No difference in total and protein-unbound pharmacokinetic parameters between severely malnourished ($n = 7$), malnourished ($n = 11$), and well-nourished ($n = 25$) patients could be demonstrated. In addition, no significant correlation between BMI and exposure (area under the concentration-time curve from 0 to 24 h [AUC_{0-24}] and maximum concentration of drug in serum [C_{max}]) was found. Females had significantly higher total AUC_{0-24} (geometric mean, 59.2 versus 48.2 h · mg/liter; $P = 0.02$) and higher unbound AUC_{0-24} (geometric mean, 6.2 versus 4.8 h · mg/liter; $P = 0.02$) than males. Overall, a marked 2-fold interindividual variation in the free fraction was observed (7.6 to 15.0%; $n = 36$). Nutritional status and BMI do not appear to have a major effect on total and protein-unbound pharmacokinetic parameters of rifampin in Indonesian subjects. The large interindividual variability in the free fraction of rifampin suggests that protein-unbound rather than total rifampin concentrations should preferably be used to study exposure-response relationships.

Inadequate exposure to rifampin and other antituberculosis (anti-TB) drugs may contribute to a suboptimal clinical response in anti-TB treatment. This follows from a recent study performed in a preclinical model, showing that pharmacokinetic variability is an important factor in the emergence of multidrug-resistant TB (1). Furthermore, a meta-analysis of clinical studies showed that pharmacokinetic variability for a single drug (isoniazid) in multidrug TB regimens is associated with therapy failure and acquired drug resistance (2). A number of clinical studies have also reported associations between low concentrations of anti-TB drugs and poor treatment response (3–8), but this association was not found in other studies (9, 10), including one of our studies on plasma rifampin concentrations in Indonesian TB patients (11).

For rifampin and other TB drugs, pharmacokinetic variability and low exposure may be affected by various factors, including gender, comorbidity (HIV/AIDS or diabetes mellitus), genetics, drug formulation, and malnutrition (3, 12–16). Malnutrition occurs frequently among TB patients. A case ($n = 121$)-control ($n = 371$) study in Indonesia documented malnutrition in 87% and 33% of cases and controls, respectively (17). A bidirectional interaction exists between malnutrition and TB (18, 19). On the one hand, malnutrition impairs immune function and increases the susceptibility to development of active TB. At the same time, TB leads to severe abnormalities in protein metabolism and loss of lean tissues and fat reserves. It is known that nutritional status can have a profound impact on the pharmacokinetics of drugs (20, 21), yet few data are available for TB drugs, and we are aware of only one publication on the effect of malnutrition on the exposure to rifampin (12).

In pharmacokinetic studies, measurement of rifampin concentrations in plasma or serum usually relates to the total (protein-unbound plus protein-bound) concentration of a drug. An equilibrium between total and protein-unbound concentrations is commonly assumed, yet free rather than total drug concentrations are preferably used in concentration-response evaluations (22), as only protein-unbound drugs are pharmacologically active and diffuse or are being actively transported into tissues and to the sites of action (23, 24). In a previous study among Indonesian TB patients (11), we confined measurements to total concentrations of rifampin, and this may be one of several possible explanations for the absence of a concentration-response relationship in that study. Importantly, malnutrition and associated low concentra-

Received 28 May 2014 Returned for modification 26 July 2014
Accepted 14 March 2015
Accepted manuscript posted online 23 March 2015
Citation te Brake LHM, Ruslami R, Later-Nijland H, Mooren F, Teulen M, Apriani L, Koenderink JB, Russel FG, Burger DM, Alisjahbana B, Wieringa F, van Crevel R, Aarnoutse RE. 2015. Exposure to total and protein-unbound rifampin is not affected by malnutrition in Indonesian tuberculosis patients. Antimicrob Agents Chemother 59:3233–3239. doi:10.1128/AAC.03485-14.
Address correspondence to L. H. M. te Brake, Lindsey.teBrake@radboudumc.nl.

doi:10.1128/AAC.03485-14