Letters to the Editor

Evaluation of High- versus Standard-Dose Rifampin in Indonesian Patients with Pulmonary Tuberculosis

We previously found peak plasma concentrations of rifampin below 4 mg/liter in 70% of Indonesian tuberculosis (TB) patients treated with 10 mg rifampin/kg of body weight daily (6), much below the reference concentration of ≥ 8 mg/liter (5). In addition, both murine models (1) and studies with TB patients (3) suggest that the typical 10-mg/kg dose of rifampin may be too low and that a higher dose may reduce treatment duration (4). Indeed, a regimen incorporating a higher dose of 1,200 mg rifampin daily yielded much faster conversion of sputum culture (2). Based on these findings, we decided to investigate the effect of increasing the dose of rifampin in terms of pharmacokinetics and tolerability.

In an open-label phase II randomized clinical trial in an urban clinic in Indonesia, consecutive patients with microbiologically proven pulmonary TB were randomized to a standard (450 mg; 10 mg/kg) or high (600 mg) dose of rifampin. High and standard doses of rifampin were administered every day in the intensive phase and three times weekly in the continuation phase of treatment. All other TB drugs were dosed according to the protocols of the Indonesian National TB Program. All patients provided written informed consent, and the study was approved by the local institutional review board. After 4 and 8 weeks of treatment, blood samples were collected at the time of peak plasma concentration of rifampin, 2 hours (5) after the witnessed intake of TB drugs on an empty stomach. Plasma was separated immediately and stored at -80°C until measurement of rifampin concentrations with a validated high-performance liquid chromatographic assay. Patients were questioned actively for possible adverse events, and liver transaminases

were monitored. The simultaneous effects of the dose of rifampin and the week of treatment on the rifampin peak plasma concentrations were evaluated with a two-way mixed analysis of variance.

Fifty patients were included, and 46 completed the study (54% male; median age, 25 years; range, 18 to 50 years). Patients from both groups had similar body weights, and the median dose of rifampin corresponded to 13.3 mg/kg in the 600-mg-dose group and 10.3 mg/kg in the 450-mg-dose group. The mean peak plasma concentration of rifampin was higher in the 600-mg-dose group (11.1 versus 8.0 mg/liter; $F = 8.77$; $P = 0.005$). Mean plasma concentrations were similar in weeks 4 and 8. In week 4, the percentages of patients with rifampin peak plasma concentrations of ≥ 8 mg/liter were 48% (for the 450-mg dose) and 78% (for the 600-mg dose) (χ^2 ; $P = 0.03$) (Fig. 1). One patient receiving 600 mg developed a reversible elevation of the liver transaminase level to >5 times normal, while four patients (two in each study arm) showed mildly elevated transaminase levels. No differences were noted in terms of tolerability.

In conclusion, this trial in Indonesia shows that a higher dose of rifampin significantly increases the proportion of patients with rifampin peak plasma concentrations above the reference value of 8 mg/liter. Blinded studies with more-extensive pharmacokinetic assessments will provide more insight into the merits of high-dose rifampin and may pave the road for studies evaluating high-dose rifampin in shorter treatment regimens.

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FIG. 1. Two-hour plasma rifampin concentrations after 4 weeks of TB treatment in Indonesian patients randomized to standard-dose (450 mg) or high-dose (600 mg) rifampin daily. Rifampin doses were combined with standard-dose isoniazid, pyrazinamide, and ethambutol. Depicted are data for individual patients (bullets) and means for both groups (horizontal bars).

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