

## Letter to the Editor

### Bioavailability of Rifampin in Experimental Murine Tuberculosis

Grosset et al. have reported that the combination of rifampin (RMP) and pyrazinamide (PZA) was more active than the combination of isoniazid (INH), RMP, and PZA in experimental murine tuberculosis models intended to simulate both chemoprophylaxis (4) and the intensive and continuation phases of chemotherapy (3) of tuberculosis in humans. The apparent antagonism between INH and RMP-PZA was thought to be due to the lower concentrations of RMP in the sera of mice treated with the triple-drug combination than in the sera of those treated with RMP-PZA. We have encountered similar but more general problems with *Mycobacterium tuberculosis* H37Rv-infected BALB/c mice treated with RMP-containing regimens by oral gavage three times weekly. The dosages of the drugs were 15 mg/kg of body weight (RMP), 25 mg/kg (INH), 300 mg/kg (PZA), and 100 mg/kg (ethambutol [EMB]). Mean RMP concentrations in sera of six mice at 1, 2, 3, 6, 24, and 29 h after the dose of drugs were determined microbiologically with *Staphylococcus aureus* at each time point (Fig. 1). The levels of RMP found with each drug combination were lower than that found with RMP alone, the lowest occurring after a dose of RMP-INH-PZA-EMB. Analysis of variance after logarithmic transformation showed the differences between the regimens to be highly significant ( $P < 0.0001$ ), regardless of whether the RMP-alone regimen was included. Limited experience suggests considerable day-to-day variation in RMP bioavailability in such regimens. We then determined serum drug concentrations after administration by gavage of RMP alone followed by administration by gavage of the remaining drugs 5 to 10 min later. We found that the mean of the 1- and 3-h serum RMP concentrations increased from 4.1 mg/liter following RMP-INH-PZA-EMB administration in a single gavage solution to 11.1 mg/liter after separate administrations of RMP and INH-PZA-EMB, nearly as high as the 13.8 mg/liter found after administration of RMP alone. Mice

were treated with the same drug combinations as those described in the legend to Fig. 1, except the RMP gavage was followed after 10 min by gavage with the remaining drugs. No significant differences in serum drug concentrations were found by analysis of variance ( $P > 0.05$ ) between the four double- or quadruple-drug regimens, which yielded overall means of 8.1, 8.3, 0.59, and 0.36 mg of RMP per liter at 1.5, 3, 24, and 27 h, respectively (AUC, 115 mg/h/liter), though the concentrations after administration of RMP alone were higher (15.0, 11.6, 1.53, and 0.73 mg of RMP per liter, respectively; AUC, 175 mg/h/liter).

It seems likely that the bioavailability problems encountered in the murine models resemble those found with some combined preparations of RMP-INH-PZA (2) but not with other preparations (1) in humans. We conclude that (i) exploration of RMP-containing regimens in murine models should always include measurement of serum RMP levels and (ii) the experiments indicating antagonism between INH-RMP-PZA and RMP-PZA should be repeated with separation of the RMP dose from the dose of the other drugs to determine whether the antagonism is due entirely to the bioavailability difference. Even so, when RMP is given separately from the other drugs, the RMP concentrations may be lower than those obtained when RMP is given alone.

#### REFERENCES

1. Ellard, G. A., D. R. Ellard, B. W. Allen, D. J. Girling, A. J. Nunn, T. Seng-kee, T. Tiong-har, N. G. Hin-kwong, and C. Siu-lun. 1986. The bioavailability of isoniazid, rifampin, and pyrazinamide in two commercially available combined formulations designed for use in the short-course treatment of tuberculosis. *Am. Rev. Respir. Dis.* 133:1076-1080.
2. Fox, W. 1990. Drug combinations and the bioavailability of rifampicin. *Tubercle* 71:241-245.
3. Grosset, J., C. Truffot-Pernot, C. Lacroix, and B. Ji. 1992. Antagonism between isoniazid and the combination pyrazinamide-rifampin against tuberculosis infection in mice. *Antimicrob. Agents Chemother.* 36:548-551.
4. Lecoeur, H. F., C. Truffot-Pernot, and J. H. Grosset. 1989. Experimental short-course preventive therapy of tuberculosis with rifampin and pyrazinamide. *Am. Rev. Respir. Dis.* 140: 1189-1193.

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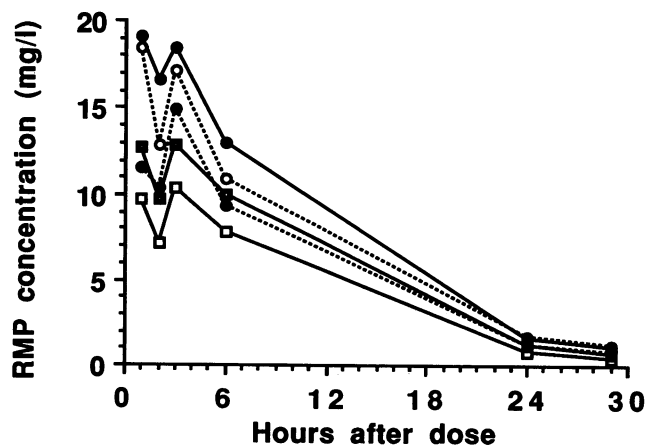


FIG. 1. Concentrations of RMP in sera of mice given oral gavage with RMP alone (—●—), RMP-INH (---○---), RMP-PZA (—■—), RMP-EMB (---●---), and RMP-INH-PZA-EMB (—□—). The AUCs were 236, 216, 170, 169, and 129 mg/h/liter, respectively.

#### Author's Reply

We are pleased to learn that Dickinson et al. have confirmed our observations that concentrations of rifampin

(RMP) in sera of mice treated with the combination of INH, RMP, and PZA are lower than those in sera of mice treated with RMP-PZA. In order to avoid the possible bioavailability problem of RMP in mice treated with RMP-containing combined regimens, we fully agree with them that (i) the serum RMP levels should always be measured in such experiments and (ii) the comparison of the bactericidal activities of the combinations INH-RMP-PZA and RMP-PZA against *M.*

*tuberculosis* should be repeated in mice in which the administration of RMP is separated from that of other drugs.

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