

Enhanced Elimination of Ciprofloxacin after Multiple-Dose Administration of Rifampin to Rabbits

STEVEN L. BARRIERE,^{1*} GLENN W. KAATZ,² AND SUSAN M. SEO²

Departments of Pharmaceutical Services and Pharmacology and Division of Infectious Diseases,
Department of Medicine, UCLA Center for the Health Sciences, Los Angeles, California 90024,¹
and Department of Internal Medicine, Division of Infectious Diseases,
Wayne State University School of Medicine, Detroit, Michigan 48201²

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The combination of ciprofloxacin and rifampin is potentially useful for the treatment of selected infections. However, rifampin may induce the metabolism of ciprofloxacin. Ciprofloxacin was given in single doses to healthy rabbits before and after six daily doses of intramuscular rifampin. Total clearance of ciprofloxacin increased from 0.96 ± 0.32 (standard deviation) to 1.57 ± 0.63 liters/h per kg ($P < 0.05$). This change in elimination is potentially significant for the outcome of experimental infections in rabbits.

Rifampin is frequently used as an adjunctive antistaphylococcal agent in chronic or deep-seated infections caused by susceptible strains (7). The addition of rifampin enhances the bactericidal activity of many antistaphylococcal regimens and provides intracellular killing of the infecting organisms (6). However, rifampin is also a potent inducer of oxidative metabolism in mammals (1, 2). Since ciprofloxacin is partially (20%) metabolized (11), concomitant use of rifampin may have an effect on its biodisposition. To investigate this possibility prior to an evaluation of the efficacy of ciprofloxacin plus rifampin in experimental *Staphylococcus aureus* endocarditis, we assessed the pharmacokinetic disposition of ciprofloxacin before and after chronic rifampin administration to healthy rabbits.

Ciprofloxacin powder (Miles Pharmaceuticals, West Haven, Conn.) and rifampin (formulation for intravenous use; Merrell Dow Research Institute, Cincinnati, Ohio) were dissolved in 5% glucose in water at concentrations of 25 and 60 mg/ml, respectively. The preparations were filter sterilized and frozen in aliquots until used. All administered doses were prepared from the same reconstituted solutions.

On day 1, 25 mg of ciprofloxacin per kg (body weight) was administered by intravenous bolus injection into an ear vein to each of six male New Zealand White rabbits (2.5 to 3.5 kg). Blood samples for determination of ciprofloxacin content in serum were collected from the contralateral ear at 0.0167, 0.0833, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after the bolus dose. On days 2 to 6, 10 mg of rifampin per kg was administered intramuscularly once daily. On day 7, a final dose of rifampin was administered, followed by an intravenous bolus injection of 25 mg of ciprofloxacin per kg. Blood samples for determination of rifampin content were obtained at 2 h (peak) and 24 h (trough) after each dose. Serum samples for determination of ciprofloxacin concentration were also obtained after the last dose at the same time points as after the first dose. Urine was not collected from these animals.

Ciprofloxacin concentrations in serum were determined by bioassay using an agar well diffusion method (8). *Klebsiella pneumoniae* ATCC 10031 (resistant to ≥ 25 μg of rifampin per ml) was used as the test organism, and the lower assay limit was 0.02 $\mu\text{g}/\text{ml}$. Metabolite concentrations were

not assessed and would not be expected to contribute significantly to serum activity of the drug. The assay variation was 4.2%. Rifampin concentrations were determined by a standard bioassay method with *Micrococcus luteus* ATCC 9341 as the assay organism (8). Variation for this assay was approximately 8%. The assay organisms were exposed to various concentrations of both ciprofloxacin and rifampin, and neither was synergistically inhibited by the combination.

Serum ciprofloxacin concentration-versus-time curves were plotted, and the elimination half-life was calculated by dividing the natural logarithm of 2 by the terminal elimination rate constant (λ_z) or slope of the plotted line.

Other pharmacokinetic parameters were determined by model independent methods (5). The area under the plasma concentration-versus-time curve (AUC) for ciprofloxacin was calculated by the log trapezoidal rule. The AUC was calculated from time zero to infinity for each dose. The AUC beyond the last measured point was estimated by dividing the predicted value of the last point by the terminal elimination rate constant. Estimates of total clearance (CL) and apparent steady-state volume of distribution (V_{ss}) were calculated from the equations $CL = \text{dose}/\text{AUC}$ and $V_{ss} = (\text{dose} \times \text{AUMC})/\text{AUC}^2$, where AUMC is the area under the first moment of the serum concentration-versus-time curve calculated by the log trapezoidal rule. Comparison of mean data was performed by the Wilcoxon signed rank test. A P value of ≤ 0.05 was considered significant.

Peak and trough rifampin concentrations did not change after multiple doses. Peak (2-h) and trough values for the first and last doses were 4.41 ± 1.34 (standard deviation) and 0.33 ± 0.18 $\mu\text{g}/\text{ml}$ and 4.81 ± 2.45 and 0.30 ± 0.37 $\mu\text{g}/\text{ml}$, respectively.

With the exception of the 12-h serum sample, concentrations of ciprofloxacin before rifampin administration were greater than those found after six doses of rifampin. The pharmacokinetic analysis is detailed in Table 1.

As noted above, rifampin is a potent inducer of drug metabolism (2). It has been shown to produce a proliferation of the smooth endoplasmic reticulum and an increase in the cytochrome P-450 content in mammalian liver (1). However, there appears to be selectivity in the enzyme induction effect so that not every drug metabolized by oxidation is affected. Ciprofloxacin undergoes oxidative metabolism in the liver. Approximately 20% of a dose in humans is converted to

* Corresponding author.

TABLE 1. Pharmacokinetic parameters of ciprofloxacin before and after rifampin administration

Time	Half-life	Clearance (liters/h per kg)	Vol of distribution at steady state (liters/kg)
Prerifampin	2.21 (0.77) ^{a,b}	0.96 (0.32) ^c	1.47 (0.39) ^b
Postrifampin	1.83 (0.36) ^b	1.57 (0.63) ^c	2.00 (0.72) ^b

^a Values in parentheses are standard deviations.

^b Not significantly different.

^c $P < 0.05$.

three different metabolites which possess weak antibacterial activity (11).

We have shown a substantial increase in the clearance of ciprofloxacin in rabbits after 6 days of rifampin administration. This effect may be important in the outcome of infection. It has been determined from experimental models of infection that, as with aminoglycosides, pharmacokinetic correlates of efficacy with quinolones are the AUC and the ratio of achievable concentration to MIC (10). Since our results indicated an average decrease in AUC of approximately 60%, this is potentially significant.

Additionally, mean levels of ciprofloxacin in serum before rifampin administration were 40% higher than those achieved after rifampin administration. Changes in concentrations in serum of this magnitude could have a significant impact on the treatment of certain infectious diseases. These include staphylococcal infections, tuberculosis, and infections caused by *Mycobacterium avium-M. intracellulare* and *Legionella* species. Combinations of ciprofloxacin plus rifampin with or without other agents are potential treatment regimens for each of these diseases (4, 9, 12, 13). Moreover, the MICs of ciprofloxacin for the causative organisms are relatively high, which makes changes in achievable concentrations even more important.

It should be noted that two factors may negate the effects of the drug interaction we have demonstrated between ciprofloxacin and rifampin. First, since rifampin and ciprofloxacin may exert a synergistic effect against certain organisms, reduction in the achievable concentrations of ciprofloxacin in serum may be counterbalanced by apparent reduction in the MIC resulting from a synergistic interaction. Although this was not observed with our test organisms, other bacteria may be affected. Second, we previously noted alterations in the disposition of ciprofloxacin after multiple doses in rabbits (3). We found the clearance of ciprofloxacin to be decreased by 20% after 13 doses. This may at least partially negate the increase in clearance produced by concomitant rifampin. Finally, it is unclear whether results of

pharmacokinetic interaction studies in rabbits are applicable to humans. However, such interactions may be important for the outcome of experimental infections and should serve as an impetus to explore the interaction in healthy human subjects and patients. Multiple-dose pharmacokinetic and pharmacodynamic studies with both drugs in animals and humans are needed to fully assess and characterize the potentially significant interaction that we have observed.

LITERATURE CITED

1. Acocella, G. 1983. Pharmacokinetics and metabolism of rifampin in humans. *Rev. Infect. Dis.* 5(Suppl. 3):S428-S432.
2. Baciewicz, A. M., and T. H. Self. 1984. Rifampin drug interactions. *Arch. Intern. Med.* 144:1667-1671.
3. Barriere, S. L., G. W. Kaatz, D. R. Schaberg, and R. Fekety. 1987. Altered pharmacokinetic disposition of ciprofloxacin and vancomycin after single and multiple doses in rabbits. *Antimicrob. Agents Chemother.* 31:1075-1078.
4. Henry, N. K., M. S. Rouse, A. L. Whitesell, M. E. McConnell, and W. R. Wilson. 1987. Treatment of methicillin-resistant *Staphylococcus aureus* experimental osteomyelitis with ciprofloxacin or vancomycin alone or in combination with rifampin. *Am. J. Med.* 82(Suppl. 4A):73-75.
5. Jusko, W. J. 1986. Guidelines for collection and pharmacokinetic analysis of drug disposition data, p. 9-54. In W. E. Evans, J. J. Schentag, and W. J. Jusko (ed.), *Applied pharmacokinetics*, 2nd ed. Applied Therapeutics, San Francisco.
6. Mandell, G. L. 1983. The antimicrobial activity of rifampin: emphasis on the relation to phagocytes. *Rev. Infect. Dis.* 5(Suppl. 3):S463-S467.
7. Norden, C. W., J. Fierer, R. E. Bryant, and the Chronic Osteomyelitis Study Group. 1983. Chronic staphylococcal osteomyelitis: treatment with regimens containing rifampin. *Rev. Infect. Dis.* 5(Suppl. 3):S495-S501.
8. Reeves, D. S., and M. J. Bywater. 1976. Assay of antimicrobial agents, p. 21-78. In J. De Louvois (ed.), *Selected topics in clinical bacteriology*. Bailliere Tindall, London.
9. Saito, A., H. Koga, H. Shigeno, K. Watanabe, K. Mori, and S. Kohno. 1986. The antimicrobial activity of ciprofloxacin against *Legionella* species and the treatment of experimental *Legionella* pneumonia in guinea pigs. *J. Antimicrob. Chemother.* 18:251-260.
10. Vogelmann, B. R., S. Gudmundson, J. Leggett, J. Turnidge, S. Ebert, and W. A. Craig. 1988. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. *J. Infect. Dis.* 158:831-847.
11. Wise, R., and I. A. Donovan. 1987. Tissue penetration and metabolism of ciprofloxacin. *Am. J. Med.* 82(Suppl. 4A):103-107.
12. Young, L. S. 1988. *Mycobacterium avium* complex infection. *J. Infect. Dis.* 157:863-867.
13. Young, L. S., O. G. W. Berlin, and C. B. Inderlied. 1987. Activity of ciprofloxacin and other fluorinated quinolones against mycobacteria. *Am. J. Med.* 82(Suppl. 4A):23-26.