ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2004, p. 4473–4475 Vol. 48, No. 11
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.11.4473–4475.2004

Decreased Bioavailability of Rifampin and Other Antituberculosis Drugs in Patients with Advanced Human Immunodeficiency Virus Disease

Prema Gurumurthy,[1]† Geetha Ramachandran,[1] A. K. Hemanth Kumar,[1] S. Rajasekaran,[2] C. Padmapriyadarsini,[1] Soumya Swaminathan,[1]* S. Bhagavathy,[1] P. Venkatesan,[1] L. Sekar,[1] A. Mahilmaran,[2] N. Ravichandran,[2] and P. Paramesh[2]

Tuberculosis Research Centre (Indian Council of Medical Research), Chetput,[1] and Government Hospital for Thoracic Medicine, Tambaram,[2] Chennai, India

Received 30 April 2004/Returned for modification 2 July 2004/Accepted 1 August 2004

We evaluated the effects of human immunodeficiency virus (HIV) disease on pharmacokinetics of antituberculosis medications by measuring concentrations of isoniazid and rifampin in blood and of pyrazinamide and ethambutol in urine. Peak concentration and exposure were reduced for rifampin, and rapid acetylators of isoniazid had lower drug levels. HIV and HIV-tuberculosis patients who have diarrhea and cryptosporidial infection exhibit decreased bioavailability of antituberculosis drugs.

Most patients with tuberculosis (TB) but without other illnesses absorb antimycobacterial drugs reliably (1, 5). However, patients with advanced human immunodeficiency virus (HIV) disease with or without diarrhea may not adequately absorb anti-TB drugs (3, 13–15). Also, the degrees of malabsorption appear to differ across populations (4, 6, 17, 19). We recently observed that HIV-infected patients with and without TB had malabsorption of rifampin (RMP) and isoniazid (INH), as determined on the basis of the urinary excretion of the drugs (7). We further wanted to evaluate the pharmacokinetics of RMP and INH in HIV-infected patients with and without TB in relation to the acetylator status of INH. We also wanted to study the absorption of pyrazinamide (PZA) and ethambutol (EMB) by estimating the percentage of the dose excreted in urine, which has not been previously reported.

The study was conducted at the Government Hospital for Thoracic Medicine, Tambaram, Chennai, India. The participants comprised 13 HIV-seronegative, pulmonary TB patients (group 1), 13 patients with advanced HIV infection (group 2), and 15 patients with HIV-TB (group 3). These study subjects were distinct from those reported earlier (7). Participants in groups 2 and 3 had history of recurrent episodes of watery stools six to eight times a day for at least 10 consecutive days in a month at the start of the study. All participants in groups 1 and 3 were sputum smear positive for acid-fast bacilli and were receiving standard anti-TB regimens. None of the patients in group 1 had complaints of diarrhea or vomiting for at least 3 days before start of the study. The study was approved by the Institutional Ethics committee, and informed written consent was obtained from all the patients.

All the patients received RMP (450 mg), INH (600 mg), PZA (1,500 mg), and EMB (1,200 mg) orally, and blood samples were collected at 1, 2, 3, 6, and 8 h after drug administration. Urine excreted up to 8 h after drug administration was also collected.

The concentrations of RMP and INH in plasma and of PZA and pyrazinoic acid (PZC) and EMB in urine were estimated using techniques previously described (8, 9, 10, 12). The INH acetylator status was also determined (16). All estimations were undertaken after coding the samples.

Certain pharmacokinetic variables were calculated on the basis of plasma concentrations of RMP and INH by noncompartmental methods using WinNonlin software (Pharsight Corporation, Mountain View, Calif.). The percentages of the doses of PZA (PZA and PZC) and EMB excreted in urine were also calculated. Analysis of data was performed using SPSS (version 10.5) software.

The baseline demographic and laboratory data of all study participants are shown in Table 1. The mean plasma RMP concentrations at various time points were significantly lower in both groups of HIV-positive patients than in TB patients ($P < 0.05$). There was a significant decrease in mean peak con-

TABLE 1. Baseline demographic characteristics of study participants

Characteristic	Value for group[a]		
	Pulmonary TB ($n = 13$)	HIV ($n = 13$)	HIV-TB ($n = 15$)
Mean age (yr)	40 (28–50)	30 (25–38)	38 (29–50)
Mean body wt (kg)	43 (32–65)	42 (34–50)	42 (23–62)
Mean $CD4^+$ cell count (cells/mm^3)		98 (4–255)	60 (15–330)
INH acetylator status (no. of participants)			
Slow	8	4	7
Rapid	5	9	8

[a] Ranges are given in parentheses.

* Corresponding author. Mailing address: HIV-AIDS Division, Tuberculosis Research Centre (Indian Council of Medical Research), Mayor V.R. Ramanathan Rd., Chetput, Chennai 600 031, India. Phone: 91-044-28362442. Fax: 91-044-28362528. E-mail: doctorsoumya@yahoo.com.

† Present address: K.J. Hospital Post Graduate & Research Foundation, Chennai, India.

TABLE 2. Pharmacokinetics of rifampin

Group	Mean (95% CI)					
	C_{max}[a] (μg/ml)	T_{max}[b] (h)	AUC_{0-8}[c] (μg/ml · h)	$AUC_{0-\infty}$[c] (μg/ml · h)	Cl[d] (ml/min)	$t_{1/2}$[e] (h)
Pulmonary TB (n = 13)	7.2 (5.5–8.9)	2.4 (1.7–3.1)	33.0 (26.7–39.4)	44.6 (36.3–52.9)	15.0 (11.8–18.2)	3.0 (2.1–3.9)
HIV (n = 13)	3.4[f] (2.5–4.3)	3.9 (2.7–5.0)	14.1[f] (9.9–18.2)	21.2[f] (14.8–27.6)	35.8[f] (27.3–44.2)	3.2 (2.6–3.7)
HIV-TB (n = 15)	3.4[f] (2.7–4.2)	3.6 (2.7–4.5)	16.5[f] (12.4–20.6)	28.2[f] (18.1–38.4)	37.3[f] (21.4–53.2)	2.6 (1.7–3.5)

[a] C_{max}, peak concentration.
[b] T_{max}, time to attain C_{max}.
[c] AUC, area under the plasma concentration versus time curve.
[d] Cl, clearance.
[e] $t_{1/2}$, elimination half-life.
[f] $P < 0.05$ (versus pulmonary TB results).

centration of drug in plasma (C_{max}) and exposure (area under the time curve from 0 to 8 h [AUC_{0-8}] and $AUC_{0-\infty}$) accompanied by a significant increase in clearance of RMP with HIV and HIV-TB patients compared to the results seen with TB patients ($P < 0.05$) (Table 2). The INH concentrations in rapid acetylators for both the HIV groups of patients were lower than those seen with TB patients ($P < 0.05$). Although mean C_{max} and AUC values of INH were lower and mean clearance values of INH were higher in HIV and HIV-TB patients than in TB patients, the differences were not statistically significant. The differences between HIV (with and without TB) and TB patients were more pronounced with rapid than with slow acetylators of INH (Table 3 and Table 4).

The percentages of the doses of PZA (PZA and PZC) and EMB excreted in urine were reduced by 35 and 43% and by 48 and 19% in patients with HIV and HIV-TB, respectively, compared to the results seen with TB patients.

Stool examination for opportunistic enteric pathogens was performed for seven patients with HIV and nine patients with HIV-TB. All 16 patients had *Cryptosporidium parvum* in their stool samples.

Response to RMP-based antimycobacterial therapy is generally good in HIV-infected patients with TB (18). However, this study demonstrated that the bioavailability of RMP in HIV-infected patients with and without TB was decreased, as evidenced by a significant reduction in peak concentration and exposure. Similar findings have been reported by Sahai et al. (17), who conducted a pharmacokinetic study of Canadian subjects with HIV infection. Low concentrations of RMP in blood could be due to malabsorption of the drug (2). Also, cryptosporidiosis has been suggested as one of the specific factors that may play a role in drug malabsorption in AIDS patients (11). Acetylator status had an impact on the bioavailability of INH in HIV-positive patients. While the decreases in C_{max} values in rapid acetylators of HIV and HIV-TB patients were 34 and 36%, respectively, compared to the results seen with TB patients, the corresponding values were 11 and 22% for slow acetylators of INH. Similar observations were made with respect to AUC values.

Our study further showed that the absorption of PZA and EMB is affected in patients with HIV infection, since the percentage of the dose excreted in urine was significantly lower than that seen with TB patients. This is in agreement with results reported by others (3, 6, 13, 17).

Of the 15 patients with HIV-TB studied, 7 had been admitted with a second episode of TB. All of them had received supervised anti-TB therapy during the first episode. All seven patients had peak plasma RMP concentrations below 5 μg/ml, a value which is lower than the therapeutic range of the drug (8 to 24 μg/ml) (3). Further, urinary excretion of PZA and EMB was low, suggesting that poor outcome of treatment with these drugs could be due to malabsorption and decreased bioavailability of these drugs. Therapeutic drug monitoring may be considered for patients with suboptimal response to treatment.

In conclusion, our study has found definitive evidence of malabsorption of anti-TB drugs, particularly RMP, in patients with advanced HIV infection and with diarrhea and evidence of cryptosporidial infection. The bioavailability of INH is affected more in rapid acetylators, and absorption of PZA and EMB is also reduced. These findings confirm and extend a previous observation of malabsorption of anti-TB drugs in patients with HIV, TB, and diarrhea (7) and suggest that this may be one of the factors affecting the success of anti-TB therapy in this group. Further studies are required to assess whether increasing the dosages of anti-TB drugs can help overcome the effect of malabsorption in patients with advanced HIV disease and to correlate plasma drug levels with treatment outcome and emergence of mycobacterial drug resistance.

TABLE 3. Pharmacokinetics of isoniazid in rapid acetylators

Group	Mean (95% CI)[a]					
	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-8} (μg/ml · h)	$AUC_{0-\infty}$ (μg/ml · h)	Cl (ml/min)	$t_{1/2}$ (h)
Pulmonary TB (n = 5)	11.0 (7.6–14.3)	1.4 (0.6–2.2)	39.0 (23.7–54.4)	42.5 (25.9–59.2)	17.5 (11.5–23.5)	1.8 (1.5–2.0)
HIV (n = 9)	7.3 (5.0–9.5)	1.8 (1.3–2.2)	24.2 (18.1–30.3)	26.2 (19.7–32.7)	28.3 (16.8–39.8)	1.9 (1.7–2.1)
HIV-TB (n = 8)	7.0[b] (5.5–8.6)	1.4 (1.0–1.7)	22.9 (17.8–28.0)	24.4 (18.6–30.2)	34.5 (15.3–53.8)	1.9 (1.4–2.4)

[a] For definitions of abbreviations, see Table 2, footnote *a*.
[b] $P < 0.05$ (versus pulmonary TB results).

TABLE 4. Pharmacokinetics of isoniazid in slow acetylators

Group	Mean (95% CI)[a]					
	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-8} (μg/ml · h)	$AUC_{0-\infty}$ (μg/ml · h)	Cl (ml/min)	$t_{1/2}$ (h)
Pulmonary TB ($n = 8$)	12.9 (10.6–15.2)	1.6 (1.1–2.1)	61.1 (50.0–72.3)	79.6 (63.1–96.0)	9.7 (7.6–11.9)	3.1 (2.8–3.5)
HIV ($n = 4$)	11.5 (9.4–13.6)	3.5 (0.5–6.6)	56.1 (42.2–70.0)	72.4 (56.4–91.8)	11.2 (8.7–13.7)	4.2[b] (3.8–4.6)
HIV-TB ($n = 7$)	10.1 (8.3–11.8)	2.0 (1.3–2.7)	52.4 (44.9–59.8)	69.3 (62.7–75.8)	11.3 (9.7–13.0)	3.3 (2.8–3.7)

[a] For definitions of abbreviations, see Table 2, footnote *a*.
[b] $P < 0.05$ (versus pulmonary TB results).

We are grateful to S. P. Tripathy and P. R. Narayanan for all the support. We acknowledge the secretarial assistance rendered by B. Doraiswamy. We thank the staff members of the HIV and Bacteriology Departments for carrying out investigations. We acknowledge the help rendered in patient management by clinic nurses J. Nagalakshmi and A. Komathi and for special bacteriological investigations by Ranjani Ramachandran. We thank the Department of Clinical Pharmacology, Seth GS Medical College, and KEM hospital, Mumbai, India, for pharmacokinetic analyses using WinNonlin software.

REFERENCES

1. **Acocella, G., A. Nonis, G. Perna, E. Patane, G. Gialdroni-Grassi, and C. Grassi.** 1988. Comparative bioavailability of isoniazid, rifampin, and pyrazinamide administered in free combination and in a fixed triple formulation designed for daily use in antituberculosis chemotherapy. Am. Rev. Respir. Dis. **138:**886–890.
2. **Barakat, M. T., J. Scott, J. M. Hughes, M. Walport, J. Calam, J. S. Friedland, P. W. Ind, and C. McKenna.** 1996. Persistent fever in pulmonary tuberculosis (clinical conference). Br. Med. J. **313:**1543–1545.
3. **Berning, S. E., G. A. Huitt, M. D. Iseman, and C. A. Peloquin.** 1992. Malabsorption of antituberculosis medications by a patient with AIDS. N. Engl. J. Med. **327:**1817–1818.
4. **Choudhri, S. H., M. Hawken, S. Gathua, G. O. Minyiri, W. Watkins, J. Sahai, D. S. Sitar, F. Y. Aoki, and R. Long.** 1997. Pharmacokinetics of antimycobacterial drugs in patients with tuberculosis, AIDS, and diarrhea. Clin. Infect. Dis. **25:**104–111.
5. **Ellard, G. A., D. R. Ellard, B. W. Allen, D. J. Girling, A. J. Nunn, S. K. Teo, H. K. Ng, and S. L. Chan.** 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.
6. **Gordon, S. M., C. R. Horsburgh, Jr., C. A. Peloquin, J. A. Havlik, Jr., B. Metchock, L. Heifets, J. E. McGowan, Jr., and S. E. Thompson III.** 1993. Low serum levels of oral antimycobacterial agents in patients with disseminated *Mycobacterium avium* complex disease. J. Infect. Dis. **168:**1559–1562.
7. **Gurumurthy, P., G. Ramachandran, A. K. Hemanth Kumar, S. Rajasekaran, C. Padmapriyadarsini, S. Swaminathan, P. Venkatesan, L. Sekar, S. Kumar, O. R. Krishnarajasekhar, and P. Paramesh.** 2004. Malabsorption of rifampicin and isoniazid in HIV infected patients with and without tuberculosis. Clin. Infect. Dis. **38:**280–283.
8. **Gurumurthy, P., T. N. Gayathri, S. Bhagavathy, and P. Venkatesan.** 2004. Standardisation of the method for the estimation of ethambutol in pharmaceutical preparations and in biological fluid. Ind. J. Exp. Biol. **42:**68–73.
9. **Gurumurthy, P., N. G. K. Nair, and G. Raghupati Sarma.** 1980. Methods for the estimation of pyrazinamide and pyrazinoic acid in body fluids. Ind. J. Med. Res. **71:**129–134.
10. **Hemanth Kumar, A. K., C. Immanuel, G. Ramachandran, K. Silambu Chelvi, L. Victor, and P. Gurumurthy.** 2004. A validated high performance liquid chromatography method for the determination of rifampicin and desacetyl rifampicin in plasma and urine. Ind. J. Pharmacol.
11. **Kotler, D. P., A. Francisco, F. Clayton, J. V. Scholes, and J. M. Orenstein.** 1990. Small intestinal injury and parasitic diseases in AIDS. Ann. Intern. Med. **113:**444–449.
12. **Olson, W. A., P. G. Dayton, Z. H. Israili, and A. W. Pruitt.** 1977. Spectrophotofluorimetric assay for isoniazid and acetylisoniazid in plasma adapted to paediatric studies. Clin. Chem. **23:**745–748.
13. **Patel, K. B., R. Belmonte, and H. M. Crowe.** 1995. Drug malabsorption and resistant tuberculosis in HIV-infected patients. N. Engl. J. Med. **332:**336–337.
14. **Peloquin, C. A., A. A. MacPhee, and S. E. Berning.** 1993. Malabsorption of antimycobacterial medications. N. Engl. J. Med. **329:**1122–1123.
15. **Peloquin, C. A., A. T. Nitta, W. J. Burman, K. F. Brudney, J. R. Miranda-Massari, M. E. McGuinness, S. E. Berning, and G. T. Gerena.** 1996. Low antituberculosis drug concentrations in patients with AIDS. Ann. Pharmacother. **30:**919–923.
16. **Raghupati Sarma, G., M. Kannapiran, A. S. L. Narayana, S. Radhakrishna, and S. P. Tripathy.** 1976. Determination of acetylator phenotype based on the ratio of acetylisoniazid to isoniazid in urine following an oral dose of ordinary isoniazid. Ind. J. Med. Res. **64:**1–8.
17. **Sahai, J., K. Gallicano, L. Swick, S. Tailor, G. Garber, I. Seguin, L. Oliveras, S. Walker, A. Rachlis, and D. W. Cameron.** 1997. Reduced plasma concentrations of antituberculosis drugs in patients with HIV infection. Ann. Intern. Med. **127:**289–293.
18. **Small, P. M., G. F. Schecter, P. C. Goodman, M. A. Sande, R. E. Chaisson, and P. C. Hopewell.** 1991. Treatment of tuberculosis in patients with advanced human immuno-deficiency virus infection. N. Engl. J. Med. **324:**289–294.
19. **Taylor, B., and P. J. Smith.** 1998. Does AIDS impair the absorption of antituberculosis agents? Int. J. Tuberc. Lung Dis. **2:**670–675.