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Two- and Four-Day Rifampin Chemoprophylaxis Regimens Induce Oxidative Metabolism

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The effects of two short-term chemoprophylaxis regimens of rifampin (2 or 4 days) on oxidative metabolism were investigated in 14 healthy subjects. Seven subjects received 600 mg of rifampin twice daily on study days 6 and 7 (group A), and seven subjects received 600 mg of rifampin once daily on days 4, 5, 6, and 7 (group B). Antipyrine (18 mg/kg of body weight) was administered orally on days 1, 8, and 15. Short-term rifampin regimens increased oral clearance of antipyrine in both groups compared with the baseline value ($P < 0.05$), and group B displayed a larger percent increase over the baseline value than group A did (70.5 ± 14.3 versus 33.1 ± 18.1; $P < 0.05$). The partial metabolic clearance (CL_M) of antipyrine to 3-hydroxymethylantipyrine (HMA) on day 8 increased 71 and 108% for regimens A and B, respectively ($P < 0.05$ for both). The corresponding increases in CL_M to norantipyrine (NORA) were 57 and 98% ($P < 0.05$ for both). CL_M to 4-hydroxyantipyrine (OHA) on day 8 increased 64% for regimen A ($P = 0.08$) and 97% for regimen B ($P < 0.05$) compared with the baseline. Although CL_M to HMA and OHA on day 15 remained >50% over the baseline with both regimens, CL_M to NORA on day 15 was <25% over the baseline with both regimens. Thus, both short-term rifampin chemoprophylaxis regimens increased antipyrine clearance for at least 1 week. The increase tended to be higher with the 4-day regimen. The pattern observed for the CL_Ms suggests that more than one P-450 enzyme is affected.

Rifampin is a broad-spectrum semisynthetic antibiotic used in the treatment of tuberculosis and other infectious diseases. It is also recommended as short-term chemoprophylaxis against *Haemophilus influenzae* type b and *Neisseria meningitidis* infections (14, 24). The recommended dosage for adults as chemoprophylaxis against *H. influenzae* type b is 600 mg of rifampin given orally once daily for 4 days. Currently, one of two dosing regimens is recommended in adults for chemoprophylaxis against *N. meningitidis* infection: 600 mg of rifampin given orally every 12 h for 2 days or once daily for 4 days (12, 14, 24, 25). Rifampin is a well-known inducer of the hepatic cytochrome P-450 oxidase system in humans (7, 30, 31). Hepatic P-450 induction is characterized by an increase in hepatic P-450 enzyme content and activity as well as proliferation of hepatic smooth endoplasmic reticulum (21, 30, 31). Induction of hepatic P-450 microsomal enzyme activity with rifampin may lead to clinically important alterations in the therapeutic responses to other drugs metabolized by these enzymes (3, 4). For example, several cases of acute graft rejection in transplant patients because of enhanced cyclosporine clearance during concomitant rifampin therapy have been reported (1, 15, 26, 41).

Antipyrine possesses several qualities that make it a useful marker of hepatic oxidative metabolism. For example, it exhibits negligible protein binding and its elimination is almost totally dependent on hepatic metabolism (42, 43). Furthermore, the partial metabolic clearances (CL_Ms) for the major metabolites of antipyrine, 3-hydroxymethylantipyrine (HMA), 4-hydroxyantipyrine (OHA), and norantipyrine (NORA), provide information on the activity of the P-450 enzyme(s) responsible for different metabolic pathways (8, 19, 40).

Studies of enzyme induction with rifampin using antipyrine as a marker have typically used 7- to 14-day regimens (27, 33, 40). Although there is limited in vitro and in vivo evidence that hepatic enzyme induction occurs within 2 to 4 days after exposure to rifampin (13, 20, 27, 35), the short-term 2- and 4-day chemoprophylaxis regimens have not been thoroughly evaluated for their effects on hepatic oxidative metabolism. Therefore, the aim of this study was to evaluate the effects of the two approved rifampin chemoprophylaxis regimens on antipyrine pharmacokinetics and the formation of antipyrine metabolites.

MATERIALS AND METHODS

Subjects. Fourteen healthy male volunteers, ranging in age from 23 to 31 years (mean age, 25.7 years) and ranging in weight from 66 to 98 kg (mean weight, 82.0 kg), participated in the study. Subjects were screened by physical examination, medical history, and routine laboratory tests. All subjects were nonsmokers (for at least 2 years) and were not passively exposed to smoke from other smokers to any significant extent during their daily activities, as assessed by a questionnaire. Individuals who worked routinely with laboratory or other chemicals were excluded from the study. The subjects were asked to abstain from any over-the-counter drugs and ethanol for 3 days prior to and during the study procedures and to abstain from possible dietary P-450 enzyme inducers (i.e., cabbage, brussels sprouts, and charcoal-broiled foods) for 7 days prior to and during the study procedures. All subjects were asked to refrain from caffeine

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intake for 24 h before and during blood sampling. The protocol was approved by the University of Tennessee's Institutional Review Board, and each subject gave written informed consent before participating in the study.

Study design. On the mornings of study days 1 (baseline), 8, and 15, each subject received a single oral dose (18 mg/kg of body weight) of antipyrine crystals USP (City Chemical Corp., New York, N.Y.) dissolved in 150 ml of water. Subjects were asked to fast for 8 h before and 3 h after each antipyrine dose. A table of random numbers was used to assign subjects to one of two rifampin treatment groups. The seven subjects in group A received 600 mg of rifampin (Rifadin; Marion Merrell Dow, Cincinnati, Ohio) orally at 7 a.m. and 7 p.m. on study days 6 and 7. The seven subjects in group B received 600 mg of rifampin orally once daily at 7 p.m. on study days 4, 5, 6, and 7. All subjects were instructed to take rifampin on an empty stomach 1 h before or 2 h after meals.

Sampling and analysis. Venous blood samples (10 ml each) were collected into heparinized tubes immediately before and at 20 and 40 min and 1, 2, 4, 6, 8, 12, 24, and 32 h after each antipyrine dose. Plasma was separated from whole blood by centrifugation and stored at −20°C until analysis. After antipyrine administration, urine was collected for 32 h in containers to which 3 g of sodium metabisulfite, an antioxidant, had been previously added. The total volume of urine collected for each subject was determined, and aliquots were frozen at −20°C until analysis. Plasma samples were prepared for injection by a previously described method (9). Antipyrine concentrations in plasma were determined by high-performance liquid chromatography (HPLC) by a modified version (38) of the method of Danhof et al. (17). At plasma antipyrine concentrations of 6 and 30 mg/liter, the assay was determined to be accurate (bias < 4.5%) and precise (between- and within-day coefficients of variation < 4.0%). After hydrolysis with β-glucuronidase and sulfatase (Glusulase; DuPont Biomedical, Boston, Mass.), the concentrations of antipyrine and its three major metabolites (HMA, OHA, and NORA) in urine were determined by HPLC by previously described procedures (6).

Pharmacokinetic calculations. Standard noncompartmental methods were used to calculate pharmacokinetic parameters. The terminal rate constant of antipyrine was determined by linear regression from the log-linear portion of the plasma antipyrine concentration-time curve. The half-life was calculated as (ln 2)/k, where k is the terminal rate constant. The area under the plasma antipyrine concentration-time curve was determined by the linear trapezoidal method for the ascending portion of the curve and by the logarithmic trapezoidal method for the descending portion; this value was then extrapolated to infinity by using the ratio of the last measured plasma antipyrine concentration to the terminal rate constant. Oral clearance (CL_O) was calculated as antipyrine dose/area under the concentration-time curve. The renal clearance of antipyrine and the CL_Ms for the antipyrine metabolites were determined by A_{e0-32}/AUC_{0-32}, where A_e is the total amount of antipyrine or metabolite excreted in 32 h (in terms of antipyrine equivalents) and AUC_{0-32} is the area under the concentration-time curve from 0 to 32 h. Calculation of CL_M with the above equation assumes the following: the metabolites are formed exclusively in the liver, their formation rates are rate limiting with respect to urinary excretion, they are not further metabolized except to conjugates (which can be hydrolyzed), and they are entirely excreted in urine. These assumptions appear to be valid for antipyrine (8, 33). It was further assumed that rifampin does not alter antipyrine bioavailability.

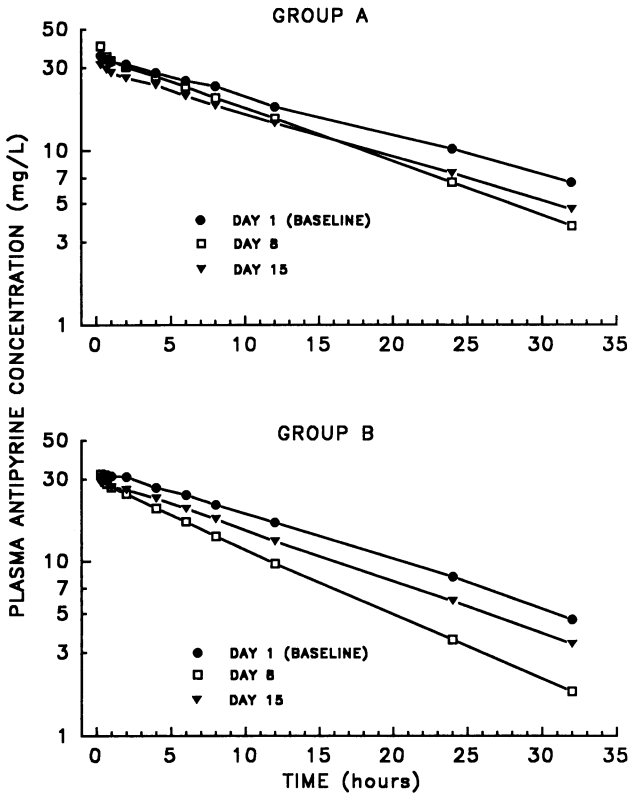

FIG. 1. Plasma antipyrine concentration-time curves after a single oral dose of antipyrine (18 mg/kg) on study days 1, 8, and 15. Group A was given 600 mg of rifampin orally every 12 h for 2 days (n = 7); group B was given 600 mg of rifampin orally once daily for 4 days (n = 7). The mean plasma antipyrine concentrations on days 1 (baseline), 8 (immediately after rifampin administration), and 15 (1 week after rifampin discontinuation) are shown.

Statistical analysis. Mean pharmacokinetic parameters were compared by analysis of variance utilizing a nested factorial design. When a significantly different value was observed with the analysis of variance, comparisons between study days and between rifampin treatment groups were made by using the least significant difference test after a Bonferonni correction for multiple comparisons (23). All statistical analyses were done with the SAS statistical package (37). Unless otherwise indicated, data are reported as mean values ± standard deviations.

RESULTS

Figure 1 illustrates the plasma antipyrine concentration-time curves for both rifampin treatment groups. Faster elimination of antipyrine is evident on day 8 than on day 1 (baseline) for both groups. This effect was more prominent for subjects receiving rifampin daily for 4 days (group B). Faster elimination was still evident 1 week after rifampin had been discontinued (day 15) than on day 1 (baseline), although the effect was less prominent. These observations are consistent with the pharmacokinetic parameters in Table 1. The half-life on day 8 was significantly shorter than on day 1 (baseline) for both groups ($P < 0.05$). The half-life on day 15 was significantly shorter for group A ($P < 0.05$), but the

TABLE 1. Antipyrine pharmacokinetic data[a]

Study day	$t_{1/2}$ (h)		CL_O (ml/min/kg)	
	Group A	Group B	Group A	Group B
1 (baseline)	13.5 ± 1.8	11.1 ± 1.3	0.467 ± 0.061	0.561 ± 0.089
8	9.8 ± 1.2*	8.0 ± 0.9*	0.614 ± 0.053*	0.952 ± 0.129*
15	12.1 ± 1.6*	10.0 ± 1.5	0.607 ± 0.054*	0.719 ± 0.120*

[a] The data are mean values ± standard deviations for pharmacokinetic parameters for seven subjects given 600 mg of rifampin orally every 12 h for 2 days (group A) and seven subjects given 600 mg of rifampin orally once daily for 4 days (group B). The terminal half-life ($t_{1/2}$) and CL_O were measured on study days 1 (baseline), 8 (immediately after rifampin was administered), and 15 (1 week after rifampin had been discontinued). The asterisks indicate that the values were significantly different from the baseline (day 1) value ($P < 0.05$).

value for group B was not statistically significantly different from the baseline.

Antipyrine CL_O increased significantly on day 8 compared with the baseline for both treatment groups ($P < 0.05$). The percent increase in CL_O from the baseline for group B was greater than for group A (70.5 ± 14.3 versus 33.1 ± 18.1; $P < 0.05$). One week after rifampin discontinuation, CL_O remained higher than the baseline for both groups ($P < 0.05$); however, the percent increases from the baseline were similar (28.4 ± 14.6 versus 31.2 ± 13.5 for groups B and A, respectively). Differences in the extent and time course of induction are further illustrated in Fig. 2, which shows the individual changes in CL_O. It is noteworthy that antipyrine CL_O increased for all subjects in both groups. The mean renal clearances of antipyrine were 0.015 ± 0.006 ml/min/kg for group A and 0.018 ± 0.008 ml/min/kg for group B, and it was not altered by either rifampin regimen.

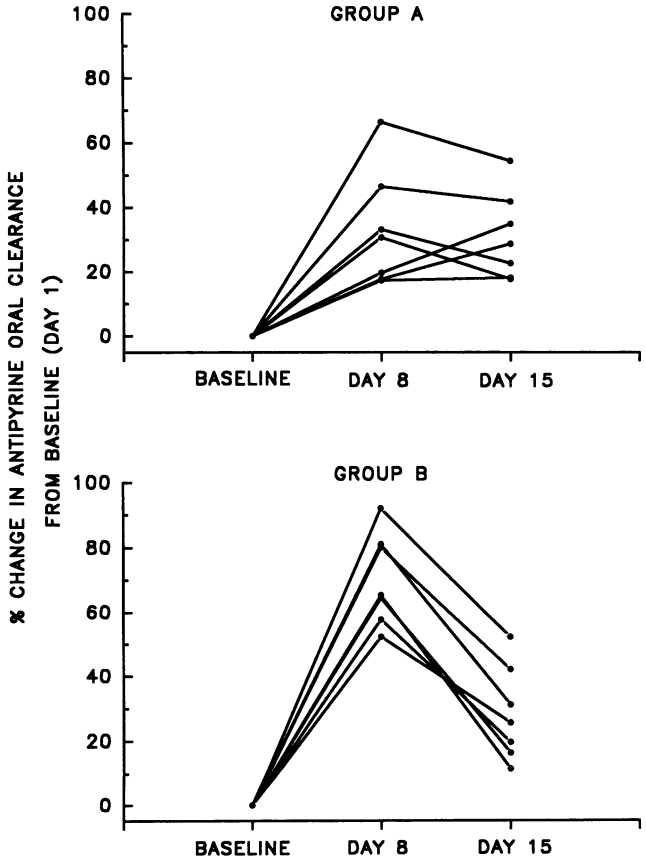

FIG. 2. Percent change in antipyrine CL_O from the baseline (day 1). Group A was given 600 mg of rifampin orally every 12 h for 2 days ($n = 7$); group B was given 600 mg of rifampin once daily for 4 days ($n = 7$). The percent changes from the baseline (day 1) on days 8 (immediately after rifampin administration) and 15 (1 week after rifampin discontinuation) are shown.

Table 2 shows that the group A CL_Ms for HMA and NORA were increased on day 8 compared with the baseline ($P < 0.05$). The mean increases were 71.3 and 56.8% for HMA and NORA, respectively (Fig. 3). A similar increase in CL_M for OHA was also observed (64.1% over the baseline); however, the value was not statistically different from the baseline ($P = 0.08$) because of the greater variability in the data. The group B CL_Ms for all three antipyrine metabolites were higher on day 8 than on day 1 (baseline) ($P < 0.05$; Table 2). Mean increases of 107.5, 98.4, and 96.9% were observed for HMA, NORA, and OHA, respectively (Fig. 3).

One week after rifampin discontinuation, group A CL_Ms for HMA and OHA were still 64.8 and 53.5% over the baseline, although the difference was statistically significant only for HMA (Table 2 and Fig. 3). Similarly, group B CL_Ms for HMA and OHA remained 79.7 and 70.0% over the baseline on day 15 ($P < 0.05$). However, it is noteworthy that for both groups the percent increases in NORA CL_Ms on day 15 were less than half the values observed on day 8 (Fig. 3) and were no longer statistically different from the baseline (Table 2).

DISCUSSION

Previous studies have examined the effects of 7 or more days of rifampin treatment on the pharmacokinetics of antipyrine and its metabolites. These studies reported a dose-related P-450 enzyme induction, as measured by increases in antipyrine clearance (5, 27–29, 33, 40). In this study, chemoprophylactic doses of rifampin administered either twice daily for 2 days or once daily for 4 days for a total dose of 2,400 mg induced antipyrine metabolism. Additionally, the increase in antipyrine CL_O remained statistically significant 1 week after rifampin discontinuation. Thus, a relatively prolonged effect on hepatic drug metabolism was produced in every subject with short-term administration of rifampin.

Enzyme induction is affected by the dosage regimen of the inducing agent (10, 28, 29) and this is underscored by the difference in CL_O we observed between the two groups. The same total rifampin dose administered over 4 days caused an approximately 2.5-fold greater percent increase in antipyrine CL_O on day 8 (immediately after rifampin administration) than the 2-day regimen did. Furthermore, a more rapid return toward the baseline was evident during the week after rifampin discontinuation for the group receiving the 4-day regimen than for the group receiving the 2-day regimen. The

TABLE 2. CL_Ms for antipyrine metabolites[a]

Study day	CL_M (ml/min/kg)[b]					
	HMA		NORA		OHA	
	Group A	Group B	Group A	Group B	Group A	Group B
1 (baseline)	0.017 ± 0.004	0.022 ± 0.005	0.083 ± 0.035	0.108 ± 0.029	0.089 ± 0.036	0.123 ± 0.048
8	0.028 ± 0.003*	0.046 ± 0.008*	0.127 ± 0.048*	0.220 ± 0.086*	0.125 ± 0.020	0.233 ± 0.065*
15	0.029 ± 0.012*	0.040 ± 0.008*	0.107 ± 0.056	0.131 ± 0.049	0.124 ± 0.048	0.202 ± 0.059*

[a] Seven subjects were given 600 mg of rifampin orally every 12 h for 2 days (group A), and seven subjects were given 600 mg of rifampin orally once daily for 4 days (group B). CL_Ms were measured on study days 1 (baseline), 8 (immediately after rifampin was administered), and 15 (1 week after rifampin had been discontinued).

[b] Means ± standard deviations. The asterisks indicate that the values were significantly different from the baseline (day 1) value ($P < 0.05$).

respective types and amounts of P-450 enzymes induced may differ after 2 and 4 days of treatment and could explain the differences in the time course of enzyme induction. Although enzyme induction persisted at least 1 week after rifampin was discontinued, it is unclear when the increased enzyme activity would return to baseline values.

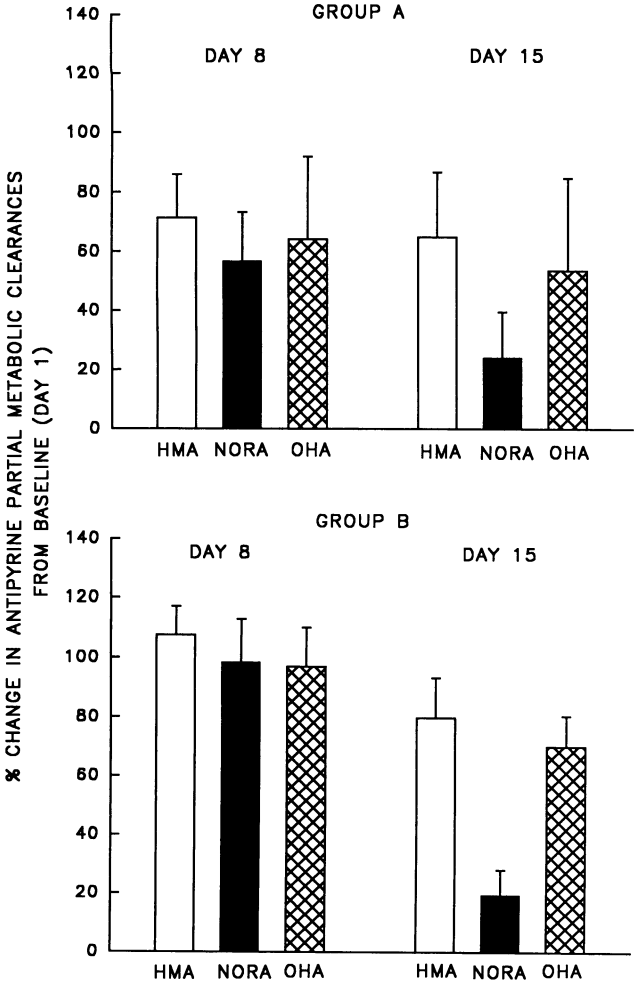

FIG. 3. Percent change in antipyrine CL_Ms from the baseline (day 1). Group A was given 600 mg of rifampin orally every 12 h for 2 days ($n = 7$); group B was given 600 mg of rifampin orally once daily for 4 days ($n = 7$). The percent changes from the baseline (means ± standard errors of the means) on days 8 (immediately after rifampin administration) and 15 (1 week after rifampin discontinuation) are shown.

In vitro and in vivo studies have indicated that hepatic enzyme induction occurs within 2 to 4 days after exposure to rifampin (13, 20, 27, 35). Prober (36) reported decreases in serum chloramphenicol concentrations by 85.5 and 63.8% within 3 days of the start of a 4-day rifampin regimen in two pediatric patients. Similarly, Kelly et al. (22) observed two pediatric patients with decreases in serum chloramphenicol concentrations below the accepted therapeutic range by the third day of a 4-day rifampin treatment. Ohnhaus et al. (27) examined the time course of enzyme induction during administration of 600 or 1,200 mg of rifampin for 7 or 14 days in 26 healthy volunteers. An increase in the ratio of 6β-hydroxycortisol to free cortisol in urine provided evidence of hepatic enzyme induction by day 2 to 3 of treatment with these regimens. The current study, however, is the first to characterize the effects of short-term rifampin administration on the pharmacokinetics of another drug.

There is evidence that antipyrine can produce a relatively small increase in its own clearance when administered daily for at least 1 week (11, 18). Although antipyrine autoinduction could have confounded our results on days 8 and 15, Andreason et al. (2) and Vesell et al. (44) have reported no evidence of autoinduction when antipyrine (18 mg/kg) was administered in two doses spaced 7 days apart. Similarly, Crom et al. (16) administered antipyrine on days 1, 8, and 22, with no change in the mean clearance of antipyrine.

We are unaware of other studies evaluating antipyrine metabolite formation after short-term rifampin administration. Previous reports have indicated that treatment with rifampin for at least 7 days induced NORA formation to a greater extent than OHA or HMA formation (28, 33, 40). These findings contrast with our results, in which the percent increase from the baseline in NORA, OHA, and HMA CL_Ms were similar after rifampin treatment (day 8) for both groups. Incomplete induction of the enzyme(s) responsible for production of NORA after a short-term course of rifampin could explain the discrepancy with previous studies. The relatively larger decline in CL_M to NORA after discontinuation of rifampin adds to the growing body of evidence that different P-450 enzymes are involved in the production of antipyrine metabolites (18, 32, 40).

Although studies with specific drugs will be needed, it is highly probable that chemoprophylactic regimens of rifampin will alter the disposition of other drugs which, like antipyrine, are eliminated by oxidative metabolism. The specific P-450 enzymes responsible for antipyrine oxidative metabolism have yet to be identified. Immunochemical studies have demonstrated that the P450IIIA gene subfamily encodes for rifampin-inducible enzyme activity, and in vitro induction has been observed after oral administration of rifampin (13, 34, 35). Consequently, drugs metabolized by

this enzyme subfamily may be affected by short-term rifampin administration. A strong correlation between the CL_M for OHA and the total clearance of theophylline has been reported (17, 39), providing one example of a widely used drug whose clearance will likely be increased in patients who receive rifampin chemoprophylaxis.

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