Single-dose Pharmacokinetics of Rifapentine in Elderly Men

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Purpose. This study was undertaken to characterize the pharmacokinetic profiles of rifapentine and its active metabolite, 25-desacetyl-rifapentine, in elderly men.

Methods. Fourteen healthy, nonsmoking male volunteers between the ages of 65 and 82 years received a single oral 600 mg dose of rifapentine. Plasma samples were collected at frequent intervals for up to 72 hours postdose. The control group consisted of 20 healthy, young (18–45 years) male volunteers from a previous, single-dose (600 mg) rifapentine pharmacokinetic study.

Results. Plasma rifapentine concentrations above the minimum inhibitory concentration for *M. tuberculosis* were observed at 2 hours after dosing. Disposition of rifapentine was monophasic with a mean terminal half-life of 19.6 hours. The peak plasma concentration of 25-desacetyl-rifapentine was found 21.7 hours, on average, after the rifapentine dose; the mean 25-desacetyl-rifapentine $t_{1/2}$ was 22.9 hours. Compared to the younger subjects, apparent oral clearance of rifapentine (24%) was lower in the elderly male ($p < 0.05$), and Cmax (28%) was higher. The only adverse event reported in both the older and younger subjects in these single-dose studies was discoloration of the urine.

Conclusions. Because the age-related changes in the pharmacokinetic profile of rifapentine observed in this study were modest and unlikely to be associated with toxicity, no dosage adjustments for this antibiotic are recommended in elderly patients.

KEY WORDS: rifapentine; rifamycin antibiotics; elderly; absorption; disposition.

INTRODUCTION

Rifapentine is an orally active rifamycin antibiotic with *in vitro* and *in vivo* activity against a variety of microorganisms, including *Mycobacterium tuberculosis* and *M. avium* (1–3). Similar to its homologue, rifampin (4), rifapentine most likely exerts its antibacterial activity by binding to a single and highly specific site on the bacterial DNA-dependent RNA polymerase enzyme and ultimately inhibiting bacterial RNA synthesis. Rifapentine is currently under development for the treatment of pulmonary tuberculosis and for the prevention of *M. avium* complex infections.

Previous investigations that evaluated the absorption and disposition of rifapentine in healthy male subjects found that the drug undergoes deacetylation by esterases found throughout the body (5) to a metabolite, 25-desacetyl-rifapentine (6–9), which has *in vitro* antibacterial activity comparable to rifapentine. Parent drug and metabolite are then eliminated primarily through fecal excretion. In contrast to rifampin (10), oral absorption of rifapentine was enhanced by coingestion with food (7–9). Mean elimination half-life ($t_{1/2}$) of rifapentine following oral administration in healthy young men was between 13 and 14 hours (6–9), much longer than the $t_{1/2}$ of 1.9 to 5.1 hours reported with rifampin (10).

A number of physiologic changes occur with advancing age that have the potential to alter the pharmacokinetic profile of a drug (11–14). These physiologic changes include alterations in body composition, gastrointestinal function (including decreased gastrin secretion), hepatic metabolism, and glomerular filtration rate (15–18). There is considerable variation, however, in the effect aging can have on drug absorption and disposition (11,19). In addition, with the exception of drugs that depend exclusively on glomerular filtration rate, no markers exist that help predict the extent to which the pharmacokinetic parameters of a drug will be influenced by diminishing organ function. For these reasons, pharmacokinetic assessments of individual drugs are required to determine appropriate dosage requirements for elderly patients (11,20).

Over the last few decades, tuberculosis has become a disease of the elderly in industrialized countries as the median age of tuberculosis patients has progressively increased (21,22). In addition, similar risks for *Mycobacterium avium* complex infection are seen when HIV-infected persons are compared by age (23). Because of the prevalence of mycobacterial infections in elderly persons, the pharmacokinetic assessment of the drugs used to treat the infections in this age group is an important step in optimizing therapy. This study was undertaken, therefore, to characterize the pharmacokinetics of rifapentine and its active 25-desacetyl metabolite in elderly men. The 600 mg dose of rifapentine chosen for this pharmacokinetic study is the dose under investigation in the clinical studies. The rifapentine dosage regimen for the treatment of tuberculosis is 600 mg twice weekly during the first 2-month intensive phase, followed by 600 mg once weekly during the subsequent continuation phase.

METHODS

Subjects and Study Design

In this open-label study, 14 healthy male volunteers who were at least 65 years of age and within 10% of ideal body weight were eligible for enrollment. The prestudy screening procedures (conducted within 14 days prior to study initiation) included a medical history, physical examination, hepatitis B surface antigen, and human immunodeficiency virus (HIV) antibody screen. A urine drug abuse screen was conducted on the evening before study drug administration. Each subject enrolled was free from any clinically significant prestudy laboratory test abnormality or organ dysfunction or disease, and had a fasting serum gastrin concentration greater than 100 pg/ml. Written informed consent was obtained from each study participant. The data obtained from these 14 elderly male subjects were compared to data obtained in 20 healthy, young (18–45 years) male volunteers from a previous, single-dose (600 mg) rifapentine pharmacokinetic study (7).

Subjects reported to the clinic the day before rifapentine dosing and remained in the clinic for 4 days after the dose was given. Following an overnight fast, a single 600 mg oral dose of rifapentine (four 150 mg film-coated tablets) was adminis-

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tered at 8:00 a.m. with 240 ml of deionized water. Standard caffeine-free meals were provided throughout the clinic stay, starting with lunch given 5 hours after the rifapentine dose on day 1. A 5 ml blood sample was collected for rifapentine and 25-desacetyl-rifapentine plasma concentration determinations immediately before and 2, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, and 72 hours following drug administration.

To assess safety, blood pressure, heart rate, and electrocardiogram measurements were obtained prior to rifapentine dosing and at the completion of the study. In addition, adverse events were collected and recorded throughout the clinic stay.

Plasma Sample Analysis

High performance liquid chromatography (HPLC) with visible detection was used to analyze the plasma samples for rifapentine and 25-desacetyl-rifapentine concentrations. A structurally related compound, 25-desacetyl-rifampin, was used as an internal standard. This bioanalytical method had been previously validated in human plasma (with heparin as an anticoagulant) by Hoechst Marion Roussel, Inc. Sample preparation consisted of adding 100 μL of plasma sample, 100 μL of methanol (containing drug as appropriate for calibration standards), and 500 μL of internal standard in methanol together in an autosampler vial. The contents of the vial were mixed to precipitate the plasma proteins, centrifuged at 3000 rpm for 5 minutes, then a sample of the supernatant (20 μL) was injected directly into the HPLC system.

The HPLC system consisted of a Waters Model 610 pump (Waters Chromatography, Milford, Massachusetts) connected to a Gilson Model 233-XL autosampler (Gilson Medical Electronics, Middleton, Wisconsin) unit equipped with a 20 μL Rheodyne injection loop. The autosampler used a Gilson Model 401 dilutor with a 1-ml syringe to perform liquid transfers. The analytical HPLC column was a Primesphere ODS-HC column (150 × 2.0 mm, 5 μ, high carbon loading, Phenomenex, Inc., Torrance, California), with a matching 30 × 2.0 mm guard. A 5.0 μm in-line filter was placed prior to the guard column to trap any particulate matter. Analytes were detected using a Spectra-Physics model UV2000 Ultraviolet detector (Thermo-Separation Products, Fremont, California). Mobile phase consisted of 40% methanol, 25% acetonitrile, 35% water, and 0.5% glacial acetic acid. Flow was isocratic at 0.45 ml/min and the column temperature was maintained at ambient. The ultraviolet detector was set at a wavelength of 480 nm, rise time was 5 minutes, and range was 0.1 AUFS.

The validated assay has nominal standard curve ranges of 0.5 to 60 μg/ml using 0.1 ml of plasma for both analytes. The batch-to-batch mean percent accuracies of the quality control samples of rifapentine and 25-desacetyl-rifapentine were 93.1 to 97.0% and 94.0 to 104%, respectively. The respective mean percent coefficients of variation (precision) of the quality control samples were 2.9 to 5.3% and 2.4 to 5.2%.

Data Analysis

Model-independent methods were used to calculate pharmacokinetic parameters for rifapentine and 25-desacetyl-rifapentine from plasma concentration-time data. For the calculation of 25-desacetyl-rifapentine parameters, a dose correction factor (0.952) based on molecular weight was applied. The parameters, C_{max} and t_{max}, were observed directly from the plasma concentration-time profiles. The terminal elimination rate constant (λ_Z) was estimated by the linear least squares regression of log plasma concentration-time data during the terminal elimination phase and $t_{1/2}$ was calculated by dividing 0.693 by λ_Z. The linear trapezoidal rule was applied to calculate the cumulative AUC from time zero to the last data point and the AUC from the last data point to infinity was estimated by dividing the last plasma concentration by λ_Z. Systemic apparent oral clearance (CL_{po}) was calculated by dividing the dose by $AUC(0 \rightarrow \infty)$.

Descriptive statistics (mean, standard deviation, and coefficient of variation) were calculated and used to characterize the pharmacokinetic parameters within each group. Comparisons between the two sets of data were performed to summarize age differences in the pharmacokinetic parameters of rifapentine and 25-desacetyl-rifapentine. The Wilcoxon Rank-Sum test was used to compare pharmacokinetic data between elderly and young subjects, with $p < 0.05$ as the level of significance.

RESULTS

Fourteen healthy, nonsmoking male volunteers between the ages of 65 and 82 years (mean age, 71 years) were enrolled and completed all of the pharmacokinetic and safety assessments. The volunteers who served as the control group for comparison consisted of 20 healthy, nonsmoking men between the ages of 18 and 45 years old (mean age, 25.7 years) and weighing within 10% of ideal body weight. All subjects in both study groups were Caucasian. No concomitant medications were used.

Figures 1 and 2, respectively, present the mean plasma rifapentine and 25-desacetyl-rifapentine concentration versus time profiles for the elderly and the young healthy male subjects. Plasma rifapentine concentrations were quantifiable for up to 72 hours after rifapentine dosing in 13 of the 14 elderly men. Two peaks for plasma rifapentine concentration were found at approximately 5 and 10 hours postdose. The second peak plasma concentration of rifapentine was coincident with dinner time on day 1. The mean plasma 25-desacetyl-rifapentine concentration versus time profile peaked later than the rifapentine concentration versus time profile, but followed the same terminal profile.

Mean rifapentine and 25-desacetyl-rifapentine pharmacokinetic parameters in the two groups of subjects are summarized in Table 1. Individual rifapentine AUC(0-72) accounted for more than 90% of the total $AUC(0 \rightarrow \infty)$, indicating that the sampling scheme was appropriate for the determination of $AUC(0 \rightarrow \infty)$. Plasma concentrations of rifapentine exceeded the minimum inhibitory concentration for *M. tuberculosis* (0.25 μg/ml) (1,2) by 2 hours after dosing in the elderly male subjects, with a mean t_{max} of 6.6 hours. Disposition of rifapentine was monophasic with a mean terminal half-life of 19.6 hours. The terminal portion of the rifapentine plasma concentration-time curve started at about 10 hours postdose. The active 25-desacetyl metabolite was formed slowly following oral administration of rifapentine, with a t_{max} of 21.7 hours. The disposition of 25-desacetyl-rifapentine was also monophasic, with a mean terminal half-life of 22.9 hours. At 72 hours after dosing, concentrations of 25-desacetyl-rifapentine present in plasma were approximately 90% of the parent drug.

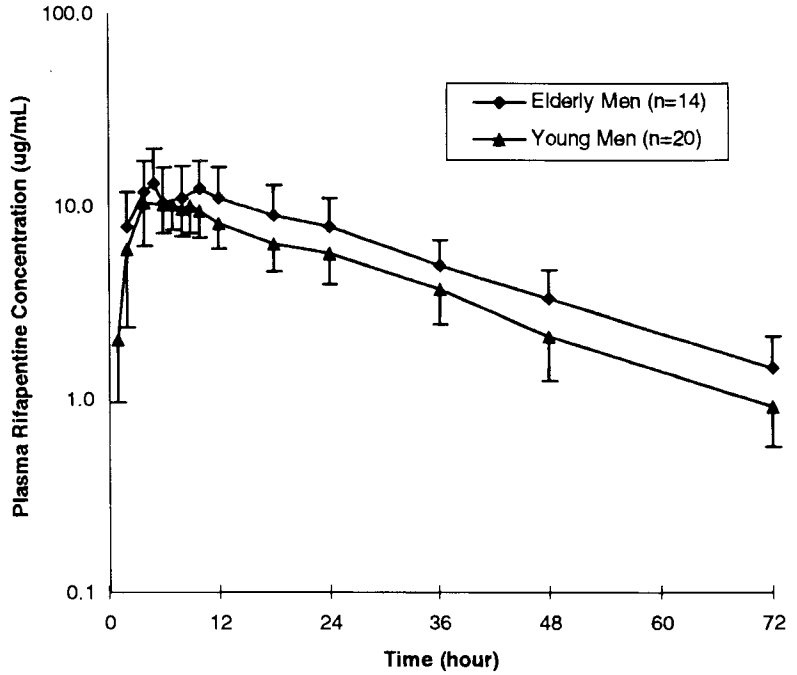

Fig. 1. Mean plasma rifapentine concentration versus time profiles for healthy elderly (mean age, 71 years; n = 14) and young (mean age, 25.7 years; n = 20) male subjects.

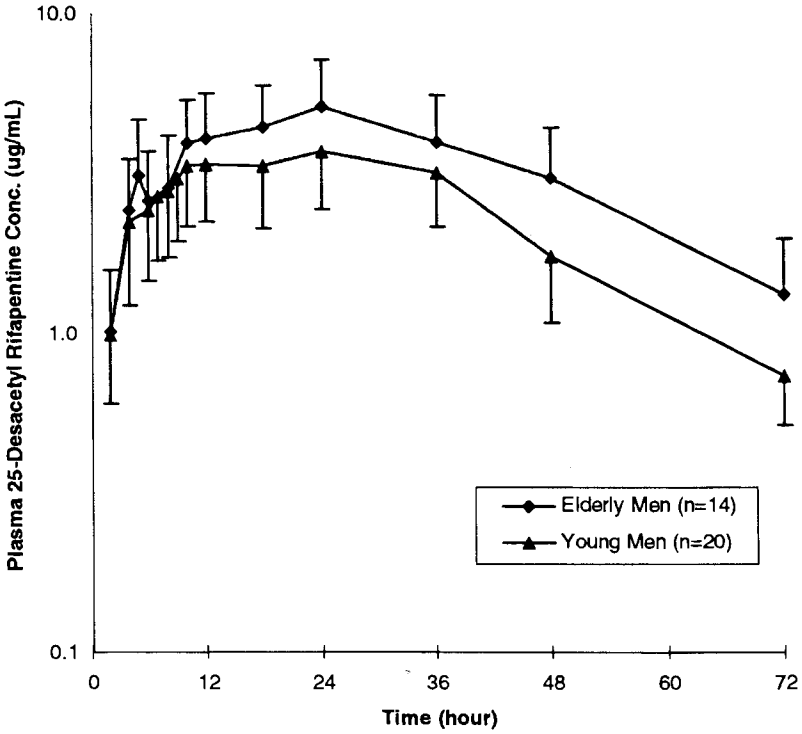

Fig. 2. Mean plasma 25-desacetyl-rifapentine concentration versus time profiles for healthy elderly (mean age, 71 years; n = 14) and young (mean age, 25.7 years; n = 20) male subjects.

Table 1. Mean (%CV) Rifapentine and 25-Desacetyl-Rifapentine Pharmacokinetic Parameters in Young and Elderly Men

Parameter	Rifapentine		25-Desacetyl-rifapentine	
	Elderly men[a] (N = 14)	Young men[b] (N = 20)	Elderly men[a] (N = 14)	Young men[b] (N = 20)
AUC (0 → ∞) (μg•h/ml)	449[c] (34)	319 (27)	279[d] (33)	177 (33)
C_{max} (μg/ml)	15.1 (41)	11.8 (27)	5.2 (37)	4.0 (30)
t_{max} (h)	6.6 (52)	5.0 (41)	21.7 (22)	19.3 (44)
CL_{po} (L/h)	1.53[c] (42)	2.20 (28)	ND	ND
$t_{1/2}$ (h)	19.6[c] (23)	15.9 (26)	22.9[d] (47)	14.3 (24)
C_{24h} (μg/ml)	7.8	5.6	5.1	3.7

[a] Mean age, 71 years.
[b] Mean age, 25.7 years; data from Reference 7.
[c] $p < 0.05$ compared to younger subjects.
[d] $p < 0.01$ compared to younger subjects AUC(0 → ∞) = area under the plasma concentration-time profile from time 0 extrapolated to infinity; C_{max} = maximum plasma concentration; CL_{po} = apparent oral clearance; C_{24h} = plasma concentration 24 hours after dosing; t_{max} = time to maximum plasma concentration; and $t_{1/2}$ = elimination half-life; BQL = below lower limit of quantitation (0.5 μg/ml); ND = not determined.

Pharmacokinetic Comparison to Healthy Subjects

Lower apparent oral clearance of rifapentine (24%) was observed in the group of elderly male subjects compared to the group of younger male volunteers ($p = 0.015$). In addition, mean rifapentine AUC(0 → ∞) and C_{max} were 41% and 28% higher in the elderly men; the difference in AUC(0 → ∞) between elderly and young subjects was statistically significant ($p = 0.015$). Similarly, mean 25-desacetyl-rifapentine AUC(0 → ∞) was 58% higher ($p = 0.004$) and C_{max} was 30% higher in the elderly male volunteers compared to the younger subjects. The ratios of metabolite to parent AUC(0 → ∞), C_{max}, and C_{24h} were similar in the groups of elderly and younger male volunteers (Table 2).

Safety

Single doses of rifapentine were well tolerated in the elderly male subjects. The only adverse event assessed as being possibly related to rifapentine was an orange-red discoloration of the urine. Discolored urine, which resolved within 4 days, occurred in all 14 elderly men. Since urine discoloration occurs with all rifamycin analogs, this was an expected event. No other adverse events were reported.

Table 2. Mean 25-Desacetyl-Rifapentine/Rifapentine Pharmacokinetic Parameter Ratios (%)

Parameter	Subject group	
	Elderly men[a] (N = 14)	Young men[b] (N = 20)
AUC(0 → ∞) (μg·h/ml)	62	54
C_{max} (μg/ml)	35	34
C_{24h} (μg/ml)	66	66

[a] Mean age, 71 years
[b] Mean age, 25.7 years; data from Reference 7. AUC(0 → ∞) = area under the plasma concentration-time profile from time 0 extrapolated to infinity; C_{max} = maximum plasma concentration; C_{24h} = plasma concentration 24 hours after dosing; ND = not determined.

DISCUSSION

Many changes occur with aging that could theoretically affect drug absorption and disposition. However, the effects that aging may have on absorption, distribution, metabolism, or excretion are not always predictable. In this study, the absorption and disposition of rifapentine and its 25-desacetyl metabolite following single-dose administration of rifapentine were evaluated in elderly men. Mean rifapentine AUC(0 → ∞) and C_{max} were 41% and 28% higher, respectively, in healthy elderly male volunteers compared to a group of healthy young male volunteers, and mean $t_{1/2}$ was about 19% longer. Mean 25-desacetyl-rifapentine AUC(0 → ∞) and C_{max} were similarly higher in elderly men. Despite the age-related pharmacokinetic differences, however, rifapentine was well tolerated in the group of elderly volunteers.

The metabolic fate of rifapentine includes deacetylation, followed by fecal and renal excretion of parent drug and metabolite (6). Based on this metabolic scheme, changes in the pharmacokinetic profile of rifapentine that might occur with advancing age are not readily predictable. In general, secretion of gastric acid and gastric emptying decreases with increasing age (15). Except for drugs whose solubility is pH-dependent, however, the extent of drug absorption is generally not compromised in the elderly, although absorption may be delayed (12,14,15,20). In previous studies, ingestion of rifapentine with food produced higher rates of oral bioavailability compared to ingestion on an empty stomach (7–9), which suggests that absorption of rifapentine may be pH-dependent. In this study, two peak plasma rifapentine concentrations were found, with the second peak occurring coincident with the ingestion of dinner. The most likely explanation for the second rifapentine peak is enterohepatic recycling of the drug. Following a large meal, any rifapentine still present would be secreted into the duodenum along with bile, where it would then be available for reabsorption.

The plasma 25-desacetyl-rifapentine concentration versus time profile peaked later than that of rifapentine, but followed the same terminal profile. Depending on which process is slower after administration of parent drug, the apparent (observed) plasma $t_{1/2}$ for a metabolite can represent either the true elimination of the metabolite or the conversion of parent to metabolite.

The similar and parallel terminal phases for rifapentine and 25-desacetyl-rifapentine support the latter explanation.

The esterases responsible for the deacetylation of rifapentine are found in many tissues, including blood. The effect that increasing age might have on the activity of this group of enzymes has not been evaluated. Data on age-related changes in biliary excretion of drugs in humans are also lacking, but limited animal data are available. In rats, the biliary excretion of eosin (24) and ouabain (25) decreased progressively with age. Concomitant reduction in portal venous blood flow found in the eosin study may have contributed to the reduced hepatobiliary function (24).

The higher systemic exposure of elderly men to rifapentine compared to that observed in younger subjects is consistent with findings for the other rifamycin derivatives used clinically, rifampin and rifabutin. Compared to pooled healthy control data, the single-dose C_{max} and AUC of rifabutin were 14% and 43% higher in elderly subjects; the differences between age groups were not significant, however (28). Similarly, rifampin AUC and C_{max} were both 20% higher in a group of 18 patients at least 65 years of age compared to a group of patients less than 65 years old (27). In a second rifampin study, Advenier et al. (28) found lower rates of rifampin renal clearance in elderly subjects compared to younger ones, but no difference in the pharmacokinetic profile of desacetyl-rifampin. Their conclusions from these data were that age-related changes in kidney function could explain the differences in renal clearance, but age had no effect on the deacetylation of rifampin.

The dosage regimens of rifapentine under investigation are 600 mg daily for the management of MAC infections and 600 mg twice weekly for the initial treatment of pulmonary tuberculosis followed by 600 mg weekly in the continuation treatment phase. Therefore, the plasma rifapentine concentration 24 hours after the dose (C_{24}) represents C_{min} for the MAC regimen and the 72-hour plasma rifapentine concentration (C_{72}) represents C_{min} for the initial pulmonary tuberculosis regimen. In the elderly subjects given a single 600-mg dose of rifapentine, rifapentine C_{24} was greater than the MIC for *M. avium* (2,3) and C_{72} was greater than the MIC for *M. tuberculosis* (1,2). It is also of interest to note that the ratios of metabolite to parent C_{24} were similar in the groups of elderly and younger male subjects (Table 2).

We acknowledge the limitations in extrapolating pharmacokinetic and safety results from a single-dose study in otherwise healthy subjects to chronic therapy in patients. Mean rifapentine AUC($0 \rightarrow \infty$) was significantly higher in elderly men compared to a group of younger men, and $t_{1/2}$ was significantly longer. However, the age-related changes in the pharmacokinetic profile of rifapentine observed in this study were relatively small and unlikely to be of clinical relevance when rifapentine is dosed once or twice weekly in patients with tuberculosis. With regard to safety, uncommon adverse events are generally not revealed in single-dose studies. Rifamycin antibiotics are associated with serious adverse effects, including a 'flu-like' syndrome, renal toxicity, and hepatic toxicity, that occur infrequently. However, these serious events appear to be idiosyncratic in nature, rather than concentration dependent.

Adjustments of drug dosages in the elderly should depend on several factors, including the degree of pharmacokinetic changes, alterations in pharmacodynamic response, and the serum concentration relationship between efficacy and toxicity (19). Considering these factors, available data regarding the pathways involved in the absorption and disposition of rifapentine, and the results of this investigation, no change in the initial dosage regimen of rifapentine in elderly subjects is recommended.

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