The intrapulmonary pharmacokinetics of rifapentine were studied in 30 volunteers who received a single, oral dose of rifapentine (600 mg). Subgroups of five subjects each underwent bronchoscopy and bronchoalveolar lavage (BAL) at timed intervals following drug administration. Drug concentrations, including the concentration of the primary metabolite 25-desacetyl rifapentine, were determined in plasma, BAL fluid, and alveolar cells (AC) by high-pressure liquid chromatography. The concentrations in epithelial lining fluid (ELF) were calculated by the urea diffusion method. The concentration-time data were fit to two-compartment (plasma) or one-compartment (AC and ELF) models. The peak concentrations in plasma, ELF, and AC, 26.2, 3.7, and 5.3 μg/ml, respectively, occurred at 5, 5, and 7 h after drug administration, respectively. The half-lives and areas under the curve for plasma, ELF, AC, were 18.3, 20.8, and 52.0 h, 20.8 and 133 μg · h/ml, respectively. Although the intrapulmonary rifapentine concentrations were less than the plasma rifapentine concentrations at all time periods, they remained above the proposed breakpoint for M. tuberculosis (0.5 μg/ml) for the 48-h observation period. These data provide a pharmacokinetic rationale for extended-interval dosing. The optimum dosing regimen for rifapentine will have to be determined by controlled clinical trials.

MATERIALS AND METHODS

Subjects. The protocol was approved by the Human Research Committee of the University of California, San Francisco. Written informed consent was obtained from each subject by an experienced research nurse. Subjects were required to be 18 to 45 years of age. If the subjects were female, they were required to be nonlactating and not pregnant and to agree to use adequate contraception (e.g., barrier methods or abstinence) during the study and for 2 weeks following completion of the study. Women using oral contraceptives were required to agree to use a barrier method in addition for 1 month following the study. Subjects who were lactating or pregnant, had a history of intolerance to rifampin is virtually complete (15). Rifapentine and rifampin is virtually complete (15). Cross-resistance between rifapentine and rifampin is virtually complete (15). Rifapentine has a longer elimination half-life than rifampin, allowing the possibility of less frequent (twice- or once-weekly) administration (17).

There have been no previous reports of the intrapulmonary concentrations or pharmacokinetics of rifapentine in humans. The purpose of this study was to compare the concentrations of rifapentine in plasma, alveolar cells (ACs), and epithelial lining fluid (ELF) of normal volunteers and to compare the drug’s pharmacokinetics in these three compartments.

Single-Dose Intrapulmonary Pharmacokinetics of Rifapentine in Normal Subjects

JOHN E. CONTE, JR., 1,2,3 a JEFFREY A. GOLDEN, 2 MARI McQuITTy, 1 JULIANA KIPPS, 1 EMIL T. LIN, 4 AND ELISABETH ZURINDEN 1

Infectious Diseases Research Laboratory, Department of Epidemiology & Biostatistics, 1 and Departments of Medicine, 2 Microbiology & Immunology, 3 and Biopharmaceutical Sciences, 4 University of California, San Francisco, San Francisco, California 94117

Received 12 May 1999/Returned for modification 18 September 1999/Accepted 10 January 2000

Rifapentine is an orally administered rifamycin derivative that has antituberculous activity and that is similar to rifampin (11, 12, 16, 27). The MICs for sensitive strains are usually in the range of 0.03 to 0.12 mg/liter, and MICs for resistant strains are ≥8 mg/liter (15). Cross-resistance between rifapentine and rifampin is virtually complete (15). Cross-resistance between rifapentine and rifampin is virtually complete (15). Rifapentine has a longer elimination half-life than rifampin, allowing the possibility of less frequent (twice- or once-weekly) administration (17).

There have been no previous reports of the intrapulmonary concentrations or pharmacokinetics of rifapentine in humans. The purpose of this study was to compare the concentrations of rifapentine in plasma, alveolar cells (ACs), and epithelial lining fluid (ELF) of normal volunteers and to compare the drug’s pharmacokinetics in these three compartments.

MATERIALS AND METHODS

Subjects. The protocol was approved by the Human Research Committee of the University of California, San Francisco. Written informed consent was obtained from each subject by an experienced research nurse. Subjects were required to be 18 to 45 years of age. If the subjects were female, they were required to be nonlactating and not pregnant and to agree to use adequate contraception (e.g., barrier methods or abstinence) during the study and for 2 weeks following completion of the study. Women using oral contraceptives were required to agree to use a barrier method in addition for 1 month following the study. Subjects who were lactating or pregnant, had a history of intolerance to rifampin drugs or topical lidocaine, had clinically significant organ dysfunction, or were required to take chronic medications other than self-prescribed vitamins, birth control pills, or thyroid replacement therapy or who were smoking on a regular basis within 6 months of the study were excluded. Subjects who reported drug or alcohol dependence or who had psychiatric problems that would interfere with participation in the study were also excluded. Twenty subjects were women, and 10 subjects were men. The subjects’ age, height, and weight (mean ± standard deviation [SD]) were 29.7 ± 6.2 years, 169 ± 9 cm, and 66.7 ± 13.8 kg, respectively. All subjects had normal renal function as measured by determination of the plasma creatinine level (0.8 ± 0.1 mg/dl).

Study design. The investigation was prospective but not randomized or blinded. Thirty normal volunteers divided into six subgroups of five subjects each were assigned to undergo standardized bronchoscopy and bronchoalveolar lavage (BAL) at specified time intervals from 4 to 48 h following oral administration of a single dose of rifapentine. Rifapentine (600 mg) was administered by a research nurse in the Endoscopy Unit, followed by a timed bronchoscopy, as indicated in Table 1. All patients were observed for at least 30 min after taking the antibiotic for any signs of an allergic reaction. Bronchoscopy and BAL were performed at 4, 5, 7, 12, 24, and 48 h. Baseline data included the results of a medical history and physical examination; blood tests including a complete blood count with differential and a platelet count and alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, albumin, blood urea nitrogen, serum creatinine, and electrolyte level determinations; and urinalysis, including specific gravity, pH, albumin, glucose, ketone, and bilirubin level determinations, and microscopic examination of spun sediment. The postbronchoscopy assessment included a medical history and physical examination, a review of voluntarily described and observed adverse experiences, collection of a sample for antibiotic concentration determination, and a repeat of the laboratory testing of blood and urine. Major adverse reactions were defined as those that were fatal or life-threatening, resulted in permanent disability, required hospitalization, were the result of drug overdose, or suggested significant hazard to the subject.

Bronchoscopy and BAL. Bronchoscopy and BAL were performed in the Endoscopy Unit of the Moffitt-Long Hospital. The blood pressure, respiratory rate, and heart rate of each subject were recorded before, at the completion of, and at approximately 1 h after bronchoscopy. Oxygenation was monitored by finger-tip oximetry throughout the procedure. A 4% topical lidocaine gargle followed by a 4% topical lidocaine spray was used to prepare the subjects for the procedure. Four percent topical lidocaine was then applied to each side of the posterior pharynx, followed by the application of topical 1% lidocaine more distally. Systemic sedation was not used. A fiberoptic bronchoscope (Pentax FB-19H) was inserted into the right middle lobe. The instrument was in place for an average of 4.8 min (range, 3 to 9 min). Four 50-ml aliquots of normal saline were instilled into the right middle lobe, and each was immediately aspirated into a trap.

Specimen handling. All specimens were kept in ice until they were frozen. The blood was centrifuged, and the plasma was separated and then frozen until it was assayed.

Since the BAL fluid aspirated from the first instillation contains significant contamination with cells from the proximal airways (3) it was discarded. The
Aspirates from the second, third, and fourth instillations were pooled. The volume of the pooled aspirates from the instillations was measured and recorded. Two-milliliter aliquots drawn from the pooled specimens were sent to the clinical laboratory for cell count and differential. Measured volumes were placed in 30-ml polypropylene tubes, and the tubes were immediately spun in a refrigerated centrifuge at 400 × g for 5 min. After separation of the supernatant from the cells, the supernatant was stored at −80°C until assay. The cells were immediately resuspended into 200 μl of acetonitrile with 200 μl of ascorbic acid per ml (acetonitrile/aa) and frozen at −80°C until they were assayed. A small aliquot of each supernatant was frozen separately for urea concentration determination.

**Assay for rifapentine concentrations.** The rifapentine concentration in plasma was measured by the laboratory at Hoechst Marion Roussel, Inc. (Kansas City, Mo.) by a high-pressure liquid chromatography method that was reported previously (18). Briefly, plasma proteins were precipitated with methanol containing internal standard (25-O-desacetyl rifampin). After centrifugation the supernatant was injected onto a 5-μm Primesphere C18-HC column (2.0 by 150 mm; Phenomenex, Inc., Torrance, Calif.) preceded by a matching guard column. Analyses were eluted with a mobile phase consisting of 40% methanol, 25% acetonitrile, and 35% water containing 0.5% acetic acid. Drug peaks were detected at 480 nm. The validation statement provided by personal communication from an internal research and development report of 5 January 1996 (Marion Merrell Dow Inc., Kansas City, Mo.) stated the following: the assay was validated over the concentration range of 0.5 to 60 μg/ml. Two replicates of seven freshly prepared calibration standards (0.0, 0.5, 1.0, 15, 30, 45, and 60 μg/ml) and 30 replicates of four validation quality control sample pools (0.5, 1.0, 30, and 60 μg/ml) were assayed in each of three batches run over a period of 2 days. The intra- and interday coefficients of variation ranged from 2.8 to 6.2% for rifapentine and 2.7 to 5.8% for 25-desacetyl rifapentine. The linearity of the assay ranged from 0.4 to 4.4% for rifapentine and 0.8 to 5.7% for 25-desacetyl rifapentine. The linearity of the assay (R^2) ranged from 0.9993 to 0.9998.

**BAL fluid supernatants and ACs were analyzed in the Infectious Diseases Research Laboratory at the University of California, San Francisco.** The BAL fluid supernatant was extracted through a Varian (Hobart Harbor, Calif.) Bond Elut C18 solid-phase extraction column. Diazepam, (Sigma Chemical Co., St. Louis, Mo.) was added to the eluant as an internal standard, and then the eluant was evaporated and resuspended in 200 μl of acetonitrile containing 200 μg of ascorbic acid per ml (methanol/aa). This preparation was injected onto a 5-μm Beckman Ultrasphere octyl column (4.6 mm [inner diameter] by 15 cm). The column was connected to the detector by tubing (polytetrafluoroethylene Teflon; 0.5 mm [inner diameter]) wrapped around a UV lamp (San Gabriel, Calif.) to preheat the sample to 80°C until they were assayed. A small aliquot of each supernatant was frozen separately for urea concentration determination.

**ELF volume was determined by the urea dilution method (29).** The ELF volume was derived from the following relationships:

\[ V_{\text{ELF}} = \frac{V_{\text{BAL}} \times \left( \text{UREA}_{\text{BAL}} / \text{UREA}_{\text{ser}} \right)}{\text{UREA}_{\text{ser}}} \]

where \( V_{\text{ELF}} \) is the volume of ELF, \( V_{\text{BAL}} \) is the volume of aspirated BAL fluid, \( \text{UREA}_{\text{BAL}} \) is the concentration of urea in BAL fluid, and \( \text{UREA}_{\text{ser}} \) is the concentration of urea in serum. The volume of ACs collected in the pellet suspension was determined from the cell
count in the BAL fluid. The cells were counted in a hemocytometer which has a lower detection limit of 1.0 × 10⁶/liter. The number of cells from which drug was extracted was calculated by multiplying the number of cells per milliliter in BAL fluid by the volume (in milliliters) of BAL fluid that was centrifuged to produce the pellet. It has been noted, however, that centrifugation causes an average loss of 21% of the cells (33), so that the actual number of cells recovered postcentrifugation may be less than the number counted, and the actual antibiotic concentration may be proportionately more than we report here. The volume of ACs in the pellet suspension was calculated by using a mean macrophage cell volume of 2.42 μm³/10⁶ cells (2). The concentration of antibiotic in alveolar cells, ABXₐc, was calculated from the following relationship (7, 10):

\[
\text{ABX}\text{ₐc} = \frac{\text{ABX}_{\text{PELLETS}}} {V_{\text{PELLETS}}} \text{V}_{\text{AC}}
\]

where ABXₐc is the antibiotic concentration in the 1-ml cell suspension, and Vₐc is the volume of ACs in the 1-ml cell suspension.

**RESULTS**

None of the 30 subjects experienced a major adverse reaction. Systemic sedation was not required for any of the subjects. During the postbronchoscopy observation period, eight subjects (27%) experienced self-limited lightheadedness of unclear etiology, possibly a lidocaine effect. Transient shortness of breath, cough, fatigue, and headache were reported by one (3%), two (7%), four (13%), and one (3%) of the subjects, respectively. None of the subjects experienced postbronchoscopy fever. Fifteen of the 30 subjects (50%) experienced an elevation in the level of one of the liver enzymes, but the level returned to normal on retesting. Two of the subjects experienced mildly abnormal total bilirubin concentrations (mean ± SD) ranging from 4.5 ± 1.7 to 13.9 ± 3.6 μg/ml at 2 h following drug administration and from 4.1 ± 2.6 to 10.7 ± 4.0 μg/ml at 20 to 24 h following drug administration. At the time of bronchoscopy, the concentrations in plasma ranged from a low of 3.4 ± 3.2 μg/ml at 48 h to a high of 26.2 ± 6.1 μg/ml at 5 h. The corresponding concentrations of 25-desacetyl rifapentine were less at all time periods (Table 2). The plasma rifapentine concentrations determined at the time of bronchoscopy (at 4, 5, 7, 12, 24, and 48 h) declined biexponentially \((r² = 0.98; \text{log likelihood of the fit} = 6.97; \text{residual sum of squares} = 3.59)\), with a \(t_{1/2}\) of 18.3 h and an \(\text{AUC}_{0-\infty}\) of 520 mg · h/ml (Fig. 1 and Table 3).

**TABLE 2. Concentrations of rifapentine and its main metabolite (25-desacetyl rifapentine) in plasma**

| BAL group and drug | Concen in plasma | At 2 h postdosing | At time of BAL | At 20–24 h postdosing |
|--------------------|------------------|-------------------|---------------|----------------------|
| 4 h                |                  |                   |               |                      |
| RFP                | 13.9 ± 3.6       | 14.9 ± 4.9       | 6.7 ± 1.7     |
| 25-dR              | 1.5 ± 0.7        | 6.3 ± 2.1        | 5.0 ± 2.6     |
| 5 h                |                  |                   |               |                      |
| RFP                | 9.7 ± 5.5        | 15.5 ± 4.4       | 10.7 ± 4.0    |
| 25-dR              | 0.5 ± 0.5        | 7.6 ± 2.2        | 7.6 ± 3.1     |
| 24 h               |                  |                   |               |                      |
| RFP                | 9.1 ± 4.7        | 8.2 ± 1.9        | 7.9 ± 2.9     |
| 25-dR              | 0.6 ± 0.7        | 7.7 ± 4.7        | 5.8 ± 4.3     |
| 48 h               |                  |                   |               |                      |
| RFP                | 0.7 ± 2.2        | 3.4 ± 3.2        | 9.8 ± 7.4     |
| 25-dR              | 1.1 ± 0.5        | 5.1 ± 4.7        | 7.3 ± 5.3     |

* RFP, rifapentine; 25-dR, 25-desacetyl rifapentine.

* For 7-h rifapentine group versus 4-h rifapentine group, \(P < 0.05\).

* For 5-h 25-desacetyl rifapentine group versus 4-h 25-desacetyl rifapentine group, \(P < 0.05\).

* For 5-h rifapentine group versus 24-h and 48-h rifapentine groups, \(P < 0.05\).
those in ACs at all time points except 48 h and were less than the corresponding concentrations in plasma. 25-Desacetyl rifapentine was detectable in ELF at low concentrations at all time periods. The concentrations in ELF declined monoexponentially ($r^2 = 0.80$, log likelihood of the fit $= -2.4$, residual sum of squares $= 0.78$), with a $t_{1/2}$ of 20.8 h and an AUC$_{0\rightarrow\infty}$ of 111 mg·h/ml (Fig. 3 and Table 4). The AUC$_{0\rightarrow\infty}$ for ELF/AUC$_{0\rightarrow\infty}$ for plasma ratio was 0.21.

**DISCUSSION**

The observations presented here confirm our previous experiences (6, 7, 9, 10) and those of others (13, 14, 25, 26) that bronchoscopy and BAL for research purposes can safely be carried out with healthy volunteers. The standardized technique that we use for bronchoscopy and BAL results in adequate and reliable recovery of ACs and ELF. The number of cells (approximately $100 \times 10^6$ to $150 \times 10^6$), the cell type (approximately 80 to 90% monocytes/macrophages), and the volume of ELF (approximately 1 ml) are similar to the values that we and others have reported previously (1, 2, 4, 7, 10, 26, 29, 33). Used with sensitive and specific drug assay techniques, this procedure permits an accurate estimation of the intrapulmonary drug concentrations in these compartments.

It is noteworthy that the $C_{\text{max}}$ (26.2 μg/ml), $T_{\text{max}}$ (5 h), $t_{1/2-LZ}$ (18.3 h), and AUC (520 mg·h/ml) values derived from this study were very similar to those reported in earlier studies with normal volunteers (19–21).

These data confirm that the long plasma $t_{1/2}$ of rifapentine also appears to result in a long intrapulmonary $t_{1/2}$, i.e., 13.0 h in ACs and 20.8 h in ELF. We believe that these estimates of
In this study we observed reversible abnormalities in liver function that we hypothesized were related to the dosing interval, and drug effectiveness requires further investigation. The relationship between the MIC of rifapentine for Mycobacterium tuberculosis and the plasma drug concentrations in Fig. 1 resulting from the administration of a single 600-mg dose remain above the MIC breakpoint for M. tuberculosis for 48 h. The data suggest a pharmacologic rationale for extended-interval dosing. Whether these pharmacokinetic estimates would be materially affected by the presence of pulmonary tuberculosis is unknown. The optimum dosing interval and the effect of multiple-dose administration on the intrapulmonary pharmacokinetics of rifapentine have not been determined. The relationship between the MIC of rifapentine for M. tuberculosis, dosing interval, and drug effectiveness requires further investigation. The reversible abnormalities in liver function that we observed in this study have been reported previously (17).

We have recently completed a steady-state study of intrapulmonary pyrazinamide concentrations (8). The $t_{1/2}$ of pyrazinamide is also long and has been reported to be from 9 to 23 h (5, 22, 28, 31). We found that pyrazinamide, unlike rifapentine, is highly concentrated in ELF. After the administration of five daily 1.0-g doses, the concentration in ELF/concentration in plasma ratio at 4 h was 22, whereas the concentration in ELF/concentration in plasma ratio was 0.2 for rifapentine in this study. The concentration in ACs/concentration in plasma ratio at 4 h was 0.6 for pyrazinamide, whereas it was 0.26 for rifapentine.

Determination of whether drugs such as pyrazinamide that achieve greater concentrations in the lungs and that therefore have greater inhibitory or killing ratios are more effective will require controlled trials. In general, high inhibitory or killing ratios are viewed as favorable in the treatment of infectious diseases. It is likely that the prolonged intrapulmonary rifapentine concentrations above the MIC for M. tuberculosis observed in these subjects are in part responsible for this drug’s effectiveness for the treatment of pulmonary tuberculosis. The significance of the low (usually below 1.0 μg/ml) but detectable concentrations of rifapentine’s main metabolite, 25-desacetyl rifapentine, in ACs and ELF is unknown. This was a single-dose study, and multiple doses may result in higher intrapulmonary concentrations than we observed in the subjects in the present study.

ACKNOWLEDGMENTS

This work was carried out with funds provided by Hoechst Marion Roussel, Inc.

We acknowledge Margareta Andersson for performing the assays and Eve Benton for manuscript preparation.

REFERENCES

1. Baldwin, D. R., J. M. Andrews, R. Wise, and D. Honeybourne. 1992. Bronchoalveolar distribution of cefuroxime axetil and in-vitro efficacy of observed concentrations against respiratory pathogens. J. Antimicrob. Chemother. 30:377–385.
2. Baldwin, D. R., R. Wise, J. M. Andrews, J. P. Ashby, and D. Honeybourne. 1990. Azithromycin concentrations at the sites of pulmonary infection. Eur. Respir. J. 3:586–590.
3. Baldwin, D. R., R. Wise, J. M. Andrews, M. Gill, and D. Honeybourne. 1993. Comparative bronchoalveolar concentrations of ciprofloxacin and lomefoxacin following oral administration. Respir. Med. 87:595–601.
4. Baldon, D. R., R. Wise, J. M. Andrews, and D. Honeybourne. 1991. Micro-lavage: a technique for determining the volume of epithelial lining fluid. Thorax 46:558–662.
5. Bareggi, S. R., R. Cerutti, R. Pirola, R. Riva, and M. Cistermino. 1987. Clinical pharmacokinetics and metabolism of pyrazinamide in healthy volunteers. Arzneimittelforschung 37:849–854.
6. Conte, J. E., Jr., J. A. Golden, M. McQuitty, J. Kipps, E. T. Lin, and E. Zurlinen. The effect of AIDS and gender on the steady state plasma and intrapulmonary concentrations of ethionamide. Antimicrob. Agents Chemother., in press.
7. Conte, J. E., Jr., J. Golden, S. Duncan, E. McKenna, E. Lin, and E. Zurlinen. 1996. Single-dose intrapulmonary pharmacokinetics of azithromycin, clarithromycin, ciprofloxacin, and cefuroxime in volunteer subjects. Antimicrob. Agents Chemother. 40:1617–1622.
8. Conte, J. E., Jr., J. Golden, S. Duncan, E. McKenna, and E. Zurlinen. 1999. Intrapulmonary concentrations of pyrazinamide. Antimicrob. Agents Chemother. 43:1329–1333.
9. Conte, J. E., Jr., and J. A. Golden. 1995. Intrapulmonary and systemic pharmacokinetics of aerosolized pentamidine used for prophylaxis of Pneumocystis carinii pneumonia in patients infected with the human immunodeficiency virus. J. Clin. Pharmacol. 35:1166–1173.
10. Conte, J. E., Jr., J. Golden, S. Duncan, E. McKenna, and E. Zurlinen. 1995. Intrapulmonary pharmacokinetics of clarithromycin and of erythromycin. Antimicrob. Agents Chemother. 39:334–338.
11. Dhillon, J., J. M. Dickinson, J. A. Guy, T. K. Ng, and D. A. Mitchison. 1992. Activity of two long-acting rifamycins, rifapentine and FCE 22807, in experimental murine tuberculosis. Tuber. Lung Dis. 73:116–123.
12. Dhillon, J., and A. Mitchison. 1992. Activity in vitro of rifabutin, FCE 22807, rifapentine, and rifampin against Mycobacterium microti and M. tuberculosis and their penetration into mouse peritoneal macrophages. Am. Rev. Respir. Dis. 145:212–214.
13. Ettensohn, D. B., M. J. Jankowski, P. G. Duncan, and P. A. Lalor. 1988. Bronchoalveolar lavage in the normal volunteer subject. I. Technical aspects and intersubject variability. Chest 94:275–280.
14. Ettensohn, D. B., M. J. Jankowski, A. A. Redondo, and P. G. Duncan. 1988. Bronchoalveolar lavage in the normal volunteer subject. 2. Safety and results of repeated BAL, and use in the assessment of intrasubject variability. Chest 94:281–285.
15. Heifets, L., T. Sanchez, J. Vanderkolk, and V. Pham. 1999. Development of rifapentine susceptibility tests for Mycobacterium tuberculosis. Antimicrob. Agents Chemother. 43:25–28.
16. Heifets, L. B., P. J. Lindholm-Levy, and M. A. Flory. 1990. Bactericidal activity in vitro of various rifamycins against Mycobacterium avium and Mycobacterium tuberculosis. Am. Rev. Respir. Dis. 141:626–630.
17. Jarvis, B., and H. M. Lamb. 1998. Rifapentine. Drugs 56:607–616.
18. Kenny, M. T., D. L. Reynolds, M. A. Brackman, and J. K. Dulworth. 1997. Comparison of biological and chemical assays for the quantitation of rifapentine in human plasma. Diagn. Microbiol. Infect. Dis. 27:107–111.
19. Keung, A. C., M. G. Eller, and S. J. Weir. 1998. Pharmacokinetics of rifapentine in patients with varying degrees of hepatic dysfunction. J. Clin. Pharmacol. 38:517–524.
20. Keung, A. C., M. G. Eller, and S. J. Weir. 1998. Single-dose pharmacokinetics of rifapentine in elderly men. Pharm. Res. 15:1286–1291.
21. Keung, A. C., M. G. Eller, and S. J. Weir. 1998. Single-dose pharmacokinetics of rifapentine in women. J. Pharmacokin. Biopharm. 26:75–85.
22. Lacroix, C., T. P. Hoang, J. Nouveau, C. Guyonnaud, G. Laine, H. Duwoos, and O. Lafont. 1989. Pharmacokinetics of pyrazinamide and its metabolites in healthy subjects. Eur. J. Clin. Pharmacol. 36:395–400.
23. Lacroix, C., J. L. Tranvouez, H. T. Phan, H. Duwoos, and O. Lafont. 1990. Pharmacokinetics of pyrazinamide and its metabolites in patients with hepatic cirrhotic insufficiency. Arzneimittelforschung 40:76–79.
24. Leonard, T. 1979. Why do we need significance levels? MRC Technical Report. University of Wisconsin, Madison.
25. Limper, A. H., U. Specks, W. M. Brutinel, W. J. Martin, and M. S. Rohrbach. 1993. Interlobar variation in the recovery of bronchoalveolar lavage fluid, cell populations, and angiotensin-converting enzyme in normal volunteers. J. Lab. Clin. Med. 121:785–791.
26. Merchant, R. K., D. A. Schwartz, R. A. Helmers, C. S. Dayton, and G. W. Hunninghake. 1992. Bronchoalveolar lavage cellularity. The distribution in normal volunteers. Am. Rev. Respir. Dis. 146:448–453.
27. Mor, N., B. Simon, N. Mezo, and L. Heifets. 1995. Comparison of activities of rifapentine and rifampin against Mycobacterium tuberculosis residing in human macrophages. Antimicrob Agents Chemother 39:2073–2077.
28. Peloquin, C. A., A. E. Bul litt, G. S. Jaresko, R. W. Jelliff, G. T. James, and D. E. Nix. 1998. Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. Pharmacotherapy 18:1205–1211.
29. Rennard, S. L., G. Basset, D. Lecossier, K. M. O'Donnell, P. Pinkston, P. G. Martin, and R. G. Crystal. 1986. Estimation of volume of epithelial lining fluid recovered by lavage using urea as marker of dilution. J. Appl. Physiol. 60:532–538.
30. Schwartz, G. 1978. Estimating the dimensions of a model. Ann. Stat. 6:461–464.
31. Stamatakis, G., C. Montes, J. H. Trouvin, R. Farinotit, H. Fessi, S. Kenouch, and J. P. Mery. 1988. Pyrazinamide and pyrazinoic acid pharmacokinetics in patients with chronic renal failure. Clin. Nephrol. 30:230–234.
32. Talke, H. S. G. E. 1965. Enzymatische Harnstoffbestimmung im Blut und Serum im optischen test nach Warburg. Klin. Wochschr. 43:174.
33. Wilcox, M., A. Kervitsky, L. C. Watters, and T. E. J. King. 1988. Quantification of cells recovered by bronchoalveolar lavage. Comparison of cytocentrifuge preparations with the filter method. Am. Rev. Respir. Dis. 138:74–80.
34. Zar, J. H. 1984. Multisample hypotheses: the analysis of variance. Multiple comparisons, p. 162–205. In J. H. Zar (ed.), Biostatistical analysis. Prentice-Hall, Inc., Englewood Cliffs, N.J.