Intrapulmonary Pharmacokinetics of Telithromycin, a New Ketolide, in Healthy Japanese Volunteers

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The concentrations of telithromycin, a new ketolide antimicrobial agent, in alveolar macrophages (AMs) and bronchoalveolar epithelial lining fluid (ELF) were determined in order to investigate the transfer of the drug into target tissue, relative to plasma, following multiple oral doses of telithromycin. Twenty-four healthy male Japanese volunteers were randomly allocated to four groups. Each subject was given 600 or 800 mg of telithromycin once daily for 5 days, followed by bronchoalveolar lavage (BAL) 2 or 8 h after the last dose (group A and B: 600 mg, 2 and 8 h BAL time point; group C and D: 800 mg, 2 and 8 h BAL time point). The mean concentrations of the drug in AMs and ELF were 34.54 and 4.92 mg/liter in group A, 50.97 and 2.26 mg/liter in group B, 25.47 and 4.24 mg/liter in group C, and 108.22 and 4.31 mg/liter in group D, respectively, which markedly exceeded concentrations in plasma. These results demonstrated good transfer of telithromycin into AMs and ELF, suggesting good efficacy against common respiratory pathogens, including intracellular pathogens and atypical microorganisms.

Telithromycin is a novel ketolide which is a semisynthetic derivative of erythromycin A, having a 3-keto function instead of a 3-L-cladinose on the erythronolide A ring (8). Telithromycin, a new ketolide antimicrobial agent, has sufficient potency, with an antibacterial spectrum that covers all major respiratory tract pathogens, against isolates from respiratory tract infections (RTIs) and exhibits potent antibacterial activity against gram-positive aerobes, including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus*, fastidious gram-negative bacilli, including *Haemophilus influenzae* and *Moraxella catarrhalis*, intracellular pathogens, including *Chlamydia pneumoniae*, *Legionella pneumophila*, and atypical microorganisms, such as *Mycoplasma pneumoniae* (2, 3, 5, 21). Unlike 14- and 15-available-membered-ring macrolides, telithromycin does not induce resistance to macrolides, lincosamide, or streptogramin B. Telithromycin retains antibacterial activity against most erythromycin A-resistant isolates within the gram-positive cocci, especially against *S. pneumoniae*. Furthermore, telithromycin exhibits antibacterial activity against multidrug-resistant *S. pneumoniae*, including penicillin G- and erythromycin A-resistant isolates (2, 15), which have become a serious public health problem in Japan and many other countries worldwide; infections caused by these bacteria have become increasingly prevalent in recent years (13, 20). In addition to the potent in vitro activity of telithromycin, telithromycin exhibited a good efficacy in vivo in rodent lung infection models using bacteria isolated from patients with RTI (10, 17).

Most types of infections occur in extravascular sites surrounded by complex membrane barriers, such as the central nervous system, the prostate gland, or the respiratory tract. A

major concern for the clinician is the need for information on the concentrations of antibiotics at these foci of infection, and therapeutic success depends upon adequate distribution of the agent to the appropriate tissues of the target organ. Many models, such as surgical procedures or bronchoalveolar lavage (BAL) techniques, have been used to study the distribution of antibiotics in the respiratory tract and have provided useful information on their penetration into tissue and fluids, and as a result, extravascular distribution and tissue penetration studies have become important tools in the assessment of new antimicrobial agents (4). However, there were no data regarding this distribution and penetration in Japan. The purpose of this study was, therefore, to investigate the intrapulmonary penetration of telithromycin by measuring concentrations in alveolar macrophages (AMs) and bronchoalveolar epithelial lining fluid (ELF), relative to those in plasma, following multiple oral administration of telithromycin to healthy Japanese subjects (600 or 800 mg, once daily for 5 days).

The present study was a single-center, randomized, prospective, nonblinded, parallel-group trial with healthy adult male Japanese volunteers. All potential subjects were required to be 20 years old or older and nonsmokers or ex-smokers for more than 6 months. Subjects were excluded from the study if any of the following conditions existed: a history of intolerance to macrolides, anxiolytic (diazepam), antisialagogue (atropine) or local anesthesia (lidocaine), the presence of clinically significant organ dysfunction; respiratory system disease, such as asthma, pollinosis, or allergic rhinitis; or a chronic requirement for medications.

After giving written informed consent, 24 volunteers were assessed using a complete medical and surgical history, measurement of height and weight, physical examination, reading of vital signs, chest X-ray, lung function tests (spirometry), 12-lead electrocardiogram (ECG), and baseline laboratory testing (complete blood count, platelet count, and blood

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urea nitrogen, serum creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin concentration determinations). Twenty-four volunteers were randomly divided into four groups, A, B, C, and D, in advance, according to dose (600 or 800 mg) and time point of BAL (2 or 8 h postdose), which were selected based on a European study in which 24 healthy male volunteers, 6 subjects in each group, were recruited in order to measure the concentration of telithromycin in AMs and ELF 2, 8, 24, 48 h after the last dose of 800 mg, and the peak concentration was achieved within 8 h postdose (C. M. Series, C. Cantalloube, P. Soler, H. P. Gia, F. Brunner, A. Andremon, and B. Lenfant, Abstr. 5th Int. Conf. Macrolides, Azalides, Streptogramins, Ketolides, Oxazolidinones, abstr. 09.26, 2000). The subjects were hospitalized from day 1 (the day before dosing) to day 8 (72 h after the last dose). Each subject received telithromycin once daily for 5 days, followed by BAL after the last dose. Prior to the administration of the first dose, a blood sample was collected. The study medication was administered to subjects under direct supervision, followed by 30 min of observation for adverse events. The subjects were also monitored via systematic questioning and spontaneous reporting to further assess any adverse events. Their weight, vital signs, 12-lead ECG, and the same laboratory testing as described for screening were also checked, and a physical examination was done, on day 6 (24 h after the last dose) and 1 week after the last dose. The chest X-ray was performed within 4 h after BAL and at one week after the last dose. The study was approved by the institutional review board of the Clinical Pharmacology Center, Niizashiki Central General Hospital.

Subjects underwent fiber-optic bronchoscopy with BAL according to the standard procedure 2 or 8 h after the last dose of telithromycin: for group A, 600 mg, 2 h; for group B, 600 mg, 8 h; for group C, 800 mg, 2 h; for group D, 800 mg, 8 h.

Each subject was premedicated intramuscularly with atropine sulfate (0.5 mg) and diazepam (5 mg). After local anesthesia with 4 percent lidocaine (Xylocaine), a flexible fiber-optic bronchoscope (BF-P40; Olympus, Tokyo, Japan) was wedged into a subsegment of the right middle lobe for lavage. An aliquot of 50 ml of sterile physiological saline solution at body temperature was instilled through the bronchoscope. The fluid was immediately retrieved by gentle suction using a sterile syringe. Instillation of 50 ml of saline solution was performed three times. The instrument was in place an average of 4 min (range, 3 to 6 min). The liquid recovered after the first aliquot was discarded because it could have been contaminated by bronchial mucus and cells or Xylocaine, and the remaining lavage fluid was pooled. The volumes of the first and pooled aspirates were measured and recorded. The pooled lavage fluid was kept refrigerated, and a volume of 5 ml was analyzed for a total and differential cell count. After washing twice with phosphate-buffered saline solution, cells were suspended with 10 percent heat-inactivated fetal calf serum and counted using a hemocytometer. An aliquot was then adjusted to 2×10^5 cells per ml, and a 0.2-ml sample of each cell suspension was spun down onto a glass slide at 1,100 rpm ($160 \times g$) for 2 min using a cytocentrifuge (Cytospin 2; Shandon Instruments, Sewickley, Pa.). The slides were later dried, fixed, and then stained using the Diff-Quick method. Three hundred cells were identified under a photomicroscope in order to evaluate the

percentage of AMs. Fluid samples were centrifuged at 4°C at 2,000 rpm ($700 \times g$) for 10 min to separate cells from the fluid components. Cell pellets and supernatant fluid were stored at -80°C for the drug concentration assay, and a small aliquot of the pooled BAL supernatants was frozen at -30°C separately for urea concentration determination. The blood pressure, pulse, respiratory rate, and heart rate of each subject were recorded prior to, at the completion of, and 30 min and 2.5 h following the procedure. A blood sample was also collected at the time of bronchoscopy, and the plasma and serum were separated immediately at 4°C at 3,000 rpm ($2,000 \times g$) for 15 min and then frozen until assayed for drug and urea concentrations, respectively. Then the frozen cell pellets, supernatant fluid, plasma, and serum were sent immediately to the laboratory of clinical microbiology in Xavier Bichat-Claude-Bernard University-Hospital, Paris, France, for the assay. Prior to the assay, cell pellets were lysed by sonification on ice for 5 min and resuspended in 1 ml of phosphate buffer (pH 8.0), and the BAL supernatants were freeze-dried and resuspended in 3 ml of acetic acid-containing phosphate buffer (pH 8.0). BAL cells and lyophilized BAL supernatants were shaken in ice for 4 h in order to extract telithromycin completely, and assays were performed with the supernatants.

Telithromycin concentrations in plasma, BAL supernatant, and AMs were determined biologically in triplicate using an agar diffusion method validated in the laboratory of clinical microbiology in Xavier Bichat-Claude-Bernard University-Hospital. The medium used was Antibiomedium 11 (Difco laboratories, Detroit, Mich.) adjusted to pH 9 with NaOH solution, and *Bacillus subtilis* ATCC 6633 was used as the test organism. Plates were incubated overnight in air at 35°C . Lidocaine would not interfere with the microbiologic analysis using *B. subtilis* ATCC 6633 in the temperature conditions of the assay (lower than 40°C) (1). The limit of quantification was 0.03 mg/liter for plasma, ELF, and AMs. All samples from the same subject were analyzed in single batches to minimize assay variability. Spiked samples were included for quality controls and to provide a standard curve. Standards for plasma samples were diluted in pooled antibiotic-free human plasma, while standards for ELF and AM samples were diluted in acetic acid-containing phosphate buffer (pH 8.0). Preliminary assays were performed using different volumes at 50, 100, 150, and 200 μl of plasma and phosphate buffer (pH 8.0), which were tested in order to find the smallest volume that enabled adequate sensitivity. Standard curves were prepared with telithromycin concentrations ranging between 0.03 and 8 mg/liter. Best-fit standard curves for the telithromycin assays were obtained by linear regression analysis. The precision and accuracy of control samples were the following: the accuracy was 95 to 106% for phosphate buffer and 100.75 to 105% for plasma, and the intra-assay and interassay coefficients of variation were 3.1 to 9.8% and 0.9 to 4.1% for phosphate buffer and 3.4 to 7.3% and 1.8 to 2% for plasma, respectively. The linearity and R-square values were 0.981 to 0.999 for phosphate buffer and 0.980 to 0.998 for plasma. All samples were analyzed within 1 month of collection. Telithromycin is stable in plasma in frozen conditions for at least 1 year and in urine for at least 6 months, although no data are available on stability of telithromycin in other matrices.

The urea concentrations in the serum and BAL samples

TABLE 1. Demographic data for healthy male Japanese volunteers

Dose (mg)	Group (n ^a)	BAL time point (h) ^b	Age (yr) ^c	Wt (kg) ^c	Ht (cm) ^c	Obesity index ^c
600	A (6)	2	22.0 ± 1.1	61.9 ± 8.3	171.6 ± 7.3	-3.7 ± 12.3
600	B (6)	8	23.0 ± 2.3	59.6 ± 8.7	169.4 ± 7.8	-4.5 ± 9.0
800	C (6)	2	23.0 ± 2.0	62.7 ± 6.8	171.8 ± 4.9	-2.8 ± 10.1
800	D (6)	8	24.0 ± 4.0	62.4 ± 5.0	171.1 ± 2.1	-2.4 ± 10.3

^a n, number of subjects.^b Time after the last dose.^c Mean ± SD; calculated as weight/(height - 100) × 0.9 × 100 - 100.

were measured with a colorimetric enzymatic test (Boehringer Test-combination Urea S, Ref. 777510; assay sensitivity was 0.015 mmol/liter for both serum and BAL). The volume of ELF was determined by the urea dilution method (18). The apparent ELF volume obtained by BAL was quantified on the basis of the following formula: ELF volume (ml) = BAL volume (ml) × (urea concentration in BAL fluid/urea concentration in serum). The concentration of telithromycin in the ELF was calculated based on the telithromycin concentration in BAL fluid as follows: telithromycin concentration (mg/liter) = telithromycin concentration in BAL fluid (mg/liter) × (BAL volume/ELF volume).

The volume of AM cells in the cell pellet suspension was calculated using a mean macrophage cell volume of 2.5 μ l/10⁶ cells (7). The concentration of telithromycin in AM cells was determined as follows: AM concentration of telithromycin (mg/liter) = telithromycin concentration in the 1-ml cell pellet suspension/AM cell volume in the 1-ml cell pellet suspension.

All data were presented as mean ± standard deviation (SD). Descriptive statistics and statistical analysis were performed using SAS (version 6.12) software (SAS Institute Inc., Cary, N.C.). The intergroup homogeneities of the demographic parameters (age, height, body weight, and obesity index) and the BAL characteristic parameters (the total numbers and percentages of AMs and ELF volumes) were evaluated using Kruskal-Wallis tests, with a significance level of 10%. Statistical evaluation of the effect of the dose (600 or 800 mg) and sampling time (2 or 8 h) on the measured telithromycin concentration was performed by an analysis of variance with Scheffe's multiple comparison for each of the parameters. A *P* value of <0.05 was regarded as statistically significant.

Twenty-four healthy Japanese males between 20 and 32 years old (mean age, 23.0 years) were recruited. Demographic characteristics of the study group are shown in Table 1. The results showed no significant intergroup differences in any item, indicating that the comparability between two dose levels or among four groups was reasonable. Medical history or hypersensitivity to drugs that could have caused a problem when conducting and evaluating the present study was not found in any subjects. Self-declaration made at the time of the screening test and the results of measurements of urinary cotinine (metabolite of nicotine) concentration indicated that all subjects were nonsmokers (data not shown). There were no problems of compliance with the study medication. One subject in group A was excluded from pharmacokinetic analysis due to withdrawal before BAL. Therefore, pharmacokinetic and statistical analysis were performed on the remaining 23 subjects.

The total numbers of AMs recovered from the BAL aspirates for the four groups were $6.2 \times 10^6 \pm 4.6 \times 10^6$ cells in

group A, $6.3 \times 10^6 \pm 1.2 \times 10^6$ cells in group B, $6.6 \times 10^6 \pm 3.6 \times 10^6$ cells in group C, and $8.2 \times 10^6 \pm 7.1 \times 10^6$ cells in group D. The percentages of AM cells among all leukocytes recovered from the BAL fluids were $68.9\% \pm 15.3\%$ for group A, $81.1\% \pm 5.2\%$ for group B, $83.6\% \pm 11.8\%$ for group C, and $74.2\% \pm 16.0\%$ for group D. There were no statistically significant differences in AMs from the BAL fluid among the four study groups. The calculated volumes of ELF in the BAL aspirates of all samples from the four groups were 1.25 ± 0.84 ml in group A, 2.05 ± 1.27 ml in group B, 2.05 ± 0.95 ml in group C, and 2.18 ± 0.64 ml in group D. No statistically significant differences in the volumes of ELF were observed. These results are in agreement with findings from previous studies performed with healthy subjects (6, 16).

The concentrations of drug in plasma before the initial study dose were all below the limit of quantification (0.03 mg/liter) in the four groups, and those before telithromycin administration on day 5 were 0.04 ± 0.03 mg/liter in group A, 0.04 ± 0.02 mg/liter in group B, 0.06 ± 0.01 mg/liter in group C, and 0.09 ± 0.03 mg/liter in group D. Individual concentrations of telithromycin in plasma, AMs, and ELF at the BAL time point (time after the last study dose) are plotted in Fig. 1. The mean concentrations of telithromycin in AMs in the 600-mg-dose group were $34.54 (\pm 25.80)$ mg/liter and $50.97 (\pm 15.89)$ mg/liter 2 and 8 h postdose, respectively, while those in the 800-mg-dose group were $25.47 (\pm 13.46)$ mg/liter and $108.22 (\pm 35.18)$ mg/liter 2 and 8 h postdose, respectively, which far exceeded those in plasma. The telithromycin concentration in AMs 8 h postdose in the 800-mg-dose group was significantly higher than those 8 h postdose in the 600-mg-dose group ($P < 0.01$) and in 2 h postdose in the 800-mg-dose group ($P < 0.0005$). The mean concentrations of telithromycin in ELF in the 600-mg-dose group were $4.92 (\pm 4.00)$ mg/liter and $2.26 (\pm 1.17)$ mg/liter 2 and 8 h postdose, respectively, while those in the 800-mg-dose group were $4.24 (\pm 3.14)$ mg/liter and $4.31 (\pm 1.87)$ mg/liter 2 and 8 h postdose, respectively. The ratios of the mean concentration in AM cells/mean concentration in plasma were ca. 50/1 and ca. 35/1, 2 h postdose, in the 600- and 800-mg-dose groups, respectively, and were less than 100/1 at 8 h postdose in both groups. A significant difference was observed in the mean concentration ratios between 2 h postdose (37.2 ± 12.1) and 8 h postdose (156.0 ± 58.0) in the 800-mg group ($P < 0.005$). The mean concentration ratios of ELF to plasma were ca. 5/1 to 6/1, 2 and 8 h postdose, in both the 600-mg and 800-mg dosage groups.

All 24 subjects were included in the safety analysis. Of these, 5 (21%) subjects reported a total of five treatment-emergent adverse events, usually of mild intensity and involving the gastrointestinal tract (diarrhea and strange sensation of the pharynx). BAL-related adverse events were observed in 10 subjects of the 600-mg-dose group and 8 subjects of the 800-mg-dose group with alveolar opacity of the right middle lobe on the chest X-ray performed within 4 h after BAL procedure, but chest X-ray was normal 1 week later. No severe or serious adverse events were reported in the present study. There were no clinically significant changes in ECG parameters, lung function tests (spirometry), vital signs, or laboratory safety data.

In the present study, we demonstrated that telithromycin concentrations were higher in both AMs and ELF than in plasma at each dose and BAL time point. Although no statis-

FIG. 1. Distribution of telithromycin concentrations in plasma (a), AMs (b), and ELF (c) in healthy male Japanese volunteers. The mean concentration of telithromycin in AMs in group D was significantly higher than that in groups B ($P < 0.01$) or C ($P < 0.0005$).

tically significant difference was observed in the drug concentration in AMs or ELF 2 h postdose between the two dose levels, 600 and 800 mg, the mean drug concentration in AMs in the 800-mg-dose group 8 h postdose was significantly higher than those in the 600-mg-dose group 8 h postdose and in the 800-mg-dose group 2 h postdose. According to clinical data other than that generated with Japanese subjects using the same design as this study, the mean concentrations in AMs and

ELF after telithromycin administration only for a dose of 800 mg were 65 and 5.4 mg/liter, respectively, 2 h postdose and 100 and 4.2 mg/liter, respectively, 8 h postdose, thereafter declining to 41 and 1.17 mg/liter, respectively, 24 h postdose (Serieys et al., Abstr. 5th Int. Conf. Macrolides, Azalides, Streptogramins, Ketolides, Oxazolidinones). These results did not differ greatly from ours for the 800-mg dose. The telithromycin concentration at 8 h postdose in AMs was half or one-third of that seen with clarithromycin or azithromycin, respectively (6, 16) yet quite a bit higher than that for erythromycin (6), and the concentration at 12 h for telithromycin, recently observed with patients without active lung diseases (14), was similar to those at 8 h for clarithromycin and azithromycin (6, 16). In ELF, the concentration of telithromycin was lower than that of clarithromycin but higher than those of both azithromycin and erythromycin at 8 and 12 h postdose. Considered together, the findings of this study indicate that there was good penetration of telithromycin into both AMs and ELF.

Based on the mouse thigh infection model with *S. pneumoniae* (O. Vesga, C. Bonnat, and A. W. Craig, Abstr. 37th Int. Conf. Antimicrob. Agents Chemother., abstr. F255, 1997), it has been shown that efficacy of telithromycin is concentration dependent rather than time dependent, with AUC/MIC and maximum concentration of drug in serum (C_{max})/MIC ratios being considered the key parameters for determining efficacy. Furthermore, population pharmacokinetic analysis performed from clinical data has shown that achieving a C_{max} /MIC ratio higher than 0.19 was predictive of a good outcome (9). Pulmonary disposition studies in which BAL can be collected at a single time per subject cannot provide any information on individual C_{max} or area under the concentration-time curve values in ELF and AMs. Although this type of study cannot show accurately when peak concentration is reached in AMs and ELF, one can say without any doubt that individual C_{max} values are at least equal to or superior than the concentrations observed in AMs and ELF. In the present study, individual concentrations of telithromycin in AMs are largely exceeding the MIC at which 90% of the isolates are inhibited (MIC_{90}) of intracellular pathogens such as *C. pneumoniae* strains (0.25 mg/liter) (19) or *Legionella* spp. (0.03 to 0.06 mg/liter) (21), whatever the group (600 or 800 mg) or the time of sampling (2 or 8 h). In the same way, any individual concentrations of telithromycin in ELF measured 2 or 8 h after dosing with 600 or 800 mg are higher than the MIC_{90} s of typical respiratory pathogens, such as *S. pneumoniae* (0.12 mg/liter) (2) and *M. catarrhalis* (0.12 mg/liter) (5). Concerning *H. influenzae* (MIC_{90} , 4 mg/liter, or 3.13 mg/liter obtained in Japan) (5; S. Arai, K. Noguchi, H. Okamoto, S. Furuta, and M. Inazu, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-135, 1998), the threshold of 0.19, predictive of a good clinical outcome, is achieved regardless of the individual concentration of telithromycin in ELF, measured 2 or 8 h after dosing with 600 or 800 mg.

In addition, telithromycin also reaches a high concentration in plasma. There were no differences at the first sampling time, 2 h postdose. A possible reason for this is that this early time postdosing had been prior to the time to maximum concentration of drug in serum, since the time to maximum concentration of drug in serum is 3 h in both 600- and 800-mg oral dosing with the mean C_{max} of 0.910 and 1.180 mg/liter, validated by

Aventis Pharma. Nevertheless, this is critically important in the treatment of respiratory tract infections accompanied by bacteremia, which are associated with a greater risk of mortality (11, 12).

The greatest difference in ratios of drug concentration to that in plasma was noted with AMs, where a ratio of 156.0 was observed in the 800-mg group. However, the clinical utility of penetration ratios is somewhat misleading, especially with the limited sampling times of 2 or 8 h, and bacterial eradication is a function of the drug concentration at the site of infection rather than penetration ratios, although many investigators have used the ratios of penetration of antimicrobial agents into various body sites and fluids to assess the clinical utilities of these agents.

Although the present study was performed with healthy volunteers, it is unlikely that the concentrations of telithromycin in ELF and AMs would be reduced in infected patients. Indeed, blood flow, in situ transport, intracellular penetration, capillary permeability, and chemotaxis of white blood cells resulting from inflammation are usually increased by infection; therefore, it would rather lead to an increase of penetration of telithromycin into the lung compared to results with healthy subjects.

Overall, the present results suggest good intrapulmonary penetration of telithromycin and make this agent a good candidate, even at a 600-mg dose in Japan, for the empirical treatment of community-acquired respiratory tract infections caused by such typical bacterial pathogens as *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*, intracellular pathogens, including *C. pneumoniae* and *L. pneumophila*, and atypical microorganisms, such as *M. pneumoniae*.

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REFERENCES

1. Abdelaziz, A., and M. El-Nakeeb. 1988. Sporicidal activity of local anaesthetics and their binary combinations with preservatives. *J. Clin. Pharm. Ther.* **13**:249–256.
2. Barry, A. L., P. C. Fuchs, and S. D. Brown. 1998. In vitro activities of the ketolide HMR 3647 against recent gram-positive clinical isolates and *Haemophilus influenzae*. *Antimicrob. Agents Chemother.* **42**:2138–2140.
3. Bebear, C. M., H. Renaudin, M. D. Aydin, J. F. Chantoin, and C. Bebear. 1997. In vitro activity of ketolides against mycoplasmas. *J. Antimicrob. Chemother.* **39**:669–670.
4. Bergogne-Berezin, E. 1993. Interpretation of pharmacologic data in respiratory tract infections. *Int. J. Antimicrob. Agents* **3**:S3–S14.
5. Biedenbach, D. J., M. S. Barrett, and R. N. Jones. 1998. Comparative antimicrobial activity and kill-curve investigations of novel ketolide antimicrobial agents (HMR 3004 and HMR 3647) tested against *Haemophilus influenzae* and *Moraxella catarrhalis* strains. *Diagn. Microbiol. Infect. Dis.* **31**:349–353.
6. Conte, J. E., Jr., J. A. Golden, S. Duncan, E. McKenna, and E. Zurlinden. 1995. Intrapulmonary pharmacokinetics of clarithromycin and of erythromycin. *Antimicrob. Agents Chemother.* **39**:334–338.
7. Crapo, J. D., B. E. Barry, P. Gehr, M. Bachofen, and E. R. Weibel. 1982. Cell numbers and cell characteristics of the normal human lung. *Am. Rev. Respir. Dis.* **126**:332–337.
8. Denis, A., C. Agouridas, J. M. Auger, Y. Benedetti, A. Bonnefoy, F. Bretin, J. F. Chantoin, A. Dussarat, C. Fromentin, S. Gouin d'Ambriere, S. Lachaud, P. Laurin, O. Le Martret, V. Loyau, N. Tessot, J. M. Pejac, and S. Perron. 1999. Synthesis and antibacterial activity of HMR 3647, a new ketolide highly potent against erythromycin-resistant and susceptible pathogens. *Bioorg. Med. Chem. Lett.* **9**:3075–3080.
9. Drusano, G. 2001. Pharmacodynamic and pharmacokinetic considerations in antimicrobial selection: focus on telithromycin. *Clin. Microbiol. Infect.* **7**:24–29.
10. Edelstein, P. H., and M. A. Edelstein. 1999. In vitro activity of the ketolide HMR 3647 (RU 6647) for *Legionella* spp., its pharmacokinetics in guinea pigs, and use of the drug to treat guinea pigs with *Legionella pneumophila* pneumonia. *Antimicrob. Agents Chemother.* **43**:90–95.
11. Finch, R. G., and M. A. Woodhead. 1998. Practical considerations and guidelines for the management of community-acquired pneumonia. *Drugs* **55**:31–45.
12. Fine, M. J., M. A. Smith, C. A. Carson, S. S. Mutha, S. S. Sankey, L. A. Weissfeld, and W. N. Kapoor. 1996. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *JAMA* **275**:134–141.
13. Jacobs, M. R., S. Bajaksouzian, A. Zilles, G. Lin, G. A. Pankuch, and P. C. Appelbaum. 1999. Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 U.S. surveillance study. *Antimicrob. Agents Chemother.* **43**:1901–1908.
14. Khair, O. A., J. M. Andrews, D. Honeybourne, G. Jevons, F. Vacheron, and R. Wise. 2001. Lung concentrations of telithromycin after oral dosing. *J. Antimicrob. Chemother.* **47**:837–840.
15. Pankuch, G. A., M. A. Visalli, M. R. Jacobs, and P. C. Appelbaum. 1998. Susceptibilities of penicillin- and erythromycin-susceptible and -resistant pneumococci to HMR 3647 (RU 6647), a new ketolide, compared with susceptibilities to 17 other agents. *Antimicrob. Agents Chemother.* **42**:624–630.
16. Patel, K. B., D. Xuan, P. R. Tessier, J. H. Russomanno, R. Quintiliani, and C. H. Nightingale. 1996. Comparison of bronchopulmonary pharmacokinetics of clarithromycin and azithromycin. *Antimicrob. Agents Chemother.* **40**:2375–2379.
17. Piper, K. E., M. S. Rouse, J. M. Steckelberg, W. R. Wilson, and R. Patel. 1999. Ketolide treatment of *Haemophilus influenzae* experimental pneumonia. *Antimicrob. Agents Chemother.* **43**:708–710.
18. Rennard, S. I., 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 a marker of dilution. *J. Appl. Physiol.* **60**:532–538.
19. Roblin, P. M., and M. R. Hammerschlag. 1998. In vitro activity of a new ketolide antibiotic, HMR 3647, against *Chlamydia pneumoniae*. *Antimicrob. Agents Chemother.* **42**:1515–1516.
20. Sahm, D. F., M. E. Jones, M. L. Hickey, D. R. Diakun, S. V. Mani, and C. Thornsberry. 2000. Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated in Asia and Europe, 1997–1998. *J. Antimicrob. Chemother.* **45**:457–466.
21. Schulz, T., C. B. Wennersten, M. J. Ferraro, R. C. Moellering, Jr., and G. M. Eliopoulos. 1998. Susceptibilities of *Legionella* spp. to newer antimicrobials in vitro. *Antimicrob. Agents Chemother.* **42**:1520–1523.