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In Vivo Efficacy of Telithromycin (HMR3647) against *Streptococcus pneumoniae* and *Haemophilus influenzae*

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The in vivo activity of telithromycin against erythromycin A- and penicillin G-resistant *Streptococcus pneumoniae* was superior to that of azithromycin, clarithromycin, cefdinir, and levofloxacin. In respiratory tract infections caused by erythromycin A-susceptible *S. pneumoniae* or *Haemophilus influenzae* in mice, telithromycin was more effective than clarithromycin and comparable to azithromycin.

Telithromycin, a new antibacterial agent, is a semisynthetic derivative of erythromycin A. Many reports indicate that telithromycin has potent antibacterial activity against 14- and 15-member macrolide- and/or penicillin G-resistant *Streptococcus pneumoniae* (1, 8). It was also reported that the in vitro activity of telithromycin against *Haemophilus influenzae* is comparable to that of azithromycin and greater than that of clarithromycin (1, 2).

Because there were few reports about its vivo activity, we investigated the in vivo therapeutic effects of telithromycin in several experimental respiratory tract infection models, including penicillin G-resistant *S. pneumoniae* (PRSP) pneumonia and bronchopneumonia due to cell-bound *H. influenzae* (6, 10).

Samples of the following antimicrobial agents of known potency were kindly provided by the indicated companies: telithromycin (Aventis Pharma Ltd., Tokyo, Japan), clarithromycin (Taisho Pharmaceutical Co., Ltd., Tokyo, Japan), azithromycin (Pfizer Laboratories, Groton, Conn.), cefdinir (Fujisawa Pharmaceutical Co., Osaka, Japan), and levofloxacin (Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan).

The bacterial strains used in the present experiments, i.e., erythromycin A- and penicillin G-susceptible *S. pneumoniae* (PSSP) TUH39, erythromycin A-resistant PRSP TUM741 (*mef* gene-positive strain), erythromycin A-resistant PSSP TOH117 (*ermB* gene-positive strain), and *H. influenzae* TUM8, were obtained from our hospital.

MICs were determined as reported previously (8).

One day after infection with PSSP TUH39, mice (three or four in each group) were orally administered a single dose of the compounds at 100 mg/kg. Samples of plasma and lung tissues were obtained at 10, 30, 60, 180, 360, and 1,440 min after administration. Levels of the compound in plasma and tissues were determined by a paper disk method. For telithromycin, *Micrococcus luteus* ATCC 9341 was used as the indicator organism with Heart Infusion Agar (Nissui, Tokyo, Japan). Levels of the reference compounds were determined as reported previously (7, 9, 11, 12). The linear ranges for telithromycin and the reference compounds were 0.002 to 0.064 and 0.05 to 100 μg/ml, respectively. The relative error of the assay was less than 15%. The quantification limits were 0.05 μg/ml for plasma and 0.25 μg/g for lung tissue. Pharmacokinetic parameters were calculated by the WinNonlin (Belgium Science) program.

The in vivo activities against erythromycin A-susceptible PSSP TUH39 were evaluated in 4-week-old male ICR mice (Japan SLC, Inc.). The mice (eight in each group) were infected by intranasal inoculation of 50-μl bacterial suspensions (4.1×10^5 CFU/mouse) under ketamine-xylazine anesthesia. Oral compound administration was initiated at 16 h after infection and continued once a day for 3 days. The animals were observed for deaths for 7 days after the final administration. A twofold serial dose (6.25 to 200 mg/kg) of each compound was used so that the respective 50% effective dose (ED_{50}) could be calculated by the Probit method (5).

In the erythromycin A-resistant PRSP TUM741 and PSSP TOH117 models, 5-week-old male CBA/J mice (five mice in each group; Charles River Japan, Inc.) were intranasally infected with bacterial suspensions (6.45×10^4 to 7.0×10^5

TABLE 1. Values of pharmacokinetic parameters for telithromycin and reference compounds in plasma and lungs of *S. pneumoniae*-infected mice[a]

Specimen and compound	C_{max} (μg/ml or μg/g)	AUC_{0-24} (μg · h/ml or μg · h/g)	$t_{1/2}$ (h)
Plasma			
Telithromycin	8.5	103.3	2.5
Clarithromycin	6.8	36.6	2.0
Azithromycin	1.1	11.3	5.1
Cefdinir	4.5	7.4	1.5
Levofloxacin	4.6	18.9	4.6
Lung			
Telithromycin	13.3	118.4	2.8
Clarithromycin	130.9	544.5	1.7
Azithromycin	48.5	593.8	16.0
Cefdinir	1.6	13.7	2.6
Levofloxacin	18.7	60.6	4.7

[a] Values were caluculated from mean concentrations in plasma and lung tissue taken at 10, 30, 60, 180, 360, and 1,440 min after compound administration (three or four mice). C_{max}, maximum drug concentration in plasma or lung tissue; AUC_{0-24}, AUC from 0 to 24 h; $t_{1/2}$ half-life.

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TABLE 2. Therapeutic effects of telithromycin and reference compounds on respiratory tract infection caused by erythromycin A-susceptible PSSP TUH39[a]

Compound	MIC (μg/ml)	ED_{50} (mg/kg)	95% confidence limits
Telithromycin	0.008	6.5	3.7–9.9
Clarithromycin	0.032	15.9	4.8–24.9
Azithromycin	0.125	6.9	4.9–9.7
Cefdinir	0.5	46.4	27.9–76.2
Levofloxacin	1	>200	

[a] The compounds were administrated orally once a day for 3 days, and the ED_{50}s were expressed as one dose. The challenge dose was 4.1×10^5 CFU/mouse.

CFU/mouse). In the *H. influenzae* model, ICR male mice (eight mice in each group) were infected by intranasal inoculation with cell-bound *H. influenzae* TUM8 organisms (1.7×10^4 CFU/mouse) (6). In those infections, oral administration started 40 h after infection and continued twice a day for 3 days. Respiratory tracts were removed under anesthesia at 16 h after the final drug administration, and the bacteria were counted. Statistical analysis was performed by Dunnett's method (4). The dose administered was 100 mg/kg, except for that of levofloxacin (10 mg/kg) in the *H. influenzae* TUM 8 model, and each experiment was performed once.

The pharmacokinetic parameters of compounds in the plasma and lungs of mice after administration of 100 mg/kg are presented in Table 1. The maximal concentration of telithromycin in plasma was 8.5 mg/liter, which is 4.6-fold higher than that of humans (1.84 ± 1.14 mg/liter) (3). However, the dose used in this study was relevant to humans because the volume of distribution (1.41 liters/kg) and the free compound (15%) in mouse plasma were both about twofold lower than those of humans (3 liters/kg and 30%) (3, 3a; C. Perret and D. H. Wessels, 10th European Congress of Clinical Microbiology and Infectious Diseases., abstr. 922, 2000; O. Vesga, W. A. Craig, and C. Bonnat, Program Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-255, p. 189, 1997). For lung tissue, the maximum concentration, the area under the concentration-time curve (AUC), and the half-life of telithromycin were 13.3 μg/ml, 118.4 μg · h/g, and 2.8 h, respectively.

TABLE 3. Therapeutic effects of telithromycin and reference compounds on respiratory tract infection caused by erythromycin A-resistant PRSP TUM741[a]

Compound	MIC (μg/ml)	Log CFU/lung (mean ± SD)
Control		6.95 ± 0.35
Telithromycin	0.063	1.49 ± 0.32[b]
Clarithromycin	1	6.46 ± 0.22
Azithromycin	2	6.96 ± 0.60
Cefdinir	2	6.45 ± 0.19
Levofloxacin	2	5.73 ± 1.65[c]

[a] The compounds, at a dose of 100 mg/kg, were administered orally to five mice twice a day for 3 days. Because the limit of detection was 20 CFU/lung, specimens that were below the limit of detection were recorded as containing 19 CFU/lung. The challenge dose was 7.0×10^5 CFU/mouse.

[b] $P < 0.01$ represents a statistically significant difference in comparison with the control.

[c] $P < 0.05$ represents a statistically significant difference in comparison with the control.

TABLE 4. Therapeutic effects of telithromycin and reference compounds on respiratory tract infection caused by *H. influenzae* TUM8[a]

Compound	MIC (μg/ml)	Dose (mg/kg)	Log CFU/lower respiratory tract (mean ± SD)
Control			6.30 ± 0.85
Telithromycin	1	100	3.10 ± 0.68[b]
Clarithromycin	4	100	4.16 ± 1.67[b]
Azithromycin	1	100	2.73 ± 0.72[b]
Levofloxacin	≤0.063	10	2.89 ± 1.13[b]

[a] The compounds were administration orally to eight mice twice a day for 3 days. Because the limit of detection was 200 CFU/lower respiratory tract, specimens that were below the limit of detection were recorded as containing 190 CFU/lower respiratory tract. The challenge dose was 1.7×10^4 CFU/mouse.

[b] $P < 0.05$ represents a statistically significant difference in comparison with the control.

The ED_{50} of telithromycin (6.5 mg/kg) was similar to that of azithromycin and lower than those of clarithromycin, cefdinir, and levofloxacin in the erythromycin A-susceptible PSSP TUH39 model (Table 2).

In the respiratory tract infection by erythromycin A-resistant PRSP strain TUM741, telithromycin treatment significantly reduced the viable count in the lungs compared with the control (Table 3). However, the reference compounds hardly showed any therapeutic effects. In this model, the AUC/MIC parameters of telithromycin, clarithromycin, azithromycin, and levofloxacin in lung tissue were 1,879, 545, 297, and 30, respectively. This result suggested that telithromycin might achieve an effective concentration in the infected region in the PRSP TUM741 model. When the infection was induced by inoculation with erythromycin A-resistant PSSP strain TOH117 (MIC of telithromycin, 0.125 μg/ml), the mean number of bacteria recovered from the lungs of untreated mice was 6.73 ± 1.52 log CFU/lung (data not shown). Treatment with telithromycin significantly reduced the bacterial count to 1.61 ± 0.43 log CFU/lung.

In the respiratory tract infections caused by *H. influenzae* TUM8, treatment with telithromycin led to significant reductions in viable bacterial counts in the lower respiratory tract compared with those of untreated mice (Table 4), which was more effective than clarithromycin but slightly less effective than azithromycin, although the differences were not significant.

The present results show that clinical trails are needed to determine the therapeutic potential of telithromycin in the treatment of respiratory tract infections by *S. pneumoniae* and *H. influenzae*.

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