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ORIGINAL ARTICLE

Aerosol-based efficient delivery of telithromycin, a ketolide antimicrobial agent, to lung epithelial lining fluid and alveolar macrophages for treatment of respiratory infections

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Abstract

Purpose: The efficacy of aerosol-based delivery of telithromycin (TEL), as a model antimicrobial agent, for the treatment of respiratory infections was evaluated by comparison with oral administration. *Method*: The aerosol formulation (0.2 mg/kg) was administered to rat lungs using a Liquid MicroSprayer®. *Results and discussion*: The time courses of the concentration of TEL in lung epithelial lining fluid (ELF) and alveolar macrophages (AMs) following administration of an aerosol formulation to rat lungs were markedly higher than that following the administration of an oral formulation (50 mg/kg). The time course of the concentrations of TEL in plasma following administration of the aerosol formulation was markedly lower than that in ELF and AMs. These results indicate that the aerosol formulation is more effective in delivering TEL to ELF and AMs, compared to the oral formulation, despite a low dose and it avoids distribution of TEL to the blood. In addition, the antibacterial effects of TEL in ELF and AMs following administration of the aerosol formulation were estimated by pharmacokinetics/pharmacodynamics analysis. The concentrations of TEL in ELF and the AMs time curve/minimum inhibitory concentration of TEL ratio were markedly higher than the effective values. *Conclusion*: This study indicates that an antibiotic aerosol formulation may be an effective pulmonary drug delivery system for the treatment of respiratory infections.

Key words: *Aerosol-based pulmonary drug delivery system; lung epithelial lining fluid and alveolar macrophage; PK/PD; respiratory infection; telithromycin*

Introduction

Alveolar macrophages (AMs) treat pathogenic microorganisms in lungs and are associated with biophylaxis. However, several microorganisms, such as *Haemophilus influenzae* and *S. pneumoniae*, avoid uptake and digestion by AMs and survive or multiply in lung epithelial lining fluid (ELF)[1–5]. Also, intracellular parasites, such as *M. avium*, *C. pneumonia,* and *L. pneumophila*, are taken up by AMs; however, they are resistant to the biocidal mechanisms of AMs and survive or multiply intracellularly in AMs[6–11]. Thus, severe respiratory infections are frequently induced by these pathogenic microorganisms in ELF and AMs[12–20]. For sterilization of these pathogenic microorganisms in ELF and AMs, the concentration of antimicrobial agents in ELF and AMs must be higher than the minimum inhibitory concentration (MIC). Consequently, efficient delivery of antibiotics to ELF and AMs is required to produce an antimicrobial effect against pathogenic microorganisms resisting sterilization systems of AMs. Antimicrobial agents are generally given by the oral route for the treatment of respiratory infections. However, because antimicrobial agents distribute too many different tissues through blood after oral administration, systemic side effects are frequently induced[21–27]. In contrast, aerosolization may be an

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efficient method for delivering antimicrobial agents directly to the lung. Therefore, an enhancement of the antimicrobial effect, a reduction in the dose, and avoidance of systemic side effects could be achieved by the aerosolization of antimicrobial agents.

In this study, telithromycin (TEL) was chosen as a model antimicrobial agent because it has a wide antimicrobial spectrum[28–32] against the pathogenic microorganisms resisting sterilization systems of AMs. Then, the efficacy of aerosol-based delivery of TEL for the treatment of various respiratory infections caused by these pathogenic microorganisms in ELF and AMs was evaluated by comparison with an oral administration.

Materials and methods

Materials and animals

TEL was supplied by Sanofi-Aventis (Paris, France). All other reagents were commercially available and of analytical grade. Male SD rats (200–230 g) were purchased from Japan SLC (Shizuoka, Japan). The animal experimental plan used has been approved by the Committee of Laboratory Animal Center (No. 09-009) and conforms to the Guiding Principles for the Care and Use of Experimental Animals in Hokkaido Pharmaceutical University.

Animal experiments

TEL dissolved in phosphate-buffered saline solution (pH 7.4) was aerosolized into rat lungs at a dose of 0.2 mg/0.25 mL/kg through the nasal cavity using Liquid MicroSprayer® (Model IA-1C, PennCentury, Inc., Philadelphia, PA, USA) under pentobarbital anesthesia. At each designated time point, blood was collected from the jugular vein. The trachea was immediately cannulated and the lungs were lavaged three times with 5 mL ice-cold phosphate-buffered saline solution (pH 7.4)[33]. The bronchoalveolar lavage fluid was immediately centrifuged at 4°C (650 × *g*, 5 min) to separate AMs from the ELF. AMs were extracted with 1 mL 0.1 M NaOH for high-performance liquid chromatography (HPLC) analysis. To calculate the concentrations of TEL in ELF, the apparent volume of ELF was estimated using urea as an endogenous marker of ELF dilution[34]. The mean value estimated in this study was 393 μL/215 g of rat. To calculate the concentrations of TEL in AMs, the intracellular volume in AMs was determined by a velocity-gradient centrifugation technique using ^{3}H-water[35], and this was estimated to have a mean value of 4.2 μL/mg cell protein. The concentration of TEL in each sample was measured by HPLC as described below. The protein concentration in the AM extracts was determined using Coomassie protein Assay reagent (Pierce Chemical Company, Rockford, IL, USA) with bovine serum albumin as a standard[36]. For the pharmacokinetic analysis, the area under the concentration (AUC) of TEL–time curve from time 0 to time 24 h was calculated by the trapezoidal rule. Also, therapeutic availability (TA) in ELF and AMs was calculated from Equation (1) using the data following the intravenous injection[37].

$$\mathrm{TA}=\frac{D_{\text{iv injection}}\times \mathrm{AUC}_{\text{formulation}}}{D_{\text{formulation}}\times \mathrm{AUC}_{\text{iv injection}}}, \tag{1}$$

where $D_{\text{formulation}}$ is the dose of formulation, $D_{\text{iv injection}}$ is the dose of intravenous injection, $\mathrm{AUC}_{\text{formulation}}$ is the AUC following administration of formulation, and $\mathrm{AUC}_{\text{iv injection}}$ is the AUC following intravenous injection. $D_{\text{iv injection}}$ was 50 mg/kg wt, $\mathrm{AUC}_{\text{iv injection}}$ in ELF and AMs were 159 and 2815 μg·h/mL, respectively.

Pharmacokinetics/pharmacodynamics analysis

The antibacterial effects of TEL in ELF and AMs following the administration of the formulation were estimated by pharmacokinetics (PK)/pharmacodynamics (PD) analysis. The AUC/MIC ratio was calculated as the PK/PD parameters of an antibacterial effect. The MIC values against pathogenic microorganisms resisting sterilization systems of ELF and AMs were taken from the literature. The effective values of AUC/MIC are larger than 100[38]. Also, the requirement dose (RD) for effective therapy (a dose required for winning 100 that is effective AUC/MIC value) was calculated from Equation (2).

$$\mathrm{RD}=\frac{D_{\text{formulation}}}{(\mathrm{AUC}/\mathrm{MIC})/100}. \tag{2}$$

Determination of TEL by HPLC

The concentration of TEL in samples was measured by HPLC. The sample (40 μL), a diphenylamine solution (as an internal standard, 20 μL), methanol (40 μL), and 250 mM ammonium acetate solution (10 μL) were mixed, and a 50 μL aliquot was subjected to HPLC using a system (Shimadzu Co., Kyoto, Japan) involving a Purospher RP-18e column (4.0 × 125 mm; Merck, Darmstadt, Germany). The mobile phase was 50 mM ammonium acetate/methanol/acetonitrile (5:4:2, v/v/v). The separation was performed at a flow rate of 1.0 mL/min at 50°C and the eluate from the column was monitored by fluorescence detection (excitation wavelength of 263 nm and emission wavelength of 460 nm). The concentrations were determined with respect to a standard curve of TEL.

Results

Pharmacokinetics of TEL

The time courses of the concentrations of TEL in ELF, AMs, and plasma after administration of the aerosol and oral formulations to rats are shown in Figure 1. The time courses of the concentrations of TEL in ELF and AMs following administration of the aerosol formulation were markedly higher than those following administration of the oral formulation. On the contrary, the time course of the concentration of TEL in plasma following administration of the aerosol formulation was significantly lower than that following administration of the oral formulation. The pharmacokinetic parameters of TEL in ELF, AMs, and plasma following administration of the aerosol and oral formulation are summarized in Table 1. The AUC in ELF and AMs following administration of the aerosol formulation were 106 and 3097 μg·h/mL, respectively, and the AUC ratios of ELF and AMs to plasma were 4750 and 139,049, respectively. The AUC of ELF and AMs to plasma following administration of the oral formulation was 31.5 and 836 μg·h/mL, respectively, and the AUC ratios of ELF and AMs to plasma were 3.1 and 82.6, respectively. The TA of the aerosol formulation in ELF and AMs were 166 and 275. These values indicate that the aerosol formulation has a pharmacokinetic efficacy of 166- and 275-fold that of the intravenous injection. On the contrary, the TA of the oral formulation in ELF and AMs were 0.20 and 0.30, respectively.

Estimation of antibacterial effect

The estimated antibacterial effects of TEL in AMs and ELF following administration of the aerosol and oral formulation to rats are summarized in Table 2. In the case of the aerosol formulation, despite a low dose, the AUC/MIC ratios against most pathogens in ELF and AMs were larger than 100 that is the effective value. Only the AUC/MIC against *H. influenzae* (26.5) was lower than the effective value. However, fortunately, the RD was 0.755 mg/kg (one-thirteenth of the general clinical dose). The oral formulation also had an effective AUC/MIC value against most pathogens except *H. influenzae*. Interestingly, the RD of the aerosol formulation against each pathogen for effective therapy was markedly lower than those of the oral formulation.

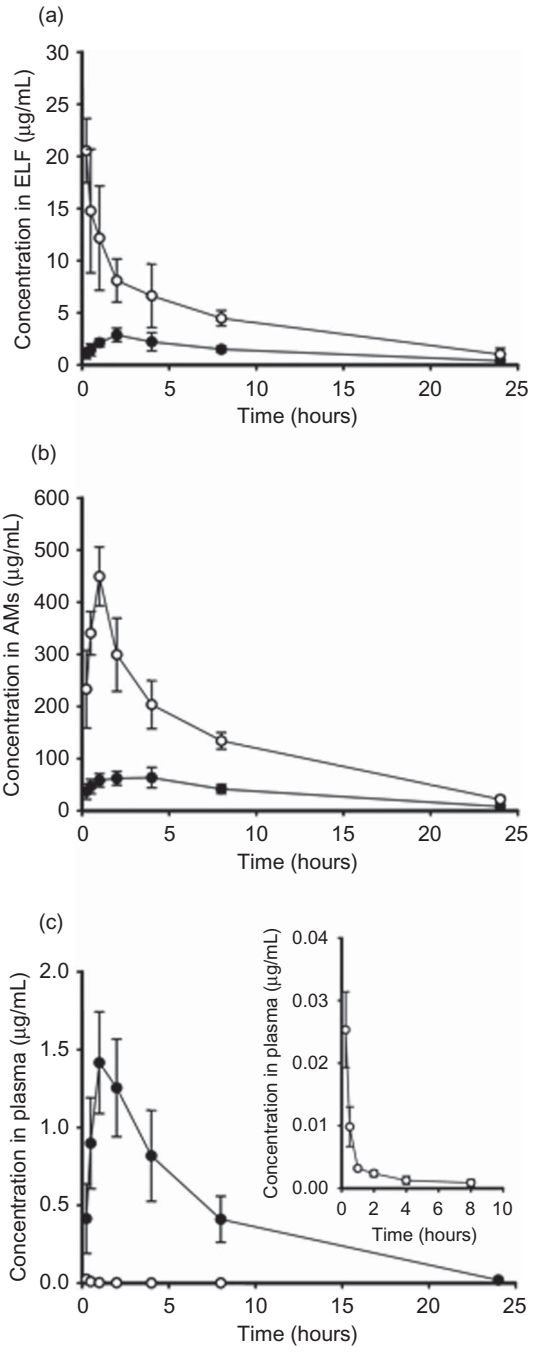

Figure 1. Time courses of concentrations of TEL in (a) ELF, (b) AMs, and (c) plasma after administration of the aerosol (○) and oral (●) formulation of TEL to rats. The aerosol formulation (0.2 mg/kg) was administered to rat lungs using a Liquid MicroSprayer®. At each time point after administration, the plasma, ELF, and AMs were collected, and then concentrations of TEL in each sample were determined. Each point represents the mean ± SD (n = 4–7). Time courses of TEL after administration of the oral formulation (50 mg/kg) were taken from the published literature[39].

Discussion

The PK of TEL in ELF, AMs, and plasma following administration of the aerosol and oral formulation to rats were examined (Figure 1 and Table 1). TEL given by the oral route distributes in the alveolus through vascular endothelial cells and alveolar epithelial cells from the blood side. The alveolar barrier consists of three layers: the capillary lumen, connected tissue, and alveolar

Table 1. Pharmacokinetic parameters of TEL in ELF, AMs, and plasma following administration of the aerosol and oral formulation to rats.

Formulation	Tissue	AUC (μg·h/mL)	AUC ratio[a]	TA
Aerosol (0.2 mg/kg)	ELF	106 ± 21	4750	166
	AMs	3097 ± 620	139,049	275
	Plasma	0.0223 ± 0.0048	1	—
Oral (50 mg/kg)	ELF	31.5 ± 6.2	3.1	0.20
	AMs	836 ± 101	82.6	0.30
	Plasma	10.1 ± 1.6	1	—

Each pharmacokinetic parameter was calculated from data shown in Figure 1.
[a] The ratio of AUC in plasma. AUC is represented as mean ± SD (n = 4–7).

epithelial cells[40]. The alveolar epithelial cells that are tightly connected by numerous zonulae occludins are considered to provide a significant barrier between the plasma and the ELF[41]. There are several efflux transporters expressed in alveolar epithelial type I cells in the human and rat lung, including *P*-glycoprotein and breast cancer-resistant protein[42–44]. TEL is a multidrug resistance protein (MDR1) substrate, and thus, TEL can cross from the alveolar epithelium to ELF through an MDR1 transporter[39]. However, transport of TEL to ELF across the alveolar barrier after oral administration may not be so efficient. In contrast, in the case of aerosolization, TEL was efficiently delivered to ELF and AMs because it was sprayed into the alveolus directly. Thus, a reduction in the dose and avoidance of distribution to the blood became possible. The AUC ratio of ELF to plasma following administration of the aerosol formulation was 4750 (Table 1). According to our recent report, this significant asymmetry is based on the fact that transport of TEL from ELF to blood is inhibited by the MDR1 transporter on the alveolar epithelial type I cells[39]. These findings suggest that aerosolization can avoid systemic side effects as well as provide efficient delivery of antimicrobial agents to AMs and ELF.

The AUC in AMs following administration of the aerosol formulation was 29-fold greater than that in ELF (Table 1). This result indicates that TEL is able to concentrate intracellularly in AMs. Recently, we have reported that the uptake of TEL by AMs is mediated by active transport systems in the same way as clarithromycin, a macrolide antimicrobial agent, which has similar structure[39]. According to previous reports[45,46], TEL may be transported to the intracellular region of AMs through active transport systems that require Ca^{2+} and protein kinase A-dependent phosphorylation, the same as other phagocytes such as human polymorphonuclear neutrophils and J774 murine macrophages[45,47,48], in addition to passive diffusion. In another study, we have also confirmed that TEL distributes to the entire intracellular area of AMs and not the local area (data not shown). This shows that intracellular parasitic microorganisms in AMs are exposed to TEL.

For sterilization of pathogenic microorganisms resisting sterilization systems of AMs, it is required that TEL is stable in ELF and AMs following aerosolization.

Table 2. Antibacterial effects of TEL against the respiratory pathogens in ELF and AMs.

Formulation (dose)	Microorganisms (MIC; μg/mL)	AUC/MIC (hours)	RD (mg/kg)
Microorganisms avoiding uptake by AMs in ELF			
Aerosol (0.2 mg/kg)	*H. influenzae* (4 μg/mL)[a]	26.5	0.755
	S. pneumoniae (0.25 μg/mL)[b]	423	0.047
	Peniciline G resistant *S. pneumoniae* (0.5 μg/mL)[b]	212	0.094
	Erythromycin A resistant *S. pneumoniae* (0.5 μg/mL)[b]	212	0.094
	Levoflaxacin resistant *S. pneumoniae* (0.125 μg/mL)[b]	846	0.024
Oral (50 mg/kg)	*H. influenzae* (4 μg/mL)[a]	7.9	633
	S. pneumoniae (0.25 μg/mL)[b]	126	39.7
	Peniciline G resistant *S. pneumoniae* (0.5 μg/mL)[b]	63	79.4
	Erythromycin A resistant *S. pneumoniae* (0.5 μg/mL)[b]	63	79.4
	Levofloxacin resistant *S. pneumoniae* (0.125 μg/mL)[b]	252	19.8
Intracellular parasitic microorganisms in AMs			
Aerosol (0.2 mg/kg)	*C. pneumoniae* (0.125 μg/mL)[c]	24,776	0.0008
	L. pneumophila (0.125 μg/mL)[d]	24,776	0.0008
	M. avium (1.25 μg/mL)[e]	2478	0.008
Oral (50 mg/kg)	*C. pneumoniae* (0.125 μg/mL)[c]	6688	0.748
	L. pneumophila (0.125 μg/mL)[d]	6688	0.748
	M. avium (1.25 μg/mL)[e]	669	7.48

AUC values in ELF and AMs mentioned in Table 1 were used for calculation of PK/PD parameters. The MIC values were taken from the literature. (a) Wootton et al.[32]; (b) Felmingham et al.[29]; (c) Miyashita et al.[30]; (d) Edelstein and Edelstein[28]; (e) Rastogi et al.[31]

We have shown that TEL was stable in ELF and AMs for a long time (data not shown). Although AMs produce and secrete various bioactive substances, such as enzymes, cytokines, complements, proteins, lipids, and reactive oxygen species[49–54], these bioactive substances may not affect the stability of TEL. In addition, it is important that the aerosolized TEL does not injure lung tissues. The aerosol formulation of TEL was found to be nontoxic following administration because no release of lactate dehydrogenase from lung tissue was observed (data not shown). This indicates that the aerosolized TEL does not injure lung tissues, at least at the dose used in this study.

The antibacterial effects of TEL in ELF and AMs following administration of the aerosol and oral formulation to rats were evaluated (Table 2). Recently, there has been increasing interest in the relationship between the PK and PD of antimicrobial agents, and therefore, the use of PK/PD parameters is now widespread[55,56]. It is proposed that the PK/PD analysis of an antibiotic treatment is important for selecting a dose and optimizing the treatment of individual patients. The effects of antimicrobial agents are concentration- and/or time-dependent and the PK/PD parameters used generally are the maximum concentration/MIC (C_{max}/MIC), AUC/MIC, and the time above the MIC. Because the antibacterial effects of TEL depend on the AUC/MIC[38,57], the AUC/MIC values in ELF and AMs were calculated in this study. Also, the RD was calculated to obtain information regarding an effective dose. The AUC/MIC and RD values showed that efficient antibacterial effects of TEL in ELF and AMs are obtained by aerosolization of a dose lower than that used clinically. The antibacterial effect of TEL following aerosol formulation to animals used as models of respiratory infection should be investigated in the future as it was not examined in this study.

In conclusion, this study evaluated the efficacy of aerosol-based delivery of TEL for the treatment of respiratory infections. We have shown that efficient delivery of TEL to ELF and AMs is possible by aerosolization. Furthermore, it was shown that the efficient antibacterial effect of TEL against various pathogenic microorganisms following administration of aerosol formulation was obtained at a dose lower than that used clinically. These findings suggest that aerosolization of antimicrobial agents is an efficient method for the treatment of a variety of respiratory infections.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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