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Presence of infection influences the epithelial lining fluid penetration of oral levofloxacin in adult patients☆

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ABSTRACT

Although epithelial lining fluid (ELF) is the presumed site for pulmonary infections, most antibiotic penetration studies are conducted in uninfected patients or healthy volunteers. Levofloxacin concentrations in plasma and ELF were collected from two previous studies involving 18 infected patients with acute exacerbations of chronic bronchitis and 15 uninfected elderly patients undergoing diagnostic bronchoscopy. Concentration data were population modelled using the BigNPAG algorithm, and a 5000-patient Monte Carlo simulation was conducted to simulate ELF exposure for a dosing regimen 750 mg every 24 h for five doses in plasma and ELF of infected versus uninfected patients. Mean ± S.D. model parameters for plasma in infected patients were similar to uninfected patients (volume of central compartment, 68.4 ± 36.3 vs. 50.2 ± 17.3 L; clearance, 6.0 ± 2.5 vs. 6.8 ± 3.3 L/h; and absorption rate, 5.4 ± 2.5 vs. 4.7 ± 2.7 h^{-1}), resulting in similar simulated AUC in plasma (infected, 140.5 ± 54.8 vs. uninfected, 133.7 ± 61.6 μg h/mL). The volume of ELF was 57.2 ± 25.0 and 14.8 ± 9.0 L in infected and uninfected patients, respectively, resulting in a lower simulated AUC_{ELF} exposure for infected patients (189.1 ± 210.5 vs. 461.0 ± 558.7 μg h/mL). Penetration ratios for infected and uninfected patients were, respectively, 1.4 ± 1.8 and 3.5 ± 3.7, with median values of 0.9 and 2.4. ELF penetration in infected patients was approximately one-half that of uninfected adults. These data highlight the importance of confirming exposure in infected patients to further support dosage regimen selection.

1. Introduction

Penetration of antimicrobials to the site of infection is vital towards achieving a positive outcome (e.g. pathogen eradication and rapid patient recovery). Thus, it is critical to identify the exposure of an antimicrobial at the primary affected site in order to determine the optimal dosing regimen. For lower respiratory tract infections (LRTIs), the epithelial lining fluid (ELF) is the presumed target site of infection for extracellular organisms such as *Staphylococcus aureus* and *Streptococcus pneumoniae* [1–4].

Due to its broad spectrum of activity against Gram-positive and Gram-negative bacteria as well as its availability as intravenous (i.v.) and oral formulations, levofloxacin is widely used to treat respiratory tract infections [5]. Penetration of levofloxacin into the ELF of the respiratory tract has been studied in several populations, including healthy adult volunteers, uninfected elderly patients requiring diagnostic or therapeutic bronchoscopy, and infected patients with acute exacerbations of chronic bronchitis (AECB), chronic obstructive pulmonary disease or LRTIs [6–11]. In general, the mean ratio of the area under the concentration–time curve (AUC) in ELF to that in plasma in these studies has been >1 [6–9,11], suggesting exposure at the site of infection that is similar to or greater than that in plasma. However, most of these studies have utilised a composite of concentrations from a single bronchoalveolar lavage (BAL) at specified time points to determine the mean AUC in plasma and ELF; this methodology does not account for variability in exposure between patients. Lastly, penetration into the ELF may be different between infected and uninfected hosts [12,13]; however, no studies have directly compared ELF exposure between uninfected and infected patients, which is critical since early dosing regimens are frequently determined using healthy uninfected volunteers.

In the current analysis, population pharmacokinetic methods using levofloxacin plasma and ELF concentration data from two previous studies conducted by our group were employed to determine whether differences in ELF exposure were apparent in the presence of infection.

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2. Methods

2.1. Study design and setting

This was a retrospective population pharmacokinetic analysis of levofloxacin plasma and ELF concentration data collected from two previously published, prospective, open-label, multidose studies to assess the penetration and exposure into ELF [7,11]. Each protocol was approved by the Institutional Review Board of Hartford Hospital (Hartford, CT), and all participants provided written informed consent prior to screening.

2.2. Study population, dosing and pharmacokinetic sampling

Briefly, the first study consisted of 15 uninfected adult patients with co-morbidities undergoing diagnostic bronchoscopy for lung mass/rule out cancer (n = 9), haemoptysis/chronic cough (n = 4) or left lower lobe infiltrate (n = 2) who received oral levofloxacin 500 mg every 24 h (q24h) for five doses before sampling [7]. A single BAL and blood sample was collected from each patient at 4 h (n = 4 patients), 8 h (n = 3 patients), 12 h (n = 4 patients) or 24 h (n = 4 patients) after the fifth dose. The second study comprised 18 infected patients with AECB who received oral levofloxacin 750 mg q24h for five doses before sampling [11]. A single BAL and blood sample was collected from each patient at 4 h (n = 6 patients), 12 h (n = 6 patients) or 24 h (n = 6 patients) after the third dose; dosing was then continued to complete treatment of their AECB. Both studies utilised identical methodology for sampling and processing the plasma and BAL fluid (i.e. right middle lobe). All levofloxacin concentrations were determined by high-performance liquid chromatography (HPLC) at the Center for Anti-Infective Research and Development, Hartford Hospital. Furthermore, both studies used the urea dilution method to calculate the concentrations of levofloxacin in ELF. The only difference was the methodology used to determine urea concentration between studies. Capitano et al. used the clinical laboratory to determine the plasma urea concentration and a modified enzymatic assay to determine the BAL urea concentration [7], whilst Nicolau et al. employed a colorimetric assay both for plasma and BAL samples [11]. However, it was felt that results would be comparable since the standard curves were linear over the range of 0.1–2.0 mg/dL and the intraday and interday coefficients of variation were ≤10% for both assays. Additional study details, including HPLC methodology, can be found in the original publications [7,11,14].

2.3. Population pharmacokinetic modelling

The original studies employed non-compartmental (NCA) pharmacokinetic methods and used mean concentrations of the composite profile at each sampling time. Thus, we could not quantify the variability in exposure with that NCA approach. In the current analysis, levofloxacin concentrations in plasma and ELF compartments were co-modelled using population pharmacokinetic methods via the non-parametric adaptive grid (BigNPAG) algorithm with adaptive γ of Leary et al. [15]. Multiple models (two- versus three-compartment) were evaluated and discriminated employing the Akaike information criterion [16], the likelihood ratio test, and visual predictive checks of observed versus predicted concentrations. Since blood samples were not collected during the absorption phase, we assumed that the range of likely values for levofloxacin's absorption rate constant (K_a) would be between 0.1 h^{-1} and 10 h^{-1} based on data from previous population studies [6,17,18], and let BigNPAG determine the value with the greatest likelihood. Weighting of the concentration data was performed using the interday assay standard deviation (S.D.). For plasma, the equation for the assay variance was S.D. = 0.00218 + 0.0182 × (concentration). For ELF, the equation for the assay variance was S.D. = 0.00107 + 0.0186 × (concentration). Individual parameter estimates were evaluated by the empirical Bayesian estimates utility in BigNPAG. Bias and imprecision were employed to determine the final model statistics. In BigNPAG, bias represents the mean-weighted error, which is calculated as the sum of the weighted prediction error/N, where the weighted prediction error is (predicted − observed)/S.D. for each prediction/observation and N is the number of observations. Weighting is according to the S.D. based on the assay variance above. Imprecision is the bias-adjusted mean-weighted squared error, which is calculated as the sum of the weighted squared prediction error/N minus the bias squared.

2.4. Monte Carlo simulation

The final mean parameter estimates and covariance matrix from the population analyses were loaded in Subroutine Prior of the ADAPT 5 package of D'Argenio and Schumitzky [19] to perform a Monte Carlo simulation. Plasma and ELF concentrations for 5000 patients receiving five doses of oral levofloxacin 750 mg q24h were simulated in 0.5-h intervals from 96 h to 120 h. During simulation, a log-Gaussian distribution was applied to all parameters.

2.5. Statistics

Pharmacokinetic parameters were compared between uninfected and infected patients using Student's t-test if normally distributed or the Mann–Whitney rank-sum test if a test for normality failed. All tests were performed in SigmaPlot v.12.0 (Systat Software Inc., San Jose, CA). A P-value of <0.05 was considered statistically significant. The AUC from 96–120 h ($AUC_{96–120h}$) in plasma and ELF was calculated by the trapezoidal rule. Penetration into ELF was calculated as the $AUC_{96–120h}$ in ELF for each simulated patient divided by the $AUC_{96–120h}$ in plasma for that subject. A second analysis was conducted correcting the $AUC_{96–120h}$ in plasma using a protein binding estimate of 30% [20]. The proportion of the

Table 1
Comparative characteristics between infected and uninfected patients receiving oral levofloxacin[a].

Characteristic	Total (n = 33)	Infected patients (n = 18)	Uninfected patients (n = 15)	P-value
Age (years)	54.9 ± 15.4	51.8 ± 12.9	58.6 ± 17.7	0.215
Male [n (%)]	12 (36.4)	2 (11.1)	10 (66.7)	0.003
Race [n (%)]				0.004
Caucasian	21 (63.6)	7 (38.9)	14 (93.3)	
African–American	12 (36.4)	11 (61.1)	1 (6.7)	
Weight (kg)	85.3 ± 22.3	87.2 ± 24.9	83.1 ± 19.3	0.613
Height (inches)	66.0 ± 3.6	64.9 ± 2.1	67.4 ± 4.6	0.049
CL_{Cr} (mL/min)	N/A	98. ± 28	95. ± 26	0.754

CL_{Cr}, creatinine clearance; N/A, not available.
[a] All data are presented as the mean ± standard deviation unless otherwise stated.