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Penetration of Orally Administered Prulifloxacin Into Human Lung Tissue

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Abstract

Objective: To evaluate the distribution in lung tissue of ulifloxacin, the active metabolite of prulifloxacin, a new once-daily fluoroquinolone administered orally in a single 600mg dose.

Design: Open-label, randomised study.

Patients: Twenty-seven patients (25 males, 2 females; mean age 65.7 years [range 49–79 years]) with a lung neoplasm requiring lobectomy or pneumonectomy.

Methods: Patients were randomly assigned to five treatment groups and received a single oral dose of prulifloxacin 600mg at 2, 4, 6, 12 or 24 hours preoperatively. During surgery, blood and healthy lung (based on macroscopic appearance) samples were collected at the same time. Ulifloxacin concentrations in plasma and lung tissue were determined by a validated reversed-phase high-performance liquid chromatography assay. Lung tissue ulifloxacin concentrations were adjusted for blood contamination, by measuring haemoglobin in the supernatant of each tissue sample and applying a corrective equation.

Results: Ulifloxacin concentration in lung tissue exceeded plasma concentration at every timepoint. Following administration of prulifloxacin 600mg, the overall mean corrected lung/plasma ratio over the 24-hour period was 6.9 (range 1.2–14.1). When sampling intervals were assessed, the corrected lung/plasma ratios were 7.5 (2 hours after dosing), 6.3 (4 hours), 4.3 (6 hours), 7.0 (12 hours) and 9.2 (24 hours). The mean corrected lung/plasma area under the concentration-time curve ratio was 6.3, demonstrating the ability of the drug to penetrate lung tissue and confirming the high exposure of this target tissue to ulifloxacin. However, the limitation of the lung tissue sampling method and the high interpatient variability should be considered. Over the 24-hour period, the concentrations of ulifloxacin in lung tissue were higher than the minimum inhibitory concentration (MIC) values for pathogens frequently involved in community-acquired respiratory tract infections.

Conclusion: Lung tissue penetration data may have a supportive value when considered jointly with MICs and efficacy results. The findings from this lung penetration study could explain the efficacy of once-daily prulifloxacin 600mg observed in clinical trials conducted in patients with exacerbation of chronic bronchitis.

Prulifloxacin, a new once-daily fluoroquinolone antimicrobial agent with a broad spectrum of antibacterial activity against Gram-negative and Gram-positive strains, has been developed to manage respiratory and urinary tract infections.[1]

After oral administration, prulifloxacin is rapidly absorbed and quantitatively transformed by esterases into its active metabolite, ulifloxacin.[2] Following a single oral dose of prulifloxacin 600mg, the maximum plasma concentration (C_{max}) of ulifloxacin was 1.6 μg/mL after 1 hour, with an area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) of 7.3 μg • h/mL.[3] At steady state, ulifloxacin C_{max} was 2 μg/mL after administration of prulifloxacin 600mg once daily for 12 days; time to reach C_{max} (t_{max}) was 0.75 hours and AUC was 7.6 μg • h/mL.[1] The steady-state binding to human serum proteins *ex vivo* was 45%.[4] Unchanged ulifloxacin is predominantly eliminated via the kidneys,[1] and urinary concentrations of ulifloxacin were >3 μg/mL 48 hours after a single dose of prulifloxacin 600mg.[1] The elimination half-life is 10–12 hours,[3] allowing prulifloxacin to be administered once daily, thus ensuring good patient compliance with treatment.[5]

Ulifloxacin peak plasma levels exceed the 90% minimum inhibitory concentration (MIC_{90}) values of common respiratory tract pathogens, such as *Haemophilus influenzae* (≤0.015 μg/mL), *Klebsiella pneumoniae* (0.015–0.12 μg/mL) and *Moraxella catarrhalis* (0.015–0.06 μg/mL).[6] The *in vitro* activity of prulifloxacin against *Streptococcus pneumoniae* was variable (MIC_{90} ranging from 1 to 4 μg/mL),[6,7] although *in vivo* data in patients with acute exacerbation of chronic bronchitis showed a high rate of *S. pneumoniae* eradication.[8] This result may also be related to good penetration of ulifloxacin into the target tissue.

Although complicated by technical difficulties, lung penetration studies of antimicrobials are generally thought to be useful in predicting efficacy in the treatment of lower respiratory tract infections, particularly when considered in conjunction with *in vitro* susceptibility data.[9,10] The aim of the present study was to assess and compare ulifloxacin concentrations in lung and plasma after a single oral dose of prulifloxacin 600mg, in order to verify its potential usefulness in treating pulmonary infections.

Patients and Methods

The study was approved by the Ethics Committee of the USSL 25 of Verona, Italy. Prior to being admitted, patients were informed of the study procedures and written informed consent was obtained.

The study was open-label and randomised in design and enrolled 27 Caucasian patients (25 males and 2 females) aged between 49 and 79 years with neoplastic lung disease requiring lobectomy or pneumonectomy. Patients with known hypersensitivity to quinolone antimicrobials, or who had received treatment with antimicrobial agents <72 hours or antacids <4 hours prior to study drug dosing, and patients with impaired liver or renal function, or with pleural or lung infection, were excluded from the study.

Two weeks before administration of prulifloxacin, the patients were assessed by medical history taking, physical examination, ECG, haematology and biochemistry investigations and urinalysis. Almost all patients had a positive medical history for chronic respiratory and cardiovascular diseases.

Patients were randomised to five treatment groups and received a single oral dose of prulifloxacin 600mg at approximately 2, 4, 6, 12 or 24 hours prior to surgery. Owing to technical and logistical problems (i.e. the time required for anaesthesia and surgery), 2 hours after dosing was chosen as the earliest time for sampling. Prulifloxacin tablets were swallowed with 100mL of water, in fasting conditions.

Tissue Sampling and Assays

During surgery, healthy lung samples (based on macroscopic appearance) with different spatial locations were collected. Tissue specimens were rinsed three times with saline to remove blood, then dried with sterile paper, weighed, homogenised in a Waring homogeniser (International PBI S.p.A., Milan, Italy), adding 5mL of 0.9% sodium chloride solution for each gram of tissue. The homogenate was cen-

trifuged at 3000 rpm for 15 minutes at 25°C. The supernatant was immediately stored at −20°C until analysis.

Blood samples were collected at the same time as lung tissue was removed. Plasma was separated by centrifugation at 2500 rpm for 1 minute at 4°C and stored at −20°C until analysis.

After oral administration, the prodrug prulifloxacin is undetectable in biological fluids. Ulifloxacin concentrations in plasma and lung tissue were determined by reversed-phase high-performance liquid chromatography coupled with UV detection at 275nm.

Plasma samples (0.5mL) spiked with the internal standard solution (pipemidic acid; Sigma-Aldrich, Milan, Italy) were extracted at room temperature (below 25°C) with dichloromethane containing 1% (v/v) ethyl chloroformate. During the extraction (15 minutes using a horizontal shaker) the two analytes reacted with ethyl chloroformate to form the relevant carbamate derivatives. After extraction, the organic phase was separated by centrifugation, withdrawn, made anhydrous by adding sodium sulphate, and evaporated to dryness under nitrogen. The residue was dissolved with 150µL of methyl alcohol (methanol), then sonicated, centrifuged and the clear solution transferred into a micro vial. Before injection, 150µL of distilled water was added. The chromatographic separation was achieved using a Suplex pKb-100 analytical column, 25cm × 4.6mm internal diameter, 5µm particle size, (Supelco; Sigma-Aldrich, Milan, Italy) at 40°C. The analytes were eluted within 30 minutes at a 2 mL/min flow rate in isocratic mode (mobile phase 31% acetonitrile, 69% 0.01 mol/L potassium phosphate buffer at pH 2.0). The lower limit of quantitation (LLQ) [signal-to-noise ratio = 10] was 43 ng/mL in plasma. The standard calibration curve was linear over the plasma concentration range of 43–7570 ng/mL (R^2 obtained on four different occasions ranged from 0.9999 to 0.9978). Precision (percentage coefficient of variation [CV]) of quality controls measured on three different occasions at low (65 ng/mL), medium (653 ng/mL) and high (6537 ng/mL) concentrations (n = 6) ranged from 3.81% to 9.71%, 2.08% to 3.46% and 1.51% to 3.18%, respectively. Accuracy (percentage deviation) ranged from −0.75% to −20.2%, −3.66% to −5.80% and −0.64% to −2.65%, respectively. The precision and accuracy of the method at LLQ (43 ng/mL) were also tested. Based on the results of four replicates, the accuracy was +10.3% deviation, and the precision was 2.92% (as relative standard deviation).

Previously centrifuged tissue homogenates (1mL) were extracted following the same procedure used for the plasma samples. The standard and quality control samples were prepared in human lung tissue obtained from the Department of Infectious Diseases, Ospedale Civile Maggiore, University of Verona, Italy. The chromatographic separation was achieved using a Suplex pKb-100 analytical column 25cm × 4.6mm internal diameter, 5µm particle size (Supelco; Sigma-Aldrich, Milan, Italy) at 40°C. The analytes were eluted within 20 minutes at 2 mL/min flow rate in isocratic mode (mobile phase 40% acetonitrile, 60% 0.01 mol/L potassium phosphate buffer at pH 2.5). The efficiency of the extraction after homogenisation was determined in blank samples spiked with ulifloxacin. The recovery rate was dependent on dilution volume and not on ulifloxacin concentration and homogenising time. Thus, a corrective factor was applied to calculate the actual tissue concentrations. The LLQ (signal-to-noise ratio = 10) was 0.7 µg/g lung tissue. The standard calibration curve was linear over the concentration range of 0.7–89 µg/g lung tissue (R^2 obtained on four different occasions ranged from 0.9998 to 0.9959). Precision (CV) and accuracy (percentage deviation) of quality controls measured on one occasion at low (1.00 µg/g), medium (6.68 µg/g) and high (53.34 µg/g) concentration (n = 6) were 13.3% and 11.4%, 3.22% and −1.13%, 0.68% and 1.08%, respectively.

To detect any blood contamination of tissue samples, haemoglobin was assayed in the supernatant of each lung tissue sample. After calculation (based on tissue weight and results of the assay), the mean ± standard error haemoglobin concentration was 1.12 ± 0.14 g/100g. The following equation was used to perform this correction (equation 1):[10]

$$C_{corr,t} = \frac{[C_t - C_p\,(Ht/Hb)(1 - P)]}{1 - Ht/Hb} \quad \text{(Eq. 1)}$$

where $C_{corr,t}$ is the corrected tissue drug concentration (μg/g), C_t is the measured tissue drug concentration (μg/g), C_p is the plasma drug concentration at the time of tissue procurement (μg/mL), Ht is the tissue haemoglobin concentration (g/100g), Hb is the blood haemoglobin concentration (g/dL) and P is the haematocrit (%). The values of Hb and P were those obtained at the screening visit.[10]

The degree of drug penetration into the lung was assessed by calculating the penetration ratio, i.e. the ratio of uncorrected or corrected lung tissue concentration to concurrent plasma drug concentration.

The AUCs from 0 to 24 hours in plasma (AUC_p) and lung tissue (before and after correction for blood contamination [$AUC_{in\ toto,\ t}$ and $AUC_{corr,\ t}$]) and their ratios were also calculated. Since patients were assigned to a specific timepoint for collection of plasma and lung specimens, only one plasma and lung concentration value was obtained from each patient. Therefore, the AUCs were calculated on the mean concentration versus time data, as in other studies.[11,12]

Results

The baseline characteristics of the 27 patients with neoplastic lung disease requiring lobectomy or pneumonectomy are reported in table I.

Table II and figure 1 illustrate the individual ulifloxacin concentrations in plasma and lung tissue following a single oral dose of prulifloxacin 600mg. Table III and figure 2 show these data pooled into five groups, according to the sampling time.

Based on the sampling times, peak ulifloxacin concentrations seem to be achieved in both plasma and lung tissue samples about 2 hours after dosing. However, the peak ulifloxacin concentrations in plasma are probably underestimated as the t_{max} of ulifloxacin is observed 1 hour after single-dose administration.[1,3]

The overall mean penetration ratios over the 24-hour period in the whole (*in toto*) lung tissue and after correction for blood contamination, were 3.0 and 6.9, respectively (table II). The corrected lung/plasma ratios did not show linearity over time (table III). This is probably related to interindividual variability and data pooling.

The mean AUC values were 7.2 μg • h/mL (AUC_p), 18.2 μg • h/g ($AUC_{in\ toto,\ t}$) and 45.6 μg • h/g ($AUC_{corr,\ t}$), and the relevant ratios were 2.5 ($AUC_{in\ toto,\ t}/AUC_p$) and 6.3 ($AUC_{corr,\ t}/AUC_p$).

Lung tissue concentrations of ulifloxacin consistently exceeded those in plasma throughout the 24-hour sampling period, both in the whole lung tissue and after correction for blood contamination. Values after correction for blood contamination were higher than those observed in whole lung tissue, indicating a consistent dilution effect exerted by blood.

During the study, no prulifloxacin-related adverse events were reported.

Discussion

Data obtained from the studies of antibacterial lung penetration have provided very useful information that may aid in the selection of the most appropriate therapy for respiratory infections.[13] Several techniques have been proposed to measure drug levels in lung tissue (i.e. measurements in the whole lung tissue, bronchial mucosa, sputum, bron-

Table I. Baseline characteristics of the study population (n = 27)

Value	Age (y)	Weight (kg)	Height (cm)	Respiratory rate (breaths/min)	Heart rate (beats/min)	Diastolic BP (mm Hg)	Systolic BP (mm Hg)
Mean	65.7	71.8	170.1	13.6	78.7	78.9	142.6
SD	6.68	8.26	29.05	2.49	15.69	7.64	11.28
Minimum	49	60	160	10	56	60	120
Maximum	79	91	181	21	148	95	180

BP = blood pressure; **SD** = standard deviation.

Table II. Individual concentrations of ulifloxacin in plasma and lung tissue after oral administration of a single dose of prulifloxacin 600mg

Sampling time (h:min)	Patient no.	Concentration			LT/P	L[a]/P
		plasma (μg/mL)	lung *in toto* (μg/g)	lung[a] (μg/g)		
2:00	6	0.51	1.12	3.74	2.2	7.3
2:00	9	0.18	0.21	1.02	1.2	5.7
2:00	15	1.59	1.88	3.48	1.2	2.2
2:05	2	0.31	1.01	4.19	3.3	13.5
2:30	19	0.69	1.97	5.98	2.9	8.7
4:00	3	0.49	0.80	4.01	1.6	8.2
4:00	4	0.79	2.39	4.59	3.0	5.8
4:00	26	0.33	0.99	2.52	3.0	7.6
4:00	27	0.54	0.57	1.82	1.1	3.4
4:10	24	0.21	0.36	1.39	1.7	6.6
6:00	5	0.39	1.25	2.24	3.2	5.7
6:00	7	0.70	1.67	5.27	2.4	7.5
6:00	11	0.10	0.18	0.45	1.8	4.5
6:00	13	0.27	0.33	0.33	1.2	1.2
6:00	29	0.53	1.24	1.24	2.3	2.3
12:00	8	0.28	0.60	1.31	2.1	4.7
12:00	10	0.32	0.96	2.48	3.0	7.7
12:00	18	0.47	0.29	1.71	0.6	3.6
12:10	1	0.32	1.58	3.08	4.9	9.6
12:30	12	0.32	1.02	3.63	3.2	11.3
13:30	20	0.09	0.29	0.46	3.2	5.2
22:00	14	0.29	1.38	3.00	4.8	10.3
23:30	23	0.03[b]	0.28	0.28	9.3	9.3
24:00	16	0.16	0.42	1.22	2.6	7.6
24:00	17	0.1	0.42	0.66	4.2	6.5
24:00	21	0.03[b]	0.23	0.42	8.2	14.1
25:00	22	0.05	0.14	0.35	2.8	7.0
Mean ± SE	NA	0.37 ± 0.06	0.87 ± 0.12	2.25 ± 0.32	3.0 ± 0.12	6.9 ± 0.6

a After correction for blood contamination.

b Estimated value (limit of quantitation = 0.04 μg/mL).

L/P = lung/plasma concentration ratio; **LT/P** = lung *in toto*/plasma concentration ratio; **NA** = not applicable; **SE** = standard error.

choalveolar lavage fluids, epithelial lining fluid and alveolar macrophages) but the results obtained have not always correlated with clinical efficacy data.[9,13,14] Objective technical difficulties and theoretical assumptions may originate controversial results and limit the predictive value of tissue penetration studies.

Based on *in vitro* MIC data, the correlation observed between quinolone concentrations in sputum or bronchial secretions and clinical results was very poor,[9] while the high degree of lung tissue penetration of ciprofloxacin was evoked to explain the very good results against pneumococcal infections reported in patients with serious respiratory infections.[15,16]

Whole lung drug concentrations are thought to be a nonspecific predictor of clinical efficacy as these represent a mixture of different tissue compartments.[17] Conversely, the investigation of bronchoscopically obtained samples may not reflect the condition in deep invasive respiratory infections. Thus, lung tissue samples might provide additional information about these conditions.[18]

The use of bronchoalveolar lavage, especially when associated with microlavage,[19] provides the opportunity to discriminate between intra- and ex-

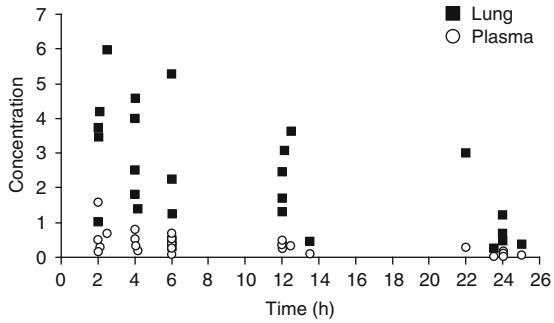

Fig. 1. Individual ulifloxacin concentrations in plasma (μg/mL) and lung tissue (μg/g), after correction for blood contamination, following a single oral dose of prulifloxacin 600mg.

tracellular sites representative of pneumonia, by sampling the epithelial lining fluid. However, measurements of antibacterial concentrations in the epithelial lining fluid involve many logistical problems[20] and do not provide longitudinal pharmacokinetic data that can only be derived by interindividual data pooling.[17]

Currently, a clear determination of antibacterial concentrations in the interstitial space fluid of lung tissue, the target site of infection, seems possible only when a microdialysis-based approach is used. This technique requires an intraoperative placement of microdialysis probes, which can be left in place for several hours, allowing a continuous sampling, but this may cause pain to the patients, particularly when they are removed.[17,20,21]

As reported for other fluoroquinolones,[9,17,20] in this study ulifloxacin concentrations in the lung tissue greatly exceeded plasma concentrations. After the administration of prulifloxacin 600mg, the overall mean penetration ratio over the 24-hour period was 6.9 (table II), higher than that observed with levofloxacin (3.9) in a similar study[10] and higher than those reported for other fluoroquinolones (1.5–4).[16,18,22,23] Furthermore, the $AUC_{corr,\,t}/AUC_p$ ratio of 6.3 demonstrates the ability of the drug to penetrate lung and confirms the high exposure of this target tissue to ulifloxacin, even if the above-mentioned specific limitations of the technique are taken into account.

When sampling times were assessed (table III), the corrected lung/plasma ratios ranged from 4 to 9. The highest lung/plasma ratio occurred after 24 hours, which may indicate different time-course profiles of ulifloxacin in lung tissue and plasma and its accumulation in lung tissue. However, these findings may also be related to the timing of lung/plasma ratio determinations when the ulifloxacin concentrations in plasma had already begun to decline. In fact, the ulifloxacin C_{max} in plasma is reported to occur 1 hour after dosing,[3] whereas in this study the first plasma sampling was performed 2 hours after dosing. For these reasons, the lung/plasma concentration ratios should be cautiously considered.

The slight time-course variability of ulifloxacin lung/plasma concentration ratios reflects the interindividual variability, as reported in other studies.[10,22] In fact, for obvious ethical and practical reasons, it is not possible to obtain serial tissue samples from the same patient at various timepoints after drug administration. Hence, different groups of patients must be employed for each tissue sampling timepoint, which makes the interpatient variability unavoidable.[9]

Table III. Ulifloxacin concentrations in lung tissue and plasma after oral administration of a single dose of prulifloxacin 600mg

Sampling time intervals (h:min)	No. of patients	Concentration[a]			LT/P	L^b/P
		plasma (μg/mL)	lung *in toto* (μg/g)	lung[b] (μg/g)		
2:00–2:30	5	0.66 ± 0.25	1.24 ± 0.32	3.68 ± 0.80	2.1 ± 0.4	7.5 ± 1.9
4:00–4:10	5	0.47 ± 0.10	1.02 ± 0.36	2.87 ± 0.62	2.1 ± 0.4	6.3 ± 0.8
6:00	5	0.40 ± 0.10	0.93 ± 0.29	1.91 ± 0.91	2.2 ± 0.3	4.3 ± 1.1
12:00–13:30	6	0.30 ± 0.05	0.79 ± 0.20	2.11 ± 0.48	2.9 ± 0.5	7.0 ± 1.2
22:00–25:00	6	0.11 ± 0.04	0.48 ± 0.19	1.0 ± 0.43	5.3 ± 1.1	9.2 ± 1.6

a Values are expressed as mean ± standard error.

b After correction for blood contamination.

L/P = lung/plasma concentration ratio; **LT/P** = lung *in toto*/plasma concentration ratio.

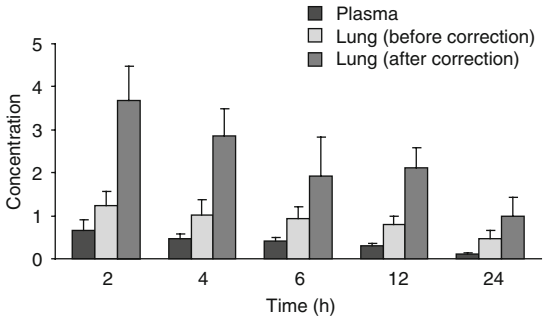

Fig. 2. Mean (± standard error) ulifloxacin concentrations in plasma (μg/mL) and lung tissue (μg/g), before and after correction for blood contamination, following a single oral dose of prulifloxacin 600mg.

A direct correlation between drug concentrations in the whole lung tissue samples and clinical efficacy may have some limitation owing to the fact that lung tissue samples are a mixture of different compartments. However, when tissue concentrations are considered in conjunction with MIC and clinical data, the drug efficacy profile may become more complete. Moreover, drug tissue concentrations represent a valid aid in the interpretation of efficacy data, at times not fully explainable on the basis of MICs and drug plasma levels alone.

The ulifloxacin mean concentrations in lung tissue after correction for blood contamination ranged from 3.68 μg/g 2 hours after dosing to 1 μg/g 24 hours after dosing (see table III). These values, definitely higher than MICs for pathogens frequently involved in respiratory tract infections,[6,7] may explain the very good efficacy of prulifloxacin observed in patients with acute exacerbation of chronic bronchitis, even when infected by *S. pneumoniae* strains.[8]

Conclusion

The results of the present lung penetration study may explain the efficacy data reported in clinical trials performed in patients with exacerbation of chronic bronchitis treated with prulifloxacin 600mg once daily for 10 days.[1,8] Nevertheless, it should be taken into account that this study was carried out in macroscopically healthy lung samples, and it is known that lung tissue penetration of antimicrobials may be influenced by the state of the tissue (i.e. inflammation) and the severity of the disease process.[9,24] On this basis, lung tissue penetration data should have a supportive value, and should be jointly considered with MICs and clinical efficacy data.

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