Penetration of prulifloxacin into sinus mucosa of patients undergoing paranasal sinus elective endoscopic surgery

Michele De Benedetto[1], Desiderio Passali[2], Giovanni Tomacelli[1], Alessandro Ruggieri[3], Maria Teresa Rosignoli[3], Rossella Picollo[3], Luisa Bellussi[2], Paolo Dionisio[3]

[1]Hospital 'Vito Fazzi', ENT Division, Lecce, Italy, [2]University of Siena, Policlinico Le Scotte, ENT Division, Siena, Italy, [3]R&D Division, Angelini Pharmaceuticals ACRAF S.p.A., Rome, Italy

The aim of this study was to assess the concentration of ulifloxacin, the active metabolite of prulifloxacin, in sinuses mucosa and plasma of patients with chronic rhinosinusitis, requiring sinus elective endoscopic surgery. Thirty-nine patients (30 males, 9 females; age range 22–77 years) with chronic sinusitis were enrolled, 35 were treated with the investigational medication. Samples from four untreated patients were used to validate the analytical method, while four treated patients dropped out before surgery. One 600 mg prulifloxacin tablet once daily was administered for 5 days before surgery. The last dosing was scheduled from 2 to 12 hours from tissue and plasma sampling. In each patient, two samples of paranasal sinus mucosa (from ethmoid and turbinate, respectively) and one blood sample were collected. Concentrations of ulifloxacin in plasma and sinuses mucosa were measured using validated bioanalytical LC/MS/MS methods. Individual and mean ulifloxacin concentrations in tissues were always higher than the relevant plasma levels. The highest concentrations were observed between 2.5 and 4.5 hours after the last dosing in all districts. The mean tissue/plasma ratios were 2.5 and 3.0 for ethmoid and turbinate, respectively. Data expressed as Area Under the Curves (AUC±SD) showed that ulifloxacin concentrations in the ethmoid were slightly higher (18.68±6.48 μg/g*h) than in turbinate (15.00±2.89 μg/g*h), and definitely higher than in plasma (6.32±1.14 μg/ml*h). The AUC ratios between tissues and plasma were 3.0 for ethmoides and 2.4 for turbinates. One patient reported two treatment-related episodes of diarrhea, which spontaneously resolved after the drug suspension. Results from this study seem to suggest that prulifloxacin showed good distribution in sinus tissues, where it reaches concentrations significantly higher than in plasma. These findings strongly call for confirmatory clinical trials in patients with bacterial rhinosinusitis.

Keywords: Prulifloxacin, Pharmacokinetics, Sinus mucosa

Introduction

The antibacterial activity and the capability of antimicrobial drugs to penetrate into tissues are important factors influencing their efficient therapeutic use.

Prulifloxacin, the pro-drug of ulifloxacin, is indicated for the treatment of respiratory and urinary tracts infections.[1] It has the aptitude to penetrate several target tissues,[2–4] particularly lung tissue with a mean ratio of 6.9 between tissue and plasma concentrations, observed over a 24-hour period.[2] Following a single 600 mg oral administration of prulifloxacin, ulifloxacin reaches the maximum plasma concentration of 1.6 μg/ml after 1 hour, with an $AUC_{0-\infty}$ value of 7.3 μg/ml*h.[5]

Correspondence to: Paolo Dionisio, R&D Division, Angelini Pharmaceuticals, ACRAF SpA, P.le della Stazione snc, S. Palomba Pomezia, Rome I-00040, Italy. Email: p.dionisio@angelini.it

After 10-day repeated once daily administrations of prulifloxacin, the ulifloxacin C_{max} was 2 μg/ml, with 0.75 hours and 7.6 μg/ml*h of t_{max} and AUC_{ss} corresponding values.[1] Unchanged ulifloxacin is predominantly eliminated via the kidneys, reaching very high urinary concentrations up to 48 hours after a single administration.[5] At the steady-state, achieved on the third treatment day, the binding to human serum proteins is 45%.[6] The elimination half-life is approximately of 10 hours.[5]

Rhinosinusitis is defined as the symptomatic inflammation of paranasal sinuses and nasal cavity.[7] Most acute rhinosinusitis begins when a viral upper respiratory infection extends into the paranasal sinuses, which may be followed by bacterial infection. Acute Bacterial Rhinosinusitis (ABRS) is one of the most common conditions encountered by primary care

DOI 10.1179/1120009X12Z.0000000009

clinicians.[7] The importance of ABRS relates not only to prevalence, but to the potential for rare, but serious, sequelae that include meningitis, brain abscess, orbital cellulitis, and orbital abscess.[7,8] The most common bacterial species isolated from sinus of adult patients with ABRS are *Streptococcus pneumoniae* (20–43%), *Haemophilus influenzae* (22–35%), *Moraxella catarrhalis* (2–10%) by us called 'Infernal Trio', and other streptococcal species (3–9%).[9]

The *in vitro* activity of prulifloxacin against community isolates of Gram-negative strains responsible for ABRS is often higher than that of other fluoroquinolones.[10–12] The drug MIC_{90} for *H. influenzae* and *M. catarrhalis* were 0.015 and 0.03–0.06 mg/l, respectively.[10,11] Previous studies showed an MIC_{90} value of ulifloxacin of 1–2 mg/l against community isolates of *S. pneumoniae*.[10,11] In a recent study, the MIC_{90} value of ulifloxacin against *S. pneumoniae* was equal to 0.75 mg/l, fully comparable with that observed with levofloxacin.[13] Clinical trials in exacerbation of chronic bronchitis confirmed very good results in the prulifloxacin-treated patients, even when infected by *S. pneumoniae* strains.[14–16] Thus, prulifloxacin may also have a potential therapeutic role in the treatment of ABRS.

However, a study to assess the prulifloxacin concentrations in sinuses mucosa was needed to further strengthen the rationale for the use of the drug in patients suffering from ABRS.

Patients and Methods

Patients

The trial was approved by the Local Health Unit Ethics Committee of Lecce, on 31 March 2007, and was performed in accordance with the Good Clinical Practice guidelines, applicable regulatory rules, and requirements of the Declaration of Helsinki updated version.

Patients entered the study if Caucasian males or females aged between 18 and 65 years, with chronic sinusitis requiring elective endoscopic sinus surgery, and willing to sign the written informed consent. The following main exclusion criteria were used: positivity to HIV test or hepatitis B and C tests; administration of other antibiotics or antibacterials in the week prior to surgery; body temperature higher than 38°C, or other evidence of infection within 48 hours before surgery; known or suspected hypersensitivity towards any of the constituents of the study medication, or allergy to the fluoroquinolone class of antimicrobials; childbearing potential with positive urine pregnancy test (β-HCG), or lactation; known moderate-to-severe hepatic or renal insufficiency; history of tendinopathy associated with use of fluoroquinolones; recent or past history of cardiac disease or rhythm disorders; concomitant treatment with hypoglycaemic drugs.

Study design and procedures

This was a single centre, randomized, open study. Six groups of patients were enrolled: Group A (untreated patients whose tissue samples were used to validate the analytical method), Groups B, C, D, E, and F receiving one prulifloxacin 600 mg tablet daily for 5 days, in which the last dosing was expected at 2, 4, 6, 8 and 12 hours before the tissue sampling, respectively.

However, due to the complexity of surgical procedures, some deviations between theoretical and actual times of tissue and blood sample collections were registered. In addition, some blood samples were not simultaneously collected with tissue, but anticipated within a maximum range of two hours. For these reasons, data were stratified on the basis of the actual collection time from the last dosing, according to the following ranges: <2.5, 2.5–4.5, 4.5–6.5, 6.5–8.5, 8.5–10.5, and >10.5 hours from dosing. As a consequence, an unbalanced distribution of patients in each time interval occurred.

Three visits were scheduled, Visit 0 (V0, 7–10 days before surgery), Visit 1 (V1, 1–5 days before surgery) and Visit 2 (V2, the day of surgery).

At V0, the eligibility of the patients was determined on the basis of medical history, physical examination, vital signs recording (blood pressure and heart rate), virological tests for hepatitis B and C and HIV antibody screens. Patients were also questioned about any concomitant pharmacological treatment.

At V1, one blood sample was collected for the standard pre-surgical haematological analyses. Patients were hospitalized before surgery. The tests for hepatitis B and C and HIV antibody screens were checked to confirm the patient's eligibility. Concomitant medications and the occurrence of adverse events were also assessed. During the hospitalization period, the investigational drug was administered (only Groups B, C, D, E, and F) under the supervision of the investigator or delegates.

Patients were submitted to ethmoidectomy. When needed, surgery was completed with sphenoid and/or frontal sinusotomy. Following surgery, patients were monitored according to the institution standard procedures, and questioned on the occurrence of adverse events. Emergent symptoms and signs were reported in the individual case report form.

Tissue sampling and analysis

Two samples of mucosa from ethmoid and middle turbinate respectively, were removed in each patient. Samples were washed for 30 seconds in 0.9% sodium chloride solution to minimize blood contamination, dried on gauze, then placed in glass tubes and immediately frozen at -20°C until analysis. A blood sample of at least 6 ml was withdrawn and centrifuged at about 3900 g, within 20 minutes from collection. The supernatant plasma (about 4 ml) were

transferred into two polypropylene plastic tubes, and then stored at −20°C until analysis.

Concentrations of ulifloxacin in plasma and mucosa were measured using validated bioanalytical methods by LC/MS/MS, using ciprofloxacin as internal standard (IS). Human sinus mucosa was weighted (about 50 mg), diluted 1 : 9 (w/v) with phosphate buffer solution and homogenized using an Ultrasonic Processor. Aliquots of the tissue homogenates (40 µl) and aliquots of plasma (10 µl) were transferred into 96 well plates and then added with 20 µl of IS (1000 ng/ml) and 400 µl of acetonitrile containing 0.1% formic acid. After capping and vortex mixing, the plates were centrifuged at 6°C (20 minutes at 2060 g for tissues and 15 minutes at 3700 g for plasma). After centrifugation, an aliquot of the supernatants (0.28 ml) was transferred into 96 well plates and the organic phase was dried under nitrogen gas at 40°C. The residue was reconstituted with 150 µl of a mixture of water, acetonitrile and formic acid (79.9 : 20 : 0.1, v/v/v) and injected onto the LC/MS/MS system.

Chromatography was performed using a Chromolith RP C18 column (50 × 4.6 mm) under gradient conditions, using a mobile phase containing 0.1% formic acid in MilliQ water and methanol. The flow rate was 1 ml/minute and a split was used to reduce at 0.3 ml/minute the flow rate directed to MS. Retention times of ulifloxacin and IS were about 1.8 and 1.7 minutes, respectively. Total cycle time was 4 minutes. MS detection used a PE-SCIEX API 3000 with Turbo Ion spray interface and MRM (350.2→248.20 m/z for ulifloxacin, 332.20→288.20 m/z for IS) operating in positive ion mode. Calibration curves, constructed by plotting peak area ratios (ulifloxacin/IS) against ulifloxacin concentrations, were analysed by weighed ($1/x^2$) linear regression (calibration range 50–10 000 ng/ml or g). Duplicate quality controls were assayed at three concentrations (150, 2000 and 7500 ng/ml or g) to assess the precision and accuracy of the back-calculated ulifloxacin concentrations.

The limits of quantification of analytical methods were 50 ng/g for tissue and 50 ng/ml for plasma. The validation results demonstrated adequate sensitivity (in terms of lower limit of quantitation), selectivity, carry-over, extraction recovery (≥80%), matrix effect, linearity, precision and accuracy over the nominal range of 50–10 000 ng/ml or g in plasma and sinus mucosa. The intra-study results confirmed a good performance of the bioanalytical method. Calibration curves were linear with accuracy of the calibrators within 100±15% of the nominal values and determination coefficients (R^2) always >0.99. The accuracy of the quality control samples was within 100±20% of the nominal values in at least five out of six samples analysed within each bioanalytical session. Precision (CV%) was always within 15%.

Statistical analysis

Population characteristics were reported as mean and standard deviation. An analysis of variance for repeated measures was applied to compare the concentrations in plasma, ethmoides and turbinates. Data were analysed all together independently on the sampling time. Prulifloxacin plasma concentrations were plotted against tissue concentrations and a linear regression analysis was performed. Ratios between tissue and plasma concentrations were individually calculated and reported as the mean value. The Area Under the Curve (AUC) for tissues and plasma concentrations and the relevant ratio (tissue/plasma) were calculated using the Bailer's method.[17] For these parameters, descriptive statistics (mean and standard deviation) were reported.

Adverse events were coded according to the MedDRA classification, and tabulated by body system, severity and correlation with the investigational medication.

Results

Thirty-nine Caucasian patients (30 males, 9 females) with chronic sinusitis were enrolled, and 35 treated with the investigational medication. Four patients dropped out before surgery. Patients' disposition and reasons for withdrawal are reported in Fig. 1. Demographic characteristics and vital signs are reported in Table 1.

At the baseline medical assessment, the most frequently reported alterations were previous surgical procedures (17 patients), and hypersensitivity/allergy (11 patients). Concomitant nasal polyposis was reported in 20 patients. Virological tests for hepatitis B and C and HIV were negative. All but two baseline laboratory tests were judged as clinically significant, but not affecting the clinical study. Fourteen out of 35 patients were treated with concomitant medications, mainly corticosteroids for systemic use.

Table 2 shows the allocation of patients according to the time ranges of collection, and the average tissue and plasma concentrations. Figure 2 shows the time course of ulifloxacin concentrations in ethmoid, turbinate and plasma.

The analysis of variance evidenced statistically significant higher concentrations in both tissues with respect to plasma ($P<0.0001$) and no differences between ethmoides and turbinates ($P=0.075$). The highest concentrations were observed between 2.5 and 4.5 hours after the last dosing in all districts. The mean tissue/plasma ratios were 2.5 and 3.0 for ethmoid and turbinate, respectively.

Data expressed as Area Under the Curves (AUCs±SD) showed that ulifloxacin concentrations in the ethmoid were slightly higher (18.68±6.48 µg/g*h) than in turbinate (15.00±2.89 µg/g*h), and

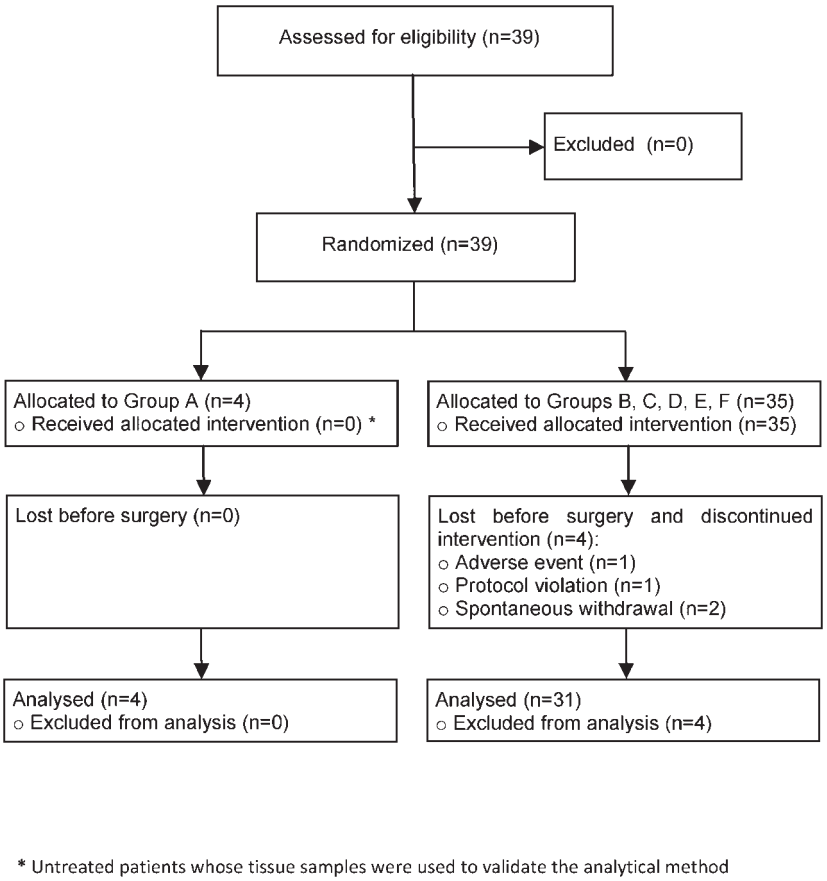

Figure 1 Flow diagram of the enrolled patients progress through the trial.

definitely higher than in plasma (6.32±1.14 μg/ml*h). The AUC ratios between tissues and plasma were 3.0 for ethmoides and 2.4 for turbinates.

Plasma concentrations were plotted against tissue concentrations and a linear trend was interpolated. Statistical analysis showed a significant slope and a not significant intercept for both tissue samples (Figs. 3 and 4), indicating a good relationship between ulifloxacin concentration in sinuses mucosa and plasma levels.

No serious Adverse Events (AEs) occurred throughout the study. One prulifloxacin-treated patient reported two treatment-related episodes of diarrhea, which spontaneously resolved after the drug suspension. For this reason, the patient was withdrawn from the study.

Discussion

The present study confirmed the ability of prulifloxacin to penetrate the mucosa of ethmoides and turbinates, as previously reported for other target tissues, such as lung, prostate and gynaecological tissues.[2–4]

Differently from other antibacterial agents, fluoroquinolones have excellent pharmacokinetic properties which give high concentrations in various body tissues, including sinus mucosa. After 1–3 hours from a single 500 mg levofloxacin administration, average paranasal sinus mucosa-to-plasma ratios ranged approximately between 1.5 and 2.5.[18] Moxifloxacin 400 mg once daily for 5 days produced higher tissue concentrations at 3 hours post-dose, reaching tissue/plasma ratios of 2.0, 2.1 and 2.6 for maxillary sinus

Table 1 Demographic characteristics and vital signs of untreated (Group A) and prulifloxacin-treated patients (Groups B, C, D, E, and F)

		Group A		Groups B, C, D, E, F	
		Mean (SD)	*n*	Mean (SD)	*n*
Age	(years)	48.0 (17.7)	4	46.8 (13.7)	31
Height	(cm)	172.0 (10.4)	3*	171.6 (7.9)	27*
Weight	(kg)	67.7 (12.7)	3*	75.2 (12.4)	28*
Heart rate	(beats/minute)	72.3 (3.3)	4	70.4 (3.5)	31
Systolic BP	(mmHg)	125.0 (10.0)	4	130.7 (12.8)	31
Diastolic BP	(mmHg)	76.3 (4.8)	4	80.8 (9.1)	31

Note: *missing data; BP, blood pressure.

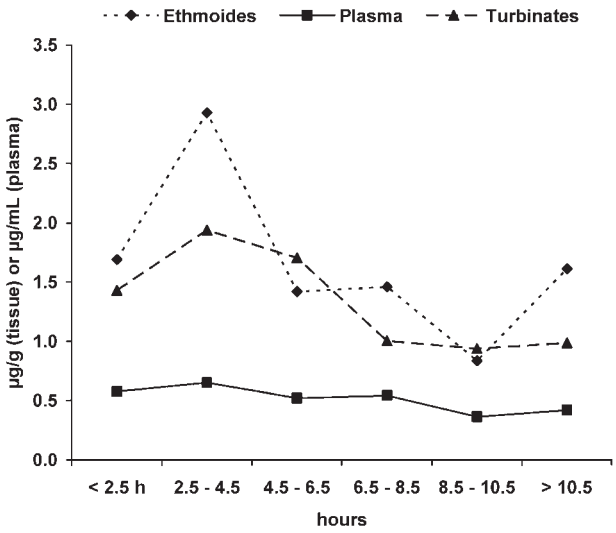

Figure 2 Average concentrations in plasma, ethmoides and turbinates after administration of one tablet daily of 600 mg prulifloxacin for 5 days.

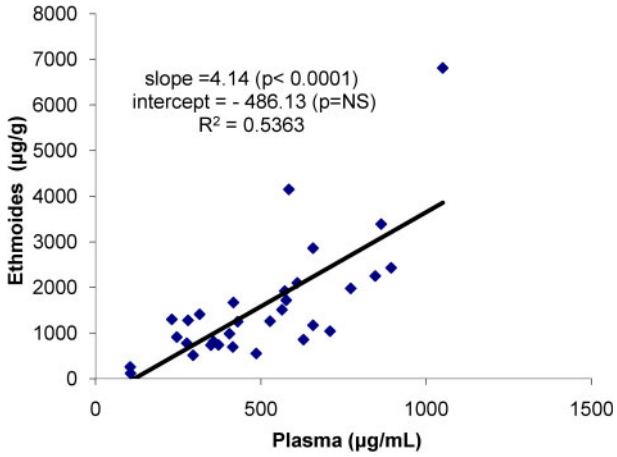

Figure 3 Correlation between ethmoid tissue and plasma ulifloxacin concentrations.

mucosa, anterior ethmoid mucosa and nasal polyps, respectively.[19]

Results from this study, in terms of tissue-to-plasma ratio, were at least comparable or even better than those reported with levofloxacin and moxifloxacin.[18,19] In fact, the average tissue/plasma ratios over the 12-hour period were 2.5 and 3.0 for turbinate and ethmoid, respectively. The regression analysis also showed that ulifloxacin concentrations in tissue increased proportionally with plasma levels.

Because a single tissue to plasma ratio of antibiotic concentration does not account for the distribution kinetics within the tissue, it has been suggested to calculate the concentration versus time profile for both tissue and plasma and to determine the ratio of the AUC (tissue to plasma).[17,20] Data expressed as AUC values covering a maximum period of about 14 hours, lower than the usual 0–24 dosing interval, confirmed that ulifloxacin concentrations in the ethmoid appeared slightly higher than in turbinate, with a relevant higher ratio with plasma (3.0 and 2.4, respectively). Minor differences in drug concentrations were already reported for moxifloxacin in collections from different sinus specimens (maxillary, ethmoid, and polyps).[18]

Given the time needed for anaesthesia and surgery, the collection time of two hours from dosing, was the earliest practicable sampling point. In addition, the complexity of pre-surgical and surgical procedures, occasionally unexpected, produced some deviations between theoretical and actual times of sample collections. Thus, a re-allocation of patients, according to the actual time of samples collection was required. The consequent unbalanced allocation within time ranges may be considered as a study limitation. However, it is minimized when results are evaluated in terms of AUC, since this parameter represents the measurement of the whole ulifloxacin bioavailability within the same definite time interval in the three compartments.

Fluoroquinolones exhibit a concentration-dependent mechanism of bacterial killing, and are characterized by a prolonged and persistent effect. In this context, the AUC-to-MIC ratio has been suggested as a good parameter in predicting the efficacy of fluoroquinolones.[9,21,22] Based on drug tissue concentrations observed in this study, and considering the most recent MIC_{90} data of prulifloxacin against *S. pneumoniae* (0.75 mg/l),[13] a theoretical AUC-to-MIC ratio of 20–25 can be anticipated. This range is only slightly lower than the target plasma AUC-to-MIC ratio of fluoroquinolones for *S pneumoniae*, that was established to approximately 25 to 30.[9] Consistently, the activity of prulifloxacin against *S. pneumoniae* strains was confirmed in clinical trials.[14–16] When the drug MIC_{90} values against *H. influenzae* and *M.*

Table 2 Average tissue and plasma concentrations

	Ethmoid (µg/g)		Turbinate (µg/g)		Plasma (µg/ml)	
Hours from dosing	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*
<2.5	1.69 (0.40)	3	1.43	1	0.58 (0.35)	4
2.5–4.5	2.93 (2.71)	4	1.94 (1.30)	4	0.65 (0.22)	3
4.5–6.5	1.42 (0.57)	4	1.70 (1.00)	6	0.52 (0.24)	11
6.5–8.5	1.46 (1.10)	9	1.00 (0.74)	8	0.54 (0.24)	3
8.5–10.5	0.84 (0.51)	5	0.94 (0.33)	6	0.37 (0.25)	4
>10.5	1.61 (1.27)	6	0.99 (0.18)	6	0.42 (0.13)	6

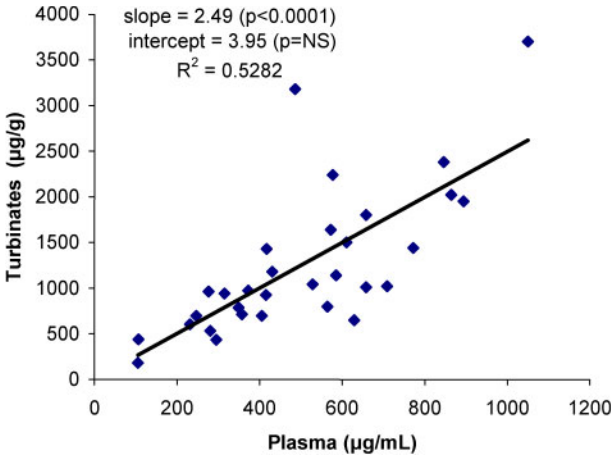

Figure 4 Correlation between turbinate tissue and plasma ulifloxacin concentrations.

catarrhalis are considered (0.015 and 0.03–0.06 mg/l, respectively),[10,11] the tissue prulifloxacin AUC-to-MIC ratios turn out to over 250.

However, the specific limitations of this study should be considered. Tissue samples were collected in patients with chronic rhinosinusitis, and it is known that respiratory tissue penetration of antimicrobials may be influenced by the state of the tissue (i.e. inflammation), and the severity of the disease process.[23] Particularly, the presence of fibrotic tissue in chronic rhinosinusitis may negatively influence the drug penetration.

In addition, the assessment of drug concentrations in whole tissue samples may have some limitation due to the fact that they represent a mixture of different compartments and for the inability to discriminate free drug concentrations in interstitial space fluid.[24] Although these constraints may have an influence in the assessment of the study results, it can be reasonably assumed that prulifloxacin distributes well in sinuses mucosa where it reaches concentrations significantly higher than in plasma, and that these results suggest for confirmatory clinical trials in patients with ABRS.

Acknowledgements

This work was supported by a grant from Angelini Pharmaceuticals, ACRAF S.p.A. (Rome, Italy).

References

1 Keam SJ, Perry CM. Prulifloxacin. Drugs. 2004;64(19):2221–34.
2 Concia E, Allegranzi B, Ciottoli GB, Orticelli G, Marchetti M, Dionisio P. Penetration of orally administered prulifloxacin into human lung tissue. Clin Pharmacokinet. 2005;44(12):1287–94.
3 Gorlero F, Lorenzi P, Rosignoli MT, Picollo R, Ruggieri A, Barattè S, *et al*. Penetration of prulifloxacin into gynaecological tissues after single and repeated oral administrations. Drugs R D. 2007;8(6):373–81.
4 Giberti C, Gallo F, Rosignoli MT, Ruggieri A, Barattè S, Picollo R, *et al*. Penetration of orally administered prulifloxacin into human prostate tissue. Clin Drug Investig. 2009;29(1):27–34.
5 Picollo R, Brion N, Gualano V, Millérioux L, Marchetti M, Rosignoli MT, *et al*. Pharmacokinetics and tolerability of prulifloxacin after single oral administration. Arzneimittelforschung. 2003;53(3):201–5.
6 Nakashima M, Uematsu T, Kosuge K, Okuyama Y, Morino A, Ozaki M, *et al*. Pharmacokinetics and safety of NM441, a new quinolone, in healthy male volunteers. J Clin Pharmacol. 1994;34:930–7.
7 Rosenfeld RM, Andes D, Bhattacharyya N, Cheung D, Eisenberg S, Ganiats TG, *et al*. Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg. 2007;137(3 Suppl):S1–31.
8 Clayman GL, Adams GL, Paugh DR, Koopmann CF Jr. Intracranial complications of paranasal sinusitis: a combined institutional review. Laryngoscope. 1991;101:234–9.
9 Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngology – Head and Neck Surgery. 2004;130(Suppl 1):1–45.
10 Montanari MP, Mingoia M, Varaldo PE. In vitro antibacterial activities of AF 3013, the active metabolite of prulifloxacin, against nosocomial and community Italian isolates. Antimicrob Agents Chemother. 2001;45(12):3616–22.
11 Prats G, Roig C, Mirò E, Navarro F, Mirelis B. In vitro activity of the active metabolite of prulifloxacin (AF 3013) compared with six other fluoroquinolones. Eur J Clin Microbiol Infect Dis. 2002;21(4):328–34.
12 Roveta S, Schito AM, Marchese A, Schito GC. Microbiological rationale for the utilisation of prulifloxacin, a new fluoroquinolone, in the eradication of serious infections caused by *Pseudomonas aeruginosa*. Int J Antimicrob Agents. 2005; 26(5):366–72.
13 Pallecchi L, Riccobono E, Montagnani F, Di Maggio T, Mantengoli E, Pollini S, *et al*. Antipneumococcal activity of ulifloxacin compared to levofloxacin and ciprofloxacin. J Chemother. 2011;23(5):308–9.
14 Cazzola M, Salvatori E, Dionisio P, Allegra L. Prulifloxacin: a new fluoroquinolone for the treatment of acute exacerbation of chronic bronchitis. Pulm Pharmacol Ther. 2006;19(Suppl 1):30–7.
15 Pasqua F, Biscione G, Crigna G, Cazzola M. Prulifloxacin in the treatment of acute exacerbations of COPD in cigarette smokers. Ther Adv Respir Dis. 2008;2(4):209–14.
16 Grassi C, Salvatori E, Rosignoli MT, Dionisio P. Randomized, double blind study of prulifloxacin versus ciprofloxacin in patients with acute exacerbation of chronic bronchitis. Respiration. 2002;69:217–22.
17 Bailer AJ. Testing for equality of area under the curves when using destructive measurement techniques. J Pharmacokinet Biopharm. 1988;16(3):303–9.
18 Pea F, Marioni G, Pavan F, Staffieri C, Bottin R, Staffieri A, *et al*. Penetration of levofloxacin into paranasal sinus mucosa of patients with chronic rhinosinusitis after a single 500 mg oral dose. Pharmocol Res. 2007;55:38–41.
19 Gehanno P, Darantière S, Dubreuil C, Chobaut JC, Bobin S, Pages JC, *et al*. A prospective, multicentre study of moxifloxacin concentrations in the sinus mucosa tissue of patients undergoing elective surgery of the sinus. J Antimicrob Chemother. 2002;49(5):821–6.
20 Carbon C. Significance of tissue levels for prediction of antibiotic efficacy and determination of dosage. Eur J Clin Microbiol Infect Dis. 1990;9:510–6.
21 Scaglione F, Mouton JW, Mattina R, Fraschini F. Pharmacodynamics of levofloxacin and ciprofloxacin in a murine pneumonia model: peak concentration/MIC versus area under the curve/MIC ratios. Antimicrob Agents Chemother. 2003;47(9):2749–55.
22 Andes D, Craig WA. Pharmacodynamics of the new fluoroquinolone gatifloxacin in murine thigh and lung infection models. Antimicrob Agents Chemother. 2002;46(6):1665–70.
23 Ritrovato CA, Deeter RG. Respiratory tract penetration of quinolone antimicrobials: a case in study. Pharmacotherapy. 1991;11(1):38–49.
24 Muller M, dela Pena A, Derendorf H. Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: distribution in tissue. Antimicrob Agents Chemother. 2004;48(5):1441–53.