ORIGINAL RESEARCH ARTICLE

Drugs R D 2007; 8 (6): 373-381
1174-5886/07/0006-0373/$44.95/0

Penetration of Prulifloxacin into Gynaecological Tissues after Single and Repeated Oral Administrations

Franco Gorlero,[1] *Paola Lorenzi,*[1] *Maria Teresa Rosignoli,*[2] *Rossella Picollo,*[2] *Alessandro Ruggieri,*[2] *Simona Barattè*[3] and *Paolo Dionisio*[2]

1 Obstetrics and Gynaecological Department, Imperia Hospital, Imperia, Italy
2 R&D Division, Angelini Pharmaceuticals ACRAF SpA, Rome, Italy
3 Nerviano Medical Sciences Srl, Milan, Italy

Abstract

Objective: This study aimed to evaluate the penetration into gynaecological tissues of ulifloxacin, the active metabolite of prulifloxacin, a once-daily fluoroquinolone administered once or in repeated doses.

Methods: This was an open-label, randomised study that included 20 consenting female inpatients (age range 40–65 years) requiring total simple hysterectomy as a result of benign disease. Three groups of patients were enrolled: group A (four patients whose gynaecological tissue samples were used to set up the bioanalytical method); group B (eight patients treated 3 hours before surgery with one 600mg tablet of prulifloxacin); group C (eight patients treated with prulifloxacin 600mg once daily for 3 days and undergoing surgery 3 hours after the last dose). Patients to be treated with prulifloxacin were randomly allocated to group B or C. During surgery, samples of blood were collected jointly with healthy tissue removed from the endometrium, proximal fallopian tube, vaginal posterior fornix and portio vaginalis. Ulifloxacin concentrations in plasma and gynaecological tissues were determined by a liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method. An intrastudy assessment of the bioanalytical method performance was also conducted for plasma and tissues using calibration and quality control data (spiked samples).

Results: Ulifloxacin mean concentrations were always higher in group C than in group B patients, both in plasma (0.76 vs 0.53 μg/mL) and in gynaecological tissues, namely fallopian tube (1.38 vs 0.81 μg/g), posterior fornix (1.48 vs 1.05 μg/g), portio vaginalis (1.46 vs 1.45 μg/g) and endometrium (2.20 vs 1.39 μg/g), as expected after repeated drug administrations. Tissue concentrations observed after repeated administrations were generally higher than the ulifloxacin minimum inhibitory concentrations for pathogens more frequently involved in

gynaecological bacterial infections. The mean tissue/plasma ratios ranged between 1.5 and almost 3.

Conclusion: The results of this study are promising but not fully predictive of clinical or microbiological efficacy for prulifloxacin. There is a need for appropriate clinical trials confirming that prulifloxacin is a useful therapeutic tool in patients with gynaecological bacterial infections.

Introduction

Prulifloxacin is an oral once-daily fluoroquinolone antimicrobial agent with a broad spectrum of antibacterial activity against Gram-negative and Gram-positive strains.[1]

After oral administration, prulifloxacin is rapidly absorbed and quantitatively transformed by esterases into ulifloxacin, the active metabolite.[2] Following a single oral dose of prulifloxacin 600mg, ulifloxacin reaches a maximum plasma concentration (C_{max}) of 1.6 μg/mL after 1 hour, with an area under the concentration-time curve from time zero to infinity (AUC_{∞}) value of 7.3 μg/mL • h.[3] After administration of prulifloxacin 600mg once daily for 12 days, the ulifloxacin C_{max} was 2 μg/mL, with corresponding time to reach C_{max} (t_{max}) and steady-state AUC (AUC_{ss}) values of 0.75 hours and 7.6 μg/mL • h, respectively.[1] Unchanged ulifloxacin is predominantly eliminated via the kidneys,[1] achieving very high urinary concentrations up to 48 hours after a single administration.[1] At steady-state, which is achieved on the third treatment day, binding to human serum proteins is 45%.[4] The elimination half-life ($t_{1/2}$) is approximately 10 hours.[3]

The antibacterial activity and ability of an antimicrobial drug to penetrate into tissues are important factors in determining its therapeutic use. Achievement of high antimicrobial tissue concentrations may represent a helpful therapeutic tool in the treatment of bacterial vaginosis and aerobic vaginitis, which are mainly associated with group B streptococci and *Escherichia coli* infections, the so-called 'intermediate' flora.[5,6] Bacterial vaginosis (the most common vaginal infection) and intermediate flora have been associated with increased risk of adverse pregnancy outcome,[7] while aerobic vaginitis may cause a severe form of desquamative inflammatory vaginitis.[6]

A previous study, carried out to evaluate the *in vitro* activity of ulifloxacin and its penetration into gynaecological tissues after oral administration of 200mg, demonstrated that ulifloxacin had a very good antimicrobial effect and achieved concentrations in tissues that exceeded the minimum inhibitory concentration for 90% (MIC_{90}) of pathogens most frequently involved as causative agents of obstetric and gynaecological infections.[8] However, this study evaluated a prulifloxacin dosage (200mg as a single dose) which is not the same as that recommended in European countries (equivalent to 600mg once daily).

The aim of the present study was to evaluate the extent of ulifloxacin penetration into gynaecological tissues after two different schedules of oral administration of prulifloxacin 600mg in patients undergoing total simple hysterectomy.

Participants and Methods

The clinical part of the study was carried out at the Obstetric and Gynaecological Department of the Imperia Hospital, Imperia, Italy, in accordance with Good Clinical Practice guidelines. It was approved by the Ethics Committee of the institution. Prior to being admitted to the study, patients were informed of the study procedures and provided written informed consent.

Table I. Characteristics of the study population (mean ± SD)

Variable	Group A (n = 4)	Group B (n = 8)	Group C (n = 8)
Age (y)	58.0 ± 9.1	49.4 ± 7.0	50.8 ± 6.6
Weight (kg)	71.5 ± 10.5	66.6 ± 8.2	63.8 ± 10.0
Height (cm)	162.5 ± 5.3	166.5 ± 5.7	163.1 ± 3.7
Heart rate (beats/min)	85.0 ± 5.8	79.9 ± 5.9	79.1 ± 5.1
Diastolic pressure (mm Hg)	77.5 ± 16.6	80.0 ± 7.1	81.9 ± 7.5
Systolic pressure (mm Hg)	140.0 ± 25.8	123.1 ± 15.8	126.3 ± 21.3
Serum creatinine (mg/dL)	NA	0.75 ± 0.13	0.74 ± 0.11
Creatinine clearance (mL/min)[a]	NA	99.0 ± 27.0	92.1 ± 20.6

a Estimated value according to the Cockcroft and Gault formula.[9]

NA = not available.

This non-blind, randomised study was carried out in female patients requiring total simple hysterectomy because of benign disease. Patients with known hypersensitivity to quinolone antimicrobials, who had received treatment with antimicrobial agents within 1 week before administration of prulifloxacin, who had impaired liver or renal function, who had malignant neoplasms or who had evidence of infection within 48 hours before surgery were excluded from the study.

Ten to 7 days before administration of prulifloxacin, patients were screened by medical history taking and physical examination to determine their eligibility. Twenty Caucasian female patients aged between 40 and 65 years were enrolled. The baseline characteristics of the patients are reported in table I. Analysis of variance using Tukey's test for multiple comparisons did not show differences between the groups.

The most frequent diagnosis upon admission was uterine fibroma (15/20). Four patients, whose gynaecological tissue samples were used to perform the intrastudy validation of the liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method, were included in group A. Sixteen patients were randomised to receive prulifloxacin 600mg as a single administration (group B) or as repeated (once daily for 3 days) administrations (group C).

Prulifloxacin tablets were taken with 100mL of water, in fasting conditions. Pre-operative or concomitant therapies taken by the patients were properly recorded. Surgical treatment was the same for all patients admitted to the trial, and was performed in accordance with the institution's standard procedures. Because of technical and logistic problems (i.e. time required for anaesthesia and surgery), 3 hours after administration was chosen as the sampling time. This time-point is in the range 1.4–3.5 hours, during which the highest tissue ulifloxacin concentrations were previously detected in patients who underwent total hysterectomy.[8] A half-hour margin for tissue and blood sampling was allowed (from 2.5 to 3.5 hours). The sampling times were within the accepted range, except in the case of three group C patients, for whom the times were slightly earlier or postponed because of logistic problems.

During the 24 hours following surgery, patients were monitored according to the standard procedures of the institution and questioned on the occurrence of adverse events.

Plasma concentrations were plotted against tissue concentrations. A correlation analysis and a linear regression trend were also applied.

Tissue Sampling and Assays

In each patient, one sample of healthy tissue approximately 1g in weight was removed from:

(a) the endometrium, (b) the proximal fallopian tube, (c) the vaginal posterior fornix and (d) the portio vaginalis. Samples were washed for 30 seconds in 0.9% sodium chloride solution to minimise blood contamination, dried on gauze and then placed in glass tubes and immediately frozen at −20°C pending shipment to the bioanalytical test facility for assay.

Blood samples were collected at the same time of tissue removal in lithium heparinised 10mL BD Vacutainer® tubes. The samples were centrifuged within 20 minutes of collection. The supernatant plasma (about 4mL) was separated and transferred into plastic tubes (polypropylene). Two parts of ≥1.5mL each were provided. Haemolysis of blood samples was minimised. Tissue and plasma samples were properly labelled for identification.

After oral administration the prodrug prulifloxacin is undetectable in biological fluids, being almost quantitatively transformed into the active metabolite ulifloxacin. Concentrations of ulifloxacin were determined in plasma and gynaecological tissues by an LC-MS/MS bioanalytical method in calibration ranges of 0.05–25 μg/mL and 0.055–27.5 μg/g, respectively. Samples from plasma and each tissue were analysed in separate batches. Seven calibrators, excluding blanks, and six quality control samples (QCs) [three concentrations in duplicate] were analysed within each batch. Calibrators and QCs were prepared with spiked blank matrices. Plasma samples were deproteinised with 0.1% formic acid in acetonitrile. Following centrifugation, the organic phase recovered in the supernatant was dried under nitrogen. The residue was reconstituted with a mixture of water, acetonitrile and formic acid (79.9/20/0.1, v/v) and then injected onto the LC-MS/MS system. Tissue samples were homogenised using a Polytron® Homogenizer PT-MR3100 (Kinematica, Lucerne, Switzerland) after adding 10 volumes of Dulbecco's phosphate buffered saline (DPBS), and then processed as the plasma samples.

Ciprofloxacin was used as the internal standard for both plasma and tissues. The LC-MS/MS apparatus consisted of a Hewlett Packard 1100 HPLC (high-performance liquid chromatography) system, a CTC-PAL autosampler (CTC Analytics) and a Sciex API 3000™ Triple Quadrupole Mass Spectrometer (Applied Biosystems, Monza, Italy) with a Turbo Ion Spray in positive ion mode with multiple reaction monitoring (MRM). The following mass/charge ratios (m/z) were used to monitor precursor → product ions: 350.2 → 248.2 for ulifloxacin and 332.2 → 288.2 for ciprofloxacin. A Chromolith® speed ROD RP18e analytical column (50 × 4.6mm, 3.5μm internal diameter) [Merck, Darmstadt, Germany] was used. The injection volume was 10μL; the injection cycle was 4.0 min and the total flow rate was 1.0 mL/min. The mobile phase (0.1% formic acid in water/methanol, 20/80) was generated by the HLPC system pumps. Elution was performed in isocratic conditions (with gradient wash). The column temperature was kept at 45°C by the column oven. The retention time of ulifloxacin was about 1.84 min.

Chromatograms were integrated to measure peak areas using Analyst™ version 1.2 (Applied Biosystems) and the data were transferred to Watson™ LIMS (Laboratory Information Management System) [Thermo Fisher Scientific, Waltham, MA, USA] for standard curve regression, curve fitting and data management. A linear regression (weighted $1/concentration^2$) was applied. The intrastudy performance of the bioanalytical method was evaluated within each batch by means of the calibration curve fitting and from the accuracy of the QCs. The accuracy of calibrators and QCs was established as acceptable for results within ±20% and ±15% of the nominal value, respectively. For each batch, two QCs at different concentrations with accuracy higher than ±15% of the nominal value were considered as acceptable.

Table II. Plasma and tissue concentrations of ulifloxacin

Patient no.	Plasma (μg/mL)	Fallopian tube (μg/g)	Fornix (μg/g)	Portio vaginalis (μg/g)	Endometrium (μg/g)
Group B					
2	0.81	1.77	1.64	1.27	1.30
4	0.94	1.60	1.46	1.20	3.03
5	0.63	0.54	1.47	5.24	2.52
7	0.22	0.46	0.73	0.98	1.39
10	0.22	0.23	0.49	0.50	0.74
12	0.28	0.29	0.57	0.52	0.66
13	0.53	0.96	1.05	0.63	0.17
16	0.59	0.61	1.00	1.29	1.27
Mean	0.53	0.81	1.05	1.45	1.39
SD	0.27	0.59	0.44	1.57	0.96
Min	0.22	0.23	0.49	0.50	0.17
Max	0.94	1.77	1.64	5.24	3.03
Group C					
1	1.08	1.79	1.62	2.19	6.46
3	1.05	2.35	2.11	2.27	2.04
6	0.53	0.86	1.46	1.02	1.26
8	0.23	0.23	0.62	0.27	0.41
9	0.23	0.53	0.55	0.51	0.57
11	0.37	0.60	0.74	0.95	0.88
14	1.14	2.38	2.01	1.80	2.70
15	1.44	2.32	2.76	2.71	3.29
Mean	0.76	1.38	1.48	1.46	2.20
SD	0.47	0.92	0.80	0.90	2.00
Min	0.23	0.23	0.55	0.27	0.41
Max	1.44	2.38	2.76	2.71	6.46

Results

The intrastudy validation results indicated good performance of the bioanalytical method. Seven analytical batches were accepted throughout the study (one for plasma, five for the tissues and one for repeated assays). The calibration curves, constructed with at least six calibrators (excluding blanks and including the lower and the upper calibration limits), were linear in the tested ranges and showed accuracy within 100 ± 20% of the nominal value. The determination coefficients (R^2) were higher than 0.99.

In agreement with the prefixed batch acceptance criteria, the accuracy of the quality control samples were within ±15% of the nominal value in at least four out of six samples analysed within each bioanalytical session.

Table II shows the individual plasma and tissue ulifloxacin concentrations in groups B and C. The mean ulifloxacin concentrations in plasma and tissue were in all cases higher in group C than in group B patients, as would be expected with repeated administrations. Specifically, 3 hours after single and repeated drug administrations, the mean ulifloxacin concentrations were 0.81 and 1.38 μg/g in the proximal fallopian tubes, 1.05 and 1.48 μg/g in the posterior fornix, 1.45 and 1.46 μg/g in the portio vaginalis, and 1.39 and 2.20 μg/g in the endometrium, respectively.

The tissue/plasma concentration ratio data are reported in table III. Mean gynaecological tissue

Table III. Tissue/plasma ulifloxacin concentration ratios

Patient no.	Fallopian tube	Fornix	Portio vaginalis	Endometrium
Group B				
2	2.20	2.03	1.58	1.61
4	1.70	1.55	1.27	3.21
5	0.86	2.35	8.38	4.03
7	2.11	3.38	4.53	6.44
10	1.07	2.26	2.32	3.42
12	1.01	2.00	1.82	2.33
13	1.82	2.00	1.20	0.33
16	1.03	1.71	2.21	2.17
Mean	1.47	2.16	2.91	2.94
SD	0.54	0.56	2.45	1.82
Min	0.86	1.55	1.20	0.33
Max	2.20	3.38	8.38	6.44
Group C				
1	1.66	1.50	2.03	5.98
3	2.24	2.01	2.16	1.94
6	1.62	2.75	1.92	2.37
8	1.01	2.70	1.15	1.77
9	2.29	2.37	2.18	2.48
11	1.62	2.00	2.56	2.37
14	2.09	1.76	1.58	2.37
15	1.61	1.92	1.88	2.28
Mean	1.77	2.13	1.93	2.70
SD	0.42	0.44	0.42	1.35
Min	1.01	1.50	1.15	1.77
Max	2.29	2.75	2.56	5.98

ulifloxacin concentrations were constantly higher than the relevant plasma concentrations in both groups of patients. The mean tissue/plasma ratio ranged between 1.5 and almost 3. The highest mean tissue/plasma ratio was found in the endometrium, followed by the portio vaginalis, posterior fornix and fallopian tubes, as confirmed by a significant tissue effect detected with analysis of variance for repeated measures.

Figure 1, figure 2, figure 3 and figure 4 show the results of the correlation analysis and linear regression. Statistical analysis showed a correlation coefficient different from zero between the ulifloxacin plasma and tissue concentrations.

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

Discussion

The results of this study demonstrated that after single and repeated administrations of prulifloxacin, ulifloxacin tissue concentrations higher than those in plasma were achieved. As expected, mean ulifloxacin plasma and tissue concentrations were higher after the 3-day administration of prulifloxacin than following single administration. The increase in mean values was approximately 45% in plasma, and ranged from 40% to 70% in tissues, except in the portio vaginalis, where mean ulifloxacin concentrations were very similar after single and repeated administrations.

Data reported in a previous study performed in Japanese patients receiving a single prulifloxacin 200mg dose showed high tissue ulifloxacin concen-

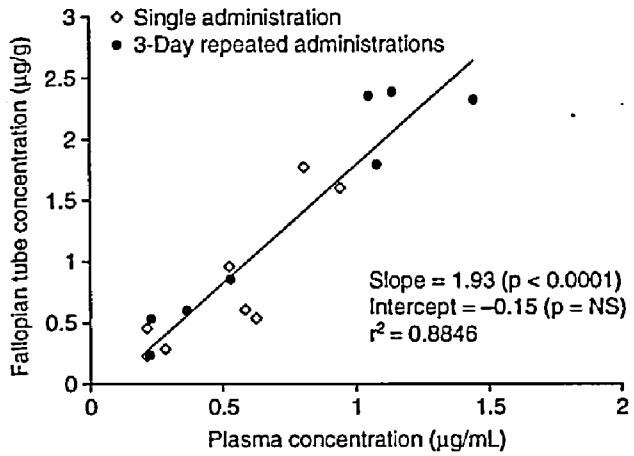

Fig. 1. Correlation between fallopian tube and plasma ulifloxacin concentrations. Symbols are the measured drug concentrations and the line is the regression fit. **NS** = not significant.

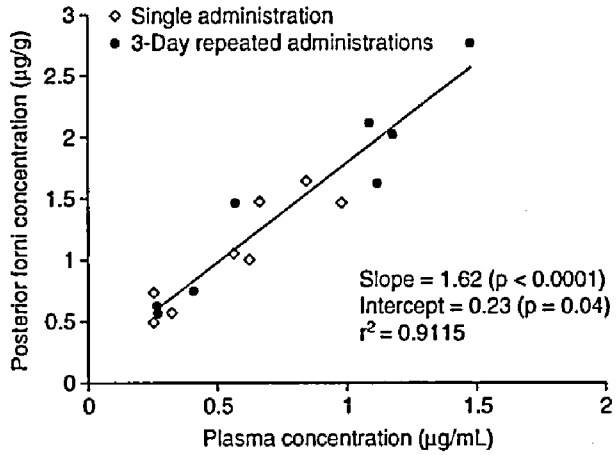

Fig. 2. Correlation between posterior fornix and plasma ulifloxacin concentrations. Symbols are the measured drug concentrations and the line is the regression fit.

trations up to 9 hours after drug administration,[8] although the concentrations were generally lower than those observed in this investigation. These differences are mainly due to the different prulifloxacin dosages (600mg vs 200mg) and study designs used in the two studies. In the previous trial, tissue and blood samples were collected from 1.40 to 9.15 hours after a single prulifloxacin 200mg administration, while in this study a single time-point was chosen and a 3-day repeated administration schedule was also implemented. Few tissue samples were collected at approximately 3 hours post-administration in the previous study, and the range of ulifloxacin concentrations was clearly lower than those observed after a single dose of prulifloxacin 600mg in the current study.

Tissue and blood samples were simultaneously collected approximately 3 hours after oral prulifloxacin administration, a time-point definitely longer than the t_{max} of the drug (which ranges from 0.75 to 1 hours).[1] However, this time-point was chosen as the earliest practicable sampling point given the time needed for anaesthesia and surgical procedures.

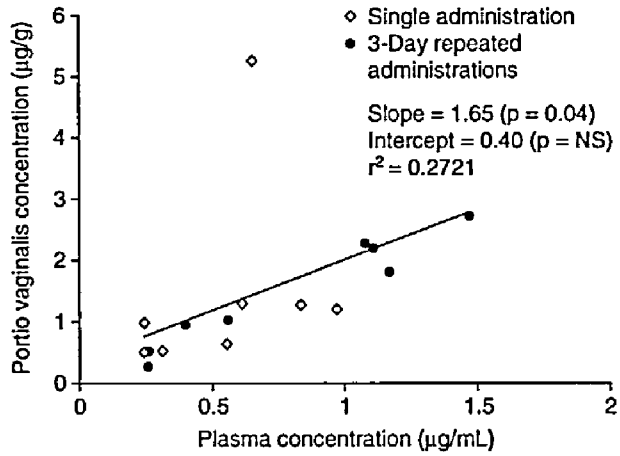

Fig. 3. Correlation between portio vaginalis and plasma ulifloxacin concentrations. Symbols are the measured drug concentrations and the line is the regression fit. **NS** = not significant.

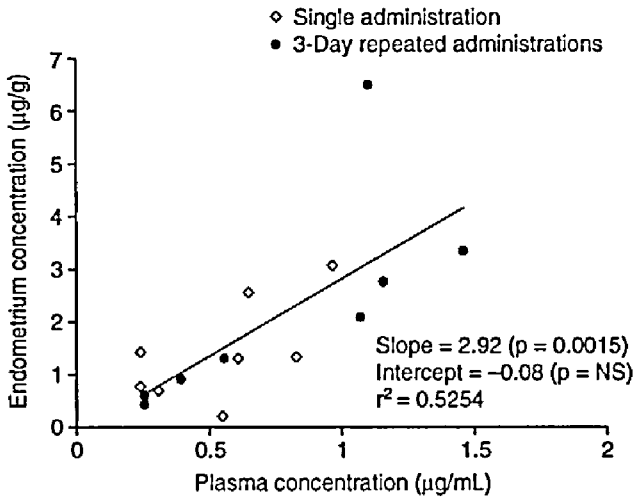

Fig. 4. Correlation between endometrium and plasma ulifloxacin concentrations. Symbols are the measured drug concentrations and the line is the regression fit. **NS** = not significant.

The delayed blood sampling time explains the relatively low plasma concentrations observed in this study compared with those previously reported at t_{max}.[3]

The ulifloxacin concentrations in gynaecological tissues in this study were constantly higher than those in plasma. These findings pointed to the ability of the drug to penetrate gynaecological tissues, and in general confirmed the high tissue exposure to ulifloxacin, as previously reported in lung tissue.[10] In this study, the highest ratio was found in the endometrium, followed by the portio vaginalis, the posterior fornix and the fallopian tubes. Statistical analysis demonstrated a significant correlation between ulifloxacin plasma and tissue concentrations. The tissue/plasma ratio ranged between 1.5 and almost 3. Similar findings were reported for penetration of telithromycin and ciprofloxacin into female genital tissues,[11,12] but not for erythromycin or trovafloxacin, which generally had lower drug concentrations in tissues compared with plasma.[13,14]

Prulifloxacin tissue concentrations, particularly those observed after repeated administrations, were generally higher than MICs for pathogens frequently involved in gynaecological bacterial infections, namely *E. coli* (MIC_{90} 0.12 μg/mL or ≤0.015 μg/mL),[15,16] *Enterococcus* spp. (MIC_{90} 1 μg/mL),[15] *Serratia* spp. (MIC_{90} 0.5 μg/mL)[15] and *Pseudomonas aeruginosa* (MIC_{90} 1 μg/mL).[16] However, according to recent data on concentration-dependent selection of resistant mutants and identification of the AUC/MIC ratio as the parameter that most closely correlates with clinical and/or bacteriological success,[17,18] ulifloxacin concentrations reported in this study may be hypothesised as being potentially most efficient in infections caused by *E. coli*.

The high tissue/plasma ratio and the extended antibacterial spectrum suggest that active concentrations of ulifloxacin are achieved in gynaecological tissues, even if the single time-point evaluated in this study places some limitations on interpretation of the data. It is possible, for example, that the higher tissue/plasma ratios observed at tissue sites may have been related to different ulifloxacin pharmacokinetics in tissue and plasma, since at the same time-point, site concentrations were probably increasing while plasma concentrations were decreasing.

Conclusion

The results of this study confirm the ability of prulifloxacin to penetrate gynaecological tissues well. However, they are promising but not fully predictive of clinical or microbiological efficacy. Thus, there is a need for appropriate clinical trials confirming that prulifloxacin may be a useful therapeutic tool in patients with gynaecological bacterial infections.

Acknowledgements

This study was supported by a grant from Angelini Pharmaceuticals ACRAF SpA, Rome, Italy. Drs Rosignoli, Picollo, Ruggieri and Dionisio are employees of Angelini Pharmaceuticals ACRAF SpA; the other authors have no conflicts of interest that are directly relevant to the content of this study.

References

1. Keam SJ, Perry CM. Prulifloxacin. Drugs 2004; 64 (19): 2221-34
2. Tougou K, Nakamura A, Watanabe S, et al. Paraxonase has a major role in the hydrolysis of prulifloxacin (NM441), a prodrug of a new antibacterial agent. Drug Metab Dispos 1998; 26 (4): 355-9
3. Picollo R, Brion N, Gualano V, et al. Pharmacokinetics and tolerability of prulifloxacin after single oral administration. Arzneimittelforschung 2003; 53 (3): 201-5
4. Nakashima M, Uematsu T, Kosuge K, et al. Pharmacokinetics and safety of NM441, a new quinolone, in healthy male volunteers. J Clin Pharmacol 1994; 34: 930-7
5. Gutman RE, Peipert JF, Weitzen S, et al. Evaluation of clinical methods for diagnosing bacterial vaginosis. Obstet Gynecol 2005; 105 (3): 551-6
6. Donders GGG, Vereecken A, Bosmans E, et al. Definition of a type of abnormal vaginal flora that is distinct from bacterial vaginosis: aerobic vaginitis. BJOG 2002; 109: 34-43

7. Leitich H, Kiss H. Asymptomatic bacterial vaginosis and intermediate flora as risk factors for adverse pregnancy outcome. Best Pract Res Clin Obstet Gynaecol 2007 Jun; 21 (3): 375-90
8. Mikamo H, Kawazoe K, Izumi K, et al. NM441: penetration into gynaecological tissues and *in vitro* activity against clinical isolates from obstetric and gynaecological patients. Drugs 1995; 49 Suppl. 2: 326-30
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41
10. Concia E, Allegranzi B, Ciottoli GB, et al. Penetration of orally administered prulifloxacin into human lung tissue. Clin Pharmacokinet 2005; 44 (12): 1287-94
11. Mikamo H, Ninomiya M, Tamaya T. Penetration of oral telithromycin into female genital tissues. J Infect Chemother 2003; 9 (4): 358-60
12. Gerstner GJ, Dalhoff A, Weuta H. Single and multiple dose pharmacokinetics of ciprofloxacin in gynecological tissues. Infection 1988; 16 Suppl. 1: S24-8
13. Lehtonen L, Wikberg R, Karhunen M, et al. Erythromycin and 2'-acetyl erythromycin concentrations in plasma and pelvic tissues after repeated doses of erythromycin acistrate. Arzneimittelforschung 1993; 43 (1): 53-6
14. Martens MG, Maccato M, Van Hook C, et al. Penetration of trovafloxacin into gynecologic tissues. Am J Surg 1998; 176 (6A Suppl.): 18S-22S
15. 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
16. Prats G, Roig C, Mirò E, et al. *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
17. Wispelwey B. Clinical implications of pharmacokinetics and pharmacodynamics of fluoroquinolones. Clin Infect Dis 2005; 41 Suppl. 2: S127-35
18. Barger A, Fuhst C, Wiedemann B. Pharmacological indices in antibiotic therapy. J Antimicrob Chemother 2003; 52 (6): 893-8

Correspondence: Dr *Paolo Dionisio*, Angelini Pharmaceuticals ACRAF SpA, P. le della Stazione snc, S. Palomba Pomezia, Rome, I-00040, Italy.
E-mail: p.dionisio@angelini.it