ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2006, p. 3947–3949 Vol. 50, No. 11
0066-4804/06/$08.00+0 doi:10.1128/AAC.00477-06

Urinary Bactericidal Activity of Extended-Release Ciprofloxacin (1,000 Milligrams) versus Levofloxacin (500 Milligrams) in Healthy Volunteers Receiving a Single Oral Dose[▽]

Florian M. E. Wagenlehner,[1*] Martina Kinzig-Schippers,[2] Uwe Tischmeyer,[1] Christine Wagenlehner,[1] Fritz Sörgel,[2,3] and Kurt G. Naber[1]

Department of Urology, St. Elisabeth Hospital, Straubing,[1] Institute for Biomedical and Pharmaceutical Research (IBMP), Nürnberg-Heroldsberg,[2] and Institute of Pharmacology, University of Essen, Essen, Germany[3]

Received 18 April 2006/Returned for modification 7 July 2006/Accepted 8 September 2006

Twelve volunteers received a single oral dose of 1,000 mg extended-release (XR) ciprofloxacin versus 500 mg levofloxacin to assess urinary bactericidal titers (UBTs) against common uropathogens. Areas under UBT-time curves were significantly larger for *Proteus mirabilis* with XR ciprofloxacin and for staphylococci with levofloxacin.

Complicated urinary tract infections (UTIs) are caused by gram-negative and -positive uropathogens (25). Fluoroquinolones are among the drugs of choice for empirical antibiotic therapy. They differ, however, in pharmacokinetic properties (11) and in antibacterial activity, and their antibacterial activity in urine is reduced significantly depending on urine pH and contents (6, 15). Extended-release (XR) ciprofloxacin and levofloxacin are given once daily (12, 23). The purpose of this study was to compare the ex vivo pharmacokinetic/pharmacodynamic properties, including urinary bactericidal titers (UBTs) of a single oral dose of 1,000 mg extended-release ciprofloxacin versus 500 mg levofloxacin against common uropathogens. The pharmacokinetic aspects of this study were recently published (24).

Twelve healthy volunteers successively received one oral dose of 1,000 mg extended-release ciprofloxacin (Bayer Vital GmbH, Wuppertal, Germany) or 500 mg levofloxacin (Sanofi-Aventis, Berlin, Germany) in a crossover design at an interval of 7 days according to the randomization schedule. All voided urine samples were collected over a 12-h interval prior to drug administration (to obtain antibiotic-free urine from each individual) and at the following time intervals after administration of the drug: 0 to 4, 4 to 8, 8 to 12, 12 to 16, 16 to 24, 24 to 28, 28 to 32, and 32 to 36 h. All samples were stored at −20°C. Levofloxacin and ciprofloxacin were analyzed in one chromatographic run by high-pressure liquid chromatography. The drug concentrations in serum and urine samples were measured by comparison with a serum and urine calibration row, respectively (24). MICs, minimal bactericidal concentrations (MBCs), and urinary bactericidal titers were determined as published previously (17, 26).

The bacterial strains used in this study and ciprofloxacin and levofloxacin MICs are depicted in Table 1. The MBCs of levofloxacin and ciprofloxacin were similar to the corresponding MICs for all strains tested. The area under the 24-h UBT-versus-time curve (AUBC) (13) was calculated as the sum of the reciprocal UBT values and the respective time intervals for each test organism and for each drug. Laboratory, UBT, and AUBC data for the two drugs were compared for each individual by the paired *t* test. The application of the paired *t* test appears adequate according to our previous analysis of the respective residuals (16). An α value of 0.05 was determined to be statistically significant. Due to the high number of tests performed, the results are of descriptive nature only. The clinical significance of the statistical results, however, should be evaluated. Statistical calculations were performed using the Microsoft Excel 97 program (1998; Microsoft Co., Redmond, Wash.).

UBTs and AUBCs of both study drugs for the test organisms were evaluated for 11 volunteers only (one volunteer showed unexplicably low UBT values) and are given in Table 2. The UBTs varied considerably between individuals and pathogens. For the gram-negative bacteria, the median reciprocal UBTs of ciprofloxacin and levofloxacin measured within the first 4 h were highest for *Escherichia coli* ATCC 25922, followed by *Proteus mirabilis*, *Klebsiella pneumoniae*, *E. coli* strain 523 (nalidixic acid resistant), and *Pseudomonas aeruginosa*; for the

TABLE 1. Bacterial strains used in this study and MICs of ciprofloxacin and levofloxacin[a]

Strain	MIC (mg/liter) of ciprofloxacin	MIC (mg/liter) of levofloxacin
E. coli ATCC 25922	0.008	0.03
E. coli 523 (NAR[b])	0.125	0.25
K. pneumoniae 595	0.008	0.03
P. mirabilis 414	0.03	0.06
P. aeruginosa 568	0.5	2
S. aureus 83	0.125	0.125
S. saprophyticus Ho94	0.25	0.25
E. faecalis 60	1	1

[a] MICs were measured in Mueller-Hinton broth.
[b] NAR, nalidixic acid resistant.

* Corresponding author. Mailing address: Department of Urology, Hospital St. Elisabeth, St. Elisabeth Str. 23, D-94315 Straubing, Germany. Phone: 49-9421-710-6702. Fax: 49-9421-710-1717. E-mail: Wagenlehner@AOL.com.
[▽] Published ahead of print on 18 September 2006.

TABLE 2. Reciprocal urinary bactericidal titers for ciprofloxacin and levofloxacin in 11 volunteers tested after a single oral dose of XR ciprofloxacin (1,000 mg) versus levofloxacin (500 mg)

Drug and strain[b]	Median UBT (range) for the following collection period:								Median AUBC (range) at 24 h
	0–4 h	4–8 h	8–12 h	12–16 h	16–24 h	24–28 h	28–32 h	32–36 h	
Ciprofloxacin (XR)									
E. coli ATCC 25922	16,384 (1,024–65,536)	4,096 (512–16,384)	4,096 (512–8,192)	2,048 (512–4,096)	1,024 (128–4,096)	512 (32–2,048)[b]	512 (32–2,048)	192 (16–1,024)	131,072 (11,264–327,680)
E. coli 523 (NAR[a])	512 (64–4,096)	256 (64–512)	256 (64–1,024)	128 (16–512)	64 (8–512)[b]	32 (4–256)[b]	16 (0–128)[b]	4 (0–64)[b]	6,656 (896–25,600)
K. pneumoniae 595	4,096 (512–32,768)	2,048 (256–16,384)	1,024 (256–4,096)	512 (256–2,048)	256 (64–2,048)	256 (16–1,024)[b]	128 (16–1,024)	64 (8–512)	36,864 (6,656–197,008)
P. mirabilis 414	8,192 (2,048–32,768)[b]	4,096 (512–8,192)[b]	2,048 (1,024–8,192)	2,048 (512–4,096)[b]	512 (256–2,048)	256 (64–1,024)	256 (32–512)	128 (32–512)	83,968 (26,624–221,184)[b]
P. aeruginosa 568	128 (16–512)	64 (16–256)	32 (16–64)	16 (8–64)	8 (2–32)[b]	2 (0–8)[b]	2 (0–8)	2 (0–4)	1,408 (240–3,712)
S. aureus 83	512 (128–4,096)	256 (64–2,048)[b]	256 (32–512)[b]	128 (32–512)[b]	64 (16–128)[b]	32 (8–64)[b]	16 (4–64)[b]	8 82–32)[b]	5,888 (1,920–19,968)[b]
S. saprophyticus Ho94	512 (128–4,096)	256 (64–512)	128 (32–512)	128 (16–256)	32 (16–128)[b]	16 (4–32)	8 (2–32)	8 (2–32)	3,328 (1,920–20,224)[b]
E. faecalis 60	128 (32–512)	32 (16–128)	32 (8–64)[b]	16 (4–64)[b]	8 (4–16)[b]	2 (2–8)[b]	2 (0–8)[b]	1 (0–4)[b]	656 (480–3,008)
Levofloxacin									
E. coli ATCC 25922	8,192 (256–65,536)	4,096 (256–16,384)	2,048 (256–16,384)	2,048 (64–4,096)	1,024 (64–8,192)	1,024 (64–2,048)[b]	256 (32–2,048)	192 (16–1,024)	81,920 (3,840–475,136)
E. coli 523 (NAR)	512 (32–8,192)	256 (32–4,096)	256 (32–4,096)	256 (8–1,024)	128 (16–2,048)[b]	128 (8–256)[b]	32 (4–512)[b]	8 (4–64)[b]	6,656 (544–86,016)
K. pneumoniae 595	4,096 (256–16,384)	2,048 (128–4,096)	1,024 (256–8,192)	1,024 (32–2,048)	512 (32–2,048)	256 (32–1,024)[b]	128 (8–1,024)	128 (16–512)	37,888 (2,816–131,072)
P. mirabilis 414	4,096 (512–8,192)[b]	2,048 (512–4,096)[b]	1,024 (1,024–4,096)	1,024 (128–2,048)[b]	512 (256–2,048)	256 (128–512)	128 (32–512)	64 (32–256)	34,816 (10,752–77,824)[b]
P. aeruginosa 568	64 (8–256)	32 (8–128)	32 (8–128)	16 (4–32)	16 (4–64)[b]	4 (2–16)[b]	2 (1–16)	2 (0–8)	896 (144–2,688)
S. aureus 83	2,048 (256–8,192)	512 (128–4,096)[b]	512 (256–4,096)[b]	256 (64–512)[b]	256 (128–1,024)[b]	128 (32–256)[b]	64 (16–256)[b]	32 (16–128)[b]	21,504 (3,840–51,200)[b]
S. saprophyticus Ho94	512 (128–4,096)	256 (64–512)	128 (128–512)	128 (32–256)	128 (32–256)[b]	32 (16–128)	32 (4–64)	32 (4–32)	4,608 (1,920–20,480)[b]
E. faecalis 60	128 (16–512)	64 (16–128)	64 (32–128)[b]	32 (8–64)[b]	32 (8–64)[b]	8 (4–32)[b]	8 (2–32)[b]	4 (1–8)[b]	1,280 (352–3,840)

[a] NAR, nalidixic acid resistant.
[b] Significantly different ($P < 0.05$, paired t test) for ciprofloxacin versus levofloxacin.

gram-positive bacteria, these values were highest for *Staphylococcus aureus*, followed by *Staphylococcus saprophyticus*, and *Enterococcus faecalis*. The AUBCs were statistically significantly ($P < 0.05$) larger for *P. mirabilis* with XR ciprofloxacin and for *S. aureus* and *S. saprophyticus* with levofloxacin. The clinical significance of these statistical calculations might, however, be different and thus has to be evaluated by appropriate clinical studies, as some authors would interpret a clinical significant difference between two antibiotics only if the MICs or MBCs were to exhibit a fourfold or greater difference in values (17, 18, 27). This has not been evaluated for UBTs or AUBCs; therefore, only the statistical calculations are presented.

Biofilm infection plays a considerable role in complicated UTIs (1–4, 5, 8–10, 19–22, 28). In an experimental model, the MBCs of ciprofloxacin and levofloxacin to eradicate *P. aeruginosa* growing in biofilms within 24 h from urine were 32-fold higher than those in planktonic growing organisms as measured under standard conditions; thus, AUC/MBC ratios for eradication were calculated to be 768 for both drugs (7). Therefore, an AUC/MBC ratio as calculated by the urinary drug concentration and the MIC or MBC measured in urine may be a helpful pharmacokinetic/pharmacodynamic index (14), which relates directly to the AUBC, while the reciprocal UBT value indicates the multiple factor of the MBC in urine. The AUC/MBCs calculated in this way derived from the experimental study (7) are close to the calculated AUBCs for *P. aeruginosa*, which were determined to be 896 for levofloxacin and 1,408 for XR ciprofloxacin in the present study (Table 2). This would also fit the experience derived from clinical studies as shown above.

In conclusion, in the treatment of complicated UTIs, an oral once-daily dose of 1,000 mg XR ciprofloxacin and a once-daily dose of 500 mg levofloxacin exhibit comparable urinary bactericidal activities against common urinary pathogens. It could therefore be assumed that these two dosages would probably also be clinically equivalent in the treatment of complicated UTIs, which should be evaluated in an appropriate clinical study.

We thank Daniela Kirchbauer for technical assistance.
The study was supported by an unrestricted grant of Bayer Vital, Leverkusen, Germany.

REFERENCES

1. **Anderson, G. G., S. M. Martin, and S. J. Hultgren.** 2004. Host subversion by formation of intracellular bacterial communities in the urinary tract. Microbes Infect. **6:**1094–1101.
2. **Andes, D., and W. A. Craig.** 2002. Animal model pharmacokinetics and pharmacodynamics: a critical review. Int. J. Antimicrob. Agents **19:**261–268.
3. **Ando, E., K. Monden, R. Mitsuhata, R. Kariyama, and H. Kumon.** 2004. Biofilm formation among methicillin-resistant Staphylococcus aureus isolates from patients with urinary tract infection. Acta Med. Okayama **58:**207–214.
4. **Bokranz, W., X. Wang, H. Tschape, and U. Romling.** 2005. Expression of cellulose and curli fimbriae by Escherichia coli isolated from the gastrointestinal tract. J. Med. Microbiol. **54:**1171–1182.
5. **Debbia, E. A., M. Dolcino, A. Marchese, A. Piazzi, and A. Berio.** 2004. Enhanced biofilm production in pathogens isolated from patients with rare metabolic disorders. New Microbiol. **27:**361–367.
6. **Drobot, G. R., J. A. Karlowsky, D. J. Hoban, and G. G. Zhanel.** 1996. Antibiotic activity in microbiological media versus that in human urine: comparison of ampicillin, ciprofloxacin, and trimethoprim-sulfamethoxazole. Antimicrob. Agents Chemother. **40:**237–240.
7. **Goto, T., Y. Nakame, M. Nishida, and Y. Ohi.** 1999. Bacterial biofilms and

catheters in experimental urinary tract infection. Int. J. Antimicrob. Agents **11:**227–231, 237–239.

8. **Jansen, A. M., V. Lockatell, D. E. Johnson, and H. L. Mobley.** 2004. Mannose-resistant *Proteus*-like fimbriae are produced by most *Proteus mirabilis* strains infecting the urinary tract, dictate the in vivo localization of bacteria, and contribute to biofilm formation. Infect. Immun. **72:**7294–7305.
9. **Justice, S. S., C. Hung, J. A. Theriot, D. A. Fletcher, G. G. Anderson, M. J. Footer, and S. J. Hultgren.** 2004. Differentiation and developmental pathways of uropathogenic Escherichia coli in urinary tract pathogenesis. Proc. Natl. Acad. Sci. USA **101:**1333–1338.
10. **Kumon, H.** 2000. Management of biofilm infections in the urinary tract. World J. Surg. **24:**1193–1196.
11. **Lubasch, A., I. Keller, K. Borner, P. Koeppe, and H. Lode.** 2000. Comparative pharmacokinetics of ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, trovafloxacin, and moxifloxacin after single oral administration in healthy volunteers. Antimicrob. Agents Chemother. **44:**2600–2603.
12. **Meagher, A. K., A. Forrest, A. Dalhoff, H. Stass, and J. J. Schentag.** 2004. Novel pharmacokinetic-pharmacodynamic model for prediction of outcomes with an extended-release formulation of ciprofloxacin. Antimicrob. Agents Chemother. **48:**2061–2068.
13. **Mouton, J. W., M. N. Dudley, O. Cars, H. Derendorf, and G. L. Drusano.** 2005. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J. Antimicrob. Chemother. **55:**601–607.
14. **Naber, C. K., M. Hammer, M. Kinzig-Schippers, C. Sauber, F. Sorgel, E. A. Bygate, A. J. Fairless, K. Machka, and K. G. Naber.** 2001. Urinary excretion and bactericidal activities of gemifloxacin and ofloxacin after a single oral dose in healthy volunteers. Antimicrob. Agents Chemother. **45:**3524–3530.
15. **Naber, K.** 1997. Antibacterial activity of antibacterial agents in urine: an overview of applied methods, p. 74–83. *In* T. Bergan (ed.), Urinary tract infections, vol. 1. Karger, Basel, Switzerland.
16. **Naber, K. G., U. Theuretzbacher, M. Kinzig, O. Savov, and F. Sorgel.** 1998. Urinary excretion and bactericidal activities of a single oral dose of 400 milligrams of fleroxacin versus a single oral dose of 800 milligrams of pefloxacin in healthy volunteers. Antimicrob. Agents Chemother. **42:**1659–1665.
17. **National Committee for Clinical Laboratory Standards.** 1999. Methods for determining bactericidal activity of antimicrobial agents. Approved guideline M26-A. National Committee for Clinical Laboratory Standards, Wayne, Pa.
18. **National Committee for Clinical Laboratory Standards.** 1993. Methods for dilution in antimicrobial susceptibility tests for bacteria that grow aerobically. Approved guideline. M7–A3. National Committee for Clinical Laboratory Standards, Villanova, Pa.
19. **Nickel, J. C., M. E. Olson, and J. W. Costerton.** 1991. Rat model of experimental bacterial prostatitis. Infection **19**(Suppl. 3)**:**S126–S130.
20. **Sabbuba, N. A., E. Mahenthiralingam, and D. J. Stickler.** 2003. Molecular epidemiology of *Proteus mirabilis* infections of the catheterized urinary tract. J. Clin. Microbiol. **41:**4961–4965.
21. **Schentag, J. J., K. K. Gilliland, and J. A. Paladino.** 2001. What have we learned from pharmacokinetic and pharmacodynamic theories? Clin. Infect. Dis. **32**(Suppl. 1)**:**S39–S46.
22. **Seno, Y., R. Kariyama, R. Mitsuhata, K. Monden, and H. Kumon.** 2005. Clinical implications of biofilm formation by Enterococcus faecalis in the urinary tract. Acta Med. Okayama **59:**79–87.
23. **Talan, D. A., K. G. Naber, J. Palou, and D. Elkharrat.** 2004. Extended-release ciprofloxacin (Cipro XR) for treatment of urinary tract infections. Int. J. Antimicrob. Agents **23**(Suppl. 1)**:**S54–S66.
24. **Wagenlehner, F. M., M. Kinzig-Schippers, U. Tischmeyer, C. Wagenlehner, F. Sorgel, A. Dalhoff, and K. G. Naber.** 2006. Pharmacokinetics of ciprofloxacin XR (1000 mg) versus levofloxacin (500 mg) in plasma and urine of male and female healthy volunteers receiving a single oral dose. Int. J. Antimicrob. Agents **27:**7–14.
25. **Wagenlehner, F. M., A. Niemetz, A. Dalhoff, and K. G. Naber.** 2002. Spectrum and antibiotic resistance of uropathogens from hospitalized patients with urinary tract infections: 1994–2000. Int. J. Antimicrob. Agents **19:**557–564.
26. **Wagenlehner, F. M., S. Wydra, H. Onda, M. Kinzig-Schippers, F. Sorgel, and K. G. Naber.** 2003. Concentrations in plasma, urinary excretion, and bactericidal activity of linezolid (600 milligrams) versus those of ciprofloxacin (500 milligrams) in healthy volunteers receiving a single oral dose. Antimicrob. Agents Chemother. **47:**3789–3794.
27. **Zhanel, G. G., I. D. Kirkpatrick, D. J. Hoban, A. M. Kabani, and J. A. Karlowsky.** 1998. Influence of human serum on pharmacodynamic properties of an investigational glycopeptide, LY333328, and comparator agents against *Staphylococcus aureus*. Antimicrob. Agents Chemother. **42:**2427–2430.
28. **Zogaj, X., W. Bokranz, M. Nimtz, and U. Romling.** 2003. Production of cellulose and curli fimbriae by members of the family *Enterobacteriaceae* isolated from the human gastrointestinal tract. Infect. Immun. **71:**4151–4158.