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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

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In a randomized crossover study, 12 volunteers (6 males, 6 females) received a single oral dose of 600 mg of linezolid or 500 mg of ciprofloxacin to assess the concentrations in plasma (up to 24 h), urinary excretion (by high-pressure liquid chromatography), and bactericidal titers in urine (UBT) at intervals up to 120 h. The mean maximum concentration of linezolid in plasma was 13.1 mg/liter, and that of ciprofloxacin was 2.46 mg/liter. The median cumulative levels of renal excretion of the administered dose of the parent drug were 44% for linezolid (range, 28 to 47%; mean ± standard deviation, 40% ± 7.8%) and 43% for ciprofloxacin (range, 20 to 56%; mean ± standard deviation, 40% ± 9.3%). The UBTs, i.e., the highest twofold dilution (with antibiotic-free urine used as the diluent) of urine that was still bactericidal, were determined for a reference strain and five gram-positive clinical uropathogens for which the MICs of linezolid and ciprofloxacin were as follows: *Staphylococcus aureus* ATCC 27278, 2 and 0.25 mg/liter, respectively; *Staphylococcus aureus* (methicillin susceptible), 1 and 16 mg/liter, respectively; *Staphylococcus aureus* (methicillin resistant), 2 and 64 mg/liter, respectively; *Staphylococcus saprophyticus* (methicillin susceptible), 1 and 0.25 mg/liter, respectively; *Enterococcus faecalis*, 2 and 1 mg/liter, respectively; and *Enterococcus faecium*, 2 and 1 mg/liter, respectively. The median UBTs of linezolid measured within the first 6 h were 1:96 for each of the two enterococcal strains and between 1:128 and 1:256 for the four staphylococcal strains. The median UBTs of ciprofloxacin were 1:64 for the two enterococcal strains; between 1:384 and 1:512 for the two ciprofloxacin-susceptible strains; and 1 (bactericidal activity of undiluted urine only) and 1:2 for the two resistant staphylococcal strains, respectively. The areas under the UBT-time curve (AUBT) for linezolid and ciprofloxacin showed no statistically significant ($P < 0.05$) differences except for a better AUBT for linezolid for the two ciprofloxacin-resistant staphylococcal strains. For linezolid there were no statistically significant differences in UBTs or AUBTs for ciprofloxacin-susceptible and -resistant strains. Thus, the bactericidal activities of linezolid and ciprofloxacin against susceptible strains in urine were comparable, whereas linezolid also exhibited the same good bactericidal activity against ciprofloxacin-resistant strains. Therefore, linezolid should be tested for use as empirical treatment for complicated urinary tract infections due to gram-positive uropathogens in an appropriate clinical trial.

The incidence of nosocomial and complicated urinary tract infections (UTIs) caused by gram-positive bacteria resistant to the antibiotics available at present is increasing (7, 19). Thus, gram-positive bacteria deserve more attention today than they did in the past. Linezolid, the first member of the class of oxazolidinones to be marketed, is active against gram-positive bacteria resistant to other drugs (1, 4, 5, 8, 9, 29) and therefore should also be considered for use in the treatment of complicated UTIs due to gram-positive uropathogens. To initiate an appropriate clinical study, one should be assured that the dose chosen exhibits bactericidal activity against the target pathogens in urine comparable to those of the standard regimen and therefore is most likely as effective as the standard regimen. Ciprofloxacin, with which there has been clinical experience over decades, can still be considered a drug of choice for the treatment of UTIs and was therefore chosen as the comparator drug. In order to combine pharmacokinetic and pharmacodynamic parameters, the concentrations in urine and the bactericidal titers in urine (UBTs) were determined to approximate more closely their antibacterial activities at the site of infection (20, 22). The purpose of the study described here was to evaluate the concentrations in plasma, urinary excretion, and bactericidal activity of linezolid (600 mg) versus those of ciprofloxacin (500 mg) in healthy volunteers receiving a single oral dose.

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MATERIALS AND METHODS

Study design and subject population. The study was approved by the Ethics Committee of the Landesärztekammer Bayern, Munich, Germany. We performed an ex vivo, open, randomized, crossover clinical trial with 12 healthy volunteers. The volunteers were considered healthy on the basis of assessment of medical history, physical examination, hematology parameters (hemoglobin concentration and erythrocyte, leukocyte, and platelet counts), serum chemistry parameters (creatinine, uric acid, γ-glutamyltransferase, alkaline phosphatase, and total bilirubin levels), and urinalysis (glucose and protein levels; white and

red blood cell counts; and lack of antibacterial activity, i.e., inhibition of *Bacillus subtilis*).

Drug administration. After giving written informed consent to participate in the study, each volunteer successively received one oral dose of 600 mg of linezolid (Pharmacia GmBH, Erlangen, Germany) or 500 mg of ciprofloxacin (Bayer AG, Wuppertal, Germany) in a crossover design at an interval of 7 days according to the randomization schedule. Study drugs were administered after an overnight fast. The subjects fasted for 2 h after drug administration. Alcohol- and xanthine-containing beverages and meals and acidic drinks, like grapefruit juice, were not allowed 12 h before and 24 h after drug administration. The volunteers were asked to drink sufficient and comparable amounts of water through both collection periods to ensure sufficient urine production. A physical examination, electrocardiography, and laboratory tests were performed before and after each phase of the study. Adverse events were recorded continuously throughout the trial period. The volunteers were monitored, and urine collection was controlled in the study center for the first 48 h and thereafter at the end of each sampling period for up to 120 h.

Sample collection. Plasma samples were collected 1, 2, 3, 4, 6, 12, and 24 h after drug intake. All urine voided was collected over a 12-h interval prior to drug administration (to ascertain that the urine was antibiotic free) and at the following time intervals thereafter: 0 to 6, 6 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 72, 72 to 96, and 96 to 120 h. All samples were stored at −20°C.

Sample preparation. All sample handling was done under protection from daylight.

(i) Linezolid. Plasma samples were precipitated with acetonitrile containing the internal standard and were diluted with ammonium acetate buffer (1:6). Urine samples were diluted with a mobile phase (1:10).

(ii) Ciprofloxacin. Plasma samples were precipitated with acetonitrile-perchloric acid containing the internal standard, and urine samples were diluted 1:100 with buffer containing the internal standard.

Assay conditions. (i) Linezolid. Chromatographic separation was performed with a reversed-phase column (50 × 4.6 mm), the column was eluted with an isocratic solvent system consisting of ammonium acetate buffer and acetonitrile (70/30; vol/vol) and monitored by mass spectrometry/mass spectrometry (linezolid, m/z 338 → m/z 296; internal standard, m/z 341 → m/z 297 [positive mode]). MacQuan software (version 1.6, 1991-1998; PE Sciex, Thornhill, Ontario, Canada) was used for evaluation of the chromatograms.

(ii) Ciprofloxacin. Chromatographic separation was performed with a reversed-phase column, and the effluent was monitored by fluorescence detection (excitation, 293 nm; emission, 490 nm). The method of measuring fluoroquinolones in biological materials has been described previously (21). Turbochrom 3 software (version 3.2, 1991; PE Nbelson, Cupertino, Calif.) was used for evaluation of the chromatograms.

Calibration row and spiked quality controls. The drug concentrations in plasma and urine samples were measured by comparison with a plasma and urine calibration row, respectively. Calibration standards were prepared by adding the defined amounts of a standard solution of linezolid or ciprofloxacin to drug-free human plasma or urine.

Spiked quality controls (SQCs) were prepared for determination of interassay variation by the addition of defined amounts of the stock solution or the spiked control of higher concentration to defined amounts of tested drug-free plasma or urine. No interference was observed in either plasma or urine for linezolid, ciprofloxacin, or the internal standard. Weighted linear regression (1/peak height ratio) was performed for calibration. The linearity of the calibration could be proven between concentrations of 0.0250 and 25.0 μg/ml for linezolid and 0.00501 and 10.0 μg/ml for ciprofloxacin in plasma and between concentrations of 0.0100 and 10.0 μg/ml for linezolid and 0.498 and 997 μg/ml for ciprofloxacin in urine. The quantification levels were identical to the lowest calibration levels. The interassay precisions of the SQCs in plasma were 2.0% (20.0 μg/ml), 1.8% (2.00 μg/ml), 2.7% (0.200 μg/ml), and 6.2% (0.0500 μg/ml) for linezolid and 2.1% (7.98 μg/ml), 2.9% (0.798 μg/ml), 3.9% (0.0638 μg/ml), and 11.7% (0.00997 μg/ml) for ciprofloxacin. The accuracies of the SQCs in plasma ranged from 99.1 to 104.2% for linezolid and from 95.3 to 102.3% for ciprofloxacin. The interassay precisions of the SQCs in urine were 2.2% (40.0 μg/ml; the sample was diluted 1:10 with blank human plasma before sample preparation), 2.2% (8.00 μg/ml), 1.5% (2.00 μg/ml), 3.8% (0.100 μg/ml), and 7.8% (0.025 μg/ml) (range of accuracy of SQCs, 99.9 to 103.8%) for linezolid and 1.0% (799 μg/ml), 4.0% (75.8 μg/ml), 1.1% (6.12 μg/ml), and 5.2% (1.02 μg/ml) (range of accuracies of SQCs, 94.9 to 102.4%) for ciprofloxacin.

Pharmacokinetic indices. The pharmacokinetic indices were estimated by standard noncompartmental methods. All indices were determined with data from each of the sample collection times and the concentrations assayed at those times. Concentrations below the lower limit of quantification were set equal to zero. The pharmacokinetic calculations were performed on a 333-MHz computer with a Pentium II processor and the Microsoft Excel 97 program (1985–1998; Microsoft Co., Redmond, Wash.). The equations were entered into the program manually and were checked by recalculation of pharmacokinetic parameters for randomly selected data sets by using the pharmacokinetic program WinNonlin Professional (version 2.0, 1994–1998; Pharsight Corporation, Palo Alto, Calif.). The following parameters were estimated: maximal concentration in plasma (C_{max}), time to C_{max} (T_{max}), half-life in plasma ($t_{1/2}$), mean residence time (MRT), area under the plasma concentration-time curve (AUC), total clearance from plasma (CL), renal clearance (CL_R), nonrenal clearance (CL_{NR}), apparent volume of distribution at the final (β) phase (V_β), and the apparent volume of distribution at steady state (V_{ss}).

Determination of MICs and MBCs. MICs and minimal bactericidal concentrations (MBCs) were determined by a microdilution test with Mueller-Hinton broth (CM 405; Oxoid, Wesel, Germany) for MICs and Mueller-Hinton broth (CM 405; Oxoid) and Columbia agar supplemented with 5% blood (Merck, Darmstadt, Germany) for MBCs. The inoculum of Mueller-Hinton broth ranged from 3.5×10^5 to 9.7×10^5 CFU/ml. The MIC was defined as the lowest concentration inhibiting visible growth after incubation at 37°C for 18 h in ambient air, while the MBC was defined in a second step by counting the numbers of CFU on Columbia agar after additional incubation for 18 h at 37°C. Bactericidal activity was defined as a >99.9% (>3-log) reduction in the numbers of CFU.

Determination of UBTs. A logarithmic serial dilution (dilution range, 1:2 to 1:1,024) was prepared by combining a 1:1 mixture of the urine sample and the individual's antimicrobial agent-free urine collected prior to drug administration (12, 20, 22). UBTs were then determined by microdilution, with each well of the microplates containing 100 μl of the prepared dilution. The final inoculum was 10^5 CFU/ml, and the bactericidal activity was determined according to the guidelines recommended by NCCLS (23). A UBT of 0 was defined as no bactericidal activity, and a UBT of 1 was used when only undiluted urine displayed bactericidal activity.

Test organisms. Five pathogens were cultured from the urine of patients with UTIs. The pathogens included two strains of *Staphylococcus aureus* (one methicillin-sensitive strain, one methicillin-resistant strain), one methicillin-sensitive strain of *Staphylococcus saprophyticus*, one strain of *Enterococcus faecalis*, and one strain of *Enterococcus faecium*. Reference strain *S. aureus* ATCC 27278, which was methicillin susceptible, was also tested.

Statistical analyses. UBTs were transformed into ordinal data by using a scale from 1 for UBTs of 0 to 12 for UBTs of 1:≥1,024. The area under the UBT-versus-time curve (AUBT) was calculated by the trapezoidal rule by using the UBT steps (ordinal data) for each test organism and for each drug phase. Laboratory, pharmacokinetic, UBT, and AUBT data for the two drug phases were compared for each individual by the paired t test. An α value equal to 0.05 was chosen to determine statistical significance. Statistical calculations were performed by using the Documenta Geigy program (13).

RESULTS

Volunteers. The volunteers were six men and six women. The mean age was 27 years (median, 25 years; range, 19 to 42 years), the mean body weight was 68.3 kg (median, 66.1 kg; range, 57.8 to 86.6 kg), and the mean height was 171.6 cm (median, 171.0 cm; range, 159 to 187 cm).

TABLE 1. Drug concentrations in plasma of volunteers[a]

Time (h) after drug intake	Mean ± SD concn (μg/ml)	
	Linezolid	Ciprofloxacin
1	11.80 ± 2.03	2.40 ± 0.6
2	12.04 ± 2.20	1.64 ± 0.47
3	10.56 ± 2.43	1.14 ± 0.27
4	9.28 ± 2.20	0.87 ± 0.22
6	7.03 ± 1.63	0.54 ± 0.13
12	3.25 ± 1.02	0.16 ± 0.06
24	0.92 ± 0.49	0.03 ± 0.01

[a] A total of 12 volunteers were tested.

TABLE 2. Pharmacokinetic indices for linezolid and ciprofloxacin in volunteers[a]

Drug and parameter	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2}$ (h)	MRT (h)	AUC_{0-last} (μg · h/ml)	$AUC_{0-\infty}$ (μg · h/ml)	CL (ml/min)	CL_R (ml/min)	CL_{NR} (ml/min)	V_β (liter)	V_{ss} (liter)
Linezolid											
Mean	13.1	1.42	6.16	8.94	109.5	118.6	87.88	34.6	53.2	46.0	46.2
SD	1.80	0.51	1.41	2.07	22.48	26.41	17.71	8.33	14.8	11.3	10.6
CV (%)	13.8	36.3	22.9	23.1	20.5	22.3	20.16	24.05	27.9	24.5	23.0
Minimum	10.5	1.00	4.29	6.11	81.89	83.56	57.75	22.8	31.3	32.2	33.9
Maximum	15.6	2.00	8.68	12.91	159.0	173.1	119.7	48.0	86.1	64.8	64.8
Median	13.3	1.00	6.09	8.80	106.2	110.8	90.30	32.5	52.7	44.6	44.3
Ciprofloxacin											
Mean	2.46	1.09	4.40	5.31	10.2	10.4	1,001	336.8	664.5	380.3	316.1
SD	0.481	0.29	0.56	0.56	1.90	1.95	220.2	138.1	131.6	91.92	60.78
CV (%)	19.5	26.4	12.8	10.6	18.7	18.8	22.0	41.0	19.8	24.4	19.2
Minimum	1.61	1.00	3.75	4.41	6.41	6.52	747.5	145.2	444.1	275.2	239.9
Maximum	3.18	2.00	5.79	6.24	13.1	13.4	1534	721.9	914.8	578.0	453.0
Median	2.50	1.00	4.20	5.31	10.5	10.7	933.7	309.3	680.9	353.5	298.7

[a] A total of 12 volunteers were tested. Abbreviations: AUC_{0-last}, AUC from time zero to the last 36 h; $AUC_{0-\infty}$, AUC from time zero to infinity; CV, coefficient of variation. The other abbreviations are defined in the text.

Safety and laboratory test results. Linezolid and ciprofloxacin were well tolerated by all volunteers. No serious adverse events occurred during the study. Neither drug caused clinically significant changes in the results of routine tests of blood and serum.

Concentrations in plasma and pharmacokinetic parameters. The concentrations in plasma and the pharmacokinetic indices for linezolid and ciprofloxacin are given in Tables 1 and 2, respectively. There were statistically significant differences ($P < 0.05$) between men and women in the $t_{1/2}$ and MRT values in the ciprofloxacin phase and the C_{max}, V_β, and V_{ss} values in the linezolid phase. However, when the pharmacokinetic indices are correlated with the body mass indices, only the V_β and V_{ss} values still showed statistically significant differences between men and women in the linezolid phase. Men and women were therefore treated as one group in the analysis of the results.

Urinary pHs and volumes and drug concentrations in urine. The medians and ranges of urinary pH and volumes, drug concentrations in urine, and cumulative renal excretion obtained in the two study phases are given in Table 3. The data for the corresponding collection periods of the respective study phases showed no marked differences in urinary pHs or volumes. In both study phases, however, the median pH for the collection period from 6 to 12 h (afternoon) was higher than those for the other collection periods.

In the first collection period (0 to 6 h) there was a statistically significant difference between the linezolid (192 mg/liter) and ciprofloxacin (407 mg/liter) concentrations. Thereafter, up to the collection period from 36 to 48 h the concentrations of

TABLE 3. Urinary pH and volume, parent drug concentration in urine and cumualtive excretion in the volunteers[a]

Drug and collection period (h)	Urinary pH	Vol (ml)	Concn (mg/liter)	% Cumulative excretion	
				Median (range)	Mean ± SD
Linezolid					
0–6	5.9[c] (5.2–6.5)	532 (182–1,135)	192.0[c] (104–497)	16.9[c] (10.0–26.6)	17.0 ± 5.0
6–12	7.7 (6.2–8.7)	947 (515–1,353)	82.0[c] (66–163)	30.6[c] (19.5–40.4)	29.7 ± 6.5
12–24	6.3 (5.5–7.1)	824 (413–954)	61.0[c] (37–139)	40.4 (26.6–45.6)	37.0 ± 7.1
24–36	6.7 (5.6–8.0)	1,236 (432–3,160)	7.8[c] (5.3–51)	43.4 (28.1–46.5)	39.3 ± 7.7
36–48	6.2[c] (5.7–6.6)	712 (334–1,630)	3.1[c] (1.2–9.4)	43.7 (28.2–46.7)	39.7 ± 7.7
48–72	6.3 (5.6–7.0)	1,432 (784–2,450)	0.6[d] (0.2–4.3)	43.9 (28.2–47.1)	39.9 ± 7.8
72–96	6.0 (5.8–6.8)	1,661 (784–3,132)	0.1[d] (0.1–1.0)	43.9 (28.2–47.2)	39.9 ± 7.8
96–120	6.1 (5.2–8.5)	1,333 (684–2,241)	0.1[d] (0.02–0.2)	43.9 (28.2–47.2)	39.9 ± 7.8
Ciprofloxacin					
0–6	6.1[c] (5.4–6.5)	353 (170–1,628)	407.0[c] (23–733)	31.5[c] (7.5–50.2)	30.5 ± 10.3
6–12	7.2 (6.2–8.9)	643 (376–1,485)	47.0[c] (19–76)	38.6[c] (14.9–53.9)	36.5 ± 9.7
12–24	6.3 (5.9–7.7)	575 (410–1,543)	24.0[c] (5.8–36)	41.4 (18.9–55.5)	39.0 ± 9.3
24–36	7.0 (5.6–8.3)	1,096 (566–2,213)	2.0[c] (0.9–4.9)	42.0 (19.4–56.0)	39.5 ± 9.3
36–48	6.5[c] (5.8–8.0)	709 (474–1,163)	1.6[c] (0.6–3)	42.2 (19.7–56.1)	39.8 ± 9.3
48–72	6.1 (5.4–7.0)	1,688 (864–2,042)	BQL[b,d] (BQL–1.6)	42.6 (19.7–56.1)	39.9 ± 9.3
72–96	6.1 (5.5–7.8)	1,448 (570–2,697)	BQL[d]	42.6 (19.7–56.1)	39.9 ± 9.3
96–120	6.5 (5.7–8.0)	1,299 (544–2,535)	BQL[d] (BQL–0.6)	42.6 (19.7–56.1)	39.9 ± 9.3

[a] A total of 12 volunteers were tested. The values are given as medians (ranges) unless indicated otherwise.
[b] BQL, below quantification limit (0.0098 mg/liter for linezolid; 0.559 mg/liter for ciprofloxacin).
[c] Significantly different ($P < 0.05$) for linezolid versus ciprofloxacin.
[d] Calculation not applicable.

TABLE 4. Reciprocal UBTs for linezolid and ciprofloxacin in the 12 volunteers tested[a]

Drug and strain[b]	UBT for the following collection period (h):								AUBT (h^{-1})
	0–6	6–12	12–24	24–36	36–48	48–72	72–96	96–120	
Linezolid									
S. aureus ATCC 27278	128[c] (16–≥1,024)	48 (16–512)	16 (4–256)	4 (1–32)	1.5 (0–8)	0 (0–4)	0 (0–2)	0 (0–2)	180 (144–390)
S. aureus 636 (MS, CR)	256[c] (64–≥1,024)	96[c] (15–512)	64[c] (8–256)	8[c] (0–32)	1.5[c] (0–4)	0[c] (0–1)	0	0 (0–1)	252[c] (120–444)
S. aureus U6991 (MR, CR)	256[c] (32–≥1,024)	64[c] (16–512)	32[c] (8–256)	6[c] (0–32)	2[c] (0–16)	0 (0–4)	0	0 (0–1)	237[c] (138–408)
S. saprophyticus Ho 94 (MS)	128[c] (32–512)	64 (32–128)	32 (16–128)	4 (1–64)	2 (0–16)	0 (0–4)	0 (0–1)	0	210 (156–420)
E. faecalis 60	96[c] (2–256)	32[c] (1–128)	24[c] (0–64)	2[c] (0–32)	1[c] (0–8)	0 (0–4)	0	0	141 (18–378)
E. faecium 106	96 (2–512)	32[c] (1–64)	16[c] (0–64)	2 (0–32)	1[c] (0–8)	0 (0–2)	0 (0–1)	0	168[c] (18–372)
Ciprofloxacin									
S. aureus ATCC 27278	512[c] (8–≥1,024)	64 (16–128)	32 (2–128)	4 (2–8)	1 (0–4)	0 (0–2)	0	0	228 (138–282)
S. aureus 636 (MS, CR)	1.5[c] (0–16)	0[c] (0–2)	0[c] (0–2)	0[c]	0[c]	0[c]	0	0	18[c] (0–60)
S. aureus U6991 (MR, CR)	1.5[c] (0–32)	0[c] (0–4)	0[c] (0–2)	0[c] (0–1)	0[c]	0 (0–1)	0	0 (0–1)	12[c] (0–66)
S. saprophyticus Ho94 (MS)	384[c] (16–≥1,024)	64 (32–256)	32 (8–128)	4 (2–8)	2 (1–4)	0 (0–2)	0	0 (0–1)	234 (150–264)
E. faecalis 60	64[c] (0–≥1,024)	16[c] (4–32)	4[c] (0–32)	0[c] (0–1)	0[c]	0	0	0	108 (66–174)
E. faecium 106	64 (2–256)	16[c] (4–32)	4[c] (2–16)	0.5 (0–2)	0[c] (0–1)	0	0	0	114[c] (66–130)

[a] The values are medians (ranges).
[b] MS, methicillin sensitive; MR, methicillin resistant; CR, ciprofloxacin resistant.
[c] Significantly different ($P < 0.05$, paired t test) for linezolid versus ciprofloxacin.

linezolid in urine were significantly higher than those of ciprofloxacin. The median proportions of cumulative renal excretion of the administered dose of the parent drug up to 120 h were 44% for linezolid (range, 28 to 47%; mean ± standard deviation, 40% ± 7.8%) and 43% for ciprofloxacin (range, 20 to 56%; mean ± standard deviation, 40% ± 9.3%). Within the first 24 h more than 90% of the total excretion of both drugs was completed. None of the urine samples collected prior to drug administration had detectable drug.

MICs and MBCs. The MICs of linezolid and ciprofloxacin were as follows: for *S. aureus* ATCC 27278, 2 and 0.25 mg/liter, respectively; for methicillin-sensitive *S. aureus* clinical strain 636, 1 and 16 mg/liter, respectively; for methicillin-resistant *S. aureus* clinical strain U6991, 2 and 64 mg/liter, respectively; for methicillin-sensitive *S. saprophyticus* clinical strain Ho94, 1 and 0.25 mg/liter, respectively; for *E. faecalis* clinical strain 60, 2 and 1 mg/liter, respectively; and for *E. faecium* clinical strain 106, 2 and 1 mg/liter, respectively. The MBCs of linezolid and ciprofloxacin were equal to the corresponding MICs for all strains tested.

UBTs and AUBTs. The UBTs and AUBTs of both study drugs for the test organisms are given in Table 4. Within the first 6 h the UBTs of linezolid for the four staphylococcal strains were between 1:128 and 1:256 and the UBT was 1:96 for each of the two enterococcal strains. During this collection interval, the UBTs of ciprofloxacin for the two susceptible staphylococcal strains were between 1:384 and 1:512 and those for the two resistant staphylococcal strains were between 1 (bactericidal activity of undiluted urine only) and 1:2; the UBT was 1:64 for each of the two susceptible enterococcal strains. Statistical analyses of the data from this period showed that ciprofloxacin had significantly better activity against the ciprofloxacin-sensitive staphylococcal strains and that linezolid had significantly better activity against the ciprofloxacin-resistant staphylococcal strains. Thereafter, the median UBTs of both drugs for the susceptible strains decreased almost in parallel for both drugs according to the concentrations in urine. For one of the ciprofloxacin-resistant staphylococcal strains, the median UBT indicated that only undiluted urine had bactericidal activity, and for the other strain no bactericidal activity in urine could be demonstrated. The AUBTs for linezolid and ciprofloxacin showed no statistically significant ($P > 0.05$) differences except for better AUBTs for linezolid for the two ciprofloxacin-resistant staphylococcal strains. No statistically significant differences in UBTs or AUBTs for ciprofloxacin-susceptible and -resistant strains were demonstrated with linezolid, however. In all but one of the volunteers, ciprofloxacin had no bactericidal activity in urine against the ciprofloxacin-resistant staphylococcal strains during one of the first three collection periods (first 24 h). The statistically significant differences indicated in Table 3 do not necessarily reflect clinical relevance.

DISCUSSION

The incidence of nosocomial UTIs caused by gram-positive bacteria is increasing, and UTIs can cause significant clinical problems (7, 19). Several new antibiotics potentially target gram-positive pathogens. However, not all of them are excreted at sufficient levels in urine to be considered for treatment of UTIs.

Linezolid is a new antibiotic very effective against gram-positive bacteria, even multiresistant ones. Linezolid has already been shown to be clinically effective against other infections, like skin and soft tissue infections (27) as well as bone and joint, blood, gastrointestinal, and respiratory tract infections (4). However, so far no pharmacodynamic study has been undertaken to determine whether linezolid has efficacy against UTIs.

In the present study we investigated a single oral dose of linezolid (600 mg) and, as a control, a single oral dose of ciprofloxacin (500 mg), with which there has been clinical experience over decades and which can still be considered a drug of choice for the treatment of complicated UTIs.

The mean maximum concentration achieved in plasma after administration of a 600-mg oral dose of linezolid was more than five times higher (13.1 mg/liter) than that achieved after administration of a 500-mg oral dose of ciprofloxacin (2.46 mg/liter). In the first 6 h the concentrations of ciprofloxacin in urine were significantly higher than those of linezolid. The

mean cumulative renal excretion rate of linezolid (40%), however, was equal to that of ciprofloxacin (40%). The ranges of urinary pH and volume, parent drug concentration, and cumulative excretion were extensive in the 12 volunteers. This shows the high interindividual variations in these parameters. Therefore, the dosage and the dosing interval of the drugs must be elected such that sufficient antibacterial activity is also obtained in those individuals with low concentrations.

In some studies the time that the concentration in serum remains above the MIC was considered the most important pharmacokinetic-pharmacodynamic index of the activity of linezolid (11, 14, 29). If this also applies to the treatment of UTIs, then the time that UBTs are positive may be relevant. With linezolid the UBTs for all except 3 of the 12 volunteers were positive for up to 24 h; in 3 of the 12 volunteers they were negative for 12 to 24 h. No UBTs were obtained in two volunteers when UBTs against *E. faecalis* were tested, and no UBTs were obtained in one volunteer when UBTs against *E. faecium* were tested. A twice-daily linezolid dosing regimen for UTIs would therefore be adequate in any case.

In a recent study, Andes et al. (2) defined the AUC in relation to the MIC (AUC:MIC) as the key pharmacodynamic index for linezolid. This parameter is independent of the dosing interval (10). The concentration and the AUC:MIC are also the best indices with which to describe the antibacterial activity of ciprofloxacin (3, 18). The estimation of UBTs by use of dilutions prepared with the individual's antimicrobial agent-free urine and the corresponding AUBTs can be considered equivalent to the concentration and AUC:MIC and therefore may be appropriate for approximation of the expected in vivo activity of an antimicrobial agent like a fluoroquinolone (20). The UBTs and AUBTs showed no statistically significant ($P > 0.05$) differences in the bactericidal activities of linezolid and ciprofloxacin in urine except for the better activity of linezolid against ciprofloxacin-resistant staphylococcal and *E. faecium* strains. In addition, there were no statistically significant ($P > 0.05$) differences in the bactericidal activities of linezolid against ciprofloxacin-susceptible and -resistant strains in urine. Thus, the activities of the two antibiotics against ciprofloxacin-susceptible strains can be considered equivalent when the doses used in the present study are used. However, randomized comparative clinical trials are also needed to ascertain the equivalence of the bacteriological and clinical efficacies of the two agents against susceptible gram-positive pathogens.

At this stage of investigation the time that the concentration remains above the MIC, AUC:MIC, and C_{max}:MIC should be considered. Whether these general pharmacodynamic principles also apply to the treatment of UTIs must be investigated in an appropriate clinical study, at least for new drugs, such as linezolid.

The UBTs of linezolid were very similar to the corresponding concentrations in urine divided by the MBC for the pathogen. This, however, was not the case with ciprofloxacin, which appeared to have UBTs of about half of that. Studies with quinolones showed that MICs and MBCs are generally higher in urine than in standard test media (17). In particular, a low pH (pH 5) and a high $MgSO_4$ concentration contribute to elevated MICs. This is apparently not the case with linezolid in urine. Some reports indicate, however, that in serum linezolid is only bacteriostatic against staphylococci and enterococci (15, 16, 24, 28). Urine is a much different environment from serum, however, with the probable result of a bactericidal effect. On the other hand, the UBT does not reflect the dynamics of bacterial killing and only describes the final result after overnight incubation, as in the case of MIC and MBC determinations. Therefore, the rates of killing may be quite different between linezolid and ciprofloxacin. Whether this is clinically relevant must also be demonstrated.

It is not known whether the same pharmacodynamic indices derived from concentrations in plasma and the susceptibility of the pathogen are necessary for the treatment of complicated UTIs as they are for other systemic infections. In the case of complicated pyelonephritis with systemic infectious reactions and most likely in the case of urosepsis, however, these pharmacodynamic indices might be very relevant. With fluoroquinolones, AUC:MIC ratios of ≥100 in plasma were associated with almost no mortality in animal models of pneumonia, peritonitis, and sepsis (10). It has also been shown in lower respiratory tract infections caused by *E. faecium* and *S. aureus* in intensive care units that AUC:MIC ratios of <125 resulted in clinical failure. In general, AUC:MIC ratios of ≥125 should probably be considered the breakpoint for infections caused by gram-positive and gram-negative pathogens in order to avoid clinical failure and the emergence of resistance (25, 26). According to the results of an experimental study with neutropenic mice, a net static effect against *S. aureus* was achieved with linezolid at a mean 24-h AUC:MIC ratio of 83 (2).

Since both antibiotics used in this study are prescribed twice daily, the time segment of the 24-h AUC which needs to be considered is two times 0 to 12 h (with a suggested cumulative factor of about 1.2). By using the results of the present study, mean ± standard deviation AUCs of 202.8 ± 38.1 μg · h/ml (median, 204.2 μg · h/ml; range, 155.0 to 282.2 μg · h/ml) for linezolid and 21.6 ± 3.9 μg · h/ml (median, 22.1 μg · h/ml; range, 14.1 to 27.7 μg · h/ml) for ciprofloxacin can then be calculated without consideration of protein binding, which is about 30% for both drugs (6).

If a 24-h AUC:MIC ratio ≥125 is the target for the treatment of systemic infections and if the minimal AUCs observed in this study are used for calculation of the MIC breakpoints, MICs of ≤1.25 mg/liter for linezolid and ≤0.125 mg/liter for ciprofloxacin should be considered the breakpoints. In this case only linezolid and not ciprofloxacin could be considered appropriate at this dosage for the treatment of systemic infections caused by gram-positive pathogens, such as staphylococci and enterococci. It is not known whether these criteria also apply to the treatment of complicated UTIs; in severe UTIs with systemic infectious reactions, however, such conditions might be relevant.

The following conclusions may be drawn from the present study. (i) The mean level of renal excretion (parent drug) of linezolid (40%) was equal to that of ciprofloxacin (40%). (ii) After administration of an oral dose of 600 mg of linezolid (13.1 mg/liter), the mean maximum concentration in plasma was more than five times higher than that after administration of an oral dose of 500 mg of ciprofloxacin (2.46 mg/liter). (iii) According to the UBTs and AUBTs there were no statistically significant ($P > 0.05$) differences in the bactericidal activities of linezolid and ciprofloxacin in urine except for the better activity of linezolid against ciprofloxacin-resistant staphylococcal

and *E. faecium* strains. (iv) According to the UBTs there were no statistically significant ($P > 0.05$) differences in the bactericidal activities of linezolid against ciprofloxacin-susceptible and -resistant strains in urine. (v) By use of an oral dose of 600 mg of linezolid twice daily, it can be expected that the drug will have bactericidal activity in urine against gram-positive uropathogens, regardless of their methicillin and fluoroquinolone resistance, throughout the complete interval of therapy.

Thus, linezolid may be a good alternative treatment and should therefore be tested for use for the empirical treatment of complicated UTIs due to gram-positive uropathogens in an appropriate clinical trial.

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