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Pharmacodynamics of Finafloxacin, Ciprofloxacin and Levofloxacin in Serum and Urine against Extended-Spectrum Beta-Lactamase Producing Enterobacteriaceae Isolated from Urinary Tract Infections

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Introduction

Resistance to antimicrobials in Gram-negative bacteria in general and in extended spectrum ß-lactamase (ESBL)-producing bacteria in particular causing UTIs increased continuously. Most of the ESBL-producers harbor enzymes belonging to the TEM- and SHV-families, although CTX-M type producers are becoming more prevalent or tend to predominate. In contrast to CTX-M type ß-lactamases, ESBLs of the TEM- and SHV-type rarely reduce quinolone-susceptibility as integrons have no major impact on the spread of TEM- or SHV-type ESBLs except those of the CTX-M type.

Therefore, it is relevant to assess the activity of the novel developmental fluoroquinolone finafloxacin, being studied clinically for the treatment of complicated UTIs or acute pyelonephritis (see poster L-1250 this conference), against TEM- and SHV-producing strains as compared to their susceptible counterparts. Ciprofloxacin and levofloxacin served as comparators.

Methods

Bacterial strains

E. coli ATCC 25922 (WT); *E. coli* ATCC 35218 (TEM-1positive); *E. coli* clinical isolate (TEM-type ESBL); *K. pneumoniae* ATCC 13883 (WT); *K. pneumoniae* ATCC 700603 (SHV-18 positive)

Experimental details

The experimental details have been published previously (Dalhoff A. et al., AAC 2011; 55: 1814-1818; Stass H., Dalhoff A. Infection 2005; 33 (Suppl 2): 29-35).

PK parameters

Agent, dose (mg)	Cmax (mg/l)		tmax (h)		t ½ (h)	
	Serum	Urine	Serum	Urine	Serum	Urine
Fina, 800, q.d.	11.0	180	1.0	2.0	10.0	7.0
CPX-IR 500, b.i.d	1.4	450	1.5, 13.5	1.5, 13.5	5.5	5.5
CPX-XR 1,000, q.d.	2.3	650	3.0	3.0	6.5	6.5
LVX 500, q.d.	5.7	580	1.0	1.5	7.5	9.0
LVX 750, q.d.	8.6	870	1.6	2.0	7.5	9.0

Table 1 Pharmacokinetic parameters simulated in the *in vitro* pharmacodynamic system following oral administration of finafloxacin (Fina) 800mg, q.d., as compared to ciprofloxacin immediate release (CPX-IR) 500mg, b.i.d., ciprofloxacin extended release (CPX-XR) 1,000mg q.d., levofloxacin 500mg, q.d., and 750mg, q.d. (q.d. = once a day; b.i.d. = twice daily)

Data evaluation

The areas under the bacterial kill- versus time-curves (AUBKC), expressed as log10 colony forming units (CFU) x h /mL, were calculated using the trapezoidal rule. In case that a discrete regrowth of a test strain at 24h, but not in between 10h to 24h was recorded. The AUBKCs were calculated for the incubation period from 0 to 10h, and the discrete data point at 24h (calculated as log10 CFU/mL /2) was added to the AUBKC-values.

Results and Discussion

Susceptibility testing

- Finafloxacin gained activity in acidic CAMHB and maintains activity in synthetic urine as compared to standard test conditions in CAMHB, pH 7.2.
- The activities of ciprofloxacin and levofloxacin were reduced in acidic CAMHB and in particular in synthetic urine.
- The differences between MICs generated at pH 7.2 and at pH 5.8 were most marked for the test strain *K. pneumoniae* ATCC 700603 for which the MICs of ciprofloxacin and levofloxacin increased by 4- to 7- and 5- >7 dilution steps, respectively.

Strain	Finafloxacin			Ciprofloxacin			Levofloxacin		
	CAMHB pH 7.2	CAMHB pH 5.8	syn.-urine	CAMHB pH 7.2	CAMHB pH 5.8	syn.-urine	CAMHB pH 7.2	CAMHB pH 5.8	syn. urine
E. coli wild type	0.06	0.03	0.06	0.03	0.06	0.5	0.06	0.25	1.00
E. coli TEM 1	0.06	0.03	0.06	0.03	0.12	0.5	0.06	0.25	2.00
E. coli TEM ESBL	2.00	0.50	1.00	2.00	8.00	16.0	1.00	8.00	32.0
K. pneumoniae wt	0.125	0.03	0.125	0.03	1.00	2.0	0.06	0.25	8.00
K. pneumoniae SHV 18	2.00	0.50	2.0	0.25	4.00	32.0	0.50	16.0	≥64

Table 2 Minimal inhibitory concentrations (mg/L) of finafloxacin, ciprofloxacin, and levofloxacin against the indicator strains studied; CAMHB = cation adjusted Mueller Hinton Broth, syn. urine = synthetic urine pH 5.8

PK-simulations

- Finafloxacin exerted a marked antibacterial activity against all indicator strains and all test conditions.
- A simulation of finafloxacin urine-PK profiles reduced under all experimental conditions viable counts of all the test strains below the limit of detection while a moderate and discrete regrowth was noticed at 24h in case the strains were exposed to the serum-PK profile.
- Finafloxacin was almost equally active against susceptible wild-type-, TEM-1 ß-lactamase-, or TEM- or SHV-type ESBL producing strains.
- Ciprofloxacin IR as well as XR urine kinetic profiles reduced the wild type indicator strains below the limit of detection under all growth conditions within four to eight hours and ten hours in synthetic urine.
- Viable counts of the TEM-1 ß-lactamase positive *E. coli* and the ESBL-producing *K. pneumoniae* strains were transiently reduced but regrew from the 10th hour onwards.
- The TEM-type ESBL producing *E. coli* strain was marginally affected; the activity of ciprofloxacin in synthetic urine was minimal.
- Levofloxacin exhibited phenotypically similar, but quantitatively stronger, activities than ciprofloxacin.
- Levofloxacin reduced viable counts of the TEM-type ESBL producing *E. coli* strain below the limit of detection within six and four hours, respectively, in the serum- and urine-PK simulation assays, provided the strain was incubated in CAMHB at a pH of 7.2. Levofloxacin lost activity by approximately one to four log10 CFU-units in acidic CAMHB and in synthetic urine in particular.

	Serum-pharmacokinetic simulations in	Urine-pharmacokinetic simulations in	Urine-pharmacokinetic simulations in	Urine-pharmacokinetic simulations in
	CAMHB pH 7.2	CAMHB pH 7.2	CAMHB pH 5.8	syn. urine pH 5.8
Fina				
E. coli wild type	4.57	2.87**	2.87**	2.78**
E. coli TEM 1	4.63	2.76**	2.76**	2.70**
E. coli TEM ESBL	21.93	16.98	6.80	7.85
K. pneumoniae wt	4.09	2.79**	2.79**	2.24**
K. pneumoniae SHV18	19.99	8.24	2.77**	4.32
CPX-IR				
E. coli wild type	84.92	4.66	18.06	24.81
E. coli TEM 1	166.54	29.52	58.96	83.08
E. coli TEM ESBL	170.06	28.32	75.00	120.86
K. pneumoniae wt	14.20	3.81	16.16	27.72
K. pneumoniae SHV18	124.80	15.44	41.00	58.11
CPX-XR				
E. coli wild type	35.40	14.26	21.39	50.08
E. coli TEM 1	153.48	19.83	54.76	97.61
E. coli TEM ESBL	153.48	13.84	101.4	183.39
K. pneumoniae wt	4.30	4.00	36.96	59.84
K. pneumoniae SHV18	79.14	4.06	62.08	99.50
LVX 500				
E. coli wild type	3.75	3.07**	6.61	6.83
E. coli TEM 1	34.65	7.93	33.35	67.56
E. coli TEM ESBL	64.52	20.79	81.86	103.26
K. pneumoniae wt	7.08	2.86**	2.98**	2.98**
K. pneumoniae SHV18	90.54	8.20	17.16	83.43
LVX 750				
E. coli wild type	3.20**	3.03**	3.23	12.56
E. coli TEM 1	3.29	2.98**	2.99**	2.98**
E. coli TEM ESBL	50.54	13.86	62.13	82.83
K. pneumoniae wt	3.29	2.98**	2.99**	2.98**
K. pneumoniae SHV18	64.74	7.57	15.16	54.72

Table 3 Comparative antibacterial activities - expressed as area under the bacterial kill curve (AUBKC, log10 CFU x h /mL) – of oral doses of finafloxacin, ciprofloxacin, and levofloxacin (* = the growth controls grew equally well in CAMHB adjusted to a pH of 7.2 and 5.8 (AUBKC=182-214) or urine (AUBKC=158-203)
** = differences in antibacterial activities under the different test conditions were not assessable, as viable counts of the test strains were reduced below the limit of detection within the time period between inoculation and first sampling at 2h).

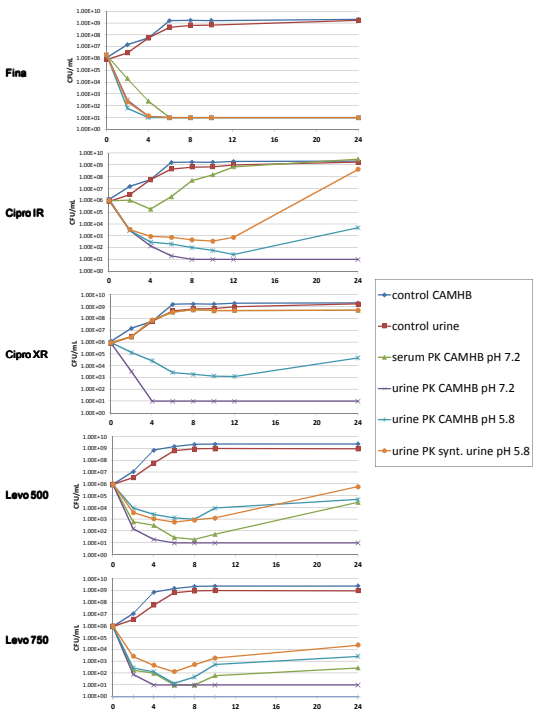

Figure 1 Time kill curves with *E. coli* clinical isolate (TEM-type ESBL)

Conclusions

- Both, low pH and divalent cations interfere negatively with the activities of ciprofloxacin and levofloxacin.
- Even the two wild type reference strains being fluoroquinolone-susceptible under routine test conditions at pH 7.2 are borderline-susceptible or even resistant in synthetic urine, so that these strains pass unnoticed under routine susceptibility test conditions.
- High urine concentrations may compensate for a loss of activity in urine provided wild type strains are exposed to ciprofloxacin or levofloxacin. However, the loss of activity against the TEM-1 ß-lactamase- and in particular the ESBL-producers is not fully compensated.
- However, the activity of finafloxacin in CAMHB increased as the pH value decreased and remained unchanged in artificial urine; the activity of finafloxacin was negligibly affected in synthetic urine.
- Finafloxacin may thus provide a safety margin for treatment of those TEM- and SHV-type ESBL-producing isolates which are borderline susceptible or resistant to ciprofloxacin or levofloxacin when tested in urine.
- The findings of this in vitro PK-simulation study may translate into the clinical arena as indicated in a phase II study presented at this conference in poster L-1250, demonstrating that finafloxacin eradicated ESBL-producing urinary pathogens in 91% (n=11), and ciprofloxacin in 0% (n=3) of the cases.