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Activity of ulifloxacin against clinical hospital isolates

Attività antibatterica di ulifloxacina nei confronti di microrganismi di isolamento ospedaliero

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INTRODUCTION

In the last years, in the field of quinolones, new molecules of increasing interest have been introduced. Among them prulifloxacin, the prodrug of ulifloxacin, characterised by a good activity against *Pseudomonas aeruginosa* and a favourable pharmacokinetic activity, has obtained considerable interest [1, 4]. Ulifloxacin has shown potent bactericidal activity against *P. aeruginosa* and the lowest MPC (mutant prevention concentration) among the quinolones most widely used [4].
In the 1990s molecules with increased activity against Gram positive and variable activity against anaerobes were developed. However, several of these molecules ended up, being limited in their clinical use due to various toxicity problem [5, 6]. Moxifloxacin was considered the drug with the best activity against anaerobes [6].
Prulifloxacin is extensively and rapidly metabolised to ulifloxacin and after administration there are no detectable concentration of prulifloxacin in plasma.
The pharmacokinetic profile of ulifloxacin is favourable, with a wide volume of distribution and a good penetration into many body tissues. In the lung, the tissue/plasma concentration is greater than 1; from 2 to 5 according to the time of assessment. Ulifloxacin is able to penetrate the macrophage, but is unable to cross the blood-brain barrier [1].
Ulifloxacin has already been studied in Italy, especially using bacterial collections, both isolated from patients with nosocomial and community infections [3, 4].
In this study, we prospectively tested ulifloxacin against all the bacterial strains isolated from laboratory of Infectious Diseases Unit of the Azienda Ospedaliera Universitaria Pisana (AOUP), Pisa Italy.

MATERIAL AND METHODS

The laboratory of the Infectious Diseases Unit at the AOUP is the reference laboratory for several wards in this hospital, including cardio-surgical and the liver transplant intensive care units, general and vascular surgery, diabetic foot clinic, cardiology unit with the national reference centre for the removal of the infected pacemakers, and infectious diseases unit.
All clinical isolates obtained in the year 2005 were included in the study. Multiple isolates from the same patients were avoided. Strains were identified using commercially and automated biochemical test systems, and when necessary the identification was confirmed by additional tests [7]. The Kirby-Bauer method was used to test the strains included in the study.
Ulifloxacin (5 μg), ciprofloxacin (5 μg), levofloxacin (5 μg) and moxifloxacin (5 μg) disks were manufactured by Oxoid Italiana (Garbagnate Milanese, MI, Italy).
The following zone diameter breakpoints were used to assess susceptibility and resistance to ulifloxacin: ≤15 and ≥19 mm for *Enterobacteriaceae*, ≤16 and ≥20 mm for non-fermenting Gram negative rods, and ≤14 and ≥18 mm for Gram positive bacteria [8].

RESULTS

A total of 647 aerobic bacteria strains were examined; 281 Gram negative and 366 Gram positive. Among Gram negative, we examined 150 *Enterobacteriaceae* (31 ESBL producers), 88 *P. aeruginosa*, 15 *S. maltophilia*, 12 *Acinetobacter baumannii.* Among Gram positive, we examined 133 *Staphylococcus aureus* strains (53 methicillin-resistant), 111 coagulase-negative staphylococci (66 methicillin-resistant), 76 enterococci (5 vancomycin-resistant strains) and 20 streptococci.

Among the 647 strains tested, 392 (60%) resulted susceptible to ulifloxacin, 350 (54%) resulted susceptible to ciprofloxacin and levofloxacin, respectively. Moxifloxacin was tested only against the Gram positive strains; in particular among the 284 Gram positive strains tested, 183 (64%) resulted susceptible to moxifloxacin. Ulifloxacin activity against Gram negative strains was equal to 65% (185/281) and was slightly superior to the other two quinolones tested. The overall susceptibility, and the susceptibility splitted in Gram positive and Gram negative strains, are listed in Table 1.

Table 1 - Activity of the four quinolones against all the strains included in the study and activity against Gram negative and Gram positive strains, respectively.

Drug	*Total susceptibility (strains - %)*	*Susceptibility against Gram negative (strains - %)*	*Susceptibility against Gram positive (strains - %)*
Ulifloxacin	392/647 - 60,5%	185/281 - 65%	207/366 - 56%
Ciprofloxacin	350/647 - 54%	180/281 - 64%	170/366 - 46%
Levofloxacin	350/647 - 54%	166/281 - 59%	184/366 - 50%
Moxifloxacin	-	-	183/284 - 64%

Table 2 - Susceptibility of Gram negative strains to different quinolones.

Gram negative (281 strains)		*Ulifloxacin*		*Ciprofloxacin*		*Levofloxacin*		*Moxifloxacin*	
		%	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*
Enterobacteriaceae									
Non ESBL+ (n=119)	R/I	18	22/119	21	25/119	20	22/111	-	-
	S	**82**	97/119	**79**	94/119	**80**	89/111	-	-
ESBL+/AmpC (n=31)	R/I	45	14/31	55	17/31	44	11/25	-	-
	S	**55**	17/31	**45**	14/31	**56**	14/25	-	-
Total (n=150)	R/I	24	36/150	28	42/150	24	33/136	-	-
	S	**76**	114/150	**72**	108/150	**76**	103/136	-	-
Pseudomonas spp (n=88)	R/I	39	34/88	42	37/88	48	37/77	-	-
	S	**61**	54/88	**58**	51/88	**52**	40/77	-	-
Acinetobacter spp (n=12)	R/I	58	7/12	64	7/11	56	5/9	-	-
	S	**42**	5/12	**36**	4/11	**44**	4/9	-	-
S. maltophilia (n=15)	R/I	80	12/15	40	6/15	14	2/14	-	-
	S	**20**	3/15	**60**	9/15	**86**	12/14	-	-
Alcaligenes spp (n=11)	R/I	64	7/11	73	8/11	70	7/10	-	-
	S	**36**	4/11	**27**	3/11	**30**	3/10	-	-

Abbreviations: R/I = resistant/intermediate; S = susceptible

Table 3 - Susceptibility of Gram positive strains to different quinolones.

Gram negative (366 strains)		*Ulifloxacin*		*Ciprofloxacin*		*Levofloxacin*		*Moxifloxacin*	
		%	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*
S. aureus									
Oxa R (53)	R/I	96	51/53	96	51/53	96	51/53	90	38/42
	S	**4**	2/53	**4**	2/53	**4**	2/53	**10**	4/42
Oxa S (80)	R/I	6	5/80	10	8/80	4	3/77	5	3/61
	S	**94**	75/80	**90**	72/80	**96**	74/77	**95**	58/61
Coagulase negative Staphylococci									
Oxacillin-R (66)	R/I	76	50/66	88	57/65	78	51/65	43	22/51
	S	**24**	16/66	**12**	8/65	**21**	14/65	**57**	29/51
Oxacillin-S (50)	R/I	18	9/50	22	11/50	14	7/49	10	4/40
	S	**82**	41/50	**78**	39/50	**86**	42/49	**90**	36/40
E. faecalis									
Vancomycin-R (2)	R/I	100	2/2	100	2/2	100	2/2	100	2/2
	S	**0**		**0**		**0**		**0**	
Vancomycin-S (67)	R/I	34	23/67	43	29/67	25	16/64	28	16/67
	S	**66**	44/67	**57**	38/67	**75**	48/64	**76**	51/67
E. faecium									
Vancomycin-R (3)	R/I	100	3/3	100	3/3	100	3/3	100	3/3
	S	**0**		**0**		**0**		**0**	
Vancomycin-S (4)	R/I	75	3/4	75	3/4	75	3/4	75	3/4
	S	**25**	1/4	**25**	1/4	**25**	1/4	**25**	1/4

Abbreviations: R/I = resistant/intermediate; S = susceptible

Among the multidrug-resistant (MDR) Gram negative rods, such as ESBL producers *Escherichia coli* and *Klebsiella spp*, ulifloxacin showed the same activity as ciprofloxacin and levofloxacin. Against *P. aeruginosa*, often MDR, ulifloxacin was superior to the other two drugs (Table 2).

Among Gram positive strains, moxifloxacin evidenced the best activity, followed by ulifloxacin, levofloxacin and ciprofloxacin. The best activity of moxifloxacin was especially observed against coagulase negative staphylococci (Table 3).

In particular, we examined the strains isolated in single wards, such as diabetic foot clinic, intensive care units and pacemaker (PM) unit, in order to understand if there were differences in susceptibility among the four quinolones studied; overall percentages of resistance are reported in Table 4. Among patients admitted at the diabetic

Table 4 - Percentage of quinolones-resistant strains isolated in different wards.

	Ulifloxacin	*Ciprofloxacin*	*Levofloxacin*
Intensive Care Unit (UTI)	43%	52%	48%
Pacemaker Unit	19%	23%	20%
Diabetic Foot Unit	41%	45%	43%

foot clinic, we observed 199 ulifloxacin-resistant strains, out of 476 isolates. Among these resistant strains, only 2 were susceptible to ciprofloxacin, 12 to levofloxacin and 12 to moxifloxacin. All of these twelve strains were Gram positive.
On the other hand, among strains susceptible to ulifloxacin, we found 24 strains resistant to ciprofloxacin and 18 strains resistant to levofloxacin. Differences were mainly among *Enterococcus faecalis* for ciprofloxacin and among *Pseudomonas aeruginosa* for levofloxacin.
Among PM infections, we studied 51 strains, 10 strains were resistant to ulifloxacin; among these, none were susceptible to ciprofloxacin and levofloxacin, and only 2 CNS were susceptible to moxifloxacin, respectively. In UTIs, we studied 160 strains, 70 resistant to ulifloxacin, among these strains, none were resistant to ciprofloxacin, only 2 were susceptible to levofloxacin and 7 to moxifloxacin, all Gram positive.

DISCUSSION

The strains studied in this study reflect the actual pattern of susceptibility that we expected to find in a large tertiary hospital in Italy, including pathogens displaying maximum incidence of resistance traits to commonly used antimicrobials. In particular, in the sample were represented units where resistant strains are frequently found, such as UTIs, diabetic foot clinic, cardiology and general surgery and transplant unit.
In this setting, ulifloxacin displays the same potency as quinolones with microbiological activity against Gram negative, included MDR strains, and was as active as moxifloxacin against nosocomial Gram positive strains.
These results are in agreement with those found by other authors, and concerning prulifloxacin activity against MDR *P. aeruginosa* strains isolated in Japan and against either Gram negative or positive strains isolated from urinary tract infections in Italy [9, 10].
Ulifloxacin has displayed high efficacy in the treatment of several infections, such as acute exacerbation of chronic bronchitis, complicated and uncomplicated urinary tract infections [1]. Furthermore, it was demonstrated its *in vitro* bactericidal activity against MDR *P. aeruginosa* strains [4]. From the pharmacokinetic point of view, this drug has shown good penetration in the lung and in the urinary tract; ulifloxacin has a long half-life that permits administration of one daily dose [11].
Ulifloxacin might be a valid alternative to the classical quinolones molecules. For example, in polymicrobial diabetic foot infections, that are usually treated at home, this drug may be a valid alternative. In those infections sustained by MDR strains, especially *P. aeruginosa*, more and more frequent in our hospitals, ulifloxacin might be the drug of choice. This drug is a good option in other community acquired infections, as well [12].
In the setting of UTIs, ulifloxacin is as effective as the other molecules. However, its administration is limited to the oral route, although once daily.
In order to understand the clinical efficacy of this useful quinolone, comparative prospective clinical study are required.

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Key words: ulifloxacin, ciprofloxacin, levofloxacin, moxifloxacin, clinical isolate

SUMMARY

We evaluated the activity of ulifloxacin in comparison with ciprofloxacin, levofloxacin and moxifloxacin against clinical isolates from a large teaching hospital in Italy.
The isolates derived from patients admitted to surgical and medical wards and intensive care units. Multi-drug resistant *S. aureus*, *P. aeruginosa*, enterococci and *Enterobacteriaceae spp.* strains were included in the study. Ulifloxacin was slightly more active than ciprofloxacin and levofloxacin against gram negative isolates. Against gram positive strains ulifloxacin was as active as moxifloxacin.

RIASSUNTO

Abbiamo valutato l'attività di ulifloxacina in confronto con quella di altri chinoloni, ciprofloxacina, levofloxacina e moxifloxacina, nei confronti di ceppi di isolamento clinico. I ceppi studiati erano stati isolati da campioni di pazienti ricoverati in reparti medici, chirurgici e di terapia intensiva. Sono stati studiati anche ceppi multiresistenti di S. aureus, P. aeruginosa, Enterobacteriaceae *ed enterococchi.*

Ulifloxacina è risultata leggermente più attiva di ciprofloxacina e levofloxacina nei confronti dei ceppi Gram negativi; nei confronti dei Gram positivi è risultata simile alla moxifloxacina.

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