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Activity of the Investigational Fluoroquinolone Finafloxacin Against Ciprofloxacin-Sensitive and -Resistant *Acinetobacter baumannii*

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Abstract

Background: *Acinetobacter baumannii* is a serious nosocomial pathogen characterised by its innate and acquired resistance to most antimicrobials, including fluoroquinolones (FQ). FQ resistance is mediated through target site mutations in *gyrA* and *parC* combined with increased efflux. Finafloxacin (FIN) is a novel fluoroquinolone which shows enhanced activity under acidic pH where all other FQ lose activity. This study investigated the activity of FIN and ciprofloxacin (CIP) against *A. baumannii* isolates with characterised resistance mechanisms.

Methods: 72 *A. baumannii* clinical isolates were included. CIP and FIN MICs were performed by agar dilution under standard conditions (pH 7.2) or at a pH of 5.8.

Results: Results are summarised in Table 1. At pH 7.2 FIN had comparable activity to CIP. Activity at pH 5.8 showed a dramatic lowering in MIC with FIN. In contrast, CIP MICs rose under these conditions. FIN MICs are raised with a GyrA substitution but are less affected by an additional ParC substitution.

Conclusions: Overall, FIN demonstrated superior activity to CIP under acidic conditions against all isolates irrespective of their resistance mechanism. Furthermore, FIN showed comparable activity to CIP at pH 7.2. Hence, FIN could be a promising new antimicrobial agent for the treatment of *A. baumannii* infections at acidic body compartments.

Introduction and Purpose

- *Acinetobacter baumannii* is a serious nosocomial pathogen characterised by its innate and acquired resistance to most antimicrobials, including fluoroquinolones.
- Fluoroquinolones resistance is mediated through target site mutations in *gyrA* and *parC* combined with increased efflux.
- Finafloxacin (Figure 1) is a novel fluoroquinolone which shows enhanced activity under acidic pH where all other fluoroquinolones lose activity.
- This study investigated the activity of finafloxacin and ciprofloxacin against *A. baumannii* isolates with characterised resistance mechanisms.

Methods

- **Bacterial isolates:** A total of 72 *A. baumannii* clinical isolates were investigated. Of these, 69 have characterised *gyrA* and *parC* genes (1). Four strains overexpress the efflux pump *adeB* compared to their isogenic parent strains (2).
- **Sensitivity testing:** Ciprofloxacin and finafloxacin MICs were determined by agar dilution under standard conditions (pH 7.2) or at a pH of 5.8. Mueller Hinton agar was prepared following the manufacturers instructions and the pH was adjusted with HCl prior to pouring into petri dishes. pH of the agar was checked once solidified.

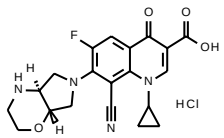
Results

Table 1. Agar dilution MICs of ciprofloxacin (CIP) and finafloxacin (FIN) under normal pH (7.2) and acidic (pH 5.8) conditions against characterised *A. baumannii* isolates.

	Amino acid substitutions		MIC (µg/ml)			
Strain No.	GyrA	ParC	CIP normal	FIN normal	CIP acidic	FIN acidic
1	-	-	0,06	0,12	2	0,06
2	-	-	0,06	0,5	2	0,12
3	-	-	0,12	0,12	2	0,06
4	-	-	0,12	0,25	1	0,03
5 - 7	-	-	0,12	0,25	2	0,06
8 - 10	-	-	0,25	0,25	2	0,12
11	-	-	0,25	0,25	4	0,06
12	-	-	0,5	1	2	0,12
13	-	-	0,5	1	4	0,12
14	-	-	0,5	1	4	0,25
15 - 17	-	-	1	1	4	0,12
18	-	-	1	1	8	0,12
19	Ser83-Leu	-	1	0,5	4	0,12
20	Ser83-Leu	-	2	1	4	0,06
21	Ser83-Leu	-	4	1	32	0,25
22	Glu87-Gly	-	4	8	32	1
23 - 25	Ser83-Leu	-	4	16	32	2
26, 27	Ser83-Leu	-	4	16	32	1
28	Ser83-Leu	-	4	32	32	4
29	Ser83-Leu	-	8	8	32	0,5
30	Ser83-Leu	-	8	16	32	1
31	Ser83-Leu	-	16	16	32	1
32	Ser83-Leu	-	8	16	128	1
33, 34	Ser83-Leu	-	8	16	128	2
35, 36	Ser83-Leu	-	16	16	128	2
37	Ser83-Leu	-	32	16	128	2
38-41	Ser83-Leu	-	16	16	>128	2
42	Ser83-Leu	-	32	16	>128	2
43	Ser83-Leu	Glu84-Lys	32	16	>128	4
44, 45	Ser83-Leu	Ser80-Leu	64	16	>128	2
46	Ser83-Leu	Ser80-Phe	64	32	>128	4
47, 48	Ser83-Leu	Ser80-Leu	128	16	>128	2
49	Ser83-Leu	Ser80-Leu	128	16	>128	4
50 - 52	Ser83-Leu	Ser80-Leu	128	32	>128	2
53 - 55	Ser83-Leu	Ser80-Leu	128	32	>128	4
56	Ser83-Leu	Ser80-Phe	128	32	>128	4
57	Ser83-Leu	Ser80-Leu	128	64	>128	4
58	Ser83-Leu	Glu84-Lys	128	64	>128	8
59 - 61	Ser83-Leu	Ser80-Leu	128	64	>128	8
62	Ser83-Leu	Glu84-Lys	>128	64	>128	2
63	Ser83-Leu	Ser80-Leu	>128	64	>128	4
64	Ser83-Leu	Ser80-Leu	>128	64	>128	8
65*	Ser83-Leu	-	32	16	128	2
66⁺	Ser83-Leu	Ser80-Leu	>128	64	>128	4
67⁺	Ser83-Leu	Ser80-Leu	>128	64	>128	4
68*	Ser83-Leu	-	4	8	32	1
69⁺	Ser83-Leu	-	128	128	>128	8
70*, 71*	nt	nt	128	32	>128	4
72⁺	nt	nt	>128	64	>128	4

*parent strain; ⁺*adeB* overexpressing; nt, not tested; strain 69 is a moxifloxacin-selected laboratory mutant derived from strain 68.

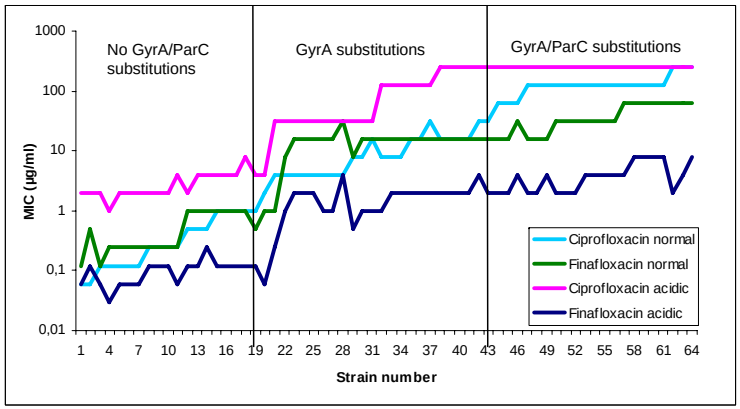
Figure 1. Structure of Finafloxacin HCl



Results cont.

- Results are summarised in Table 1 and shown graphically in Figure 1.
- At pH 7.2 finafloxacin had comparable activity to ciprofloxacin.
- Activity at pH 5.8 showed a dramatic lowering in MICs with finafloxacin. In contrast, ciprofloxacin MICs rose under these conditions (Table 1).
- Finafloxacin MICs are raised with a GyrA substitution but are less affected by an additional ParC substitution (Figure 2).

Figure 2. Chart comparing MICs of ciprofloxacin and finafloxacin under normal and acidic pH.



Conclusions

- Overall, FIN demonstrated superior activity to CIP under acidic conditions against all *A. baumannii* isolates irrespective of their resistance mechanism.
- Furthermore, FIN showed comparable activity to ciprofloxacin at pH 7.2.
- FIN could be a promising new antimicrobial agent for the treatment of *A. baumannii* infections at acidic body compartments.

References and Acknowledgements

1. Wisplinghoff et al. J. Antimicrob. Chemother. (2002). 51: 177-180
2. Higgins et al. J. Antimicrob. Chemother. (2004). 54: 821-823

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