

P1526 Activity of fluoroquinolones (finafloxacin, levofloxacin, ciprofloxacin) vs. that of imipenem against extracellular and intracellular forms of infection by *Burkholderia thailandensis*

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Background: *Burkholderia thailandensis* is a facultative intracellular bacterium thriving in the cytosol of eukaryotic cells. It is considered as a surrogate for *B. pseudomallei*, the agent of melioidosis, a lethal infection in humans. The aim of this work was to compare the activity of fluoroquinolones to that of a typical β -lactam (imipenem) against the extracellular and intracellular forms of infection by *B. thailandensis*, both antibiotic classes having access to eukaryotic cell cytosol (Cur-Opin-Drug-Discov-Devel 2006;9:218-30). For fluoroquinolones, we selected finafloxacin (showing enhanced activity at acidic pH; currently in development for the treatment of serious bacterial infections in the hospital and critical care setting), levofloxacin and ciprofloxacin.

Materials/methods: The ATCC 700388 reference strain was used. Extracellular infection: bacteria were exposed during 24h to antibiotics over a wide range of concentrations (0.003-100x MIC). Intracellular infection (human THP-1 cells): (i) phagocytosis of human serum-opsonized bacteria (1 h at 10 bacteria/cell); (ii) elimination of non-phagocytosed bacteria by incubation with gentamicin (1h; 100X MIC); (iii) 24h incubation of infected cells with antibiotics (same range of concentrations as extracellularly). Maximal efficacy (Emax) and potency (Cs [apparent static concentration]) were calculated using the Hill equation fitted to the data (change in log₁₀ cfu at 24h compared to 0h over log₁₀ of the antibiotic extracellular concentration; AAC 2006;50:841-51).

Results: See Table. Extracellularly, all antibiotics showed a Cs close to their MIC and Emax values below the detection level [apparent complete eradication]. Intracellularly, fluoroquinolones were as potent and effective as extracellularly while imipenem was less potent (Cs at 13x MIC) and considerably less effective (less negative Emax).

Conclusions: Fluoroquinolones are remarkably effective against intracellular *B. thailandensis*, consistent with their activity already demonstrated for intracellular *Listeria monocytogenes*, which also thrives in the cytosol (IJAA 2011;38:52-9). In contrast, imipenem, although part of the β -lactam class of antibiotics often recommended for the treatment of *Burkholderia* infections, was unable to eradicate intracellular bacteria. This work rationalizes the recently demonstrated efficacy of finafloxacin in an animal model of infection by *B. pseudomallei* (AAC 2017;61(7). pii: e00082-17).

antibiotic	MIC (mg/L)	Extracellular		Intracellular	
		Cs (x MIC)	Emax ^a	Cs (x MIC)	Emax ^a
Finafloxacin	4	0.8 ± 0.3	< - 5 ^b	0.4 ± 0.1	< - 5 ^b
Levofloxacin	4	0.5 ± 0.2	< - 5 ^b	0.5 ± 0.2	< - 5 ^b
Ciprofloxacin	4	0.4 ± 8.7	< - 5 ^b	0.3 ± 0.1	< - 5 ^b
Imipenem	0.5	0.5 ± 0.2	< - 5 ^b	13.4 ± 15.3	-1.7 ± 0.2

^a reduction in log₁₀ cfu from the initial inoculum (time 0)
^b below the limit of detection (5 log₁₀ cfu decrease)