

P1987 Activity of finafloxacin, ciprofloxacin, and imipenem against intracellular *Burkholderia thailandensis*, *Yersinia pseudotuberculosis*, and *Francisella philomirargia* in media at neutral or acidic pH

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Background: The bioterrorism agents *Burkholderia pseudomallei*, *Yersinia pestis*, and *Francisella tularensis* are all facultative intracellular organisms. In the laboratory, *B. thailandensis*, *Y. pseudotuberculosis*, and *F. philomirargia* can be used as their surrogates. The aim of this work was to compare the activity of the fluoroquinolone finafloxacin [more active at acid pH; in development for treatment of serious hospital infections] to that of ciprofloxacin and imipenem [both less active at acidic pH], in broth and in infected THP-1 monocytes and comparing neutral and acid acidic media.

Materials/methods: MICs were determined in MHB-CA at pH 7.4 and 5.5. For intracellular infection, human THP-1 monocytes were incubated with bacteria opsonized by human serum, after which non-phagocytosed bacteria were eliminated by incubation with gentamicin (10-100 X its MIC) during 1h. Infected cells were then incubated during 24h with antibiotics in culture media adjusted at pH 7.4 or 5.5. Maximal relative efficacy (Emax) and apparent static concentrations (Cs) were calculated using the Hill equation of concentration-response curves (AAC 2006;50:841-51). [¹⁴C]-labelled finafloxacin was used to measure its intracellular concentration.

Results: See Table. As expected, MIC of finafloxacin were 1-3 doubling dilutions lower while those of ciprofloxacin and imipenem were 2-4 and 4-7 doubling dilutions higher, respectively, at acidic pH compared to neutral pH. Intracellularly, finafloxacin Emax was at or lower than the limit of detection for all bacteria while ciprofloxacin achieved the same effect for *B. thailandensis* and *F. philomirargia* only. Imipenem was much less effective against all strains (Emax limited to 1.8 log CFU decrease). Cs were lower for cells incubated at acidic pH than at neutral pH for finafloxacin but higher for ciprofloxacin and imipenem. Finafloxacin accumulated 15-20 times in THP-1 cells when using medium adjusted to pH 5.5 but only 5 times at pH 7.4, rationalizing its increased intracellular potency in cells incubated at acidic pH.

Conclusions: This work highlights the interest of fluoroquinolones for markedly reducing the intracellular reservoirs of *B. thailandensis*, *Y. pseudotuberculosis*, and *F. philomirargia*, with finafloxacin showing additional advantage in acidic environments that are prevalent in infected tissues.

| Antibiotic | pH of the medium | strains | | | | | | | | |
|---------------|------------------|--|--|---------------------------|--|--|---------------------------|---------------------------------------|--|---------------------------|
| | | <i>B. thailandensis</i> ATCC 700388 | | | <i>Y. pseudotuberculosis</i> ATCC 29833 | | | <i>F. philomirargia</i> ATCC 25015 | | |
| | | broth MIC (mg/L) | intracellular Emax ^a (Δlog cfu) | Cs ^b (mg/L) | broth MIC (mg/L) | intracellular Emax ^a (Δlog cfu) | Cs ^b (mg/L) | broth MIC (mg/L) | intracellular Emax ^a (Δlog cfu) | Cs ^b (mg/L) |
| Finafloxacin | 7.4 | 4 | -5* | 1.6 | 0.25 | -5* | 0.15 | 0.06 | -4* | na ^c |
| | 5.5 | 1 | -5* | 0.7 | 0.12 | -5* | 0.03 | 0.008 | -4* | na ^c |
| Ciprofloxacin | 7.4 | 4 | -5* | 1 | 0.06 | -3.3 | 0.08 | 0.015 | -4* | na ^c |
| | 5.5 | 32 | -5* | 3.7 | 1 | -3.6 | 0.14 | 0.06 | -4* | na ^c |
| Imipenem | 7.4 | 0.5 | -1.7 | 0.7 | 0.25 | -0.8 | 1.9 | 0.25 | -1.8 | na ^c |
| | 5.5 | 8 | -1.5 | 2.2 | 8 | -0.9 | 2.1 | 32 | -0.1 | na ^c |

^aEmax: relative maximal efficacy: maximal decrease in inoculum (in log₁₀ units) compared to the post-phagocytosis inoculum as extrapolated for an infinitely large antibiotic concentration. When cfu counts fell below the lowest detection level within the range of extracellular drug concentrations investigated, Emax was not calculated but arbitrarily set at -5 (or -4 for intracellular *F. philomirargia*) and marked with an *.

^bCs: apparent static concentration i.e., the extracellular concentration (mg/L) resulting in no apparent bacterial growth (number of CFU identical to the initial [extracellular] or post-phagocytosis [intracellular] inoculum)

^cnot applicable because the intracellular inoculum at 24h is lower than the initial inoculum (static effect not reached)

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