References


Intracellular activity of trovafloxacin (CP-99,219) against *Enterococcus faecium*  
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Sir, *Enterococcus faecium*, a significant nosocomial pathogen, has developed resistance to multiple antibiotics, stimulating a search for new effective antimicrobials. The new quinolone trovafloxacin (CP-99,219) has good in-vitro activity against Gram-positive cocci, including *E. faecium*. As trovafloxacin is concentrated in phagocytes, we evaluated the intracellular activity of trovafloxacin inside human neutrophils (PMNs) against three vancomycin-susceptible (UWHC 2145, GE-1 and 758) and three vancomycin-resistant (SH-4, VREH-1 and E-1) strains of *E. faecium*.

Bacteria opsonized with autologous serum were phagocytosed by PMNs for 30 min; PMNs were then washed, suspended in Dulbecco's modified Eagle's medium with 10% fetal calf serum, and exposed to trovafloxacin at 0.25 × MIC or 4 × MIC. Initially and at 18 h, samples were withdrawn; PMNs were lysed in water and bacterial viability was determined. Controls without antibiotic or without PMNs were included.

Trovafloxacin at concentrations equal to 0.25 × MIC or 4 × MIC reduced the intracellular viability of all vancomycin-susceptible strains tested (Table). Declines in viability ranged from 0.33 log units at 0.25 × MIC to 0.95 log units at 4 × MIC. In contrast, trovafloxacin was unable to reduce the intracellular viability of vancomycin-resistant strains, with increases in viability ranging from 0.04 log units at 4 × MIC to 0.97 log units at 0.25 × MIC. Trovafloxacin had equal or greater activity in medium alone than intracellularly for almost all strains.

As trovafloxacin is concentrated intracellularly, with an intracellular:extracellular ratio of 8–15,3 we would have expected the intracellular levels to be above the MIC in the present experiments even when using extracellular concentrations of trovafloxacin equal to 0.25 × MIC. Despite this, at 4 × MIC, trovafloxacin had only moderate activity against intracellular vancomycin-resistant strains, and was unable to prevent growth of intracellular vancomycin-resistant strains. However, since we did not measure the intracellular concentrations of trovafloxacin inside PMNs, it is possible that features related to our assay system, such as the pH of the medium, could have resulted in a lower than expected intracellular concentration of trovafloxacin. Alternatively, the intracellular location of trovafloxacin may be different from that of phagocytosed bacteria. Our findings in this study, along with our earlier study using sparfloxacin,4 suggest a disparity between the intracellular concentration of these quinolones and their intracellular activity against *E. faecium*.

Interestingly, PMNs alone did inhibit the growth of the three vancomycin-susceptible strains significantly more than that of the three vancomycin-resistant strains (*P* < 0.001), similar to our earlier study examining RP59500 (quinupristin/dalfopristin) and sparfloxacin. The difference in intracellular killing by trovafloxacin can be attributed to the difference in killing by PMNs alone, as the additional bacterial killing due to intracellular antibiotic beyond that due to PMNs alone was almost the same for vancomycin-susceptible and vancomycin-resistant strains. The mechanism of this difference in PMN-mediated killing between vancomycin-susceptible and vancomycin-resistant strains has yet to be delineated.
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In conclusion, trovafloxacin has moderate activity inside PMNs against vancomycin-susceptible strains. As the peak serum levels of trovafloxacin following oral administration are about 3 mg/L, the concentrations used in this study, particularly for vancomycin-susceptible strains, are potentially clinically achievable. Trovafloxacin may be useful in treating infections due to *E. faecium*.

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References


Neonatal meningitis due to multi-resistant *Listeria monocytogenes*

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Sir,

*Listeria monocytogenes* can produce severe, life-threatening infections. Clinical manifestations of the disease include neonatal and perinatal listeriosis, and infections in adult immunocompromised patients as well as in normal hosts, with the CNS as the most frequent site involved. Treatment of severe listeriosis requires the combination of a cell-wall active antibiotic (ampicillin or vancomycin) and an aminoglycoside. Tetracycline, erythromycin, chloramphenicol and co-trimoxazole are possible replacements, especially when allergy to β-lactams is suspected. Most clinical isolates of *L. monocytogenes* are uniformly fully susceptible to the above antibiotics as well as to others active against Gram-positive bacteria. However, there are some recent reports of singly or multiply resistant *L. monocytogenes* isolates in France, Switzerland and the UK. We describe a case of late-onset neonatal meningitis due to a multi-resistant strain of *L. monocytogenes*.

In our laboratory we isolated a multi-resistant strain of *L. monocytogenes* from CSF of a neonate who developed meningitis 21 days after birth and was admitted to the neonatal intensive care unit of the hospital. Blood and superficial cultures showed no growth. The organism was...