

Bacteriostatic and Bactericidal Activities of Moxifloxacin against *Coxiella burnetii*

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The in vitro activity of moxifloxacin against *Coxiella burnetii* was compared to those of pefloxacin, ofloxacin, and doxycycline. MICs of moxifloxacin ranged from 0.5 to 1 µg/ml for the Nine Mile, Priscilla, and Q212 strains. Moxifloxacin was not bactericidal against *C. burnetii* at 4 µg/ml.

Coxiella burnetii, a strict intracellular bacterium, is the etiologic agent of Q fever (8). Q fever is a worldwide zoonosis and is endemic in virtually every country in the world except New Zealand (5). The incidence varies greatly between different geographical locations but seems to be highest in regions where there is medical interest in the disease. The disease is rare in northern Europe but is common in southern Europe, the United Kingdom, Canada, Japan, and Australia. In southern France, 5 to 8% of endocarditis cases are due to *C. burnetii*, and the prevalence of acute Q fever in southeast France is 50 per 100,000 inhabitants (16). In the United States, 20 to 60 Q fever cases are reported annually, but the true incidence may be greatly underestimated. The disease may present by acute manifestations, including a self-limited febrile illness, pneumonitis, or hepatitis. Chronic Q fever is typically an endocarditis. For acute Q fever, antibiotics with a bacteriostatic activity are sufficient in order to shorten the duration of the disease. Chronic Q fever is a severe disease which can relapse despite years of antibiotic treatment. In this case, bactericidal activity is required to eradicate *C. burnetii* infection. Tetracyclines remain the first-line antibiotics to treat acute Q fever. Fluoroquinolones are effective against *C. burnetii* in vitro (4, 6, 9, 12, 18) and have been used as an alternative to tetracyclines in vivo (8). Moxifloxacin is a new fluoroquinolone compound which is under investigation because of its improved intracellular pharmacokinetic properties and its good activity against both gram-positive and gram-negative bacteria (1). In this study we have evaluated the bacteriostatic and bactericidal activities of this new fluoroquinolone against three strains of *C. burnetii* as compared to the activities of pefloxacin, ofloxacin, and doxycycline.

The Nine Mile isolate, which is the reference isolate for acute infection was obtained from O. Baca (University of New Mexico, Albuquerque). The Priscilla (a goat isolate) and Q212 (a human isolate) strains, which are reference strains for chronic infection, were obtained from T. Hackstadt (Rocky Mountain Laboratory, Hamilton, Mont.). Strains were cultured in L929 murine fibroblast cells (12). The antibiotics used were moxifloxacin (Bayer AG, Leverkusen, Germany), oflox-

acin (Diamant, Puteaux, France), pefloxacin (Rhone Poulenc Rorer, Paris, France), and doxycycline (Pfizer, Neuilly, France). The bacteriostatic and bactericidal effects of antibiotics against *C. burnetii* were determined using previously described models (7, 12). Briefly, for the bacteriostatic effect, the activity of antibiotics was evaluated by their capacity to inhibit *C. burnetii* growth in shell vials as compared to a drug-free control leading to 50% infection of cell monolayers after 6 days of incubation of cultures. The bactericidal activity was assessed by a quantitative assay (7). L929 cells persistently infected with the Nine Mile and Q212 *C. burnetii* strains for 9 months were used for the quantitative bactericidal assay. Moxifloxacin was added to the culture medium at 4 µg/ml. Bactericidal activity corresponded to a significant reduction in bacterial titers (using Student's *t* test at the 95% confidence limit) after 24 h of antibiotic exposure as compared to the primary inoculum dose. All experiments were performed in duplicate and repeated to confirm results.

Moxifloxacin was not toxic during challenges for L929 and HEL cells at concentrations of up to 4 µg/ml, as determined by the trypan blue dye exclusion test (7, 12). Results for the MICs in the two independent experiments were the same. Moxifloxacin was bacteriostatic against *C. burnetii*, and complete growth inhibition was obtained at concentrations of 0.5 µg/ml for the Nine Mile and Priscilla strains and 1 µg/ml for the Q212 strain (Table 1). No bactericidal activity was demonstrated with 4 µg of moxifloxacin per ml in this assay; i.e., no significant differences in bacterial titers between untreated controls and cultures receiving 4 µg of moxifloxacin per ml for 24 h were noted.

Moxifloxacin represents a potential therapy for community-acquired respiratory tract infections (8). Moxifloxacin is a new fluoroquinolone compound which has been reported to be more effective than ofloxacin and ciprofloxacin against a wide range of pathogens, including *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* (2, 3, 13–15). The intracellular pharmacokinetic properties of moxifloxacin are improved compared to those of the oldest fluoroquinolone compounds (10). In animal models, the toxicity of moxifloxacin is comparable to that of the less toxic fluoroquinolones (17). Moxifloxacin appears to have a lower propensity than other fluoroquinolones for causing phototoxicity, hepatitis, and central nervous system excitatory effects in humans. The most common adverse effects are gastrointestinal disturbances (1). The aim of the present study was to

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TABLE 1. MICs of moxifloxacin, pefloxacin, ofloxacin, and doxycycline against *C. burnetii*

Strain	MIC ($\mu\text{g/ml}$)			
	Moxifloxacin	Ofloxacin	Pefloxacin	Doxycycline
Nine Mile	0.5	1	1	1
Priscilla	0.5	1	1	1
Q212	1	2	2	2

assess the in vitro antibiotic activity of this new, promising compound against *C. burnetii*, which is also an etiologic agent of community-acquired respiratory tract infections. Moxifloxacin was 2 times more active than pefloxacin and ofloxacin but was as effective as other fluoroquinolone compounds such as levofloxacin (9). Fluoroquinolones have been used successfully to treat patients suffering from acute Q fever (8). In contrast, in the case of chronic Q fever, a bacteriostatic regimen is not curative (8). We have found in this study that moxifloxacin was not bactericidal against *C. burnetii* at a concentration of 4 $\mu\text{g/ml}$, which is in accordance with previous reports for other fluoroquinolones (7). Recently we have demonstrated that a combination of doxycycline and the lysosomotropic agent chloroquine was bactericidal against *C. burnetii* (7, 11).

In conclusion, our results indicate that moxifloxacin possesses promising in vitro activities against *C. burnetii* and may be a safe alternative to tetracyclines in cases of acute Q fever and that clinical trials are warranted. This enlarges the spectrum of activity of this compound for the empirical treatment of atypical pneumonia. Conversely, the absence of bactericidal activity of this compound against *C. burnetii* does not substantiate a therapeutic benefit in using this drug to treat patients with chronic Q fever.

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