Reply to: Efficacy and pharmacodynamics of simulated human-like treatment with levofloxacin on experimental pneumonia induced with penicillin-resistant pneumococci with various susceptibilities to fluoroquinolones

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Sir,

Croisier et al.,1 described an experimental model of pneumococcal pneumonia in the rabbit caused by penicillin-resistant Streptococcus pneumoniae with different susceptibilities to fluoroquinolones. In this model, levofloxacin, at a dose that simulated human treatment with 500 mg twice a day, was effective against strains with levofloxacin MIC < 1.5 mg/L, but ineffective against strains with MIC ≥ 2 mg/L (strains with parC and parC+gyrA mutations).

This interesting and elaborate study raises several issues that may cast doubt on the relevance of its findings to the clinical situation: the animal model employed (rabbit) has not been used traditionally, or validated, for the study of experimental pneumococcal pneumonia, except by the same group.2 Indeed, the high bacterial inoculum used (10^10 cfu/mL), whereas certainly facilitating the emergence of resistant mutants, is far higher than inocula used for other experimental infection models of S. pneumoniae (10^6–10^8 cfu/mL)3-5 and raises the possibility of a toxic effect by the bacteria on the host.

The bacterial inoculum was introduced into the bronchus (presumably of one lung), and not into the trachea (as the authors state), yet the infection was present in both lungs, suggesting a spillover from one lung to the other, enhanced by the large bacterial inoculum. No pulmonary bacterial counts were performed early following the introduction of the inoculum (in treated and control animals), just before therapy was started, thus the ‘starting point’ for evaluating the antibiotic efficacy is unknown. No bacterial counts were performed during therapy at fixed intervals to evaluate the early effect of antibiotic therapy and to define the time at which resistant mutants were induced. The observation that levofloxacin did not reduce the bacterial count of susceptible strains in the spleen, compared with untreated animals, needs to be explained, as it casts doubt on the validity of the experimental design; that is, eradication of levofloxacin-susceptible strains would have served as a positive control in the experiment, a control that is lacking. It is unclear when the last lung samples were obtained for the qualitative cultures, at 48 h (immediately after the last dose), or ‘a few hours later’, or 24 h later. If the samples were obtained 24 h after therapy discontinuation, bacterial regrowth has certainly occurred, complicating the evaluation of the post-therapy bacterial count.

The authors designed the plasma kinetics of levofloxacin in the rabbit to be similar to that in humans, yet the protein binding of levofloxacin to rabbit proteins may not be identical to that of humans (as is the case with cefotaxime).6 As only the protein-unbound fraction of an agent is antibacterially active, a possible difference in protein binding should be included in the calculation. It is not explained why the authors chose 48 h as the optimal duration of therapy. In previous studies evaluating amoxicillin in pneumococcal infection models, 72 h of therapy was chosen, yet in other models evaluating pneumococcal empyema in the rabbit, 96 h of therapy was chosen. The diffusion/penetration of levofloxacin into the lung in man and rabbit should be compared in order to establish that the rabbit is the appropriate pharmacodynamic model for the study of pneumococcal pneumonia.

In future animal studies, these issues should be examined in order to make animal infection models more relevant to the clinical settings.

References

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dynamics in four experimental pneumococcal infection models. *Antimicrobial Agents and Chemotherapy* 45, 1078–85.

