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Letters to the Editor

Mutant Prevention Concentration of Gemifloxacin for Clinical Isolates of *Streptococcus pneumoniae*

Fluoroquinolone resistance is beginning to appear among isolates of *Streptococcus pneumoniae* (4, 7, 8, 10). We have argued that resistance arises as a consequence of dosing that places tissue concentrations between the MIC and the mutant prevention concentration (MPC), a new measure of activity related to the MIC of the least susceptible, single-step mutant (15, 16). If this is true, MPC can be used to identify fluoroquinolones that are least likely to selectively enrich resistant subpopulations. We previously estimated MPC for several fluoroquinolones with about 100 clinical isolates of *S. pneumoniae* obtained from the Royal University Hospital, Saskatoon, Canada (2). We now add gemifloxacin to the list of compounds compared and increase the number of isolates tested to 146 for all of the compounds.

Table 1 lists MICs and MPCs for gemifloxacin, moxifloxacin, gatifloxacin, and levofloxacin determined as described previously (2) using the same set of isolates for each compound. Fluoroquinolone-resistant isolates were excluded. Gemifloxacin had the lowest modal MPC (0.25 μg/ml), followed by moxifloxacin (0.5 μg/ml), gatifloxacin (1 μg/ml), and levofloxacin (2 μg/ml). The same rank order was observed when MPC was determined for 90% of the isolates. These data are consistent with gemifloxacin having more activity than the other compounds against resistant mutants (9, 14). When the MIC at which 90% of the susceptible isolates are inhibited (MIC_{90}) was determined, gemifloxacin was also more active than moxifloxacin, gatifloxacin, and levofloxacin in these comparisons by 2, 3, and 4 dilutions, respectively.

Since the effectiveness of an antibacterial agent is likely to be a function of both activity (MIC and MPC) and pathogen exposure (5, 11), comparision of compounds requires consideration of drug pharmacokinetics in human tissues. From published values of concentrations in serum, we calculated the time above MPC for each compound when dosed as recommended by the manufacturer. Moxifloxacin is expected to have a concentration in serum above the MPC at which 90% of the isolates tested are prevented (MPC_{90}) for 18 h. For gemifloxacin, gatifloxacin, and levofloxacin, those times are 4, 1 to 2, and 0 h, respectively. This suggests that moxifloxacin may be the most effective at restricting the development of resistance, even though gemifloxacin has the lowest MIC and MPC.

Table 1 also lists values of the area under the concentration-time curve from 0 to 24 h/MIC and the maximum concentration of drug in serum (C_{max})/MIC for recommended doses. For both parameters gemifloxacin exhibits higher values than moxifloxacin. If these two parameters are inversely related to the selection of resistant mutants (1, 6, 13), resistance should develop less often from treatment with gemifloxacin than with moxifloxacin. But time above MPC (Table 1) and low-concentration cycling (12) predict the opposite outcome. A clinical comparison of these two compounds may help distinguish between MPC-based ideas (15) and empirical pharmacodynamics (6, 13) for predicting the development of resistance. Such a comparison is important because neither method can be easily tested: MPC is an in vitro measure that does not take into account compartments in patients where drug concentrations and bacterial growth properties are poorly defined, and pharmacodynamic methods require examining very large numbers of patients to identify the point at which the overall prevalence of resistance does not increase.

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TABLE 1. Fluoroquinolone activity with clinical isolates of *S. pneumoniae*[a]

Compound	MIC_{90}	MPC_{50}[b]	MPC_{90}[b]	C_{max}	Half-life (h)	Time > MPC_{50}[b,c]	Time > MPC_{90}[b,c]	AUC_{0-24}/MIC_{90}[c]	C_{max}/MIC_{90}[c]
Gemifloxacin	0.03–0.063	0.25	1	1.6	7–8	14	4	140–280	27–53
Moxifloxacin	0.25	0.5	2	4.5	12–14	24	18	190	18
Gatifloxacin	0.5	1	4	4.2	8–10	12	1–2	103	8.4
Levofloxacin	1	2	8	5.7	5–7	9	0	48	5.7

[a] Of the 146 isolates tested, 43 were nonsusceptible to penicillin. Fluoroquinolone susceptibility was unaffected by loss of susceptibility to penicillin. Test cultures, growing in liquid medium, were prepared from bacterial lawns grown directly from frozen samples (2). All concentrations in the table are in milligrams per liter, and times are in hours. (Some of these data were previously reported [2].)

[b] Data taken as MPC were designated provisional in previous work (MPC_{pr}) because a twofold overestimate arises from the high inoculum used ($>10^{10}$ cells per plate). MPC_{pr} is a conservative estimate of MPC.

[c] Pharmacokinetic parameters were calculated by using total drug concentration. C_{max} applies to doses recommended by the manufacturer (listed in reference 3). AUC_{0-24}, area under the concentration-tin curve from 0 to 24 h.

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Glen T. Hansen
Kelli Metzler
Department of Microbiology and Immunology
University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Karl Drlica
Public Health Research Institute
Newark, NJ 07193

Joseph M. Blondeau*
Department of Clinical Microbiology
Royal University Hospital
103 Hospital Dr.
Saskatoon, Saskatchewan, Canada S7N OW8

*Phone (306) 655-6943
Fax: (306) 655-6947
E-mail: blondeauj@sdh.sk.ca