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Low Correlation between MIC and Mutant Prevention Concentration

Soon after the term mutant prevention concentration (MPC) was coined to define the MIC of the least susceptible mutant subpopulation of a microbial culture (2), we noticed that MPCs and MICs correlated poorly ($r^2 = 0.39$) for a set of closely related fluoroquinolones when determined with *Mycobacterium smegmatis* (9). Subsequently, isolated examples were described in which correlation was low for a variety of fluoroquinolones with strains of *Escherichia coli*, *Salmonella enterica*, and *Staphylococcus aureus* (5, 8, 10), and a set of 20 clinical isolates of *E. coli* showed a low correlation ($r^2 = 0.58$) for ciprofloxacin (6). To determine whether a low correlation between MICs and MPCs is likely to be a general phenomenon, we calculated the correlation coefficients for several quinolones with five bacterial species and for three macrolides with *Streptococcus pneumoniae* using data from published and unpublished studies of clinical isolates. As shown in Table 1, r^2, determined by linear regression, was below 0.5 for fluoroquinolones with *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *S. aureus*, and *S. pneumoniae* (an exception was levofloxacin with *K. pneumoniae* [$r^2 = 0.7$]). Values of r^2 were slightly above 0.5 for three macrolides with *S. pneumoniae* (Table 1).

TABLE 1. Relationship between MICs and MPCs

Bacterial species	Compound tested	r^2 for MPC/MIC	No. of isolates	Reference
E. coli	Garenoxacin	0.26	44	J. Blondeau, unpublished
	Gatifloxacin	0.03	44	J. Blondeau, unpublished
	Gemifloxacin	0.10	44	J. Blondeau, unpublished
	Levofloxacin	0.02	43	J. Blondeau, unpublished
	Moxifloxacin	0.03	40	J. Blondeau, unpublished
K. pneumoniae	Garenoxacin	0.09	39	J. Blondeau, unpublished
	Gatifloxacin	0.34	40	J. Blondeau, unpublished
	Gemifloxacin	0.15	39	J. Blondeau, unpublished
	Levofloxacin	0.70	41	J. Blondeau, unpublished
	Moxifloxacin	0.18	40	J. Blondeau, unpublished
P. aeruginosa	Ciprofloxacin	0.41	151	J. Blondeau, unpublished
	Levofloxacin	0.43	151	J. Blondeau, unpublished
S. aureus	Ciprofloxacin	0.11	21	11
	Garenoxacin	0.30	21	11
	Garenoxacin	0.08	82	7
	Gatifloxacin	0.04	218	7
	Gemifloxacin	0.05	218	7
	Levofloxacin	0.18	220	7
	Moxifloxacin	0.08	219	7
S. pneumoniae	Garenoxacin	0.31	524	J. Blondeau, unpublished
	Gatifloxacin	0.28	516	3
	Gemifloxacin	0.29	495	3
	Levofloxacin	0.44	528	3
	Moxifloxacin	0.17	523	3
	Azithromycin	0.58	499	J. Blondeau, unpublished
	Erythromycin	0.67	293	J. Blondeau, unpublished
	Clarithromycin	0.67	278	J. Blondeau, unpublished

Low correlations between MICs and MPCs with clinical isolates are likely to require a complex explanation. These isolates probably contain mutant subpopulations that vary considerably in relative abundance and drug susceptibility, which will contribute to a wide variation in MICs when the mutants are abundant enough to be scored. The isolates may also contain many different multistep mutants (1) which may or may not represent the least susceptible subpopulations that determine MPCs. Added complexity derives from some resistance mutations having a much larger effect on MPCs than on MICs (4). Indeed, isolates with the same MIC were found to have values of MPC that ranged over 5 twofold dilutions.

A consequence of a low correlation between MICs and MPCs is that MPCs cannot be estimated accurately from MICs on an individual patient basis. Thus, using antimutant strategies for individual patients will require measurement of the MPC. Likewise, empirical estimates of antimutant activity that are keyed to MIC-based pharmacokinetic-pharmacodynamic indices, such as area under the concentration-time curve at 24 h/MIC, will tend to exhibit more patient-to-patient variability than indices using MPCs.

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