Impact of AUC/MIC ratios on the pharmacodynamics of the des-F(6) quinolone garenoxacin (BMS-284756) is similar to other fluoroquinolones

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Sir,

Garenoxacin (BMS-284756) is a new des-F(6) quinolone that exhibits enhanced potency against Streptococcus pneumoniae compared with clinically available fluoroquinolones.1 Although this antibiotic lacks the C-6 fluorine, its antibacterial mechanism of action against DNA gyrase appears to be the same as that of other quinolones.2 It is well established that the AUC/MIC ratio is an important pharmacodynamic parameter influencing quinolone efficacy, and AUC/MIC ratios of ∼30 or higher have been shown to be sufficient to eradicate S. pneumoniae from in vitro pharmacodynamic models (IVPM).3 4 A similar minimum target has been reported for the eradication of S. pneumoniae from community-acquired respiratory tract infections.5 This study was designed to evaluate the impact of AUC/MIC ratios on the pharmacodynamics of garenoxacin.

Three isolates of S. pneumoniae were selected for this study. Susceptibility tests with levofloxacin and garenoxacin against these three isolates were carried out by macrobroth dilution methodology with THB as the test medium, since it was the medium used for the pharmacodynamic studies. In addition, MICs were determined using 0.2 mg/L increments to more accurately define AUC/MIC ratios. The MICs of garenoxacin for the S. pneumoniae isolates were 0.2 mg/L for S. pneumoniae 315, 1.4 mg/L for S. pneumoniae 316 and 3.0 mg/L for S. pneumoniae 317. The MICs of levofloxacin for S. pneumoniae were 2 mg/L for S. pneumoniae 315 and 32 mg/L for S. pneumoniae 316 and 317. Nucleotide sequence analysis of the quinolone resistance-determining regions of S. pneumoniae 316 and 317 demonstrated that these resistant strains had mutations within the genes for both DNA gyrase and topoisomerase IV.

Pharmacodynamic studies were carried out in THB at 37°C in ambient air using a previously described two-compartment IVPM.3 4 Logarithmic-phase cultures (5 × 107 cfu/mL) were introduced into the peripheral compartment of the IVPM and were exposed to the peak concentrations of garenoxacin that were approximately two- to three-fold above the MIC (0.6 or 6 mg/L). Garenoxacin was also dosed at the same concentrations at 24 h. Since garenoxacin and other fluoroquinolones kill bacteria in a concentration–dependent manner, AUC/MIC ratios were varied by altering rates of elimination rather than peak concentrations. Therefore, any differences in pharmacodynamic killing could be related to differences in AUC/MIC ratios and the time concentrations remained above the MIC, not peak/MIC ratios. Elimination half-lives of 3, 5, 8 and 12 h were simulated to provide AUC/MIC ratios of ∼15, 20, 30 and 39 for S. pneumoniae 315 (Figure 1a), and 16, 23, 33 and 50 for S. pneumoniae 316 (Figure 1b). Elimination half-lives of 3, 6, 12 and 24 h were simulated to provide AUC/MIC ratios of ∼9, 18, 27 and 36 for S. pneumoniae 317 (Figure 1c).

The low range of peak/MIC ratios (2:1 to 3:1) was selected because investigators have reported that the AUC/MIC ratio is most closely linked to treatment outcome when the peak/MIC ratios are <10:1.6 If larger peak/MIC ratios had been used, the impact of varying AUC/MIC ratios may have been obscured.

To evaluate pharmacodynamic interactions after drug exposure, samples were removed from the peripheral compartment of the IVPM at 0, 2, 4, 8, 24 and 30 h, and viable bacterial counts were measured by plating serial 10-fold dilutions of each sample into Todd–Hewitt agar (BBL) and incubating plates overnight at 37°C in 5% CO2. The lowest dilution plated was 0.1 mL of undiluted sample from the peripheral compartment. Therefore, the lowest level of detection was 1 colony per plate or 10 cfu/mL. Antibiotic carryover was prevented by first incubating samples taken from the IVPM with antibiotic-removal beads (Amberlite XAD-4; Sigma Chemical Co., St Louis, MO, USA) for 15 min. To evaluate the selection of mutants exhibiting decreased susceptibility to garenoxacin, 30 h samples were also plated into Todd–Hewitt agar containing garenoxacin at a concentration four-fold above the MIC.

Drug-free control cultures grew to a maximum of 3–7 × 108 cfu/mL by 8–12 h, and viable counts remained steady throughout the remainder of the 30 h experimental period (data not shown). With each individual strain of S. pneumoniae in this study, targeting similar peak/MIC ratios resulted in comparable initial rates of killing through 8 h (Figure 1). However, after 8 h the impact of varying AUC/MIC ratios
Figure 1. Pharmacodynamics of garenoxacin against \textit{S. pneumoniae} 315 (a), \textit{S. pneumoniae} 316 (b) and \textit{S. pneumoniae} 317 (c). Each datum point represents the number of viable bacteria (log$_{10}$ cfu/mL) for a single experiment, and numbers to the right of data lines represent the actual AUC/MIC ratios the \textit{S. pneumoniae} were exposed to in each experiment.
was evident. When AUC/MIC ratios were at least 29–32, bacterial killing continued after 8 h and bacterial eradication (viable counts decreasing below the 10 cfu/mL limit of detection) was achieved within the first 24 h dose interval for *S. pneumoniae* 317 (Figure 1c) and within 24–30 h for the other two strains (Figure 1a and b). In contrast, when AUC/MIC ratios were 23 or lower, eradication was not observed and in many experiments substantial inoculum regrowth occurred between 8 and 24 h (Figure 1). In some cultures, viable counts at 30 h exceeded the level of the initial inoculum; however, since no colonies were observed on drug selection plates, this inoculum regrowth was not caused by the selection of mutant populations. The lack of emergence of mutant subpopulations was of interest, especially since cultures were only exposed to peak antibiotic levels that were two- to three-fold above the MIC. A similar lack of emergence of resistance was reported from recent studies with gatifloxacin and levofloxacin,4 and these observations highlight the low propensity for pneumococci to mutate to quinolone resistance compared with staphylococci and some Gram-negative bacteria.

The data obtained from this study suggest that the pharmacodynamics of garenoxacin are similar to those of other fluoroquinolones3,4 in that AUC/MIC ratios of ∼30 or higher are sufficient to achieve eradication of *S. pneumoniae* from IVPM. Furthermore, the initial susceptibility of the challenge organism does not appear to influence the general pharmacodynamics of this drug. The conclusions reached from these IVPM studies support those being reported from clinical evaluations of other fluoroquinolones. In a study of levofloxacin and gatifloxacin for the treatment of community-acquired respiratory tract infections, Ambrose et al.5 reported that the probability of microbiological cure was 100% in patients where the AUC24/MIC was ∼34 or higher.

These studies were designed to specifically evaluate the impact of changing AUC/MIC ratios independently of the influence of peak/MIC ratios. However, it was not possible to separate ∼MIC from the AUC/MIC unless simulating constant static infusions, which would have required variations in peak/MIC ratios to achieve the desired range of AUC/MIC ratios. Although ∼MIC does not appear to play the most prominent role in the pharmacodynamics of fluoroquinolones from a statistical standpoint, one cannot ignore its influence. Similar to studies with gatifloxacin,4 eradication of the *S. pneumoniae* from the IVPM required that garenoxacin concentrations remain above the MIC for >8 h of the 24 h dose interval. However, since there were limited data for ∼MIC between 8 and 14 h, more specific conclusions could not be reached.

In summary, data from these studies suggest that in addition to sharing a similar mechanism of action to clinically available fluoroquinolones, garenoxacin also exhibits very similar pharmacodynamic characteristics. AUC/MIC ratios of ∼30 or higher were sufficient to achieve eradication of *S. pneumoniae* from an IVPM, and the impact of AUC/MIC ratios on pharmacodynamics was not affected by differing levels of susceptibility. Studies evaluating the impact of higher peak/MIC ratios (>10:1) on the relationship between AUC/MIC ratios and eradication would be beneficial to better delineate the linked importance of each of these two pharmacodynamic parameters in treating pneumococcal infections.

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**References**


