Gastrointestinal Bacteria Will Have Its Way

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(See the major article by de Lastours et al, on pages 1399–406.)

Louis Weinstein, the late renowned infectious diseases physician, has often been quoted (perhaps apocryphally) as stating, “We know everything we need to know about antibiotics except how much to give and how long to give them.” Since the era of that quote (roughly the 1980s), the world has changed considerably. The science of pharmacokinetics-pharmacodynamics has matured to the point that we can state with reasonable certainty how much of an antibiotic (whose pharmacokinetics are established) we need to deliver, by what route, to treat an infection of a particular body site, caused by a specific bacterial strain with a known minimum inhibitory concentration (MIC). We are familiar with terms such as “concentration-dependent killers” and “time-dependent killers.” Sophisticated computer programs can then take these data (generally derived from animal experiments) and combine them with ranges of achieved concentrations in humans to determine the likelihood that pharmacodynamic targets will be achieved with proposed dose regimens. It is, therefore, fair to say that pharmacokinetic-pharmacodynamic analysis has become essential for modern drug development and is becoming an increasingly visible component of day-to-day medical practice.

Pharmacokinetic-pharmacodynamic analysis has also been suggested as an appropriate framework for designing strategies whereby our use of antibiotics can minimize the risk of emergence of antimicrobial resistance [1]. The rationale underlying such strategies is simple and compelling: Assuming a majority susceptible population at an infection site (one that might contain within it a small minority of bacteria that have single, resistance-conferring mutations) and assuming that any single mutation can raise the MIC only by a limited amount, devising a therapeutic regimen that maintains the antibiotic concentration (the mutant prevention concentration [MPC]) in excess of the first-order mutant MIC will suppress the growth of these first-order mutants during therapy. The idea of “suppressing” the emergence of resistant strains has a rich tradition in the treatment of infectious diseases, generally involving addition of second agents with different mechanisms of action. Our successful treatment strategies for tuberculosis and human immunodeficiency virus infection both rely on the suppression of mutant strains by addition of mechanistically diverse antimicrobial agents.

Of course, not all resistance is mutational, and not all mutational resistance is incremental, so dosage-based strategies are applicable to only a subset of antibiotics. For example, the increment in ampicillin resistance associated with the acquisition of β-lactamase-producing plasmids can be several orders of magnitude, far exceeding achievable serum concentrations of β-lactam antibiotics, even at their peak [2]. Resistance to rifampin in many species is conferred by a single amino acid change in the bacterial RNA polymerase, which can also increase the MIC by orders of magnitude [3].

For some antimicrobial classes, such as the fluoroquinolones, known emergence of resistance is always incremental. Single-point mutations of topoisomerase genes, activation of efflux pumps, or acquisition of plasmid-mediated mechanisms of fluoroquinolone resistance rarely result, by themselves, in levels of resistance exceeding concentrations achievable by appropriate dosing [4]. It is, therefore, not surprising that most work done to validate pharmacodynamic suppression of resistance has employed fluoroquinolones to make the case.

In 2009, Fantin et al [5] published a study in The Journal of Infectious Diseases in which they administered doses of ciprofloxacin to healthy volunteers for 14 days. They sampled saliva and feces in these subjects over a 42-day period for the presence of levofloxacin-resistant viridans streptococci (saliva) and nalidixic acid– or ciprofloxacin-resistant Escherichia coli (feces). They were able to demonstrate the emergence of resistance at both locations. Resistance to levofloxacin emerged in streptococci...
during the course of treatment, which the investigators attributed to the fact that ciprofloxacin concentrations that would be inhibitory for first-order mutants were never achieved in the saliva during the dosing interval. In contrast, newly identified nalidixic acid-resistant E. coli strains emerged in the feces only after the course of treatment, which the investigators attributed to the fact that very high levels (above the MPC for susceptible E. coli) of ciprofloxacin were maintained in the feces during the treatment course. Treatment courses end, however, and it is predictable that the time between the end of treatment (when fecal ciprofloxacin concentrations are very high) and the day 42 sampling time (when fecal ciprofloxacin concentrations are negligible) will include a first-step means. If time (when fecal ciprofloxacin concentrations are very high) and the day 42 sampling time (when fecal ciprofloxacin concentrations are negligible) will include a period of time when fecal concentrations of ciprofloxacin are detectable but below those required to suppress first-step mutants. If first-order mutants emerge within or find their way into the gastrointestinal tract, they will probably proliferate during this period.

Although the authors’ pharmacodynamic explanations regarding the emergence of resistance are plausible up to a point, it is fair to ask how some highly resistant E. coli strains survived throughout the course of therapy if fecal concentrations of ciprofloxacin were, as reported >1000 µg/mL, whereas the MICs of the resistant strains were 32 and 64 µg/mL. As the fluoroquinolones are among our most bactericidal antibiotics, it is unclear, to me at least, how those strains persisted under such conditions. It is possible that the activity of ciprofloxacin differs between feces and broth cultures, and that the effective ciprofloxacin concentrations in the feces were somewhere between what was required to suppress the highly resistant strains and what was required to suppress the first order mutants.

In this issue of The Journal, de Lastours et al describe the dynamics of emergence of quinolone resistance in the E. coli strains identified in the study by Fantin et al. After analyzing the genotypes and resistance mechanisms in the strains that emerged resistant, they concluded, with a reasonable degree of certainty, that this emergence of resistance was unlikely to have resulted from mutation to resistance in the susceptible E. coli population present at day 0 of therapy but rather resulted from the acquisition of resistant strains. In support of this conclusion were 2 compelling pieces of data. First, the resistant strains were of genotypes distinct from those identified in the initial flora. Second, 70% of the resistant strains were also resistant to other classes of antibiotics, phenotypes that were absent from the E. coli isolated on day 0. Resistance in all cases was associated with typical mutations in the gyrA and/or parC genes.

de Lastours and colleagues provide compelling evidence that in most cases the emergence of fluoroquinolone resistance in E. coli found within the gastrointestinal tract during and immediately after courses of therapy probably results from the acquisition of resistant strains. Under these circumstances, MPC-based strategies are unlikely to be effective, because the concentrations of antimicrobial agent would need to suppress both first-order mutants and highly resistant strains (which are increasingly common in the environment). Because the study by Fantin et al [5] suggested that resistant strains cannot be eliminated from the gastrointestinal tract, even when concentrations 10-fold higher than the MIC are achieved, it is not unreasonable to conclude that resistance suppression in the gastrointestinal tract is unachievable, for fluoroquinolones at least.

These 2 important articles do not imply that pharmacodynamic strategies have no place in our efforts to reduce antimicrobial resistance in our hospitals. They are more a note of caution that our knowledge of the pharmacodynamics of antibiotics in the human body is still limited and that if we really want to understand the full impact of antimicrobial administration, we need to acquire data that will allow us to predict outcomes in all body compartments.

For bacteria that colonize the human gastrointestinal tract, giving more of an antibiotic will never prevent resistance; it will only promote it. Therapeutic regimens should most of all acknowledge this fact and focus on finding reliable ways to minimize the overall exposure to antibiotics in the first place, whether by not administering them to patients who don’t need them, by administering single agents instead of multiple agents and, most of all, by discontinuing therapy as soon as infections are successfully treated.

Notes

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References