Preventing the risk of emergence of bacterial resistance associated with antibiotic therapy: what role for pharmacokinetic and pharmacodynamic data?


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Sir,

Although convergent findings from preclinical and clinical studies suggest that pharmacokinetics (PK) and pharmacodynamics (PD) might play an important part in the emergence of antibiotic-resistant bacterial strains, the potential value of PK/PD data in the assessment of new antibiotic drugs has been largely overlooked.

Instead, PK/PD data are too often given a unique role—the theoretical basis and justification for clinical trials—and their importance in the evaluation of risk of in vivo selection of resistant strains remains an unresolved issue.

Some observations made in vitro could indicate a possible line of research in the field. Carsenti-Etesse et al.1 reported that, after serial passages of clinical strains of Streptococcus pyogenes in subinhibitory concentrations of antibiotics, final erythromycin MICs reached intermediate and resistant levels. These results, together with the demonstration by clinical studies that prior exposure to macrolides may facilitate the emergence of drug-resistant strains of streptococci, raise the question as to whether macrolides with a short or long half-life have different selection potentials.

This seems to be confirmed by a clinical trial published by Guggenbichler & Kastner.2 These authors reported very different results in terms of resistant-strain carriage after using the short half-life (5 h) antibiotic clarithromycin compared with the long half-life (48 h) azithromycin. In children treated for upper respiratory tract infection, the proportion of children with resistant strains 1 week after starting therapy was similar (70%) in those treated with azithromycin 10 mg/kg once daily over 3 days and those treated for 7 days with clarithromycin 7.5 mg/kg twice daily. However, at 6 weeks, the proportion fell to 10% in the clarithromycin group and rose to 90% in the azithromycin group. The bacteria involved were Streptococcus pneumoniae, S. pyogenes, Haemophilus influenzae and Moraxella catarrhalis, and also commensals of the oral cavity such as Streptococcus viridans, Streptococcus salivarius, etc.

In their trial assessing a single dose of azithromycin 20 mg/kg in the treatment of trachoma in an Aboriginal community, Leach et al.3 studied in parallel changes over time in pharyngeal carriage of S. pneumoniae, S. pyogenes and H. influenzae. At baseline, 54% of children were colonized by S. pneumoniae and 1% of strains were azithromycin resistant. Three weeks later, 11 children were still colonization, but 50% of strains were resistant. Those strains eventually disappeared, but not in less than 6 months. Although the study was not comparative, its results also raised the issue of long periods of exposure to subinhibitory concentrations of antibiotics as a factor of selection and/or persistence of resistant mutants. Neither the clinical impact of this carriage of resistant bacteria nor the transmission potential of such bacteria has yet been determined.

The AUC/MIC ratio is a recognized predictor of antibacterial efficacy. This ratio can also be used to determine the risk of selection of resistant bacteria if the AUC0–24 is taken into account.4 Indeed, very different AUC patterns may yield similar AUC/MIC ratios, and it would appear that the risk of selection is lower if the height of the AUC is equal to its width, the higher risk being associated with AUCs exhibiting a protracted time dimension. This could have important implications for the definition of optimal dosing.

Defining appropriate dosing and administration regimens of antibiotics is a difficult task, and much remains to be learned about the many parameters involved in the antibacterial activity of these drugs. Some factors promoting bacterial resistance could be as yet unidentified, or at least insufficiently taken into account, such as the PK/PD characteristics of antibiotics.

In particular, convergent data suggest that subinhibitory concentrations of azithromycin or other long half-life antibiotics may induce, in vitro and in vivo, the emergence of resistant mutants among both the commensal and pathogen flora.

The kinetics of the disappearance of these mutants and their clinical and epidemiological implications remain to be determined.
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References


