Bactericidal Activities of Ceftizoxime and Cefotaxime against Streptococcus pneumoniae

Patel et al. (4) compared the serum bactericidal titers (SBTs) and the time serum drug concentrations remained above the MICs ($T > MIC$) of ceftizoxime and cefotaxime against three intermediately penicillin-resistant Streptococcus pneumoniae isolates. MICs were $\leq 1.0 \ \mu g/ml$, SBTs were $> 1:2$, and $T > MIC$ exceeded 50% of dosage intervals. They concluded that ceftizoxime’s longer $T > MIC$ compensates for its lower microbiologic activity, that both agents should produce comparable clinical outcomes in the treatment of infections caused by intermediately penicillin-resistant S. pneumoniae, and that the two agents can be viewed as being therapeutically similar. While we do not dispute the accuracy of the data, some conclusions are not justified based on the information presented. Furthermore, Patel et al. (4) do not address other clinical and laboratory implications regarding the choice of a cephalosporin for hospital formularies.

Even though $T > MIC$ is important for predicting bactericidal activities and clinical success of cephalosporins, achievable concentrations in serum are also quite relevant when MICs approach or exceed such concentrations. Maximum concentrations of cefotaxime and ceftizoxime after a 1-g dose were 53.9 ± 11.2 and 56 ± 9.1 µg/ml, respectively, in Patel et al.’s study (4). In our study of 66 penicillin-resistant or intermediately resistant S. pneumoniae isolates (6), the ceftizoxime MICs were $\geq 64 \ \mu g/ml$ for 5 isolates. Haas et al. (1) reported ceftizoxime MICs of $\geq 256 \ \mu g/ml$ for some intermediately penicillin-resistant S. pneumoniae isolates versus a maximum cefotaxime MIC of 4 µg/ml. These findings, and those of others (2), indicate that the microbiologic activity of ceftizoxime can be 32-fold less than that of cefotaxime. It is unrealistic to expect uniformly favorable outcomes for infections treated with a drug when MICs exceed peak concentration ($T > MIC = 0$). Stratton et al. (5) concluded that an infection with an S. pneumoniae isolate for which the cefotaxime or ceftizoxime MIC was 0.5 to 1.0 µg/ml should respond to treatment with either agent. However, like Patel et al. (4), they provided data for organisms with minimal resistance and made no claims regarding organisms which required higher MICs. To our knowledge, no clinical trials using ceftizoxime against microbiologically documented invasive S. pneumoniae infections have been performed since the widespread dissemination of beta-lactam resistance of the past few years.

Among 121 S. pneumoniae isolates tested at the University of Alabama Hospital in 1997, 71 (55%) were susceptible, 36 (30%) were intermediately resistant, and 22 (17%) were resistant to penicillin. These numbers reflect an ever-increasing shift towards higher MICs of penicillin and other beta-lactams which is being experienced elsewhere. It is impossible to predict on a clinical basis which infections will be due to a resistant organism or what the cephalosporin MICs will be for intermediately penicillin-resistant or resistant isolates. This clinical uncertainty coupled with the fact that in many instances there may be no organisms isolated to test for susceptibility dictate that empiric treatment cover all possibilities.

Patel et al. (4) stated that S. pneumoniae has intermediate to high-level resistance to cefotaxime, ceftriaxone, and ceftizoxime as delineated by MIC breakpoints in a National Committee for Clinical Laboratory Standards (NCCLS) document (3). Although the NCCLS provides interpretive breakpoints for cefotaxime and ceftriaxone, none are published for ceftizoxime and this agent is not recommended for in vitro susceptibility testing against S. pneumoniae. This omission can be problematic for laboratories asked to provide susceptibility data for ceftizoxime. Although many laboratories use the Etest (AB Biodisk, Solna, Sweden) to determine the MICs of penicillin and cefotaxime or ceftriaxone, ceftizoxime is not available in appropriate concentrations for use against S. pneumoniae.

For the reasons stated above, we have not considered ceftizoxime for formulary inclusion with therapeutic equivalency to cefotaxime or ceftriaxone.

REFERENCES


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Author’s Reply

Unfortunately, the comments by Waites and Rivers represent the common mistake of predicting clinical responses solely based on a comparison of the microbiological activity (i.e., MIC) of one antibiotic versus that of another against a specific bacterium. An accurate prediction can occur only if one performs a pharmacodynamic analysis comparing the microbiological activity, pharmacokinetics, and mode of bacterial killing of one agent versus those of another and then correlates this information with the results of animal models of sepsis and volunteer studies and clinical outcome information.

Interestingly, these authors quote the data by Haas et al. (1) reporting higher MICs of ceftizoxime compared with those of cefotaxime against penicillin-resistant Streptococcus pneumoniae, suggesting a difference in outcomes from this microbiological observation alone without any clinical information to support such a speculation. Moreover, they fail to mention that...
the Stratton et al. study they cite comes from the same laboratory as the Haas et al. study but that the authors of this later publication predict that the clinical response would be the same whether one uses cefotaxime or ceftizoxime in the treatment of intermediately penicillin-resistant *S. pneumoniae* infection (2).

Although it has been known for years that ceftizoxime typically exhibits higher MICs against penicillin-resistant *S. pneumoniae* compared with those of the other expanded-spectrum cephalosporins cefotaxime and ceftriaxone, there are no clinical outcome data available indicating that there is any difference in clinical outcomes in the management of *S. pneumoniae* infections (penicillin sensitive or resistant, bacteremic or non-bacteremic) whether one administers any one of these expanded-spectrum cephalosporins (3). In fact, there is even no difference if one uses penicillin, amoxicillin, amoxacillin, or a narrow-spectrum cephalosporin like cefazolin (4).

Poor outcomes in the management of penicillin-resistant *S. pneumoniae* have been reported only in meningeal infections, and most of these outcomes have occurred with the use of ceftiraxone (5). This is not surprising owing to the poor penetration of all beta-lactam antibiotics into cerebrospinal fluid where it is difficult to obtain adequate time above the MIC, especially for the highly resistant strains of *S. pneumoniae* (MICs $\geq 2 \mu g/ml$), with these expanded-spectrum cephalosporins. In any case, until antibiotic susceptibility data are available, the empirical treatment for pneumococcal meningitis requires the use of vancomycin with or without any of the expanded-spectrum cephalosporins.

We have used ceftizoxime as our primary expanded-spectrum cephalosporin at Hartford Hospital, one of the largest tertiary hospitals in New England, for over 3 consecutive years without any evidence of problems in the management of both community- and hospital-acquired lung infections or any other nonmeningeal infections in which streptococci are the proven or suspected pathogens. Interestingly, compared with cefotaxime and ceftriaxone, ceftizoxime has significantly greater anaerobic activity and has even been used as monotherapy for community-acquired intra-abdominal infection.

Despite the slightly lower microbiological activity of ceftizoxime against penicillin-resistant *S. pneumoniae* and its slightly greater activity against anaerobes compared with those of cefotaxime and ceftriaxone, it still remains scientifically sound to view these three cephalosporins as therapeutically similar antibiotics and subject to competitive bidding.

REFERENCES


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