641

Pharmacokinetics/Pharmacodynamics in Otitis Media: Comparison of Time-Dependent Antibiotics in Middle Ear Fluid

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ABSTRACT

Background. An effective dosing regimen of β-lactam and macrolide antibiotics for otitis media involving *S. pneumoniae* (SP) requires that drug concentrations in middle ear fluid (MEF) remain above the MIC (T>MIC) of the isolate for at least 35-50% of the dosing interval. The purpose of these analyses was to determine the probability of obtaining 35-50% T>MIC in MEF using Monte Carlo simulation (MCS) for CDC-recommended (amoxicillin) or FDA-approved dosing regimens of AMX, cefaclor, cefprozil, cefixime, cefpodoxime, ceftibuten, ceftriaxone, and clarithromycin.

Methods. MCS (5000 subjects) was utilized to estimate the probability of attaining a free-drug (fu) T>MIC of 35-50% of a dosing interval. Fu-drug concentration probability density functions for each agent were estimated using published MEF drug concentrations collected during the interval of interest. A microbiological probability mass function for each agent was estimated from 977 clinical isolates of SP obtained from pediatric patients ≤ 5 years of age (SENTRY Program, 1997-2000).

Results.

Agent	Mean MEF (sd or range) [µg/mL]	Dosing Regimen	MIC_{50}, MIC_{90} Range [mg/L]	% Protein Bound	PK-PD Target Attainment [%]
amoxicillin (FDA dose)	0.7 0.7	15 mg/kg Q8hr	≤ 0.06, 4, ≤ 0.06–>8	20	83
amoxicillin (CDC dose)	6.1 2.1	45 mg/kg Q12hr	≤ 0.06, 4, ≤ 0.06–>8	20	95
cefaclor	0.5 (0.13-0.95)	20 mg/kg Q12hr	2, >32, ≤0.25–>32	25	5.8
cefprozil	0.25 0.04	15 mg/kg Q12hr	0.5, 16, ≤ 0.12–>16	40	18
cefixime	0.8 0.2	8 mg/kg Q24hr	0.5, >4, ≤0.03–>4	67	32
cefpodoxime	0.5 (0.35-1.6)	5 mg/kg Q12hr	0.12, 4, ≤0.03–>4	28	61
ceftibuten	3.9 1.2	9 mg/kg/d QD	>4, >4, 0.25–>4	65	2.8
ceftriaxone	19 (8-28)	50 mg/kg QTD	0.12, 2, ≤0.008-16	90	88
clarithromycin	8.3 2.5	7.5 mg/kg Q12hr	≤0.25, 8, ≤0.25–>32	60	84

Conclusions. Amoxicillin (either FDA or CDC regimens), clarithromycin and ceftriaxone demonstrated probabilities > 80% of achieving the 35-50% T>MIC target. Although there was great variability among oral cephalosporins in achieving the pharmacokinetics/pharmacodynamics (PK/PD) target, none of the agents had a probability > 65%, which may suggest that these agents are under-dosed for the treatment of otitis media in pediatric patients involving SP; thus, amoxicillin, ceftriaxone and clarithromycin may be preferable to oral cephalosporins as clinical options for otitis media.

INTRODUCTION

Streptococcus pneumoniae remains a leading cause of morbidity and mortality among infants and children worldwide. The incidence of penicillin-resistant strains of *S. pneumoniae* is rising and has made the empirical treatment of common respiratory tract infections such as otitis media more difficult (1-3). Further complicating the treatment of infants and children with otitis media is the observation that resistance to macrolides and cephalosporins among penicillin-intermediate or -resistant strains is the norm, rather than the exception (1, 4). When one considers that penicillin-resistance is related to previous antibiotic therapy, common among infants and children with acute or recurrent otitis media (2, 5, 6), then the importance of appropriate antibiotic selection becomes apparent.

For β-lactam antibiotics, the time that drug concentrations remain above the MIC (T>MIC) of the pathogen is accepted as the pharmacokinetics/pharmacodynamics (PK/PD) target for therapeutic efficacy (7). There is some evidence that the T>MIC in plasma may also be associated with drug efficacy in otitis media (1). In general, the PK/PD target for time-dependent antibiotics is a T>MIC of 40-50% of a dosing interval. Using Monte Carlo simulation, we have attempted to quantify the impact of the two most important sources of variability on PK/PD target attainment: 1) the variability in drug concentrations in the middle ear fluid (MEF) after the administration of recommended dosage regimens of several common antibiotics in children, and 2) the variability in the *S. pneumoniae* sensitivity as demonstrated through minimum inhibitory concentration (MIC) values seen clinically. This approach has two advantages: 1) it attempts to quantify the influence of drug concentrations at the site of infection (MEF), and 2) it utilizes the distribution of MIC values in the population of interest (children). This analysis uses MEF concentration and *S. pneumoniae* MIC distribution data from several drugs that exhibit time-dependent antibacterial effects: amoxicillin, cefaclor, cefprozil, cefixime, cefpodoxime, ceftibuten, ceftriaxone, and clarithromycin.

METHODS

PK/PD Target Attainment Analyses

- Monte Carlo simulation was utilized to estimate the probability of achieving the PK/PD target for CDC-recommended amoxicillin (8) or FDA-approved dosing regimens of amoxicillin, cefaclor, cefprozil, cefixime, cefpodoxime, ceftibuten, ceftriaxone, and clarithromycin.
- The PK/PD target was defined as a free-drug (fu) concentration in the MEF above the MIC of the isolate for at least 35-50% of the dosing interval (T>MIC).
- The dosing regimens modeled and simulation assumptions for each of the above agents are shown in Table 1.
- Five-thousand patient population simulations were performed for each agent using Crystal Ball 2000.1, Decisioneering, Inc., Denver, Colorado.

Clinical Isolates

- Clinical isolates of *S. pneumoniae* (n=977) used in the simulations were obtained from pediatric patients ≤ 5 years of age across North America (SENTRY Antimicrobial Surveillance Program, 1997-2000).

Pharmacokinetic Data

- Analyses were performed using previously published pharmacokinetic data obtained from pediatric patients with otitis media (9-15).
- Mean (range or standard deviation) concentrations in MEF were obtained for %Time > MIC = 33-50% of the dosing interval and are summarized in Table 1.

Table 1: Dosing Regimens Modeled and Simulation Assumptions

Agent	Regimen	Mean (% CV) Drug Concentration at 33-50% of Dosing Interval	Distribution Assumption	fu
Amoxicillin (9) (FDAdose)	45 mg/kg/d in 3 divided doses	2.7 (26)	LN	0.80
Amoxicillin (9) (CDC dose)	90 mg/kg/d in 2 divided doses	8.1 (26)	LN	0.80
Cefaclor (10)	40 mg/kg/d in 2 divided doses	0.50	Tri	0.75
Cefixime (13)	8 mg/kg/day as a single dose	0.80 (25)	LN	0.33
Cefpodoxime (12)	10 mg/kg/d in 2 divided doses	0.50	Tri	0.72
Cefprozil (11)	30 mg/kg/d in 2 divided doses	0.25 (24)	LN	0.60
Ceftibuten (13)	9 mg/kg/day as a single dose	2.9 (41)	LN	0.35
Ceftriaxone (14)	50 mg/kg x 1	19.0	Tri	0.10
Clarithromycin (15)	7.5 mg/kg Q12hr	8.3 (30)	LN	0.40

fu = fraction of unbound drug; LN = log normal, Tri = Triangular

RESULTS

- The distribution of *S. pneumoniae* isolates by patient age is summarized in Table 2.
- The MIC distributions for amoxicillin, cefaclor, cefixime, cefpodoxime, cefprozil, ceftibuten, ceftriaxone, and clarithromycin against *S. pneumoniae* are shown in Figure 1.

Table 2: Distribution of *Streptococcus pneumoniae* Isolates (n=977) by Patient Age (SENTRY Antimicrobial Surveillance Program)

Age (years)	% of Isolates
<1	27
1	37
2	14
3	10
4	7
5	35
Total ≤ 5 years	100

Figure 1: *Streptococcus pneumoniae* MIC Distributions for Amoxicillin, Cefaclor, Cefixime, Cefpodoxime, Cefprozil, Ceftibution, Ceftriaxone, and Clarithromycin (SENTRY Antimicrobial Surveillance Program)

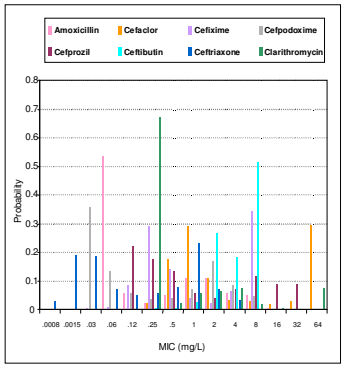

Table 3: Comparison of Overall Probability of Achieving PK/PD Target by Dosing Regimen

Agent	Probability of Achieving PK/PD Target (%)[1]
Amoxicillin (FDA dose)	83
Amoxicillin (CDC dose)	95
Cefaclor	5.8
Cefprozil	18
Cefixime	32
Cefpodoxime	61
Ceftibuten	2.8
Ceftriaxone	88
Clarithromycin	84

[1] Probability of achieving PK/PD target (%Time > MIC = 33-50%) based on entire MIC distribution.

DISCUSSION/CONCLUSIONS

- The integration of PK/PD concepts with Monte Carlo Simulation represents an advance in the paradigm of evaluating and comparing antimicrobial regimens, both during drug development and post-marketing.
- Due to the increasing number of resistant *S. pneumoniae* isolates causing otitis media, a thorough understanding of the influence of the variability inherent in antimicrobial treatment is critical to appropriate dosage regimen selection.
- Amoxicillin (either FDA or CDC regimens), clarithromycin, and ceftriaxone demonstrated overall probabilities > 80% of achieving the PK/PD target of 35-50% T>MIC in the MEF.
- Although there was great variability among oral cephalosporins in the overall probability of achieving the PK/PD target in the MEF, none of the agents compared demonstrated a probability > 65%.
- The results of these analyses suggested that the oral cephalosporins compared are generally under-dosed for the treatment of otitis media in pediatric patients involving *S. pneumoniae*.
- Amoxicillin, ceftriaxone, and clarithromycin may be preferable to oral cephalosporins as clinical options for treatment of otitis media arising from *S. pneumoniae*.

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