69

Comparison of Susceptibility Rates and Potencies for Orally Administered and Parenteral Cephalosporins Against *S. pneumoniae*: Report from the SENTRY Antimicrobial Surveillance Program (1999-2001)

A.H. Mutnick[1], R.N.Jones[1,2]. [1]The JONES Group/JMI Laboratories, N. Liberty, IA [www.jmilabs.com]; [2]Tufts Univ, Boston, MA

IDSA 2002

ABSTRACT

Background: Oral cephalosporin (CEPH) use in the ambulatory setting is predicated on their ability to treat a wide variety of infections. Compliance-friendly flexible dosing has minimized hospitalization with associated costs, but limited data in vitro exist to guide selection among these agents. Such data enhances the understanding of the great potency/spectrum differences in the class, which have been limited to narrow-focused (single drug) marketing trials. This SENTRY Program report was designed as a unique comparison of all leading oral CEPH and to parenteral counterparts.

Methods: 5,321 respiratory *S. pneumoniae* isolates were obtained from ambulatory patients, collected at 35 centers in North America. Organisms were sent to a central laboratory and tested by NCCLS methods against seven oral, and two parenteral CEPHs plus penicillin control.

Results: No oral CEPH achieved activities (MIC_{90}) or susceptible (S) rates approaching those of the parenteral CEPHs (M100-S12 criteria). Rank order of S testing for oral CEPHs was cefprozil (74.5% S) > cefpodoxime (73.4%) >cefuroxime (72.6%) > cefdinir (70.3%) > loracarbef (66.6%) > cefixime (63.7%; based on penicillin rate per NCCLS) > cefaclor (61.8%) and these S rates offer little benefit over that of penicillin alone (63.7% S, 19.2% resistance [R]). The potency of these agents ranged 32-fold from a MIC_{50} of ≤ 0.03 µg/ml (cefpodoxime) to 1 µg/ml for cefaclor and loracarbef. The best S for the oral CEPHs was 20% inferior to the two parenteral CEPHs (cefepime 95.7% S, 0.3% R; ceftriaxone 94.0% S, 1.4% R).

Conclusions: Orally administered CEPHs were less optimal for treatment of ambulatory patients suffering from contemporary *S. pneumoniae* respiratory tract infections (61.8-74.5% S; 21.6-36.3% R). Surveillance of this population of patients and oral CEPHs has largely been ignored in favor of newer compounds. Continued laboratory surveillance seems prudent (SENTRY Program) to maximize the use of the oral ß-lactams in the ambulatory setting.

INTRODUCTION

Antimicrobial agents are among the most frequently used medications in the ambulatory care setting. Increasing pressures to reduce health care costs has resulted in efforts to reduce hospitalizations among ambulatory patients. The use of oral cephalosporins in the ambulatory setting is based on their ability to treat a wide variety of infections and to improve patient compliance through flexible dosing regimens. Several members of the class have been introduced in the last few years to replace older, more familiar drugs. Although some of the newer agents may provide a broader spectrum of activity or less toxicity than older agents, there have been few studies directly comparing their relative efficacy in treating common ambulatory infections.

It has been more than 50 years since the earliest patients with serious *S. pneumoniae* infections were successfully treated with penicillin. The life-saving therapy revolutionized the treatment of these infections. We have not yet exhausted the options for treating penicillin-resistant *S. pneumoniae*, but growing concerns focusing on antimicrobial resistance have prompted many to establish action plans calling for restrictions in therapeutic choices. *S. pneumoniae* is a frequently encountered etiologic agent of pneumonia, bronchitis, otitis media, paranasal sinus infection, and meningitis, and less commonly the causative pathogen in endocarditis, septic arthritis, spontaneous bacterial peritonitis, and pleuropulmonary empyema.

This SENTRY Antimicrobial Surveillance Program report was intended to serve as a comparison amongst the leading oral cephalosporins and two parenteral cephalosporins against *S. pneumoniae* isolates from North American medical centers.

MATERIALS AND METHODS

Isolates in this study were recent clinical strains obtained from the SENTRY Program (1999-2001) which were from community-acquired respiratory tract infections. A total of 5,321 *S. pneumoniae* respiratory isolates were collected at 35 centers in North America and were sent to a central laboratory

All strains were tested and interpreted using reference broth microdilution methods as described by the National Committee for Clinical Laboratory Standards (NCCLS). MIC values for seven oral cephalosporins: cefaclor, cefdinir, cefixime, cefpodoxime, cefprozil, cefuroxime, and loracarbef; two parenteral cephalosporins cefepime and ceftriaxone; and penicillin (control) were determined using validated, dry-form panels.

The strains were inoculated with the appropriate broth delivered by automated inoculators (TREK Diagnostics, Westlake, OH). Organisms were suspended in cation-adjusted Mueller Hinton broth enriched with 5% lysed horse blood. The final concentration of inoculum present in each well of the microdilution tray was equivalent to 5 X 10^5 CFU/ml.

Regular routine testing of the following American Type Culture Collection (ATCC) strains recommended by the NCCLS was performed: *Esherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, *S. pneumoniae* ATCC 49619 and *Enterococcus faecalis* ATCC 29212.

RESULTS

- None of the oral cephalosporins tested demonstrated a MIC_{90} or susceptibility rates approaching those achieved by the parenteral cephalosporins (MIC_{90} range, 2 - >32 µg/ml versus 1 µg/ml, respectively; and susceptible rates, 64% – 75% versus 94% - 96%, respectively).

- Among the oral cephalosporins tested, cefpodoxime was the most potent with a MIC_{50} of ≤ 0.03 µg/ml followed by cefuroxime (≤ 0.06 µg/ml), cefdinir (0.12 µg/ml), cefprozil and cefixime (0.25 µg/ml), and cefaclor and loracarbef (1 µg/ml). Cefpodoxime had a four-fold greater activity (MIC_{90}, 2 versus 8 µg/ml) compared to cefuroxime.

- Rank order of susceptibility for the oral cephalosporins was: cefprozil (75%) > cefpodoxime = cefuroxime (73%) > cefdinir (70%) > loracarbef (67%) > cefixime 64% (based on penicillin rate per NCCLS) > cefaclor (62%). Rank order for lowest resistance rates was: cefpodoxime = cefprozil (22%) > cefuroxime (24%) > cefdinir (27%) > cefaclor = loracarbef (30%).

- Based on the susceptibility testing results described, oral cephalosporins offered little spectrum benefit over penicillin alone (64% susceptible and 19% resistance) against the *S. pneumoniae* isolates.

Table 1. In vitro activity and susceptibilities of seven orally administered cephalosporins compared to ceftriaxone and cefepime when tested against 5,321 respiratory tract isolates of *S. pneumoniae* (SENTRY Antimicrobial Surveillance Program, 1999-2001).

	MIC (µg/ml)			% by category	
Cephalosporin	50%	90%	Range	Susceptible	Resistant
Oral					
Cefaclor	1	>32	≤0.25->32	62	30
Cefdinir	0.12	>4	≤0.03->4	70	27
Cefixime	0.25	>4	≤0.03->4	64[a]	-
Cefpodoxime	≤0.03	2	≤0.03->4	73	22
Cefprozil	0.25	16	≤0.12->16	75	22
Cefuroxime	≤0.06	8	≤0.06->8	73	24
Loracarbef	1	>32	≤0.25->32	67	30
Parenteral					
Cefepime	≤0.06	1	≤0.06-8	96	<1
Ceftriaxone	0.03	1	≤0.008-16	94	1
Controls					
Penicillin	≤0.03	2	≤0.03->4	64	19

a. Susceptibility predicted by the susceptibility result for penicillin [NCCLS, 2002].

CONCLUSIONS

• Orally administered cephalosporins provided limited spectrum benefit as compared to penicillin or parenteral cephalosporins based on susceptibility and resistance rates against the *S. pneumoniae* isolates (USA; 1999-2001).

• Based on the current study, flexible dosing regimens, improved patient compliance, and the convenience of oral administration are all associated with the use of oral cephalosporins. However, these agents should not be considered as alternatives to parenterally administered cephalosporins or high-dose penicillin in the treatment of serious invasive *S. pneumoniae* infections.

• Longitudinal surveillance programs allow for continuous evaluation of newer as well as older antimicrobials to document changing susceptibility/resistance patterns against common, as well as, infrequent bacterial pathogens. The characterization of resistance with advanced epidemiological procedures and a wide selection of tested orally administered agents distinguishes the SENTRY Program from all others.

SELECTED REFERENCES

Bax R, Bywater R, Cornaglia G, Goossens H, Hunter P, Isham V, Jarlier V, Jones R, Phillips I, Sahm D, Senn S, Struelens M, Taylor D, White A. Surveillance of antimicrobial resistance: What, how and whither? *Clin Microbiol Infect.* 2001;7:316-25.

Butler J, Cetron M. Pneumococcal Drug Resistance: The New “Special Enemy of Old Age”. *Clinical Infectious Diseases* 1999;28:730-5.

Hoban D, Doern V, Fluit C, Roussel-Delvallez M, Jones RN. Worldwide Prevalence of Antimicrobial Resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the SENTRY Antimicrobial Surveillance Program, 1997-1999. *Clinical Infectious Diseases* 2001;32:S81-93.

National Committee for Clinical Laboratory Standards (NCCLS). Methods for dilution antimicrobial tests for bacteria that grows aerobically. Approved standard M7-A5. Wayne, PA:NCCLS. 2000.

National Committee for Clinical Laboratory Standards (NCCLS). Performance standards for antimicrobial susceptibility testing. Supplemental tables, M100-S12. Wayne, PA:NCCLS. 2002.

Reed K, Newton W. Oral or IV Antibiotics for the Treatment of Febrile Children with UTIs? The Journal of Family Practice 1999;48:912-14.