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Original Article

Cefprozil in the Treatment of Acute Upper and Lower Respiratory Tract Infections in Filipino Subjects

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ABSTRACT

Cefprozil is a new orally active semisynthetic cephalosporin with broad spectrum antibacterial activity recently introduced in the Philippines. It is highly active against *Streptococcus pnuemoniae, Neisseria sp., Moraxella cattarhalis* and *Haemophilus influenzae.* In an open-label, multicenter study, Cefprozil was evaluated to assess its efficacy and safety in 136 Filipino patients with acute upper (n=50) and lower respiratory tract infections (n=86). The overall clinical response rate was 98.5% (134/136). Cefprozil was effective, well-tolerated and safe in the treatment of respiratory tract infections.

INTRODUCTION

Cefprozil is a new orally active semisynthetic cephalosporin with broad spectrum antibacterial activity.[1,2,3,4] It is composed of cis and trans isomers in a 9:1 ratio as administered and the pharmacokinetics of both are very similar. It is rapidly absorbed, reaching a maximum concentration 0.9 to 1.2 hours post-dose. Serum half-lives are generally reported as between 1.2 and 1.4 hours and urine recovery is high, (57 to 70%). Ingestion of food has no significant effect on cefprozil pharmacokinetics as opposed to other cephalosporins where serum levels are reduced.

Against gram negative bacilli, cefprozil is at least 2- to 4-fold more active than cephalexin. Against gram positive cocci, cefprozil is at least 2- to 4- fold more active than cefaclor, cephalexin and cefixime. Cefprozil is highly active against *Streptococcus pneumoniae, Neisseria spp., Moraxella catarrhalis,* and *Haemophilus influenzae*. The balanced antimicrobial activity and reliable pharmacokinetics of cefprozil suggest that it should be efficacious in the treatment of upper and lower respiratory tract infections.

PATIENT AND METHODS

Patients

This open-label, multicenter study included patients of either sex, aged 1-64 years, with confirmed diagnosis of upper (pharyngitis/tonsillitis) and lower (secondary bacterial infection of acute bronchitis, acute exacerbation of chronic bronchitis, bacterial pneumonia) respiratory tract infections based on clinical signs and symptoms (sore throat, fever, cough, sputum production, leukocytosis, rales on auscultation, lung infiltrates in chest x-ray for pneumonia). Exclusion criteria were as follows: hypersensitivity to a penicillin or cephalosporin, concomitant antimicrobial therapy, renal impairment (creatinine clearance > 2.5mg/100ml), current hepatic disease (e.g. viral hepatitis), significant illnesses in addition to the disease being studied, antimicrobial therapy in the last 72 hours prior study start, immunosuppressive medications, pregnant or nursing females, immunodeficiency sites, uncontrolled diabetes mellitus and malabsorptive states.

Study Design

The study was carried out in 4 centers between November 1996 to April 1997. Informed consent was obtained from each patient before admission to the study. Pre-treatment laboratory assessment e.g. hematology, serum chemistry, urinalysis, sputum gram stain and culture and chest x-ray (if needed) were done on inclusion. Bacteriological specimens were taken and isolates

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tested for susceptibility to cefprozil. However, a post-treatment sputum gram staining and culture was not required if the patient exhibited clinical cure and sputum production was nil or inadequate.

Definition of Response

All patients receiving treatment were evaluated for tolerance or any adverse events. Therapeutic efficacy was determined after a minimum of 3 days treatment based on clinical evaluation before, during and after treatment. Clinical response was classified as "cured" (absence of all signs and symptoms of infection post-treatment) or "failure" (persistent, worsening or recurrence of one or more symptoms of infection). Bacterial response was defined as "eradication" (no pathogen present post-treatment) or "persistence" (isolation of initial pathogen post-treatment).

RESULTS

Demography

A total of 136 patients were included for evaluation in the study from 4 centers covering a 6-month period. The demographic details of the total population, 1-15 yrs group and 16-64 yrs group are presented in Tables 1, 2 and 3, respectively.

Table 1. Demography of total population

Total (n)	136
Sex M	75
F	61
Age (yrs) ± SD	16.4 ± 17.6
Age range (yrs)	1 - 64
Weight (kg) ± SD	33.6 ± 23.5
Height (cm) ± SD	116.3 ± 43
Concomitant medication	
Carbocysteine	3
Clemastine	1
Salbutamol	4
Terbutaline	1
Diagnosis	
URTI	50
LRTI	86

Table 2. Demography of patients aged 1-15 yrs

Total (n)	86
Sex M/F	52/34
Age (yrs) ± SD	5 ± 3.5
Weight (kg) ± SD	20 ± 14
Height (cm) ± SD	97.4 ± 33.5
Concomitant medication	
Carbocysteine	3
Clemastine	1
Salbutamol	5
Terbutaline	1
Diagnosis	
URTI	10
LRTI	76

Table 3. Demography of patients aged 16 yrs and above

Total (n)	50
Sex M/F	23/27
Age (yrs) ± SD	36.2 ± 14
Weight (kg) ± SD	58.7 ± 15
Height (cm) ± SD	152.5 ± 36.5
Diagnosis	
URTI	40
LRTI	10

Patients upon inclusion received cefprozil according to the following dose recommendation and schedule:

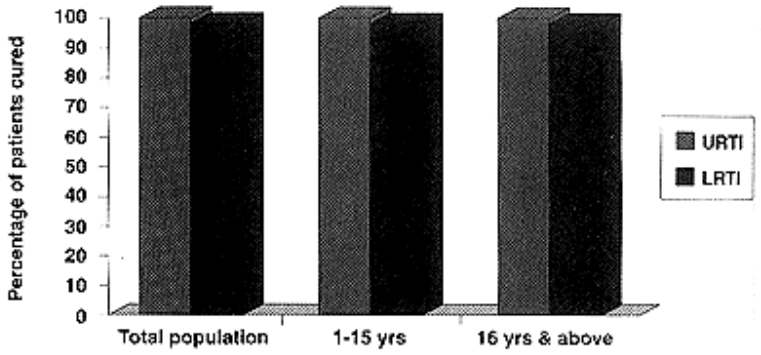
URTI (1-12 yrs) - 15mg/kg/day once a day for 10 days
(13 yrs and above) - 500mg tablet once a day for 10 days

LRTI (1-12 yrs) - 20mg/kg/day twice daily for 10 days
(13 yrs and above) - 500mg tablet twice daily for 10 days

All the 50 patients diagnosed with upper respiratory tract infections showed clinical improvement as early as 3 days of cefprozil treatment. At the end of treatment, clinical cure was observed in all. Those with lower respiratory tract infections, on the other hand, showed a 97.6% (84/86) response rate. The overall clinical response rate for upper and lower respiratory tract infections was 98.5%.

In the subgroups of patients based on age (1-15 yrs and 16-64 yrs), the clinical response rate in URTI mirrored the response rate (100%) of the whole population while lower respiratory tract infections, 74/75 (97.3%) and 84/86 (97.6%) were the respective clinical response rates (Figure 1).

Figure 1. Clinical Response Rates



Adverse Events

Adverse events were noted in 9 (6.6%) of the 136 patients (anorexia - 1, diarrhea - 5, epigastric pain - 1 and rash - 2). None of these patients discontinued treatment.

DISCUSSION

Acute lower respiratory tract infections remain an important cause of morbidity as well as mortality for all ages, especially among the children of the developing world. Pneumonias account for more than a quarter (28%) of all deaths in children above 5 years.[5] In the Philippines, lower respiratory tract infections such as bronchitis and pneumonias are the number 2 and 4 causes of illness, respectively, for all ages. Pneumonias is the number 2 killer disease (64/100,000) population, 13.2% of total deaths), and it is the most common cause of death among our infants (DOH, Phil 1992).[6]

The antimicrobial chosen in the therapeutic management of respiratory tract infections of bacterial origin must be one that is effective against the causative pathogen, well tolerated (minimal or no side effects) and rapidly acting. Additional factors include a greater assurance of compliance through an easy-to-remember once or twice daily dosage schedule, cost-effectively and, especially in the pediatric age group, palatability.

The above requirements mandate a correct diagnosis on which to base antibiotic prescription. Isolation of etiologic agents is difficult in the pediatric ages especially those below 7 years of age, because these children are unable to expectorate and an adequate sample easily obtainable non-invasively (e.g. sputum) is hardly possible, unlike in older children and adults. In acute bronchitis, which is frequently of viral origin, the presumption of a bacterial etiology is based on the clinical picture of increased sputum production and purulence, dyspnea and pleuritic chest pain. In chronic bronchitis the picture of an exacerbation is, similarly, an increase in previously existing signs and symptoms. In the former, documentation of the existence of an infection and its pathogen may be as simple as performing a gram's stain and culture of the sputum. In chronic bronchitis, however, not only do mixed flora frequently appear in the Gram's Stain, but the organisms cultured would generally be considered pathogenic in non-chronic specimens. In both acute and chronic bronchitis, as well as in pneumonia, the culturing of sputum for causative agents would yield results in no less the 48 hours. Reliance on this procedure to determine initial therapy would mean a delay in the delivery of care.

An additional consideration is the trend of increasing resistance to beta lactamases. Relative to the course of Medicine, the development of antimicrobial use has advanced rapidly; the development of antimicrobial resistance has run an even faster course. Research notes that as newer antibiotics are constantly being discovered to counter almost all known pathogens, drugs may be inactivated by bacterial enzymes. Partly as a result of this, penicillin-resistant pnuemococci are increasing in worldwide incidence.

It has also been theorized that increased antibiotic use even for non-bacterial infections has led to inappropriate or prolonged use of these agents. Antibiotics account for 15-30% of drug expenditures, the largest of any therapeutic group of drugs. A study by the WHO's Programme for Appropriate Health Care Technology (ATH) has shown a correlation between the existence of multiresistant bacteria and antibiotic resistance patterns.

In 1983, the Philippines had the highest percentage (>25%) of antibiotic utilization among countries surveyed. In the 1990 survey, the Philippine figures changed significantly.

A 1996 report on the Antimicrobial Resistance Surveillance Program (ARSP) of the Philippine Department of Health[7] garnered data from 11 hospitals. Resistance rated from 28,044 isolated reported a 24% increase from numbers reported in 1985. The respiratory system was the most common source of specimens, (25%) with *Streptococcus pneumoniae* as the most common cause of acute respiratory infections. Analysis of this group of pathogens showed a 13% resistance rate to penicillin.

In the Philippines, the inappropriate use of antibiotics whether with respect to drug dose, interval duration (singly or collectively) in the light of proper clinical situations and/or financial considerations has been cited as contributing to the problem of development of resistance. Apart from its recognized effects on the rapid emergence of resistance, additional effects include selection pressure on resistance microorganisms, adverse reactions, treatment failures, the occurrence of preventable morbidity and mortality and waste of resources.

The initial management of acute respiratory tract infections pending laboratory cultures is therefore, largely empiric and directed as a rapid response without adding to the development of drug resistance. Such a challenge implies a properly recognized bacterial infection and a high index of suspicion of the pathologic organism against which to launch an attack using an antimicrobial that is most active against the most common respiratory pathogens. In COPD patients, these are the non-typeable *Haemophilus influenzae, Moraxella cattarhalis, Streptococcus pnuemoniae* (pneumococcus) and to some extent, the atypical pathogens. In children, bacterial causes for respiratory infections outweigh viral ones with the most common causes as *Streptococcus pnuemoniae* (46%), *Haemophilus influenzae* (28%), *Staphylococcus aureus* (9%) and other gram negative agents (17%).[8] Likewise, these organisms are the most common bacterial etiologies of acute respiratory tract infections in Filipino children less than 5 years old, as documented in studies of the Research Institute of Tropical Medicine (Alabang, Philippines 1985-1992).[9] It is important that all recommended antibiotics have good activity against *S. pnuemoniae* and *H. influenzae* in

children >2 months of age. Many of these bacteria produce beta lactamases and therefore, the antibiotic of choice must be resistant to the relevant beta lactamases. Such an agent must penetrate to the site of infections and be effective with once or twice daily dosing as well as tolerated by a wide range of patients.

Few of the older antibiotics are effective against this broad microbiological spectrum. In the US, the incidence of penicillin resistance in *S. pneumoniae* has risen from about 5% in the late 1980's to 20% in 1992.[10] In the Western Pacific regions, where the Philippines is one of the member states, an increasing resistance of our common respiratory pathogens against commonly administered antimicrobials like penicillin, ampicillin, cotrimoxazole has likewise been noted.[11] In the Philippines, for 1995, the resistance rates for *S. pneumoniae* against chloramphenicol, cotrimoxazole and penicillin was 0.7%, 16% and 13% respectively.[12]

In other parts of the world, a considerable proportion (up to 50%) of *H. influenzae* and *Moxarella catarrhal*is are beta lactamase producers and are therefore resistant to ampicillin. Amoxicillin, ampicillin and few of the first generation cephalosporins are not beta lactamase resistant or active against the atypical pathogens. Erythromycin and cotrimoxazole are not active against *H. influenzae* or atypical pathogens respectively. Tetracycline is not always effective against pnuemococcus.

With the global threat of increasing resistance of common respiratory pathogens against frequently administered antimicrobials, the introduction of a second generation cephalosporin such as cefprozil (Procef) with its effective coverage against the more common respiratory pathogens and its beta lactamase stability is a welcome development. Response was noted by the 3rd to 5th day after initiation of therapy with minimal side-effects, none of which necessitated discontinuation of the drug. In addition, its twice daily dosing schedule assured compliance in our adult group of patients. For the pediatric group, its pleasant taste made administration by care-givers easier.

This study has shown that Cefprozil is an effective second generation cephalosporin with a broad spectrum of activity which affords easy administration because of its BID dosing and for children, its pleasant taste.

REFERENCES

1. Chin N-X, Neu HC. Comparative antibacterial activity of a new oral cephalosporin BMY 28100. Antimicrobial Agents and Chemotherapy 1987; 480-483.
2. Jones RN, et al. BMY 28100, a new oral cephalosporin: antimicrobial activity against nearly 7000 recent isolates Diagnostic Microbiology 1988; 9:11-26.
3. Kayser F. Comparative antibacterial activity of the new oral cephalosporin, BMY 28100. European Journal of Clinical Microbiology 1987; 6:309-312.
4. Thornsberry C. Review of the in vitro antibacterial activity of cepfrozil, a new oral cephalosporin, Clinical Infectious Disease 1992; 11(suppl 2): S189-94.
5. 1991 UNICEF State of the World's Children, p 4.
6. Philippines Health Statistics, DOH, 1992.
7. Carlos C. 1996 Antimicrobial Resistance Surveillance Data. PJMID 26(3): 139-141. July-Sept 1997.
8. WHO and UNICEF Reports, 1993.
9. Etiology of ALRI in Filipino Children, 1985-92. RITM, Alabang, Philippines.
10. Thornsberry C. et al. Increasing Penicillin Resistance Patterns of Community Acquired Infection Pathogens in the Western Pacific. Proceedings of the 4th Western Pacific Congress of Chemotherapy and Infectious Diseases. December 1994, PICC, Manila, Philippines pp 278-282.
11. Peña A. Antimicrobial Resistance Patterns of Community Acquired Infections Pathogens in the Western Pacific Proceedings of the 4th Western Pacific Congress on Chemotherapy and Infectious Diseases. December 1994, PICC, Manila, Philippines pp 278-282.
12. Carlos C. 1996 Antimicrobial Resistance Surveillance Data. PJMID 26(3): 139-141 July-Sept 1997.