CEFUROXIME COMPARED TO AMOXICILLIN - CLAVULANIC ACID IN THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

H M L Oh, A W K Ng, S K Lee

ABSTRACT

The study compared the efficacy and safety of cefuroxime (CFX) versus amoxicillin-clavulanic acid (AC) in the treatment of community-acquired pneumonia. A total of 48 patients (mean age 44 years; 32 males and 16 females) were randomised to receive sequential intravenous/oral CFX (750mg iv 8H for 48H/500mg po bid) and sequential intravenous/oral AC (1.2g iv 8H for 48H/ 750mg po tid) for 7-14 days. The two groups were well matched for age, sex and treatment duration (median 7 days).

The most frequent causative organisms were Mycoplasma (3), Klebsiella species (2), Pseudomonas aeruginosa (2) and hemolytic streptococcus (2). Clinical cure was obtained in 20 patients (83.3%) and 18 patients (75%) of CFX and AC group respectively. Clinical improvement was observed in one patient of the CFX group. There were 3 failures in the CFX group and 4 failures in the AC group. Two patients in the AC group developed adverse drug reactions (namely vomiting and rash) and were withdrawn from the study.

In conclusion, cefuroxime and amoxicillin-clavulanic acid have comparable efficacy and safety in the treatment of community-acquired pneumonia.

Keywords: cefuroxime, amoxicillin-clavulanic acid, bacterial pneumonia

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INTRODUCTION

Acute bacterial pneumoniae are commonly encountered infections in the community. The common aetiologic pathogens of community-acquired pneumonia are *Streptococcus pneumoniae, Haemophilus influenzae* and *Branhamella catarrhalis*. Some of the antibiotics traditionally used, such as ampicillin and amoxicillin, are no longer antibiotics of choice because of the increase of β-lactamase-producing organisms. Second generation cephalosporins and amoxicillin clavulanic acid are reasonable alternatives because of their β-lactamase stability.

Cefuroxime is a second generation cephalosporin available for parenteral use as cefuroxime sodium and for oral use as a pro-drug, cefuroxime axetil. The oral bio-availability of cefuroxime axetil is 50%-60% when taken shortly after food[1]. Cefuroxime is almost completely eliminated via the kidneys (renal filtration and active tubular secretion).

Clavulanic acid is an irreversible inhibitor of intracellular and extracellular β-lactamases and hence protects amoxicillin from inactivation by β-lactamases. The absolute bio-availability of clavulanic acid is 60% and the main route of elimination is via the urine[2].

This study compared the efficacy and safety of cefuroxime and amoxicillin-clavulanic acid in the treatment of community-acquired pneumonia.

MATERIALS AND METHODS

All patients admitted to the Department of General Medicine, Tan Tock Seng Hospital with a suspected diagnosis of pneumonia were evaluated for inclusion into the study. Inclusion criteria were as follows:

1. A new pulmonary infiltrate on chest roentgenogram on admission or within 24 hours.
2. Confirmatory clinical findings including at least 2 of the following criteria: fever over 37.5°C, cough, sputum production, pulmonary consolidation by examination and white blood cell count >10,000/mm^3.

Exclusion criteria included hypersensitivity to penicillins or cephalosporins, antimicrobial therapy in the three days before study entry, gastrointestinal disorders likely to interfere with drug absorption, pregnancy or lactation and serious underlying disease or other circumstances making availability of follow-up unlikely.

Routine biochemical and haematological investigations were performed before, within 72 hours and at the completion of treatment. Sputum cultures were performed before and after therapy.

Gram stain and Ziehl-Neelsen stain of respiratory secretions were performed. Blood cultures and acute and convalescent sera for antibodies against *Legionella pneumophilia* and *Mycoplasma pneumoniae* were obtained. The Gram stains were evaluated for purulence (>25 leukocytes per low power field) and relevance (<25 epithelial cells per low power field). Microbiologic identification and susceptibility testing by disk diffusion technique were performed on sputum and blood specimens.

A diagnosis of Legionella was made by demonstrating a four-fold rise in serum antibody titre or a single serum titre of ≥ 1:320 with a characteristic clinical picture. The diagnosis of

Department of Infectious Diseases
Communicable Disease Centre
Tan Tock Seng Hospital
Singapore 308433

H M L Oh, MBBS, M Med (Int Med), MRCP (UK)
Senior Registrar

Department of Respiratory Medicine
Tan Tock Seng Hospital

A W K Ng, MBBS, M Med (Int Med), MRCP (UK)
Registrar

Department of General Medicine
Tan Tock Seng Hospital

S K Lee, MBBS, FRCP (Edin), FRCP (Glas)
Senior Consultant

Correspondence to: Dr H M L Oh
Department of Medicine
Toa Payoh Hospital
Toa Payoh Rise
Singapore 298102

Mycoplasma pneumoniae was based on a fourfold rise in titre between acute and convalescent sera or a single titre ≥ 1:128 in the complement fixation test.

The patients were randomly assigned according to a computer-generated code to receive sequential intravenous/oral cefuroxime and intravenous/oral amoxicillin-clavulanic acid for 7 to 10 days. Cefuroxime was administered at a dosage of 750 mg iv 8H for 48 hours followed by cefuroxime axetil 500mg po bid. Amoxicillin-clavulanic acid was administered at a dosage of 1.2g iv 8H for 48 hours followed by 500mg/250mg po tid. A minimum of 7 days of therapy was required for evaluation. Clinical assessment of the patients was done daily for all in-patients and 1 to 2 weeks post-treatment.

DEFINITION OF RESPONSE

A cure was defined as resolution of clinical symptoms and signs at the end of treatment. Clinical improvement was defined as slow resolution of symptoms and signs during the treatment period. Failure correlated with the lack of any response to therapy. Relapse was defined as recurrence of the pathogens or clinical symptoms and signs of the initial infection during the follow-up period, after initial cure or improvement.

RESULTS

A total of 48 patients (32 males and 16 females) were evaluated. The mean age of the patients was 44 years, 39.25±17.2 years in the amoxicillin-clavulanic acid group and 43.3 ± 19.8 years in the cefuroxime group.

The underlying medical conditions included bronchiectasis (6 patients), chronic obstructive airway disease (5 patients), bronchial asthma (2 patients), hypertension (4 patients), valvular heart disease (3 patients), coronary artery disease (one patient), spinal muscular atrophy (one patient), diabetes mellitus (one patient) and alcoholic liver disease (one patient).

Twenty-four patients received amoxicillin-clavulanic and 24 received cefuroxime. The mean duration of treatment for both groups was 7 days (range 7-28 days). The 2 groups were well-matched for age and sex (Table I). In the 13 patients with a definitive aetiology, the diagnosis was established by a positive sputum culture in 10 patients and by serological methods in 4 patients. None of the patients were bacteraemic (Table II).

Table I – Characteristics of 48 patients enrolled in the study

Characteristic	Amoxicillin-clavulanic acid	Cefuroxime
No. of evaluable patients	24	24
Sex (M:F)	16:8	16:8
Race		
Chinese	13	20
Malay	5	1
Indian	5	3
Others	1	–
Age (years)	39.25±17.2	43.3±19.8
Mean duration of treatment (days)	7	7
Mean time to fever defervescence (days)	2.66	1.83

The most frequent causative organisms were *Mycoplasma pneumoniae*[3], *Klebsiella species*[2], *Pseudomonas aeruginosa*[2] and haemolytic streptococcus[2] and Legionella[2].

The type of lower respiratory tract infection treated included 34 unilateral bronchopneumonia, 10 bilateral bronchopneumonia, 2 lobar pneumonia, one empyema and one lung abscess (Table III). In the cefuroxime group, clinical cure was obtained in 20 patients (83.3%), clinical improvement in one patient and failure in 3 patients. Clinical cure was obtained in 18 patients (75%) and failure in 4 patients in the amoxicillin-clavulanic acid group (Table IV). Adverse reactions occurred in 2 patients in the amoxicillin-clavulanic acid group and consisted of urticarial rash in one patient and vomiting in the other. This resulted in the discontinuation of therapy.

Table II – Results of therapy with amoxicillin-clavulanic acid and cefuroxime by pathogens detected

Pathogens	No. of patients/No. of clinical cures	
	Amoxicillin-clavulanic acid	Cefuroxime
Mycoplasma pneumoniae	1/1	1/1
Pseudomonas aeruginosa	1/0	1/1
Hemolytic *streptococcus*	–	1/1
Klebsiella species	1/1	–
Haemophilus influenzae	–	1/1
Enterobacter species	–	1/0
Non-fermentative gram-negative bacillus	–	1/0
Legionella	–	1/1
Klebsiella species + *Mycoplasma pneumoniae*	1/1	–
Pseudomonas species + hemolytic *streptococcus*	1/0	–
Legionella + Mycobacterium tuberculosis	1/0	–
None	18/15	17/15
	24/18	24/20

Table III – Results of therapy with amoxicillin-clavulanic acid and cefuroxime by the type of lower respiratory tract infections

Type of infection	No. of patients/No. of clinical cures	
	Amoxicillin-clavulanic acid (n=24)	Cefuroxime (n=24)
Bronchopneumonia		
– Unilateral	15/12	19/16
– Bilateral	6/ 4	4/ 3
Lobar pneumonia	1/ 1	1/ 1
Empyema	1/ 0	–
Lung abscess	1/ 1	–
Total	24/18	24/20

Table IV - Therapeutic outcome

Outcome	No. of patients		P value
	Amoxicillin-clavulanic acid (n=24)	Cefuroxime (n=24)	
Cure	18 (75%)	20 (83.3%)	NS *
Improvement	–	1	NS *
Failure	4	3	
Discontinuation due to adverse effects	2	–	

* NS = not significant

DISCUSSION

Treatment of patients with community-acquired pneumonia involves the prompt administration of appropriate antimicrobial agent(s) for the appropriate duration. Bacterial resistance to antibiotics commonly used to treat community-acquired pneumonia is an increasing problem.

Beta lactamase producing organisms are becoming more important among the major causative pathogens of community-acquired pneumonia[4,5]. In the community acquired pneumonias requiring hospitalisation, a second generation cephalosporin or amoxicillin-clavulanic acid offer appropriate cover.

Classification based on sputum culture may be tenuous since isolation of an organism is not necessarily tantamount to infection by that organism. Our study utilised sputum for gram stain, blood and sputum cultures, and serologic studies to determine the aetiology of the pneumoniae. A definitive aetiology was obtained in 13 of 48 patients (27%).

Aerobic gram-negative bacillus consisting of the *Enterobactericeae* and non-fermentative organisms constituted 14.6%, and gram positive cocci, haemolytic streptococcus constituted 4.2% of the pneumonia. The pathogens of atypical pneumonia, *Mycoplasma pneumoniae* and Legionella species, are beginning to play an important role in the aetiology of community-acquired pneumonia. In our study, 10.4% of the pneumonia were caused by atypical organisms. This is in contrast with other studies of community-acquired pneumonia in which *Streptococcus pneumoniae* is the most common pathogen isolated[3].

This study was conducted in 2 comparable groups of patients with community-acquired pneumonia requiring hospitalisation. However there were clinical differences between the 2 groups.

Patients treated with amoxicillin-clavulanic acid had slower response to treatment than those treated with cefuroxime. The mean time to fever defervescence in the amoxicillin-clavulanic acid group was 2.66 days compared to 1.83 days in the cefuroxime group. However, the overall cure rate was 75% in the amoxicillin-clavulanic acid group and 83.3% in the cefuroxime group. This difference was not statistically significant.

Both treatment regimens proved effective for the types of organism isolated from sputum and were well tolerated by the patients. Only 8% of the amoxicillin-clavulanic acid patients experienced minor adverse reactions.

The results of this study is consistent with the favourable results found by O'Donoran et al and Landau et al[6,7]. Cefuroxime was as effective and as well tolerated as amoxicillin-clavulanic acid. Both antibiotics have the advantage of broad *in vitro* antibacterial activity and both intravenous and oral formulations. The results demonstrate that cefuroxime and amoxicillin-clavulanic acid are suitable as antibiotics of first choice in the treatment of community-acquired pneumonia.

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