Sequential i.v. Cefuroxime/Oral Cefuroxime Axetil versus Sequential i.v. Ampicillin-Sulbactam/Oral Amoxicillin-Clavulanate Therapy in Moderate Community-Acquired Pneumonia

Osman Nuri Hatipoğlu, Yücel Taşan**, İsmail Yüksekol**, Metin Özkan**, Arzu Balkay**, Olgaç Seber***
** Trakya University, Chest Medicine Department, Edirne-Turkey*
*** Gülhane Military Medical Academy, Chest Medicine Department, Ankara-Turkey*

We declare that this paper is not under consideration by any other journal at the same time and it has not been accepted for publication elsewhere.

The study was presented at the ERS annual congress, 1999, Madrid-Spain.

Abstract

The present study compares the efficacy and safety of sequential i.v. cefuroxime (CFX)/oral CFX-axetil versus i.v. sulbactam-ampicillin (SAM)/oral amoxicillin-clavulanate (AC) therapies in hospitalized male soldiers with moderate community-acquired pneumonia (CAP). A total of 72 patients were randomized to receive either CFX 750 mg administered i.v. tid or SAM 1000 mg administered i.v. bid, all for three days. Although WBC counting, CRP measurement and chest X-ray were performed before and three days after the therapy, only clinical response on the third day was taken into consideration to switch to oral therapy. If clinical improvement was seen with i.v. treatments, therapy continued with oral CFX-axetil 500 mg bid after i.v. CFX (CFX-CFX group) and with oral AC 625 mg tid after i.v. SAM (SAM-AC group). Among 72 patients, 67 were evaluable. WBC counts and radiographic infiltrations at switch time to oral therapy showed a statistically significant decrease that was consistent with clinical response ($p<0.05$), but CRP levels ($p>0.05$). Clinical success (cure or improvement) was obtained in 28 (90%) and 34 (94%) patients from CFX-CFX and SAM-AC groups, respectively ($p>0.05$), and maintained in the follow-up period. Both regimens were well tolerated except gastrointestinal side effects, which were observed in two patients from CFX-CFX group (3.2%) and three patients from SAM-AC group (5.5%). In conclusion, both sequential therapy modalities are of similar efficacy and safety in the treatment of moderate CAP. Clinical assessment is essential to decide when to change to oral therapy, but WBC counting and chest radiograph can also be helpful.

Turkish Respiratory Journal, 2000;1:40-45

Key words: *Cefuroxime, Sulbactam-ampicillin, Amoxicillin-clavulanate, Moderate pneumonia, Sequential therapy.*

Introduction

Community-acquired pneumonia (CAP) is a common illness causing noticeable morbidity and mortality, and forms an important economic burden. Some patients with CAP require hospitalization. Conventional treatment for hospitalized patients consists of full course i.v. antibiotic therapy that prolongs hospital stay and increases cost. Recently, efforts to reduce the costs have led to the introduction of sequential therapy, in which a relatively short course of i.v. therapy is followed by an oral

Correspondence: *Dr. Osman Nuri Hatipoğlu, Trakya University, Chest Medicine Department, Edirne-TURKEY*
E-mail:gogus@trakya.edu.tr

treatment period.1-4 Previous studies have demonstrated that, in many selected low-risk patients with CAP, the i.v. therapy can safely be changed to oral antibiotics after 2-3 days.1,5-7 The use of cefuroxime(8) (CFX) or beta-lactam/beta-lactamase inhibitor combinations, both administered as i.v. forms followed by oral forms, is the current approach. The symptoms of patients who respond to antibiotic therapy, frequently begin to resolve within 48 to 72 h.(10-12) Clinical assessment is essential to decide when to change to oral therapy, but the roles of WBC counting, CRP measurement and chest radiograph, although advised by some authors(13,14), are unclear.

The aim of the present study was to evaluate the efficacy and safety of two sequential therapy regimens in hospitalized patients with moderate CAP; i.v. CFX followed by oral CFX-axetil (CFX-CFX regimen) and i.v. sulbactam-ampicillin (SAM) followed by oral amoxicillin-clavulanate (AC) (SAM-AC regimen). In addition, we examined whether the changes in WBC counts, CRP levels and chest radiographs were consistent with clinical response at switch time.

Methods

Patients with moderate CAP requiring hospitalization and initial treatment with i.v. antibiotics were studied prospectively at Etimesgut Army Hospital from April 1997 to May 1998.

Eligibility criteria:

Eligible patients were male soldiers 18 years of age or older, doing their obligatory military service. Informed consent was obtained from all patients. Among the patients with pneumonia, moderate pneumonia cases (patients requiring hospitalization and parenteral therapy but not severely ill) were selected according to international criteria(13,14). Diagnosis of pneumonia was established on the basis of the following criteria: (1) the presence of new or progressive radiographic changes and (2) symptoms and signs consistent with pneumonia.

Exclusion criteria:

Mild (patients not requiring hospitalization and parenteral therapy) or severe (patients requiring hospitalization in intensive care units) pneumonia, history of hypersensitivity reaction to study drugs, severe renal or hepatic dysfunction, suspicion of active tuberculosis, history of pneumonia unsuccessfully treated with one of the study drugs within four weeks of the study entry, presence of clues indicating clinical improvement with a systemic antibiotic that had been started before the study entry or use of a systemic antibiotic for a period that was not enough to evaluate its efficacy, presence of potential pathogen sensitive to an antibiotic having a more narrow spectrum than the study drugs.

Treatment

Eligible patients were randomized to take either CFX-CFX or SAM-AC therapy regimens. Patients were switched to oral therapy within 72 h if they met the following clinical criteria: (1) resolution of fever; (2) improvement of cough and respiratory distress; (3) presence of normal gastrointestinal tract absorption. Table 1 shows the dose, duration and route of treatment regimens. Oral clarithromycin 500 mg bid for 10 days concomitantly used if there was a suspicion of atypical pneumonia.

Laboratory analysis

All patients were hospitalized during the treatment. The physical examination and clinical laboratory tests, such as complete blood counting, sedimentation rate, hepatic enzymes, CRP measurement (values of 5 mg/dl were considered normal), renal function tests, and chest X-ray were performed at the pre-treatment visit. Signs and symptoms of pneumonia (cough, dyspnea, auscultatory findings, pleural pain, sputum, and fever) were recorded. If available, sputum examination was performed only in patients who were not treated with antibiotics prior to hospital admission. WBC counting, CRP measurement and chest X-ray were repeated just before switching to oral therapy. Chest X-rays were also performed at the end of the entire therapy and on the follow-up assessment. Table 2 shows the days on which the clinical assessments and laboratory examinations were performed.

Chest X-ray and scoring

Chest X-rays were evaluated according to the extent of involvement. On the chest X-ray, each lung was

Table 1. Dose, duration and route of treatment regimens

CFX-CFX regimen	SAM-AC Regimen
Intravenous CFX, 750 mg tid for 3 days	Intravenous SAM, 1000 mg bid for 3 days
Oral CFX-axetil, 500 mg bid for 7 days	Oral AC 500 mg tid for 7 days

CFX: cefuroxime; SAM: sulbactam-ampicillin; AC: amoxicillin-clavulanate

Table 2. Days of the clinical assessment and laboratory examination

	Days			
	0	3	10	25-55
	i.v. therapy		oral therapy	
X-ray	+	+	+	+
WBC	+	+	-	-
CRP	+	+	-	-
Clinical Assessment	+	+ (IA)	- (PTA)	- (FA)
		Hospitalization		

IA: interim assessment; PTA: post-treatment assessment; FA: follow-up assessment

divided into upper, middle and lower zones. The boundary between the upper and middle zones was defined as a horizontal line drawn at the level of the anterior end of the second rib and the boundary between the middle and lower zones as a horizontal line at the level of the anterior end of the fourth rib(15). A score was assigned to each zone, based on the percentage of lung parenchyma involved: (0) no involvement; (1) involvement less than 25% of a zone; (2) 25 to 50%; (3) 50 to 75%; (4) more than 75%. Thus, the total score for lungs ranged between 0 and 24. Radiographic scoring was performed at the beginning of the therapy and on the third day of the treatment.

Clinical evaluation and efficacy analysis

Patients were visited every day and adverse events related to antibiotics were recorded. To assess the efficacy of the i.v. therapy, interim clinical assessment was performed 72 h after the initiation of i.v. therapy. If the clinical improvement was seen within the first 72 h of the treatment, we considered the initial therapy to be effective. If the initial therapy failed, an alternative therapy was started. Post-treatment assessment was performed within 24 h after the end of the oral therapy. Treatment efficacy was evaluated by means of the variations in clinical symptoms and signs, and was rated as cure (elimination of signs and symptoms of infection with no recurrence in the follow-up period); improvement (not complete but partial resolution of signs and symptoms of infection); success (cure+improvement) or failure (no improvement). At the post-treatment assessment, effectiveness of the treatment regimens were calculated with respect to the number of the patients, clinical success achieved. To watch whether the cure or improvement was maintained, follow-up assessment was performed within 15 to 45 days after the last dose.

Statistical analysis

Pre-treatment WBC counts, CRP levels and radiographic scores were compared with the third day values, using paired t-test. Post-treatment efficacy rates of the groups were compared by using Fisher's exact test (two-tailed). P values of 0.05 or less were considered significant.

Table 3. Parenteral, oral and overall effectiveness of the treatment regimens

Characteristics	CFX-CFX Group (n=31)	SAM-AC Group (n=36)	Total (n=67)
Sex, M	31	36	67
Age,year,mean SD (range)	20.64 ± 1.02 (20-24)	20.56 ± 0.88 (19-23)	20.60 ± 0.94 (19-24)
Smoking history, %	84	64	73
Previously antibiotic use, %	77	75	76
High WBC counts, % (>12000/dl)	77	72	75
High CRP levels, % (>5mg/dl)	93	92	92
Coexisting illness, %	16	6	10
Concomitant use of macrolide, (n)	5	4	9

CFX-CFX: i.v. cefuroxime/oral cefuroxime-axetil;
SAM-AC: i.v. sulbactam-ampicillin/oral amoxicillin-clavulanate

The two groups compared with respect to age, smoking history, previously antibiotic use, high WBC counts, high CRP levels, coexisting illnesses and use of macrolide concomitantly by using unpaired t-test.

Results

72 patients were included in the study; but, 5 patients were withdrawn from the study as the target pathogens identified were sensitive to an antibiotic having a more narrow spectrum than the study drugs. CFX-CFX and SAM-AC groups consisted of 31 and 36 evaluable patients, respectively. All patients were male, ages ranging from 19 to 24. Demographic and baseline characteristics of patients are summarized in Table 2. The two groups were well matched for age, smoking history, previous antibiotic use, high WBC counts, high CRP levels, coexisting illnesses and use of macrolide concomitantly (for all parameters, $p>0.05$). Because of the suspicion of atypical pneumonia, oral clarithromycin was used concomitantly in five patients from the CFX-CFX group and in four patients from the SAM-AC group.

Table 4. Demographic and baseline characteristics

Effectiveness	CFX-CFX group %	(n)	SAM-AC group %	(n)	Total %	(n)
Parenteral	97	(30/31)	97	(35/36)	97	(65/67)
Oral	93	(28/30)	97	(34/35)	95	(62/65)
Overall	90	(28/31)	94	(34/36)	92	(62/67)

CFX-CFX: i.v. cefuroxime/oral cefuroxime-axetil;
SAM-AC: i.v. sulbactam-ampicillin/oral amoxicillin-clavulanate

Table 5. Baseline and third day laboratory and radiographic findings in patients clinically improved with i.v. therapy

	Mean	Decreased n (%)	Unchanged n (%)	Increased n (%)
Pre-treatment WBC counts (mm^3)*	14470	52 (80%)	2 (3%)	11 (17%)
Third day	11187			
Pre-treatment CRP levels (mg/dl)^{ns}	15.49	40 (62%)	0	25 (38%)
Third day	13.97			
Pre-treatment Radiographic scores*	6.70	49 (75%)	14 (22%)	2 (3%)
Third day	5.81			

*:$p<0.05$; ns: non-significant

Clinical response

When compared with pre-treatment assessment, interim and post-treatment assessments showed significant improvement in the signs and symptoms of pneumonia. In only two of 67 evaluable patients (one in CFX-CFX group and one in SAM-AC group), the initial treatment regimen was considered to fail. After switching to oral treatment, three patients (two in CFX-CFX group and one in SAM-AC group) regressed. The treatment resulted in success in 28 of 31 patients from the CFX-CFX group (90%) and 34 of 36 (94%) patients from the SAM-AC group (Table 3).

No statistically significant difference in the clinical success rates was observed between the groups ($p=0.66$). No relapse was observed in 59 patients who returned for follow-up assessment. The remaining three patients didn't come for follow-up assessment.

Laboratory response

The mean value of pre-treatment WBC counts was 14470/mm^3 and WBC counts were higher than 12000/mm^3 in 50 out of 67 patients. After i.v. therapy, the mean WBC count decreased to 11187/mm^3. The descent rate was statistically significant ($p<00.5$). Of the 65 patients clinically improved with i.v. therapy; WBC counts decreased in 52, increased in 11 and remained unchanged in 2.

Pre-treatment CRP levels were higher than 5 mg/dl in 62 out of 67 patients. The mean CRP level was 15.49 mg/dl, which decreased to 13.97 mg/dl after the i.v. therapy. The decrease in CRP levels was statistically insignificant ($p>0.05$). After the i.v. therapy, CRP levels decreased in 40 out of the clinically improved 65 patients and increased in 25 (Table 4).

Radiographic response

The pre-treatment mean value of radiographic scores was 6.70 (range 3 to 11) and decreased to 5.81 (range 0 to 9) after i.v. therapy ($p<0.05$). Radiographic scores decreased in 49, remained unchanged in 14 and increased in 2 out of the 65 patients clinically improved with the i.v. therapy (Table 5). The other 2 patients who showed clinical progression during the i.v. therapy had also increased radiographic scores.

Post-treatment and follow-up radiographic responses were almost fully compatible with clinical responses.

Microbiological evaluation

Microbiological evaluation is not the aim of the study. Microbiological tests were not done on 51 patients who had been pretreated with antibiotics. An etiologic agent could be identified in 5 patients and *S. pneumonia* sensitive to penicillin was the only pathogen isolated.

Adverse events

Both treatment regimens were well tolerated. None of the patients was excluded from the study due to any adverse event. In only one (3.2%) patient from CFX-CFX group and two (5.5%) patients from SAM-AC group, mild abdominal discomfort and nausea occurred during the oral therapy.

Discussion

Cefuroxime, SAM and AC are known to be effective against probable organisms causing moderate CAP. If there is a suspicion of atypical pneumonia, a macrolide should be used concomitantly. The American Thoracic Society(13) (ATS) and European Study on Community-Acquired Pneumonia(14) (ESOCAP) committee guidelines for management of CAP, recommend the empirical use of these antibiotics in patients with moderate CAP. In several randomized comparative studies, sequential CFX therapy was found as effective as AC sequential therapy(16,17) and full courses of parenteral cefuroxime(1,3) or cefotaxime (18). Siegel et al(1) compared the therapeutic outcome of inpatients with CAP. They randomized patients to one of 3 treatment groups: group 1 received 2 days of i.v. and 8 days of oral CFX therapy; group 2 received 5 days i.v. and 5 days of oral CFX therapy; and group 3 received 10 days of i.v. CFX therapy. They found no differences in the clinical course, cure rates, or resolution of chest radiograph abnormalities among the three groups. Oh et al(16) compared the efficacy and safety of CFX versus AC in the treatment of CAP. In their study, the clinical cure was 83% and 75% with sequential i.v./oral CFX and sequential i.v./oral AC treatments, respectively. Brambilla et al(17) studied the same sequential therapy regimens in the treatment of lower respiratory tract infections and found that the clinical responses in the two treatment groups were very similar: 87% of the patients were cured or improved with i.v./oral CFX compared to 86% with sequential i.v./oral AC. The success rate was 90% for sequential i.v./oral CFX therapy regimen and 94% for sequential i.v. SAM/oral AC therapy regimen in our study. We found that both sequential therapy regimens were effective. Concomitant use of oral clarithromycin with the study drugs may appear to affect our results. However, we think it is negligible because the number of the patients given clarithromycin were both small and almost equal in each treatment group. Both treatment regimens were well tolerated. In only one (3.2%) patient from CFX-CFX group and two (5.5%) patients from SAM-AC group, mild abdominal discomfort and nausea occurred during the oral therapy. No patient discontinued the drug therapy because of any adverse event. Our efficacy and safety results were compatible with those of previous studies (1,16,17).

Change to oral therapy should be considered if the patient is clinically stable and has no fever(2,19). If the antibiotic used is effective, resolution of fever is expected within 48-72 h.(10-12) In patients presenting without fever or having difficulty in assessment of clinical response, some laboratory tests can be helpful to decide when to change to oral therapy. Although WBC counting and CRP measurement have been advised for this purpose, there is very little information in literature regarding the roles of these tests in sequential therapy and their correlation with clinical response, in patients with CAP. Although we decided to switch from i.v. to oral therapy only with clinical assessment, we also performed WBC counting, CRP measurement and chest X-ray on switch time. We found that WBC counts reduced significantly after i.v. therapy, and the decrease in WBC counts was consistent with clinical improvement. But, there was not a significant decrease in CRP levels. Moreover, 37% of the clinically improved patients had elevated CRP levels. As we decided to switch to oral therapy only with clinical improvement, we didn't take into consideration elevated CRP levels. If CRP measurements had been repeated on the following days, we might have found CRP levels decreased. Although chest radiographs are not suggested to be a useful determinant to decide when to change from i.v. to oral therapy(19) because of the late occurrence of the radiographic changes than the clinical response(20), we found a significant decrease in radiographic scores that switch time (radiographic infiltrations decreased in 75% of the patients). The fact that all patients in our study were young males without associated severe illnesses, may explain the early radiographic improvement.

In conclusion, sequential i.v./oral CFX and sequential i.v. SAM/oral AC therapy regimens are of comparable

efficacy and safety in the empirical treatment of hospitalized patients with moderate CAP. Clinical assessment is essential to decide when to change to oral therapy, but WBC counting and chest radiograph can also be helpful.

References

1. Siegel RE, Halpern NA, Almenoff PL, et al. A prospective randomized study of inpatient i.v. antibiotics for community-acquired pneumonia. The optimal duration of therapy. Chest 1996; 110(4):965-971
2. Ramirez JA. Switch therapy in community-acquired pneumonia. Diagn Microbiol Infect Dis 1995; 22:219-23
3. Iakovlev SV, Suvorova MP, Dvoretskii LI, et al. Stepwise therapy of community-acquired pneumonia. Results of cefuroxime and cefuroxime axetil study. Antibiot Khimioter 1998; 43(6):7-11
4. Conly JM, Low DE. Intravenous-to-oral antimicrobial step-down therapy: improving the quality of care and reducing costs. Can J Infect Dis 1995; 6(suppl A):3-5
5. Rhew DC, Hackner D, Handerson L, et al. The clinical benefit of in-hospital observation in low-risk pneumonia patients after conversion from parenteral to oral antimicrobial therapy. Chest 1998; 113:142-146
6. Weingarten SR, Riedinger MS, Hobson P, et al. Evaluation of a pneumonia practice guideline in an interventional trial. Am J Respir Crit Care Med 1996; 153:1110-1115
7. Ehrenkranz NJ, Nerenberg DE, Shultz JM, et al. Intervention to discontinue parenteral antimicrobial therapy in patients hospitalized with pulmonary infections: effect on shortening patient stay. Infect Control Hosp Epidemiol 1992; 13:21-32
8. Perry CM, Brogden RN. Cefuroxime axetil. A review of its antibacterial activity, pharmocokinetic properties and therapeutic efficacy. Drugs 1996; 52(1):125-158
9. Ramirez JA. Switch therapy with beta-lactam/beta-lactamase inhibitors in patients with community-acquired pneumonia. Ann Pharmacother 1998; 32(1):22-6
10. Van den Brande P, Vondra V, Vogel F, et al. Sequential therapy with cefuroxime followed by cefuroxime axetil in community-acquired pneumonia. Chest 1997; 112:406-415
11. Amir J, Harel L, Eidlitz-Markus T, Varsano I. Comparative evaluation of cefixime versus amoxicillin-clavulanate following ceftriaxone therapy of pneumonia. Clin Pediatr (Phila) 1996; 35(12):629-633
12. Ramirez JA, Srinath L, Ahkee S, et al. Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. Arch Intern Med 1995; 155(12):1273-6
13. American Thoracic Society. ATS guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity and initial antimicrobial therapy. Am Rev Respir Dis 1993; 148:1418-1426
14. European Study on Community Acquired Pneumonia (ESOCAP) committee. Guidelines for management of adult community-acquired lower respiratory tract infections. Eur Respir J 1998; 11:986-991
15. Currie DC, Cooke JC, Morgan AD, et al. Interpretation of bronchograms and chest radiographs in patients with chronic sputum production. Thorax 1987; 42:278-284
16. Oh HM, Ng AW, Lee SK. Cefuroxime compared to amoxicillin-clavulanate in the treatment of community-acquired pneumonia. Singapore Med J 1996; 37(3):255-257.
17. Brambilla C, Kastanakis S, Knight S, Cunningham K. Cefuroxime and cefuroxime axetil versus amoxicillin plus clavulanate in the treatment of lower respiratory tract infections. Eur J Clin Microbiol Infect Dis 1992; 11(2):118-124
18. Miller A, Hancock F. Sequential therapy for significant infection: a comparison of the efficacy, safety profile and cost of intravenous followed by oral cefuroxime versus cefotaxime (abstract 664). Seventh European Congress of Clinical Microbiology and Infectious Diseases, Vienna, 1995
19. Shalit I, Dagan R, Engelhard D, et al. Cefuroxime efficacy in pneumonia: sequential short course i.v./oral suspension therapy. Isr J Med Sci 1994; 30:684-689
20. Barlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med 1995; 333:1618-24