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COMPARATIVE EFFICACY AND SAFETY OF CEFIXIME AND CIPROFLOXACIN IN THE MANAGEMENT OF ADULTS WITH COMMUNITY-ACQUIRED PNEUMONIA IN IBADAN, NIGERIA

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ABSTRACT

Background: **Initial antibiotic therapy in upper and lower respiratory tract infections is usually empirical. However, the decreasing susceptibility of respiratory pathogens to antibacterials have raised concerns about the decreasing efficacy of currently available antibiotics.**

Objective: **This study was conducted to compare the efficacy and safety of cefixime and ciprofloxacin in the empirical treatment of community-acquired pneumonia among adult Nigerian patients in Ibadan.**

Methods: **This was an open-labelled, randomized, parallel-group study of seventy-three (73) radiologically and bacteriologically confirmed adult cases of community-acquired pneumonia, between July 1 and September 31, 2011 at two health care facilities in Ibadan, Nigeria. All of these patients had severity index (CURB 65) scores of either 1 or 2. They were treated with either Cefixime, 400mg twice daily or Ciprofloxacin 500mg twice daily for 14 days. They were evaluated four times during the course of their treatment for clinical responses, radiological and bacteriological clearances and safety of therapy.**

Results: **There were 39 (53.4%) patients in the Cefixime group and 34(46.6%) in Ciprofloxacin group. On day 7, patients on cefixime had a statistically significant lower temperature than patients on ciprofloxacin (P<0.01). By day 14, only 10.3% of patients in cefixime group still had persistent residual radiological changes compared to 38.2% in the ciprofloxacin group (P < 0.01). Bacteria cure was obtained in 96% of the patients in the cefixime group and 83% in the ciprofloxacin group.**

Conclusion: **Cefixime was found to be superior to ciprofloxacin in terms of efficacy in the treatment of community-acquired pneumonia in adults in Nigeria. However, both antibiotics were well-tolerated by all the patients as there were no reports or documentation of adverse events.**

Keywords: Cefixime, Efficacy, Safety, Community-acquired pneumonia

INTRODUCTION

Respiratory tract infections (RTIs) are amongst the most widespread and serious infections accounting for over 50 million deaths globally each year.[1] They are also the most common reason for physician's visit and antibiotic prescription.[2] The prevalence of pneumonia among adults with respiratory symptoms suggesting pneumonitis ranges from only 3% in a general outpatient setting to 28% in emergency department.[3,4] Community-acquired pneumonia (CAP) is a common cause of hospital admission in Nigeria, and, in TB patients attending a TB clinic in South-Western Nigeria, 6.4% was found to have *Streptococcal pneumoniae.*[5]

Initial antibiotic therapy in upper and lower respiratory tract infections is usually empirical, focused towards the most common aetiologic agents, which include, *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae and Moraxella catarrhalis.*[6] However,the decreasing susceptibility patterns of these pathogens, particularly *S.pneumoniae* and *H.influenzae*, to antibacterials have raised concerns about the decreasing efficacy of currently available antibiotics.[7,8] In the United States, almost 100% of clinical *M. catarrhalis* and up to 50% of *H.influenzae* isolates produce beta-lactamase. Penicillin-resistant strains have been identified worldwide,[9] and, resistance to other antibacterials such as cephalosporins, fluoroquinolones and macrolides is increasing among isolates of *S.pneumoniae.*[10-12]

Cefixime belongs to the third -generation cephalosporin antibiotics that exert their bactericidal effect by attaching to penicillin-binding proteins and inhibiting peptidoglycan synthesis, thus causing damage to the bacterial cell wall. The third-generation cephalosporins

are used all over the world because of their broad spectrum activity against all Gram-negative and positive pathogens and atypical organisms, e.g. Mycoplasma and Chlamydia.[6]

Ciprofloxacin, also a broad-spectrum, early-generation fluoroquinolone, is one of the cheap and most commonly used antibiotics for most infections including RTI in this community, and, it exhibits bactericidal activity primarily by inhibiting bacterial DNA gyrase. These drugs were acceptable standard antibiotics for the treatment of community-acquired pneumonia during the study period. Even though there are many antibiotics that require less frequent administration, some studies indicate that older antibiotics that have fallen out of favour, are still effective for treatment of community-acquired pneumonia.[13] This study was therefore conducted to evaluate the comparative efficacy and safety of Cefixime and Ciprofloxacin in the empirical treatment of CAP among adult Nigerian patients in Ibadan, Nigeria.

PATIENTS AND METHODS

Study population, enrolment and therapy

This was an open-labelled, randomized, parallel-group study conducted at the General Out Patient Department of the University College Hospital (UCH), Ibadan and Saint Mary's Catholic Hospital, Eleta, Ibadan, Nigeria, between July 1 and September 31, 2011.

The first 75 subjects who satisfied the inclusion criteria were randomised into Cefixime and Ciprofloxacin groups. However, 2 of these were lost to follow-up as they failed to turn up for subsequent visits to the clinic, leaving 73 to conclude the study.

The major inclusion criteria included: adult above 18 years of age, recent onset of fever (>38.3°C), cough with purulent expectoration, bacteriologically positive sputum, presence of an infiltrate on chest radiography performed within 72 hours after the first clinical examination, pleuritic chest pain, crackles, new onset of dyspnea, or worsening dyspnea, female of child bearing potential with a negative urine pregnancy test prior to enrolment (including those who were practising birth control, those with tube ligation and those less than 1 year post-menopausal),willingness to partake in the study and provision of a signed informed or witnessed verbal informed consent.

The key exclusion criteria included: patients with bacteriologically negative sputum, negative chest radiograph, on antibiotics for any infective conditions within the preceding 30 days, hypersensitivity to quinolones or cephalosporins or a severe allergic reaction to any other drug in the past, especially penicillin, patients with other chronic pulmonary diseases like active tuberculosis, bronchiectasis, or active pulmonary malignancies, patients with a life threatening or serious underlying disease, which is unstable, e.g. myocardial infarction, patients with known or suspected renal impairment and/or known creatinine clearance <40ml/min, patients with ALT, AST, or alkaline phosphatase levels 3 times greater than the upper limit of normal, patients who were immuno-compromised including HIV positive patients, patients whose initial clinical status justified immediate hospitalization, and these were provided with hospital admission and excluded from the study.

A complete medical history was obtained and physical examination conducted on all the patients prior to entry into the study. Patients whose severity index (CURB 65) score were 1 or 2 were enrolled and those whose scores were higher than these were excluded from the study as many of these needed to be admitted. Enrolment was made after obtaining bacteriologically positive sputum and positive chest radiograph results from any of the patients apart from other inclusion criteria. Each eligible patient was assigned by a computer-generated sequence of random numbers to receive either Cefixime, 400mg twice daily or Ciprofloxacin, 500mg twice daily for 14 days.

Enrolled patients were followed up during treatment at the Medical Out-Patient Department of the respective study hospitals. Each study participant received the first dose of any of the 2 antibiotics on the first day of the study which corresponded to the time after positive radiological and bacteriological reports were obtained.

This was supervised by the study nurse and patients were then encouraged to take subsequent doses of the respective antimicrobial agent daily till the next follow up clinic visit. Compliance with drug regimen was crosschecked by direct questioning and pill count at every follow up clinic visit. Study participants were followed up on days 1, 3, 7, and 14.

Prior to enrolment, sputum samples were collected in sterile sputum cups and were transferred to the laboratory in a cold box the same day for laboratory evaluation. Pathogens were isolated and identified from sputa using standard bacteriological methods. Identified pathogens were then subjected to antibiotics susceptibility test to cefixime and ciprofloxacin using the Kirby-Bauer disc diffusion method.[14] Sputum collection was repeated on days 3, 7 and 14 to check for bacteriological clearance.

Ten milliliters of blood was obtained by venepuncture for full blood count and blood chemistry evaluation which included aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), total bilirubin, electrolyte & urea and serum creatinine.

The laboratory investigations were conducted at the diagnostic medical microbiology, hematology and chemical pathology laboratories of University College Hospital Ibadan. Full blood count and differentials as well as biochemical parameters were again re-evaluated on day 14. Chest X-rays (posterior anterior & lateral views) were taken at the UCH or Saint Mary's Catholic Hospital, Eleta X-ray Departments prior to commencement of treatment and on day 14.

Efficacy and safety parameters

Patients were evaluated four times during the course of treatment. The primary efficacy was to evaluate the comparative clinical response at the two arms of treatment on days 3, 7 and 14. Secondary efficacy parameters included the comparative radiological response at the end of therapy and bacterial eradication rate on days 3,7 and 14. The bacterial sensitivity to Cefixime and Ciprofloxacin was determined for each isolated bacteria, irrespective of the treatment group assigned. The organisms were considered sensitive to Cefixime when the inhibition halo was equal to or greater than 19 mm and sensitive to Ciprofloxacin when the halo was equal or greater than 21 mm.[15]

The bacteriologic response was considered satisfactory if the causative organism had been eradicated with treatment. Radiologic response was considered satisfactory when the lobar consolidation noticed at the beginning of treatment has cleared completely on day 14 of antibiotics therapy as reported by the consultant radiologist.

The safety end point was to evaluate the incidence of adverse effects and laboratory parameters.

Statistical analysis

Data generated was entered using epidata program and the SPSS version 16 was used for further statistical analysis. Frequency tables, graphs and summary index were used for data presentation. The student t-test was used to investigate the statistical significance of the quantitative effects of the two drugs between the two groups.

Ethical considerations

All patients enrolled gave written informed consent and the trial was approved by the Joint Ethical Committee of the University College Hospital/ University of Ibadan, Nigeria.

RESULTS

Seventy-five patients that satisfied the inclusion criteria were recruited for this open-labelled, randomised,drug trial but two were lost to follow-up as they failed to turn up for subsequent visits to the clinics as scheduled. One was from each arm of the treatment leaving 39 in the cefixime group and 34 in the ciprofloxacin group. Table 1 shows the anthropometric characteristics of the patients from the two arms of treatment.

Primary efficacy parameter is the clinical response on follow up in each treatment group. Table 2 shows the clinical features of patients allocated to the 2 treatment groups while Table 3 shows the summary of statistics of patients' clinical characteristics on each day of follow-up in each treatment group.

The temperature pattern shows that the temperatures decreased slightly in both groups by day 3 but not statistically significant (P>0.2). However, on day 7, patients on cefixime had a statistically significant lower temperature than patients on ciprofloxacin (P<0.01). The same was observed with regards to the respiratory rate. This pattern was maintained on day 14 during the final clinical examination of the patients.

Table 1: Anthropometric characteristics of patients in the 2 arms of treatment.

Anthropometric characteristics	Drug Group	Sample Size N	Mean	Standard Deviation	T-value	P-Value
Age(yrs)	Cefixime	39	44.6	18.59	-0.50	0.62
	Ciprofloxacin	34	46.7	17.10		
Weight (kg)	Cefixime	39	62.1	12.45	-1.67	0.10
	Ciprofloxacin	34	67	14.61		
Height (cm)	Cefixime	39	162.6	8.15	0.65	0.52
	Ciprofloxacin	34	161.5	5.97		

Table 2: Summary Statistics of the duration of Symptoms in days of patients allocated to cefixime and ciprofloxacin treatment groups.

DRUG	FEVER	COUGH	COUGH WITH SPUTUM	CHILLS AND RIGORS	CATARRH	HEADACHE	CHEST PAIN
Cefixime							
Mean	6.12	9.38	5.00	4.11	8.26	5.17	5.54
Median	7.00	10.00	7.0	3.00	7.00	7.00	7.00
N	33	39	18	9	19	12	26
Ciprofloxacin							
Mean	6.87	10.50	6.32	6.86	8.82	5.7	6.65
Median	7.00	10.00	7.00	7.00	10.00	7.0	7.0
N	30	32	19	7	17	13	26
TOTAL							
Mean	6.48	9.89	5.68	5.31	8.53	5.4	6.1
Median	7.00	10.00	7.00	6.00	8.00	25	7
N	63	71	37	16	36	7	52

Table 3: Summary of statistics of patients' clinical characteristics on each day of follow-up in each treatment group.

Day of Exam.	Clinical Assessment	Cefixime Mean (SD) n = 39	Ciprofloxacin Mean (SD) n = 34	t-value	p-value
1	TEMP	37.9 (0.7)	37.8 (0.5)	0.77	0.44
	PR	110.5 (162.0)	93.0 (8.0)	0.77	0.34
	RR	21.4 (2.5)	22.1 (3.2)	-1.06	0.29
3	TEMP	37.2 (0.9)	37.5 (0.5)	-1.21	0.23
	PR	103.9 (147.6)	81.1 (18.6)	0.89	0.38
	RR	21.5 (11.2)	20.7 (2.6)	0.38	0.69
7	TEMP	36.8 (0.8)	37.2 (0.5)	-2.64	0.01*
	PR	76.0 (6.4)	79.8 (18.8)	-2.14	0.04*
	RR	17.3 (1.4)	18.7 (2.7)	-2.68	0.01*
14	TEMP	36.8 (0.4)	37.0 (0.5)	-2.36	0.02*
	PR	75.1 (6.6)	77.7 (8.0)	-1.42	0.16
	RR	16.5 (1.1)	17.7 (2.5)	-2.58	0.01*

** Statistically significant differences between the two treatment groups.*

TEMP= Temperature
PR= Pulse rate
RR= Respiratory rate

Table 4: Percentage bacteria eradication rate and radiological clearance at follow-up of patients in Cefixime and Ciprofloxacin groups.

Patients with radiological consolidations and bacterial isolates

Type of follow up	Days	Cefixime No (%)	Ciprofloxacin No (%)	χ2-value	P – value
1.Radiological clearance	1	39(100.0)	34(100.0)	-	
	14	4(10.3)	13(38.2)	7.96	0.01*
2. Microbiological	1	39(100.0)	34(100.0)	-	
(Bacterial eradication rate)	3	30(76.9)	29(85.3)	0.82	0.37
	7	5(12.8)	21(61.8)	18.98	0.0001*
	14	3(7.7)	13(38.2)	9.90	0.002*

**Statistically significant differences between the 2 treatment groups.*

Table 5: Distribution of the lung lesions and percentage clearance on days 1 and 14 in Cefixime and Ciprofloxacin drug groups.

		Cefixime No (%)	Ciprofloxacin No (%)	TOTAL No (%)
Left Lower Zone	Day 1	25 (64.1)	25(73.5)	50(68.5)
Left Lower Zone	Day 14	2(5.1)	10(29.4)	12(16.4)
Left Mid & Lower Zone	Day 1	3(7.7)	0(0.0)	3(4.1)
Right Lower Zone	Day 14	-	-	-
Left Mid Zone	Day 1	0(0.0)	1(2.9)	1(1.4)
	Day 14	-	-	-
Right Lower Zone	Day 1	10(25.6)	7(20.6)	17(23.3)
Right Lower Zone	Day 14	2(5.1)	3(8.8)	5(6.8)
Right Mid Zone	Day 1	0(0.0)	1(2.9)	1(1.4)
	Day 14	-	-	-
Right Upper Zone	Day 1	1(2.6)	0(0.0)	1(1.4)
	Day 14	-	-	-

Left lower and right lower zones were the zones mostly affected by the consolidative changes on chest-x-ray accounting for 92.1%.

Table 4 shows the results of the secondary efficacy parameters of the two drugs in terms of their bacterial eradication rates and radiological clearance at follow-up of the patients. The distribution of lung lesions and percentage clearance on days 1 and 14 in the 2 treatment groups is demonstrated in Table 5. The predominant bacterial aetiology of community-acquired pneumonia in this study was *Staphylococcus aureus 29 (39.7%)*, followed by *Streptococcus pneumoniae 11(15.1%)*, *Klebsiella pneumoniae* 10(13.7%), *Escherichia coli* 17(23.3%) and *Proteus mirabilis 6* (8.2%).

As regards the safety parameters considered for the two drugs, there were no adverse drug effects observed or reported by any of the patients in the two arms of treatment. The liver function tests, urea and creatinine, complete blood counts were essentially of normal values in all the patients at baseline and end of treatment.

DISCUSSION

Community-acquired pneumonia (CAP) is a cause of substantial morbidity, mortality, and resource utilization worldwide. Despite substantial progress in therapeutic options, CAP remains a significant cause of morbidity and death, and, there continues to be a major controversy concerning the antimicrobial management of this infection.[16] The mixed aetiology and the changing susceptibility of pathogens causing CAP, in particular, that of *Streptococcus pneumoniae,* has created a challenge, in some circumstances, to clinicians in terms of optimal outcome.[17]

Initial antimicrobial therapy is normally given empirically before the bacterial cause of the infection can be determined in the laboratory, and, in many cases, treatment is empirical throughout due to lack of reliable microbiological data. An understanding of the possible pathogens and resistant patterns is therefore helpful in guiding antibiotic choice. A detailed knowledge of the local susceptibility of the potential pathogens would ensure a more appropriate selection of the antimicrobial agent to be used.[18,19] In this environment, ciprofloxacin is the most commonly used antibiotics for management of infections including RTIs, being the most readily available and very cheap, which leads to the comparison of it's efficacy and safety with cefixime in this study.

The choice of these empirical antibiotics for CAP in this study was in conformity with the guildelines of IDSA (Infectious Disease Society of America)/ATS (American thoracic society)/Canadian guidelines (CIDS,CTS).[20-23] The major criterion that guided the management decision of the CAP patients revolved around the initial assessment of the severity since the oral route can only be recommended in these non-severe (mild to moderate) pneumonia which was the case in this study.[22,23]

The finding of persistent residual radiological changes in this study is in keeping with the observation of earlier researchers that radiographic response to treatment usually lags behind clinical improvement and pneumococcal pneumonia may take 6 weeks to clear on the chest film.[24,25] This delay of the radiographic clearing that contrasts with the rapid clinical response seen on the third day of antibiotic treatment was one of the striking findings in this study.

The results of our study show that cefixime administered at the dose of 400mg twice daily is an effective oral antibiotic treatment in the management of community-acquired pneumonia in adults. This is in keeping with most previous clinical studies that found it very effective for lower respiratory tract infections.[26-32] The efficacy of cefixime in acute exacerbation of chronic bronchitis (AECB) has also been well documented in both comparative and non-comparative clinical studies.[33,34].

In this study, the predominant cause of community-acquired pneumonia was *Staphylococcus aureus 29 (39.7%)*, followed by *Streptococcus pneumoniae 11(15.1%)*, *Klebsiella pneumoniae* 10(13.7%), *Escherichia coli* 17(23.3%) and *Proteus mirabilis 6* (8.2%).

This is contrary to a study conducted in the United States in 2006, where, in approximately 4.2 million ambulatory care visits for CAP, *Streptococcus pneumoniae* was the most commonly identified pathogen.[35-37]

None of the patients experienced vital signs of potential clinical concern or reported any adverse events during the course of study in the two arms of treatment. Cefixime was found to be safe and well tolerated in all the patients which contrasts the previous documentation of mild or moderate diarrhea and epigastric discomfort.[31-33] Thus, cefixime was shown to be superior to ciprofloxacin in the treatment of bacterial pneumonia among adults who have been properly assessed not to need hospitalization in Nigeria.

Limitation of the study

The clinical efficacy of Cefixime should also be compared with the new-generation fluoroquinolones (clionfloxacin, gemifloxacin, levofloxacin or moxifloxacin) and with another potent third-generation cephalosporins (cefpodoximeproxetil).

The on-going research will address this and help the clinicians with the right choice of empiric antibiotic treatment of CAP in Nigeria.

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