CLINICAL ROLE OF CEFIXIME IN COMMUNITY-ACQUIRED INFECTIONS

Dreshaj Sh1, Doda-Ejupi T1, Tolaj IQ1, Mustafa A4, Kabashi S2, Shala N3, Geca Nj1, Aliu A1, Daka A5, Basha N6

1Infectious Diseases Clinic, Prishtina Medical Faculty, Kosovo
2Institute of Radiology, Prishtina Medical Faculty, Kosovo
3Neurologic Clinic, Prishtina Medical Faculty, Kosovo
4ENT Clinic, Prishtina Medical Faculty, Kosovo
5Dermatovenerology Clinic, Prishtina Medical Faculty, Kosovo
6Clinical Biochemistry Institute, Prishtina Medical Faculty, Kosovo

Abstract: Cefixime is an oral third generation cephalosporin, frequently used in respiratory tract infections (RTI) in the pediatric population. However, in some publications cefixime has demonstrated poor efficacy against staphylococci and streptococci.

The aim: of this study was to evaluate the efficacy of cefixime in the treatment of community-acquired infections in a country where parenteral third generation cephalosporins have been used for a long time.

The present study was designed to assess the clinical efficacy, bacteriological eradication rates and tolerability of cefixime in children with community-acquired upper RTI (URTI), lower RTI (LRTI) and uncomplicated urinary tract infections (UTI).

Materials and methods: The study was prospective, open, and included 89 patients, from 6 months to 28 years, of both sexes, with the diagnosis of community-acquired URTI, LRTI and UTI.

Results: The treatment with cefixime was successful in 30/30 (100%) patients suffering from acute otitis media (AOM), in 10/12 (83.3%) with acute sinusitis, in 12/12 patients (100%) with pneumonia, and 31/35 (88.57) with uncomplicated UTI. The antibiotic was well tolerated. In 10 days treatment we recorded one case (1.3%) with acute gastroenteritis and two cases (2.6%) of maculopapular rash. Side-effects were transient and disappeared after finishing therapy in all three of the cases.
Conclusions: Community-acquired infections, such as AOM, LRTI and UTI, caused by susceptible pathogens, can be treated with cefixime, as a good choice for a successful clinical response.

Key words: cefixime, antimicrobial therapy, community-acquired infections.

Introduction

Cefixime was quickly established in the Western countries as a potent broad-spectrum antibiotic with a variety of indications. A multinational, worldwide study has confirmed the excellent efficacy of cefixime in children and adults [1]. Some authors recommend cefixime as a first line antibiotic in community-acquired URTI [2]. In one study susceptibility surveillance of 267 isolates of *Streptococcus pneumoniae*, 205 of *Streptococcus pyogenes*, 204 of *Hemophilus influenza*, and 147 isolates of *Moraxella catarrhalis* showed good sensitivity to cefixime and was recommended as the first line antibiotic for community infection of URTI and LRTI. [3, 4]. Other studies present good clinical efficacy of cefixime in URTI [5] and AOM [6], where community-acquired infections present a very high resistance to macrolides and high sensitivity to cefixime [7]. Also, cefixime had excellent success (92%) in the eradication of microorganisms and the side-effects which occurred were similar to therapy with other cephalosporins [8]. Other studies demonstrate similar efficacy in respiratory, urinary and community-acquired skin infections [9, 10]. Similarly, excellent efficacy of cefixime was found in adults with urinary tract infections (UTI), with a clinical cure in 80 patients (94%), improvement in 4 (5%), and failure in 1 (1%) [11]. Cefixime also demonstrated very good microbiological efficacy in 2724 isolates (urinoculture) from patients with community-acquired UTI, where all isolates were susceptible to cefixime, and the eradication rate was very high [12].

The global problem with antibiotic resistance, especially the growing resistance to first-line antibiotic treatment for community-acquired infections, has provoked many clinicians to experience other available oral antibiotics. Cefixime was offered as an alternative [13, 14]. Some other clinicians use cefixime in the prophylaxis of complicated UTI with good success [15].

However, in some publications cefixime has demonstrated poor efficacy against staphylococcus and streptococci. Therefore, they recommend avoiding it, if staphylococci or pneumococci cannot be ruled out [7].

The aim of this study was to evaluate the efficacy of cefixime in the treatment of various community-acquired infections in a country where parenteral third generation cephalosporins have been used for a long time. The pre-
sent study was designed to estimate the clinical cure, bacteriological eradication rates and tolerability of Cefixime in children with URTI, LRTI and uncomplicated UTI.

**Material and methods**

The study was prospective, randomized, open, noncomparative and included 89 patients, aged 6 months to 28 years, of both sexes, with a diagnosis of community acquired URTI, LRTI and UTI were included in the study.

**Inclusion Criteria:**

Including criteria for patients with community-acquired infections were:
- a minimum of one acute infection treated with ceftriaxone parenterally and
- a confirmed diagnosis with clinical, biochemical and radiological examinations.

The etiology was confirmed using swabs and culture from the patients. Deep nasal and deep nasopharyngeal swabs were examined in patients with acute sinusitis. If the isolation showed the same microorganisms in both swabs, we used it as a real etiological agent.

In patients with AOM, the etiology was confirmed with the fluid from the middle ear obtained by tympanocentesis, or swab from the external channel if the membrane was perforated.

In patients with LRTI, the etiology was confirmed using a culture of sputum.

In patients suffering from UTI, the etiology was confirmed using a three times positive urine culture with more than 100,000 microorganisms per ml. Patients with a history of hypersensitivity to ceftriaxone, cefpodoxime, cefixime or any other cephalosporin were excluded from the study.

**Study procedures.** Patients fulfilling the inclusion criteria received cefixime 8 mg/kg/day once per day for 10–14 days, without regard to meals. Patients were evaluated on the 1st day, after 48h, after 72h, after 96h, and at the end of therapy (on the 10th day).

Patients were considered to be compliant with the study medication if at least 80% of study medications were taken according to the prescribed regimen. Otherwise the patient was considered to be non-compliant.
Evaluation visits. The physician examined the patient and recorded adherence to therapy, any adverse drug reactions and the clinical response on the following days:

Visit 0: Day 0, study admission visit; Visit 1: Day 2, mid-therapy visit; Visit 2: Day 3; Visit 3: Day 4 and, Visit 4: Day 10–14, end of therapy.

Symptoms of infection: fever was assessed at each visit. Patients were also monitored for any complications.

Efficacy assessment. The main outcome measures were:
1. Bacteriological and clinical response of signs and symptoms of URTI, LRTI and UTI, determined at end of therapy.
2. Physician Global evaluation of patient condition (using a 5-point scale):
   1 = Excellent,
   2 = Very Good,
   3 = Good,
   4 = Fair,
   5 = Poor.

   Clinical outcome was defined as follows: Clinical cure (defined as a complete resolution of signs and symptoms); Improved (if clinical signs & symptoms diminished, but did not completely resolve); Failure (if the signs and symptoms worsened, persisted or reappeared).

Safety assessment. Patients were closely monitored for adverse clinical events. The severity of clinically adverse events was categorized as: mild, moderate, or severe.

The adverse reactions were classified as: probably drug–related, possibly drug-related, not drug-related, or with an unknown relationship to the study drug.

Statistical analysis. Collected data were processed by the Sigma Stat and Instat 2 computer program. Comparison of signs and symptoms of disease before and after therapy was done by a paired t-test. The limit of significance was set at p value < 0.05.

Results

Community-acquired infections in 89 patients of different ages and with different diagnoses were treated during a period of 6 months in the University Clinical Centre (UCC) in Prishtina, Kosovo. All isolates was susceptible to cefixime.
The cumulative data and laboratory analysis used for follow-up of the patients that fulfilled the criteria for treatment are presented in Table 1. During the treatment with cefixime we evaluated WBC, CRP and ESR. As presented in Table 1, during the treatment with cefixime the total number of WBC decreased within 72h, with a statistical significance ($p > 0.05$). The finding was similar for the CRP value, with a statistical significance after 72h ($p > 0.05$). ESR, as the parameter for evaluation of the efficacy of cefixime, did not present a statistically significant reduction comparing the value from the beginning and at the end of treatment ($p < 0.05$). (Table 1)

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Nr. of patients</th>
<th>Mean age</th>
<th>WBC Day 0</th>
<th>Day 2</th>
<th>Day 3</th>
<th>CRP Day 0</th>
<th>Day 2</th>
<th>Day 3</th>
<th>ESR Day 0</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOM</td>
<td>30</td>
<td>6.9 ± 3.87</td>
<td>15.7 ± 2.69</td>
<td>10.6 ± 2.8</td>
<td>8.05 ± 1.89</td>
<td>37.76 ± 21.9</td>
<td>32.33 ± 17.7</td>
<td>13.13 ± 5.7</td>
<td>23.8 ± 15.2</td>
<td>12.1 ± 5.79</td>
<td></td>
</tr>
<tr>
<td>Acute sinusitis</td>
<td>12</td>
<td>15.7 ± 3.79</td>
<td>15.19 ± 1.95</td>
<td>12.85 ± 1.27</td>
<td>8.2 ± 2.05</td>
<td>18.33 ± 6.08</td>
<td>12.6 ± 4.92</td>
<td>8.0 ± 2.95</td>
<td>20.58 ± 12.2</td>
<td>14.8 ± 6.56</td>
<td></td>
</tr>
<tr>
<td>LRTI</td>
<td>12</td>
<td>7.74 ± 4.84</td>
<td>17.66 ± 2.9</td>
<td>14.9 ± 2.42</td>
<td>10.59 ± 1.43</td>
<td>53.5 ± 26.88</td>
<td>45.16 ± 9.85</td>
<td>37.16 ± 6.29</td>
<td>20.5 ± 11.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>35</td>
<td>4.62 ± 3.61</td>
<td>10.2 ± 3.10</td>
<td>8.04 ± 2.58</td>
<td>7.6 ± 1.51</td>
<td>23.54 ± 9.05</td>
<td>16.8 ± 5.88</td>
<td>10.9 ± 4.53</td>
<td>27.51 ± 17.7</td>
<td>18.31 ± 7.86</td>
<td></td>
</tr>
</tbody>
</table>

WBC – white blood count, CRP – C reactive protein, ESR – erythrocyte sedimentation rate

Success of Cefixime in treatment of AOM. In this group we selected 30 patients of both sexes with a mean age 6.9 (± 3.8725 years). Of a total of 30 pts., 17 were male and 13 were female. The etiology was confirmed with a microbiological culture from the fluid of the middle ear obtained with tympanocentesis or a swab from the external channel, if the membrane was perforated. Patients with a sterile culture were eliminated from the study. In 17 (56.66%) we isolated Streptococcus pneumonia, in 5 (16.67%), in 4 (13.33%) Staph. aureus, in 2 (6.67%) Moraxella catarrhalis, in 2 (6.67%) E. Coli. The etiological agents are presented in the Graph 1.

Using a five point scale, clinically cefixime was effective in treatment of AOM in 92.4%. The clinical outcome of AOM treated with cefixime resulted in a cure in 93.33%. (Graph 4.)
Success of Cefixime in the treatment of Acute Sinusitis

In this group we selected 12 patients, 50% male and 50% female, with mean age 15.7 ± 3.79 years. In 4 pts the acute infection affected one-side maxillary sinus, in 2 pts – frontal sinus, and in another 2 pts pansinusitis was detected. Other patients had various combinations. Etiology was confirmed in 10 patients. In 4 patients we isolated *Streptococcus pneumoniae*, in 3 pts – *Moraxella catarrhalis*, in 2 pts – *Staph. aureus*, and in one patient we confirmed mixed flora with *Staph. aureus* and *Streptococcus pneumoniae*. All isolates were susceptible in Cefixime (Graph 2). Clinically using a five-point scale cefixime was effective in 83.33%. Clinical outcome of acute sinusitis treated with cefixime resulted with cure in 66.67% and failed in 0.12%. (Graph 4.)
Success of Cefixime in the treatment of LRTI

In this group we selected 12 patients, 6 male and 6 female, with mean age $7.74 \pm 4.84$ years. The etiological agent was confirmed in 5 of them from the culture of sputum: in four of them Streptococcus pneumoniae was isolated from sputum, and in one Haemophilus influenzae. Radiological changes were detected as typically pneumonia in 5 pts and as bronchopneumonia, in 7 pts. Using a five-point scale, in patients with LRTI cefixime showed excellent and very good success in 10/12 patients. (83.33%). The efficacy of cefixime in the clinical outcome of these patients showed very good results in 10/12 (83.33%), without fail. (Graph 4)

Success of Cefixime in the treatment of uncomplicated UTI

35 patients with acute urinary tract infection were included in this group. 19 patients (54.28%) were male and 16 (45.61%) were female with a mean age of $4.62 \pm 3.61$ years. E. coli was the most frequent pathogen, isolated in 48.6% of pts with UTI, and Proteus spp. in 20%. In 11.4% mixed flora was isolated (Graph 3). Using a five-point scale, in UTI, cefixime showed very good efficacy in 29/35 (83.6%). (Tables 2, and 3, Graphs 4, and 5). In 4/35 (11.43%), cefixime was not effective.

Graph 3 – Etiology of UTI in our patients

In general, using a five-point scale cefixime showed excellent and very good clinical success in 86.52% of the various community-acquired infections. The evaluation of cefixime through clinical outcome was impressive, resulting in 82.02% clinical cure. (Graph 5)
Table 2

Physicians’ global evaluation of patient condition at end of treatment (using 5-point scale)

<table>
<thead>
<tr>
<th></th>
<th>AOM (%)</th>
<th>Acute sinusitis (%)</th>
<th>LRTI (%)</th>
<th>UTI (%)</th>
<th>General (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>30 (83.33)</td>
<td>12 (58.34)</td>
<td>12 (66.67)</td>
<td>35 (71.43)</td>
<td>89 (73.034)</td>
</tr>
<tr>
<td>Very good</td>
<td>30 (10.0)</td>
<td>12 (16.67)</td>
<td>12 (16.67)</td>
<td>35 (11.42)</td>
<td>89 (13.48)</td>
</tr>
<tr>
<td>Good</td>
<td>30 (6.67)</td>
<td>12 (8.33)</td>
<td>12 (16.67)</td>
<td>35 (5.71)</td>
<td>89 (7.86)</td>
</tr>
<tr>
<td>Fair</td>
<td>0</td>
<td>12 (8.33)</td>
<td>0</td>
<td>35 (5.71)</td>
<td>89 (3.37)</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>12 (8.33)</td>
<td>0</td>
<td>35 (5.71)</td>
<td>89 (3.37)</td>
</tr>
<tr>
<td>Total</td>
<td>30 (100%)</td>
<td>12 (100.0)</td>
<td>12 (100%)</td>
<td>35 (100.0%)</td>
<td>89 (100.0)</td>
</tr>
</tbody>
</table>

Graph 4 – Physicians’ global evaluation of patients treated with cefixime at the end of treatment (using 5-point scale)

Graph 5 – Clinical outcome of patients treated with cefixime

Clinical outcome of patients treated with cefixime

<table>
<thead>
<tr>
<th></th>
<th>AOM Nr</th>
<th>%</th>
<th>Acute sinusitis</th>
<th>%</th>
<th>LRTI</th>
<th>%</th>
<th>UTI</th>
<th>%</th>
<th>General</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td>30 (28)</td>
<td>93.33</td>
<td>12 (8)</td>
<td>66.66</td>
<td>12 (10)</td>
<td>83.33</td>
<td>35 (27)</td>
<td>77.14</td>
<td>89 (73)</td>
<td>82.02</td>
</tr>
<tr>
<td>Improved</td>
<td>30 (2)</td>
<td>6.66</td>
<td>12 (3)</td>
<td>33.33</td>
<td>12 (2)</td>
<td>16.66</td>
<td>35 (4)</td>
<td>11.4</td>
<td>89 (11)</td>
<td>12.35</td>
</tr>
<tr>
<td>Failure</td>
<td>30 (0)</td>
<td>0.00</td>
<td>12 (1)</td>
<td>0.12</td>
<td>12 (0)</td>
<td>0.00</td>
<td>35 (4)</td>
<td>11.4</td>
<td>89 (5)</td>
<td>5.6</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100.0</td>
<td>12</td>
<td>100.0</td>
<td>12</td>
<td>100.0</td>
<td>35</td>
<td>100.0</td>
<td>89 (89)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Cefixime presented very good activity in the elimination of the isolated microorganisms. Streptococcus pneumonia was eliminated in 27/29 (93.1%), Moraxella catarrhalis in 100%, E. Coli, Klebsiella and Proteus in 32/35 (93%). The efficacy of cefixime in the elimination of Staph. Aureus in RTI was 82.02% and in UTI 33.33%. Through the clinical outcome, the general success with a clinical cure was 82.02% of respiratory tract and 33.33% from UTI. In total, cefixime was a well tolerated and safe drug with general side effects evidenced in 3.48% (3 pts), where severe reactions was not evidenced. The moderate and mild reactions did not require the discontinuation of therapy with cefixime. (Table 4)

Safety assessment of patients treated with cefixime

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>General</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Mild</td>
<td>89 (2)</td>
<td>2.25</td>
</tr>
<tr>
<td>Moderate</td>
<td>89 (1)</td>
<td>1.23</td>
</tr>
<tr>
<td>Severe</td>
<td>89 (0)</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>89 (3)</td>
<td>3.48</td>
</tr>
</tbody>
</table>

Discussion

Cefixime has been used for more than ten years throughout the world, with various efficacies. Pathogens causing community-acquired infections in the global population have started to develop resistance to the standard first-line recommended antibiotics. There are some publications that recommend changes in the first-line empirical therapy because of the growing rate of antibiotic resistance, and nowadays in some countries cefixime is becoming the first line antibiotic for treatment of URTI, LRTI, UTI [1, 5, 6, 13, 14,17].

The aim of this study was to define the efficacy of the oral third generations in the treatment of the most frequent infections diagnosed in general practice. Parenteral third generation cephalosporin-ceftriaxone is widely used in
Kosovo. Recently, the growing rate of antibiotic resistance to the most frequently used parenteral third generation cephalosporin in community-acquired infections was noticed in Kosovo. This study was designed to evaluate the efficacy of oral third generation cephalosporin-cefixime given as a single dose to outpatients with a confirmed community-acquired infection. Patients included in the study had been treated with ceftriaxone or other antibiotics before the prescription of cefixime. In the study, we evaluated the ESR (erythrocytes sedimentation rate), WBC (white blood cells), CRP (C-reactive protein), then the clinical outcome, the efficacy and the side effects of cefixime in the treatment of community-acquired infections and also the eradication of isolated bacteria. Results showed the best efficacy of cefixime in patients suffering from AOM and LRTI, with a cure in 93.3% and 83.33% respectively. Other authors have also presented similar results worldwide [13, 15, 17]. For sinusitis and uncomplicated UTI the rate of cure was 66.67% and 77.14% respectively. Similar results have been found by other authors where cefixime was recommended as the first line of antibiotic for treatment of UTI, partially in childhood, but not for acute sinusitis [1, 7, 12]. In our study, cefixime was prescribed in patients with recurrent UTI, who had previously been treated with several antibiotics. The gender structure of our patients presented a similar incidence of infection in both sexes. The aim of our study was not to analyse the prevalence of UTI in a large community group, but only to present the patients with recurrent UTI that we treated.

The results of the efficacy of cefixime in patients with URTI caused by Streptococcus pneumoniae were 27/29 (93.1%), but in patients where the isolation of Streptococcus pneumoniae was combined with Staphylococcus aureus, cefixime failed in treatment. Cefixime has an excellent activity against Moraxella catarrhalis, 4/4 (100%). Cefixime in infections caused by Staph. aureus was effective in 2/3 cases (66.67%). This antibiotic will not be recommended for the treatment of infections caused by Staph. aureus. Cefixime was effective in 31/35 (88.57%) of patients with uncomplicated UTI, in infections caused by susceptible pathogens such as E. coli, Proteus spp and Klebsiella. In patients with UTI caused by S. aureus, cefixime failed in the eradication of the specified pathogen in 66.67% of the cases. The effectiveness of the treatment with cefixime in community-acquired infections was evaluated with biochemical tests and improvement was noticed in a short period: WBC were normalized after 72h, CRP clearly decreased in the first 72h, with significance after 96h (p > 0.001), while CRP was completely normalized after 7 days. Radiological improvements in patients with sinusitis and pneumonia were documented after 10 days.

The drug was well tolerated. In 10-days treatment we recorded one case (1.3%) of acute gastroenteritis, and maculopapular rash in two cases (2.6%). The side-effects were transient, without the need to discontinue the therapy and they disappeared after finishing the therapy.

From these results we conclude that cefixime proves good efficiency in patients with community-acquired infections suffering from AOM, LRTI and in UTI. In cases of acute infections where Staphylococcus aureus is a suspected
pathogen, cefixime is not recommended as a therapy and needs to be replaced with another antibiotic, according to susceptibility at the antibiogram. Cefixime was well tolerated and there was no need of therapy discontinuation. Our study showed excellent compliance from the patients and parents to the protocol of cefixime in the treatment of AOM, LRTI, and UTI.

REFERENCES


Цел: Студијата имаше за цел да се процени ефикасноста на оралниот третогенерациски цефалоспорин-цефиксим во третманот на инфекциите стекнати во заедница, во држава каде што долго време се употребуваат парентерални цефалоспорини од третата генерација.

Овaa студија е дизајнирана со цел да ја прикаже клиничката ефикасност, стапката на бактериолошката ерадикација и толерантноста на цефиксим кaj деца со стекнати горни и долни респираторни инфекции (РТИ) и некомплшириани уринарни инфекции (УТИ).

Материјали и методи: Студијата е проспективна, отворена и во неа беа вклучени 89 пациенти (на возраст од 6 месеци до 28 години) од обата пола, со дијагноза за инфекции стекнати во заедницата (РТИ и УТИ).

Резултуаати: Терапијата со цефиксим беше успешна кај 30/30 (100%) од пациентите со акутен отитис медиа (AOM), кај 10/12 (83,3%) со акутен синузитис, кај 12/12 пациенти (100%) со пневмонија, кај 31/35 (88,57%) со некомплшириани УТИ. Лекот беше добро толериран. За време на 10-дневниот третман регистрираaме един случаа (1,3%) со акутен гастроентеритис и два случаа (2,6%) со макулопапуларна егзема. Кaj сите три случаи, несаканите ефекти беа благи, транзи-торни и исчезнаа по завршувањето на терапијата.

Заклучок: Студијата покажа дека цефиксимот претставува добар избор во третманот на пациенти со инфекции стекнати во заедница, пациенти кои страдаат од акутен отитис медиа, долни респираторни инфекции и некомпишириани уринарни инфекции.

Ключни зборови: цефиксим, антимикробна терапија, инфекции стекнати во заедница.

Corresponding Author:
Shemsedin Dreshaj
Infectious Diseases Clinic
Director
Qendra Klinike Universitare e Kosovës – QKUK
10000 Prishtina, Kosovo
E-mail: shemsedindreshaj@msn.com

Norma Budima-Basha
Institute of Clinical Biochemistry
Qendra Klinike Universitare e Kosovës – QKUK
10000 Prishtina, Kosovo

Приложи, Од. бил. мед. науки, XXXII/2 (2011), 143-155