The Efficacy and Safety of Cefaclor in Respiratory Infections amongst

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Abstract

Purpose: To evaluate the efficacy and safety of Cefaclor in respiratory tract infections amongst Pakistani children.
Patients and Methods: Multicenter, open label and non-comparative study was done to evaluate the response in terms of symptoms (In vivo) and bacterial cultures (In Vitro) to Cefaclor amongst children with respiratory tract infection between the ages 2 months to 12 years. Each patient was asked to visit the doctor on three occasions i.e., Day 0 (initial evaluation prior to commencement of study), Day 4 (During therapy assessment and confinnation of compliance) and Day 10 (End of therapy assessment and compliance evaluation). Representative swab specimens (Throat swabs, Ear swabs or Sputum) were collected from the infected site on day 0 and day 10 for culture and sensitivity. Patients were also assesed by the evaluators on each visit in terms of clinical symptomatic response and information collected was documented on a prescribed data base form.
Results: A total of 160 patients were enrolled in the study, of whom 15 were lost to follow-up between the first and second visit and a further 38 were lost by the 3rd visit. Thus 107 patients completed the study as per protocol. Otitis media and Upper respiratory tract infection were the predominant ailments amongst the cases enrolled. One or more bacteria were isolated in 75 (46%) instances, the maximum number of isolates being from ear swabs of Otitis media patients. Beta haemolytic Streptococcus (group A,C,F,G) seen in 18 cases was the most common pathogen reported followed by Staphylococcus aureus, H. influenzae and Streptococcus pneumoniae in 13,12 and11 cases respectively. Sensitivity of Cefaclor for bacteria commonly seen in the respiratory tract was greater than 90% in most of the cases. Evaluation of the 42 culture proven cases for patients who completed the study showed that Cefaclor had a 93% efficacy for indicated bacteria and 54 % for non-indicated bacteria. In Vivo analysis of Cefaclor (i.e. on the basis of symptomatic response) showed that 96 % cases had a symptomatic response by the second visit, which improved to 97 % by the third visit. Only 15 non-serious adverse events were observed in 160 patients, none of the cases necessitated discontinuation of drug. Mild gastrointestinal symptom was the most common adverse event reported.
Conclusion: Cefaclor was found to be a safe and efficacious drug in the treatment of bacterial respiratory tract infections amongst Pakistani children (JPMA 50:289, 2000).

Introduction

Respiratory tract infection is one of the foremost infective problems amonGst children world over with

a significant number of cases presenting a bacterial pathology necessitating the use of antibiotics [1]. Traditionally, antibiotics like Penicillins or Sulfonamides or their derivatives have been used in combating such infections, however with the advent of resistant respiratory pathogens physicians have started looking towards other alternatives. Cefaclor, a Beta Lactam antibiotic of the Cephalosporin group, has proved to be effective in dealing with various respiratory pathogens. Its antibacterial spectrum, bactericidal activity, clinical efficacy and low toxicity makes it a good antibiotic and an efficacious choice. lts efficacy being further enhanced by its ability to effectively act against penicillinase and beta-lactamase producing organisms making this group of drugs amongst one of the 1000 most frequently prescribed drugs the world over [2].

Data on epidemiology of respiratory infections amongst children in Pakistan is very scant. We studied this aspect and evaluated the efficacy of Cefaclor in dealing with respiratory tract infection[3].

A multicenter, open label, non-comparative study was conducted involving 17 physicians from 5 cities within Pakistan. Enrollment of patients was done according to a predefined inclusion and exclusion criteria (Table 1)

Table 1. Inclusion/exclusion criteria for patient enrolement.

Inclusion Criteria
1. Diagnosis of Upper respiratory tract infection or Otitis media or Lower respiratory tract Infection by the Physician, subsequently proven by microbiological analysis of the infected area specimen.
2. Patient with Upper respiratory tract infection or Otitis media or Lower respiratory tract infection due to cefaclor resistant organism on in vitro tests but are showing marked clinical improvements after 4 days of treatment.
3. Investigator will attempt to select those patients and parents or guardians who have a history of complying with instructions.
4. Patients, male and female, 2 months to 12 years of age.
5. Parents and guardian must sign an Ethical Review Board approved form.
Exclusion Criteria
1. Any condition, including significant underlying disease or concomitant infection which, in the opinion of the investigator, could preclude evaluation of response, including but not limited to: chronic diarrhoea, irritable bowel or malabsorption syndromes.
2. Anticipated requirement of systemic antibiotics other than the study antibiotic after the pre therapy and before the post therapy evaluation.
3. Inability of patient to return for follow-up examinations.
4. Hypersensitivity to cephalosporins or penicillin.
5. Use of other investigational agents within 28 days prior to entry into the study.
6. History of significant renal or hepatic impairment.
7. Treatment with an antibiotic with last dose within 72 hours of enrolment.

subject to approval by the Ethical Review Board (ERB) of the Department of Microbiology University of Karachi. The aim of the study was to establish the efficacy and safety of Cefaclor in upper and lower respiratory infections amongst children aged 2 months to 12 years. Data was collected on prescribed clinical report forms (CRF) within specific pre defined guide lines. Written informed consent was taken

prior to enrolling patients as per the ERB approved guidelines. A representative swab specimen was collected from the infected site prior to commencement of antibiotic and a second specimen was collected after the completion of a 7-10 days course of the antibiotic. All specimens were evaluated at Aga Khan University Hospital Laboratories (Karachi) or Liaquat National Hospital Laboratories (Karachi) and analyzed under independent quality control for culture and sensitivity of the organisms. Cefaclor (CECLOR® Eli Lilly Pakistan) was administered in a dose of 20-40 mg/Kg/Day in three divided doses for a period of 10 days.

Patients were evaluated on the basis of symptomatic response and the pre and post antibiotic response of the bacteriologic specimens. Each patient visited the doctor on three occasions i.e. Day 0 (Initial evaluation prior to commencement of study), Day 4 (During therapy assessment and confirmation of compliance) and Day 10 (End of therapy assessment and compliance evaluation). On each visit information collected was documented as per specific guidelines in a data base form (CRF). Cefaclor (CECLOR®) 125 mg/S ml granules were supplied to patients with specific instructions on its use by the investigators. In submitting the data patient identity was masked from the evaluators. Concomitant medication needed for therapeutic (with the exception of antibiotics) purposes was considered as acceptable. In filling out the CRF's a section was also dedicated for recording any adverse events reported by the patients or observed by the Physicians.

Results

A total of 160 patients were enrolled in the study of whom 15 were lost to follow-up between the first and second visit and a further 38 were lost by the 3rd visit. Thus 107 patients completed the study as per our protocol.

The efficacy of the drug was analyzed for both Cured (culture proven cases) and Improved (Symptomatic response) patients separately, sensitivity of the drug with the pathogens isolated and the safety of the drug (based on the reported cases of adverse effects).

The most common ailments were URTI and Otitis media (Table 2).

Table 2. Breakdown of the infection diagnosed by symptoms

Sr. no.	Otitis Media		Upper Respiratory Tract Infection (s)		Lower Respiratory Tract Infection (s)	
1	Acute	43	Tonsillitis	48	Bronchitis	29
2	Chronic	34	Pharyngitis	32	Pneumonia	3
3	Other	3	Sinusitis	8	Acute Pneumonia	1
4			Other	12	Other	1
5	Total	80	Total	100	Total	34

Cultures showed isolation of single bacteria in 57 cases and isolation of two or more bacterial pathogens in 18 cases. Out of 75 (46%) culture positive cases (Table 3),

Table 3. Bacteria Isolated Cases by the initial diagnosis.

Sr. no.	Initial diagnosis	Culture Proven Cases	% of Positive Cultures	Total number of patients tested
1.	Otitis media, upper respiratory tract and lower respiratory infection	4	100	4
2	Otitis media and upper respiratory tract infection	14	56	25
3	Both upper and lower respiratory tract infections	6	28	21
4	Otitis media only	45	88	51
5	Only Upper respiratory infections	4	8	50
6	Only Lower respiratory infections	2	22	9
	Total	75	46	160

the maximum were taken from ear swabs of patients with Otitis media, A wide spectrum of bacterial pathogens was seen amongst the cultures sent for microbiological analysis. Beta haemolytic Streptococci (group A,C,F,G) seen in 18 cases was the most common pathogen reported followed by Staphylococcus aureus, H. influenzae and Streptococci pneumoniae in 13,12 and 11 cases respectively. Sensitivity for indicated bacteria as well as non-indicated bacteria commonly seen in the respiratory tract was found to be very good for cefaclor (Table 4).

Table 4. Indicated and Non-Indicated Bacteria isolated and sensitivity with Cefaclor.

Sr. nc	Bacteria	Reaction with Cefaclor			Total	% Sensitivity
		Sensitive	Resistant	Not done		
1	**Indicated:**					
2	BHS Group A	2	-	2	4	100
3	BHS Group C	5	-	-	5	100
4	BHS Group F	4	-	-	4	100
5	BHS Group G	4	-	1	5	100
6	Branhamella. Catarrhalis	1	-	-	1	100
7	H. Influenza	8	3	1	12	73
10	K. oxytoca	1	-	-	1	100
11	Staph. Aureus	10	2	1	13	83
12	Strept pneumonia	10	1	-	11	91
	Non-Indicated:					
1	A. Iwoffi	3	1	-	4	75
2	M. morganni	1	-	-	1	100
3	Ps. Aeruginosa	1	27	6	34	4
4	Pseudomonas-sp	1	5	-	6	17

In Vitro analysis of the 42 culture proven cases for patients who completed the study showed that Cefaclor had a 93% efficacy for indicated bacteria and 54 % efficacy for Non indicated Bacteria (Table 5).

Table 5. Culture proven cases (In vitro Response).

Sr. no.	Description	Indicated bacteria	Non-indicated bacteria	Total Patients
1	Patients who had both first and second culture	29	13	42
2	Patients whose first culture report was positive and second culture report was negative	27	7	
3	Bacteria found persistent	2	6	
4	Total	29	13	
5	Efficacy	93%	54%	

In Vivo analysis of Cefaclor (i.e., on the basis of symptomatic response) showed that 96 % of cases reported a symptomatic response by the second visit, which further improved, to 97% by the third visit. Only 15 cases of non-serious adverse events were observed
in 160 patients. These events were all of a trivial nature with mild gastrointestinal
symptoms predominating. These included nausea (5 cases), vomiting (3 cases) abdominal pain (4 cases) and diarrhoea (3 cases). None of these reported adverse events were of a nature to necessitate the cessation of the drug therapy.

Discussion

Respiratory tract infection is one of the most common infections that pediatricians encounter in their every day clinical practice with a significant number of cases having bacterial origin. An interesting finding in our study was the fact that in almost 54% of the cases no growth could be obtained on specimens sent for microbiological analysis. This could be attributed to so many reasons including the fact that these may have been viral infections. Traditionally Penicillins or Sulfonamides or their derivatives have proven to be very effective in the treatment of these conditions but with the passage of time pathogens have developed resistance to the commonly used antibiotics thus necessitating the need for use of other alternative antibiotic groups.

Ampicillin resistant strains of various respiratory pathogens were first reported in 1974 in the US and reports of the same became wide spread over the following years[4-6].

Mastro et al. in a review of 87 Streptococcus pneumoniae isolates of ARI amongst children in Pakistan reported a resistance pattern of 97% to at least one of the common antimicrobial drugs used for treatment of children, with a 62% decreased susceptibility to Cotrimoxazole (31% were fully resistant) and 39% resistance to Chloramphenicol. In the same study it was found that all isolates were susceptible to Cefaclor. Further more 29% of isolates were neither vaccine types nor vaccine-related types [7].

Because of these factors, second generation cephalosporins have come to the forefront in the treatment

of such conditions. Their efficacy, safety and relatively lower cost implications make them a good choice in such conditions. An added advantage in their use is of course the Penicillinase and Beta lactamase resistant properties of some of these in dealing with some common pathogens including Haernophilus[8]. In our study we have looked at some aspects of RTJ in our setting with particular reference to one such antimicrobial agent Cefaclor.

Data Collected from various clinical trials conducted in 15 European countries, South Africa, Canada and US has shown an in vitro susceptibility pattern for Cefaclor to common respiratory pathogens of greater than 90%[1]. The question however remains whether this susceptibility is also reflected in the pathogens we encounter in our country.

Ideally the efficacy of a drug is determined by the ability of the drug to eliminate the isolated bacteria. We tested the efficacy of the drug based on two criteria i.e. the culture proven efficacy (In vitro response) and the symptomatic efficacy (in vivo response). Studies have shown that in quite a number of cases the in vivo response of a particular drug may be different from the in vitro response, therefore it is important the two be evaluated separately[3]. Cefaclor in our study fully justified its use in respiratory infection in both categories. With respect to in Vitro response the study indicated that Cefaclor eliminated the indicated bacteria in 27 out of 29 patients (93% of culture proven cases) and in case of non indicated bacteria response was also quite encouraging where 7 out of 13 patients showed bacterial clearance (54% of culture proven cases).

0Previous studies indicate that efficacy of Cefaclor ranged from 84% to 95%[9]. Based on our study estimation of 95% confidence interval for the point estimate showed about 9% margin of error, which means that the efficacy of the drug was more than 88%.

The in vivo evaluation also showed very good results where 96% of the patients had shown a symptomatic improvement by the second visit (4-5th day) and almost 97% had shown significant clinical improvement by the time they finished the course (10th day).

Adverse events were recorded on all visits after the start of treatment. Only known (i.e., previously documented for cephalosporins) adverse effect of minor nature were reported. Events encountered _3 times were considered significant for analysis. Thes were abdominal pain, diarrhoea, nausea and vomiting comprising 9% of the total study population. As mentioned the events reported in our trial were all of trivial natures thus making the use of this drug extremely safe.

The clinical efficacy of Cefaclor (Ceclor®) for its use in respiratory infections was evaluated on the basis of two categories of responses (i.e., in vivo and in vitro).

Our study showed a 93% in vitro response and a 97% in vivo response to its use. We feel that the significance of the problem is such that further large-scale studies in this regards are the need of the hour, however based on the data we were able to collect from our study, Cefaclor seems to be a good, safe and efficacious drug in the treatment of bacterial respiratory tract infections.

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