

# THE USE OF CIPROFLOXACIN AMONG FILIPINO INFANTS AND CHILDREN: EXPERIENCE AT THE UNIVERSITY OF THE PHILIPPINES - PHILIPPINE GENERAL HOSPITAL, JUNE 1993 TO OCTOBER 1995

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## ABSTRACT

A descriptive study on the use of Ciprofloxacin among Filipino pediatric patients admitted at the University of the Philippines-Philippine General Hospital (UP-PGH) from June 1993 to October 1995 was done. The demographic, clinical, bacteriological profiles of these patients as well as the indications for the use of Ciprofloxacin, outcome of the therapy and adverse reactions were studied. Review of medical records of 28 patients given Ciprofloxacin at 10-20 mg/kg per day IV/PO (15 males and 13 females with ages ranging from 19 days to 15 years) showed a cure rate of 50%. Majority of patients who received Ciprofloxacin had septicemia. *Pseudomonas* and *Klebsiella* were the predominant organisms isolated. Mild abdominal discomfort was reported in one patient. The use of Ciprofloxacin among pediatric patients is justified for treatment of life-threatening infections for whom more conventional therapy is not available, either due to resistance or toxicity. Long-term follow-up of these patients should be done. It is also recommended that a multi-center study be conducted on the use of Ciprofloxacin among pediatric patients.

Key words: Ciprofloxacin                      *Pseudomonas*  
                  Septicemia                         *Klebsiella*

## INTRODUCTION

Quinolones are synthetic antimicrobial agents that are structurally related to nalidixic acid. Quinolones consist of a bicyclic ring structure with a carboxyl group at position 3, a keto group at position 4, a fluorine atom at position 6 and a piperazinyl group or a methyl piperazinyl group at C-7. Differences in the moiety present at the N-1 position or at the C-7 position markedly influence both microbiological and pharmacokinetic properties [1].

However, rapid development of resistance prompted the synthesis of newer compounds. The introduction of fluoroquinolones during the 1980's ushered in a new era of treatment of infectious diseases. They have broad anti-bacterial coverage that includes both gram-negative and gram-positive aerobic bacteria as well as *Mycobacterium sp.*, *Chlamydia sp.*, and *Mycoplasma sp.* Also included are strains of bacteria that are multi-

resistant to B-lactam antibiotics and aminoglycosides. They have good oral absorption with excellent tissue penetration, high potency and low incidence of resistance. Though, pharmacokinetic data of fluoroquinolones in children are still incomplete [1].

In the Philippines, Ciprofloxacin, a fluoroquinolone was launched in 1986.

The use of Ciprofloxacin has been limited in children because it has been shown to induce arthropathy among juvenile animals [2]. However, review of foreign literature showed that "compassionate-use" based-protocols, were adopted for many children treated with Ciprofloxacin mainly because it is the only antimicrobial with potential activity against multiply resistant and difficult to treat infections such as resistant *Pseudomonas aeruginosa* infections in children with cystic fibrosis and extraintestinal Salmonellosis.

There has been no local study yet on the use of Ciprofloxacin in children.

This paper will describe the use of Ciprofloxacin among pediatric patients admitted at UP-PGH. Specifically, this study will describe the following:

- a. demographic profile of the study population as to age and sex;
- b. clinical profile of the study population as to admitting diagnosis, previous antimicrobials used and types of infections;
- c. indications for treatment with Ciprofloxacin;
- d. duration of treatment with Ciprofloxacin;
- e. outcomes of therapy based on clinical and bacteriologic criteria; and
- g. adverse drug reactions.

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## MATERIALS AND METHODS

### A. Study Design

This is a descriptive study of pediatric patients aged 19 days to 15 years admitted from June 1993 to October 1995 at UP-PGH who were given Ciprofloxacin at 10-20 mg/kg per day, intravenously (IV)/per os (PO). This tertiary hospital has a bed capacity of 1475, 75% of which are charity beds.

### B. Data Collection

All Infectious Disease Service (IDS) referral logbooks from June 1993 to October 1995 were reviewed for patients given Ciprofloxacin. Previous to this, no records of use of Ciprofloxacin among pediatric patients admitted in this hospital existed. After identification of patients and their case numbers, a review of their medical records was conducted. Data on age, sex, admitting diagnosis, clinical course, indications for use of Ciprofloxacin, outcome of therapy and adverse drug reactions were collected.

### C. Statistical Analysis

Frequency and percentage distribution were mainly used to quantify the results of the study.

### D. Response to Treatment

Response to treatment were evaluated based on clinical and bacteriologic criteria.

#### I. Clinical Response

- Cure** - disappearance of all pre-treatment signs and symptoms
- Improvement** - satisfactory remission but without complete disappearance of signs and symptoms
- Failure** - no signs or remission of pre-treatment signs and symptoms or if patient died during or after completion of treatment

#### II. Bacteriologic Response

- Eradication of Pathogens** - elimination of original organisms on post-treatment cultures
- Failure** - persistence of the organisms in post-treatment cultures
- Superinfection** - new organisms such as *Candida sp.* were isolated on follow-up cultures

## RESULTS

A total of 33 patients admitted at a tertiary hospital in Manila were given Ciprofloxacin (10-20 mg/kg per day) IV/PO, over a period of 28 months. However, medical records of only 28 patients were available for review. There were 15

males and 13 females. The ages ranged from 19 days to 15 years. Most of these patients were less than 12 months old (57.2%) of which 13 (46.5%) were 3 months and below (Table 1).

Table 2 shows that six of these patients were admitted for respiratory distress syndrome secondary to prematurity. The rest were admitted because of CNS, gastrointestinal, pulmonary, renal and skin infections. One patient presented with a mediastinal mass on admission.

**Table 1** Number and percentage distribution of patients treated with Ciprofloxacin as to age and sex, Tertiary Hospital, June 1993 - October 1995.

Age Group	Male	Female	Total (%)
< 1 month	2	3	5 (17.9)
1-3 months	6	2	8 (28.6)
4-6 months	1	1	2 (7.1)
7-11 months	-	1	1 (3.6)
1-2 years	1	1	2 (7.1)
3-6 years	2	1	3 (10.7)
7-12 years	1	3	4 (14.3)
13-16 years	2	1	3 (10.7)
<b>TOTAL (%)</b>	<b>15 (53.6)</b>	<b>13 (46.4)</b>	<b>28 (100.0)</b>

**Table 2** Admitting diagnosis of patients given Ciprofloxacin, Tertiary Hospital, June 1993-October 1995.

Admitting Diagnosis	No. of Patients (%)
<b>CNS</b>	8 (28.6)
• Suppurative Meningitis	2
• Post-meningitic Hydrocephalus	2
• Acute Demyelinating Disease	1
• Microcephaly with non communicating hydrocephalus	1
• Multiple Brain Abscesses	1
• Massive Cerebral Edema secondary to Hypoxic Ischemic Encephalopathy S/P CP Arrest	1
<b>Pulmonary</b>	10 (35.7)
• Respiratory Distress Syndrome secondary to Prematurity	6
• Bronchopneumonia, Community-acquired	2
• Bronchial Asthma, In acute exacerbation	1
• Empyema Thoracis, l. r/o Lung Abscess r/o TB	1
<b>Gastrointestinal</b>	4 (14.3)
• Typhoid Fever	2
• Infectious Diarrhea T/C Necrotizing Enterocolitis	1
• Intussusception	1
<b>Renal</b>	1 (3.6)
• Nephrotic Syndrome with nephritic signs	1
<b>Skin</b>	1 (3.6)
• Infected Burn Wounds	1
<b>Neoplasm</b>	1 (3.6)
• Superior Mediastinal Mass	1
<b>Multiple Organ Involvement</b>	3 (10.7)
• Multiple Congenital Anomalies with Bronchopneumonia, Community-acquired	1
• Nephrotic Syndrome with Nephritic signs with Bronchopneumonia, Community-acquired	1
• TB Meningitis Stage III with Neurogenic Bladder	1
<b>TOTAL</b>	<b>28 (100.0)</b>

Table 3 shows that indications for giving Ciprofloxacin were septicemia in 21 patients, two had recurrent UTI, another two with multi-drug resistant typhoid fever and one each with suppurative meningitis, ventriculitis and multi-drug resistant TB.

**Table 3** Clinical indications for use of Ciprofloxacin according to type of infections, previous antimicrobials given and duration of treatment with Ciprofloxacin, Tertiary Hospital, June, 1993 – October, 1995.

No. of Patients (%) N=28	Type of Infection	Previous Antimicrobials	Duration of Treatment Ciprofloxacin (days)
21 (75)	Septicemia	Piperacillin Cefuroxime Ceftazidime Aminoglycoside Metronidazole Oxacillin Imipenem	1-14
2 (7.1)	Recurrent UTI	Ampicillin Co-trimoxazole Ceftazidime Aminoglycoside	10-14
2 (7.1)	Multi-Drug Resistant Typhoid Fever	Amoxycillin Chloramphenicol Co-trimoxazole	14
1 (3.6)	Suppurative Meningitis	Chloramphenicol Oxacillin Aminoglycoside Ceftazidime	1
1 (3.6)	Ventriculitis	Ceftazidime Cefotaxime Aminoglycoside	21
1 (3.6)	Multi-drug Resistant TB	INH Rifampicin Ethambutol PZA Streptomycin	> 60

All 28 patients were previously given other antimicrobials as listed in Table 3. The duration of treatment with Ciprofloxacin differed for each type of infection. One patient with multi-drug resistant TB is currently on his third month of intake of Ciprofloxacin along with other anti-TB drugs such as INH and Rifampicin. Another patient with suppurative meningitis was given Ciprofloxacin for only 24 hours because the relative requested discharge against medical advice. Four patients with septicemia died while on their first five days of treatment with Ciprofloxacin.

Table 4 shows the bacteriologic response of isolated microorganisms to Ciprofloxacin. Majority of the isolates were *Pseudomonas sp.* (25%) and *Klebsiella sp.* (25%). Fifty percent (50%) of these isolates were eradicated on repeat cultures after treatment with Ciprofloxacin. Six patients developed superinfection with *Candida*, three of whom had previous isolates of *Klebsiella sp.*, two with *Acinetobacter sp.* and one with *Pseudomonas sp.* Three patients had negative cultures pre- and

post-treatment with Ciprofloxacin. One was a case of multi-drug resistant TB whose work-ups for TB were negative except for one specimen of urine which tested positive on AFB smear. Clinically, he had signs and symptoms referable to a possible tuberculous infection. Another patient with negative cultures (blood, urine and stool) had all the classical signs and symptoms of typhoid fever. Likewise, one patient who developed septicemia after undergoing hemicolectomy for intussusception had negative cultures.

Table 5 shows the clinical response to Ciprofloxacin according to each type of infection. There was no clinical cure among 14 (50%) of patients while 11 died with failure rate of 39.3%.

Only one patient developed adverse drug reaction to Ciprofloxacin. Mild abdominal discomfort was reported.

**Table 4** Bacteriologic response to Ciprofloxacin treatment according to distribution of isolated microorganisms, Tertiary Hospital, June, 1993 – October, 1995.

Organisms	No. of Patients (%)	Eradication of Organism	Failure	Super Infection
<i>Pseudomonas sp.</i>	7 (25.0)	3	4	1
<i>Enterobacter sp.</i>	5 (17.9)	2	3	-
<i>Klebsiella sp.</i>	7 (25.0)	5	2	3
<i>Alkaligenes fecalis</i>	1 (3.6)	1	-	-
<i>Acinetobacter sp.</i>	3 (10.7)	1	2	2
<i>Salmonella sp.</i>	1 (3.6)	1	-	-
<i>Escherichia coli</i>	1 (3.6)	1	-	-
No growth	3 (10.7)	-	-	-
<b>Total (%)</b>	<b>28 (100.0)</b>	<b>14 (50.0)</b>	<b>11 (39.3)</b>	<b>6 (21.4)</b>

**Table 5** Clinical response to Ciprofloxacin treatment according to distribution of types of infections, Tertiary Hospital, June, 1993 – October, 1995

Types of Infections	No. of Patients	Cure	Improvement	Failure
Septicemia	21	10	-	11
Recurrent UTI	2	1	1	-
Multi-drug resistant Typhoid Fever	2	2	-	-
Multi-drug resistant TB	1	-	1	-
Ventriculitis	1	1	-	-
Suppurative Meningitis *	1	-	-	-
<b>Total (%)</b>	<b>28</b>	<b>14 (50.0)</b>	<b>2 (7.1)</b>	<b>11 (39.3)</b>

\* Cannot be assessed because patient was discharged against medical advice after 24 hours of treatment with Ciprofloxacin

## DISCUSSION

There have been many reports on the use of Ciprofloxacin using "compassionate-use" based protocols. Most of these were on patients with cystic fibrosis who were previously treated with anti-*Pseudomonas* penicillins and aminoglycosides [2]. The use of Ciprofloxacin provided an added advantage against resistance to *Pseudomonas* and made oral therapy possible for these group of patients. A number of potential indications for use of Ciprofloxacin among pediatric patients were reviewed by Schaad and co-workers [2]. Our data showed that there was not much difference from foreign studies as to indications for use of Ciprofloxacin in pediatric patients. Multiply resistant and difficult-to-treat *Salmonella* infections justify the use of Ciprofloxacin specially in life-threatening clinical settings. This is an advantage over other antimicrobials being used in developing countries such as the Philippines where identification of pathogens is not always possible and therefore, treatment with an antimicrobial with a narrow spectrum of activity is inadequate. This was fully elucidated by the International Society of Chemotherapy Commission when they issued guidelines/recommendations on the use of fluoroquinolones in children as follows [4]:

1. Quinolones were indicated for the following clinical situations:
  - a. patients with cystic fibrosis with chronic *Pseudomonas aeruginosa* and *Staphylococcus* infections
  - b. urinary tract infections with multi-drug resistant *Pseudomonas aeruginosa* and other gram-negative organisms in children with genitourinary tract abnormalities
  - c. chronic suppurative otologic infections caused by *Pseudomonas aeruginosa* or *Staphylococcus aureus*
  - d. osteomyelitis caused by *Pseudomonas aeruginosa*
  - e. *Salmonella* and *Shigella* infections caused by multi-drug resistant strains found in developing countries
2. Quinolones should only be used when other alternative antibiotics are unavailable

In this study, the following were the possible causes of failure of therapy among patients with septicemia:

1. delay in referring patients with possible multiply resistant organisms;

2. immunocompromised state of the patients;
3. nutritional status of the patients; and
4. presence of co-existing metabolic problems.

In general, the clinical improvement of patients given Ciprofloxacin warrant further epidemiological investigation. This would require a larger group of study population and the use of case control studies.

The major contraindication to the use of Ciprofloxacin in children has been the question of whether this agent can cause damage to cartilage. To date, there is no evidence that Ciprofloxacin causes irreversible cartilage damage in children [4]. The only additional potential skeletal toxicity in children was greenish discoloration of teeth among two of 11 children treated as neonates for life-threatening multi-drug resistant *Klebsiella pneumoniae* sepsis [5]. Thus, the above mentioned adverse reactions cannot be assessed at this time because no follow-up study has been done yet among the study population.

## CONCLUSIONS

Ciprofloxacin is one of the newer antimicrobial agent with broad coverage that includes most gram negative organisms, many gram positives including multi-drug resistant organisms. This study followed the guidelines and recommendations set by the International Society of Chemotherapy Commission.

The use of Ciprofloxacin among pediatric patients is justified for treatment of life-threatening infections for whom more conventional therapy is not available, either due to resistance or toxicity.

## RECOMMENDATIONS

The following are the recommendations based on this study:

1. Ciprofloxacin can be used for pediatric patients in accordance with the guidelines given by the International Society of Chemotherapy Commission;
2. Long term follow-up of patients should be done; and,
3. Multi-center study should be conducted.

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*Ang paggalang sa nakakatanda ay madaling matutunan ng mga bata.*