# ADVERSE DRUG REACTION MONITORING OF CIPROFLOXACIN IN PEDIATRIC PRACTICE

**S.C. Karande**
**N.A. Kshirsagar**

**ABSTRACT**

*Ciprofloxacin, a fluoroquinolone antibacterial agent, is not recommended in pediatric population on account of its possible adverse effect on growing cartilage. It is being commonly used for treatment of variety of infections in children in our country and very little information is available on the risks involved in its use.*

*A questionnaire was sent to 750 pediatricians in the last week of November 1990, to retrospectively judge over the previous 2 month period the extent of its use and identify the adverse drug reactions (ADRs). One hundred and fifty-four pediatricians replied, of which 147 had prescribed ciprofloxacin in a total of 3341 patients under 18 years of age, enteric fever being the commonest indication for its use. One hundred and fifty-nine ADRs were reported in 104 (3.1%) patients. They were: gastrointestinal in 50% of these 104 patients, CNS in 23%, skin and allergic in 19.1%, musculoskeletal in 8.6%, hematological in 3.8%, CVS in 2.9% and nephrological in 0.9% cases. Of 159 ADRs, 8 (5%) were severe, 76 (47.8%) were moderate and 75 (47.2%) were mild. Therapy needed discontinuation in only 9 (0.3%) patients. Two new ADRs were identified, viz., sudden death after intravenous ciprofloxacin and sinus nodal arrest causing bradycardia.*

**Key words:** *Ciprofloxacin, Adverse Drug Reactions, Enteric Fever.*

The Drug Controller of India, Ministry of Health and Family Welfare, has recently started 6 Adverse Drug Reaction Monitoring (ADR) Centres, ours being the only one in Maharashtra. Unfortunately, the concept of ADR reporting is still new in India, inspite of its immense need(1). One of the main objective of this project is to identify ADRs occurring to new drugs being used in our own population for diseases endemic in India(1).

With the recent emerging problem of multiple drug resistant enteric fever(2), ciprofloxacin (CF) is being used widely, even in pediatric patients. Concern over possible joint damage is the reason that quinolones, *viz.*, nalidixic acid, norfloxacin, ofloxacin and ciprofloxacin are not recommended for routine therapy of infections in children(3). Ciprofloxacin (CF) has been used for treating enteric fever(4) and its use in children may be ethically justified for multiple drug-resistant enteric fever as a life-saving measure.

## Material and Methods

This was a retrospective survey of CF use and ADRs to CF in pediatric practice in Western India (Maharashtra). The mode of survey was a questionnaire printed on a self-addressed inland letter sent to 750 pediatricians in medical colleges and private practice in the last week of November 1990. A letter which was enclosed with

*From the ADR Monitoring Centre, Department of Pharmacology, Seth G.S. Medical College and K.E.M. Hospital, Parel, Bombay 400 012.*

*Reprint requests: Dr. (Mrs) N.A. Kshirsagar, Associate Professor of Pharmacology, Seth G.S. Medical College, Parel, Bombay 400 012.*

*Received for publication February 26, 1991; Accepted October 17, 1991*

the questionnaire explained the need to identify ADRs to CF in actual clinical practice. A short list of common ADRs to CF were also supplied, *viz.*, (*a*) nausea, abdominal discomfort, headache, and dizziness, (*b*) skin rashes, photosensitivity reactions, (*c*) arthropathy in immature animals, and (*d*) inhibition of theophylline metabolism.

The survey was intended to collect retrospective data and to be practicable, and to get a good response it was kept simple. The information sought for included (*a*) Number of cases treated with CF in last 2 months, (*b*) Indications for using CF (*e.g.*, enteric fever.....cases, PUO.....case any other..... cases), (*c*) Did any ADRs occur to CF ?, (*d*) If ADRs did take place, further details were asked for, *viz.*, diagnosis of illness, age/sex of child, description of ADR; whether ADR was certain, probable or possible; and whether ADR was mild, moderate or severe. The terms, certain (*i.e.*, ADR reappeared on rechallenge with drug after initially stopping drug), probable (*i.e.*, ADR disappeared on stopping drug, but rechallenge not done) and possible (*i.e.*, ADR suspected but did not disappear on stopping drug or when follow up was inadequate) were clearly explained in the questionnaire.

This retrospective survey on extent of use and ADRs occurring to CF has been analyzed and rarer ADRs noted. Whenever an interesting and rare ADR was reported, further details were asked for from the concerned pediatrician.

## Results

By the end of January 1991, of 750 pediatricians 154 (20.5%) filled in the questionnaire and mailed the inland letter back to us. Of 154 pediatricians, 147 (95.5%) had prescribed CF and only 7 (4.5%) had not used this new drug. One hundred and one (68.7%) reported no ADRs with CF in their clinical practice, while 46 (31.3%) did report ADRs to CF.

CF was prescribed to treat 3341 patients, under 18 years of age. Their clinical diagnosis were enteric fever (2792 patients) PUO (278 cases), bacillary dysentry (134 cases), pneumonia (24 cases), multiple abscesses (18 cases), UTI (15 cases), pyogenic meningitis (6 cases), septicemia and upper respiratory tract infection (5 cases each); neonatal septicemia, malignancy with neutropenia and acute non-tuberculous cervical lymphadenitis (4 cases each); osteomyelitis (3 cases), burns (2 cases), and septic arthritis, cholera, chronic diarrhea, and ventriculitis (1 case each). In 43 patients treated with CF no diagnosis was mentioned.

Of 3341 patients treated with CF, ADRs were observed in 104 patients, *i.e.*, in only 3.1% of patients. In these 104 patients who developed ADRs the adverse reactions noted were: gastrointestinal in 52 (50%), CNS complaints in 24 (235), skin and allergic manifestations in 20 (19.1%), musculoskeletal in 9 (8.6%), hematological in 4 (3.8%), CVS manifestations in 3 (2.9%) and 1 (0.9%) developed a nephrological adverse reaction (*Table I*).

A total of 159 ADRs were reported in 104 patients, of which 11 (6.9%) were certain, 103 (64.7%) probable and 44 (27.7%) possible (*Table I*). One neonate had a sudden death immediately after a dose of intravenous ciprofloxacin. This severe ADR, like an anaphylactic reaction, could not be labelled as certain, probable or possible. Of the total 159 ADRs reported 8 (5%) were severe, 76 (47.8%) moderate and 75 (47.2% were mild in their clinical intensity (*Table I*). Therapy with CF

**TABLE I**—*Summary of ADRs to Ciprofloxacin Reported*[++]

| System | Certain | Probable | Possible | Severe | Moderate | Mild |
|---|---|---|---|---|---|---|
| (A) *GIT* | | | | | | |
| Nausea | 1 | 19 | 7 | 1 | 16 | 10 |
| Vomiting | – | 20 | 1 | 2 | 13 | 6 |
| Diarrhea | – | 6 | 1 | 2 | 1 | 4 |
| Abdominal discomfort | – | 10 | 19 | – | 5 | 24 |
| Hematemesis | – | – | 1 | – | – | 1 |
| Abdominal distention | 1 | 2 | 1 | – | 2 | 2 |
| GI Bleeding | 1 | 1 | – | – | 1 | 1 |
| (B) *CNS* | | | | | | |
| Headache | 2 | 9 | 2 | – | 6 | 7 |
| Dizziness | 1 | 2 | 2 | – | 3 | 2 |
| Irritability/Restlessness | 1 | 4+2 * | – | – | 4 | 3 |
| Tremors | – | 1 * | – | – | – | 1 |
| Depersonalization | 1 | 2 | – | – | 3 | – |
| insomnia | – | 3 | – | – | 3 | – |
| (C) *Skin & allergic* | | | | | | |
| Rash | 1 | 3 | 6 | – | 5 | 5 |
| Pruritic rash | – | 3 | – | – | – | 3 |
| Photosensitive rash | – | 2 | – | – | 2 | – |
| Anaphylaxis | ? | – | – | 1 | – | – |
| Angioneurotic edema | – | 1 | – | – | – | 1 |
| Hot flushes | – | 1 * | – | – | – | 1 |
| Rigors and itching after IV dose | 1 | – | – | – | 1 | – |
| (D) *Musculoskeletal* | | | | | | |
| Arthralgia | – | 5 | 2 | – | 4 | 3 |
| Myalgia (Cramps) | – | 1 | – | – | 1 | – |
| Generalized weakness | – | 1 | – | 1 | – | – |
| (E) *Hematological* | | | | | | |
| Drop in Hb | – | 1 | – | – | 1 | – |
| Epistaxis | 1 | – | 2 | 1 | 2 | – |
| (F) *CVS* | | | | | | |
| Cardiac Failure | – | 1 | – | – | 1 | – |
| Sinus nodal arrest | – | 1 | – | – | 1 | – |
| Phlebitis at IV site | – | 1 | – | – | 1 | – |
| (G) *Kidney* | | | | | | |
| Nephritis | – | 1 | – | – | – | 1 |

N.B.: * Patients also on aminophyline.

[++] 104 patients experienced at least one ADR, but many experienced more than one, hence total number of ADRs is 159.

needed discontinuation in only 9 (0.27%) patients, *viz.*, in 2 due to severe vomiting and diarrhea, 1 due to marked nausea, severe epistaxis in 1, moderate pain in hip joint in 1, angioneurotic edema in 1, cardiac failure in 1, and in 1 who developed sinus nodal arrest.

## Discussion

The problem of chloramphenicol resistant strains of *S. typhi* has been reported since 1972 from different parts of the world(5). Unfortunately, due to indiscriminate use of chloramphenicol, ampicillin and cotrimoxazole for trivial infections like common cold and gastroentritis, this new problem of multiple drug-resistant *S. typhi* has emerged(2). Recently, similar experience has been reported from Shangai China, and Wang *et al.*, have reported resistance in 80% strains of *S. typhi* to commonly used drugs such as chloramphenicol, ampicillin and cotrimoxazole(6).

Ciprofloxacin (CF) is a new, second generation fluoroquinolone: norfloxacin, enoxacin and ofloxacin also belong to the same group. All are 6-fluorine derivatives of the quinolone nalidixic acid(7). CF is a broad spectrum antibacterial drug and the most potent of the new quinolones, active against most aerobic Gram-positive and Gram-negative bacteria, particularly *Enterobacteriaceae, E. coli (Klebsiella, Proteus, Salmonella, Shigella*) and *Pseudomonas aeruginosa*(8). It can be given in a convenient oral 12 hourly dosage and has good tissue penetration(8). The side effects are usually transient and subside without discontinuation of therapy(8). This drug is not recommended for use in patients under 18 years of age and in pregnant women due to its possible toxicity to growing cartilage at the ends of long bones(8). However, use of CF to treat life threatening illnesses caused by multiple drug resistant organisms, even in children, may be ethically justified(9).

Data showing that CF is a relatively safe antimicrobial drug has been gathered from extensive clinical trials with this drug(10,11). In comparative trials, ADRs generally occurred less often than with cotrimoxazole or amoxicillin and no more often than with cefotaxime(8). ADRs to CF occur in 9 to 16% patients(10,11); predominantly mild gastrointestinal symptoms like nausea, vomiting, abdominal discomfort and diarrhea in 4 to 8% patients; CNS symptoms like headache, restlessness in 1.5 to 3.5% patients and skin rash in 1.1% patients. In our survey, ADRs reported are much lower than those by information gathered from clinical trials (*Table II*). Probably, this could be explained due to under-reporting by the pediatricians. Also known ADRs like mild transient alterations in laboratory values, *viz.*, eosinophilia, neutropenia, prolonged prothrombin time, elevated SGOT and SGPT, elevated serum creatinine, blood urea were not searched for, unlike in clinical trials. A similar survey done by sending questionnaire in Germany(12) enlisting 12,205 patients treated with CF between February 1987 and January 1989, of which only 1.1% were less than 18 years of age, revealed a lower rate of ADRs (8.3%) than the ADRs seen in clinical trials.

Seven children developed pain in various joints of the body. No objective findings were seen in any of these children. Five were followed up for 2 weeks after discharge and in all of them symptoms had disappeared. Concern over possible joint damage is the reason that quinolones are not recommended for therapy of infections in those under 18 years of age and in pregnant women(3). Schluter(3) studied the

**TABLE II**—*Comparison of Our Data with Two Extensive Clinical Trials*

| | Reference 10 | Reference 11 | Our Survey |
|---|---|---|---|
| 1. Total No. of patients | 9473 | 2829 | 3341 |
| 2. No. of patients who developed ADR | 881 | 457 | 104 |
| 3. Per cent of patients who developed ADR | 9.3 | 16.2 | 3.10 |
| 4. *ADR involving (% of patients)* | | | |
| (*a*) Gastrointestinal | 4.9 | 7.8 | 1.56 |
| (*b*) CNS | 1.5 | 3.3 | 0.70 |
| (*c*) Skin and allergic | 1.1 | 1.8 | 0.59 |
| (*d*) Musculoskeletal | 0.1 | 0.2 | 0.26 |
| (*e*) Hematological | 0.9 | 1.0 | 0.12 |
| (*f*) CVS | 0.2 | 0.9 | 0.01 |
| (*g*) Kidney | 0.8 | 1.0 | 0.03 |
| (*h*) Special senses | 0.2 | 0.8 | – |
| (*i*) Respiratory | 0.1 | 0.4 | – |
| 5. *Severity of ADR(%)* | | | |
| (*a*) Severe | 6 | 6.8 | 5 |
| (*b*) Mild or moderate | 94 | 93.2 | 95 |

N.B. :* Some patients experienced ADR in more than one system.

effect of 4 orally administered quinolones, *viz.*, nalidixic acid, norfloxacin, ofloxacin and ciprofloxacin at very high doses of 100 to 500 mg/kg over 4 weeks on immature rats. Nalidixic acid caused highest percentage of cartilage alterations and ciprofloxacin the least. Also, there is a clear-cut species difference in the effect of quinolones on cartilage(3). A pilot study of immature beagles given 100 mg/kg of CF for 3 weeks, with one leg bandaged for lessening weight-bearing has postulated that, joint damage can probably be minimised by keeping the joint pressure-free during treatment(3). Whether such animal studies wherein minimum 5 times the recommended dose in humans were given, can conclusively predict permanent joint damage in young children given CF, is open to speculation. A study of adults given nalidixic acid in childhood revealed no evidence of arthritis(13). Recent studies have also shown that the original assumption that joint damage occurs only in juvenile animals is not true, as arthropathogenic effects have also been found in adult dogs(14). Mc Ewan *et al.*(15) have reported tenosynovitis occurring in a 67 year old man within 3 days of starting CF.

To date, the vast majority of patients treated with CF have been adults and there is little clinical evidence to either confirm or dispute the development of articular changes in young children. Stutman(16) treated 35 patients of cystic fibrosis under 18 years of age with CF, and only 1 developed arthropathy during the 4 weeks of treatment. Alfaham *et al.*(17) have reported arthropathy of both knees in a 15 years old girl suffering from cystic fibrosis treated with CF. The arthropathy developed after 3 weeks of CF and completely resolved within 2 weeks of stopping the drug. It has been suggested that Magnetic

Resonance Imaging studies could be used in children treated with CF as a method to monitor arthropathogenic effects, if any, even in the early stages of treatment and even subsequently on long-term follow up(14).

Rare ADRs that occur in less than 1% of CF courses(18) such as gastrointestinal bleeding, hematemesis, abdominal distention, dizziness, insomnia, tremors, depersonalization, pruritic rash, hot flushes, rigors and itching after intravenous administration, myalgia (cramps), generalized weakness, epistaxis, and phlebitis at intravenous site of drug administration were reported to us (*Table I*). Other interesting rare ADRs such as angioneurotic edema (1 case); photosensitive rash (2 cases); nephritis with edema face and feet, microscopic hematuria and mild hypertension (1 case); unexplained drop in Hb (1 case); cardiac failure (1 case) and sinus nodal arrest with bradycardia (1 case) were also reported to us (*Table I*). Davis *et al.* have reported anaphylactoid reactions to CF in 15 cases(19). But, none of their patients died during therapy. In the present series, a 7 day-old baby reported to us died immediately after receiving ciprofloxacin. The exact cause of death could not be ascertained.

In our survey, 2 patients who developed restlessness and irritability, and 1 patient who developed hot flushes and tremors during CF therapy (*Table I*), were also on aminophylline prophylaxis for bronchial asthma. In this context, the drug interaction of ciprofloxacin with theophylline, wherein CF inhibits theophylline metabolism by approximately 30% is worth remembering(20). Five patients on CF therapy, without any simultaneous aminophylline also developed irritability and restlessness as an ADR to CF (*Table I*). The safety of intravenous ciprofloxacin is comparable to that of the oral formulation of the drug(21), though intravenous administration can cause phlebitis and rigors(10). We received 1 report each of phlebitis and rigors after intravenous ciprofloxacin.

On further enquiry from pediatricians who reported these rare and interesting ADRs, we were informed that CF dosage used was the recommended(22) one (7.5 to 15 mg/kg/day orally and 5 to 10 mg/kg/day intravenous in 12 hourly divided doses) for a duration of 7 to 10 days, or lesser duration whenever the drug required to be omitted.

Our survey was specific to identify ADRs to CF in patients below 18 years of age. A thorough review of literature could not locate a similar study. Also, we could not find any literature describing ADRs to CF in Indian patients. Hence, after comparing our results with known literature on ADRs to CF(10-12,18) we conclude that incidence of ADRs to CF in children is no greater than in adults, including musculoskeletal reactions. The ADRs observed in our study were only during the course of treatment and for a short period thereafter of 1 to 2 weeks. However, the long term effect of CF on linear growth and joint structure integrity, or any other structure or organ can only be judged by follow up over many years. We do not advocate or even remotely justify shotgun therapy with CF for enteric fever or PUO, without culture and sensitivity studies done on the isolates. Inappropriate and random use of CF for short-term benefit of quick cure and to avoid hospitalization is reprehensible.

Only use of CF for multiple drug resistant enteric fever or other serious infections,as a life-saving measure, can be ethically justified, as the benefit from CF use will outweigh the potential risk of

damage to juvenile cartilage. It would be interesting to know that CF has been used even in premature infants with multi-resistant *Enterobacter cloacae* septicemia with no evidence of adverse effects(23).

**Acknowledgements**

The authors wish to thank their Dean, Dr. (Mrs) P.M. Pai for granting them permission to publish this article. They also wish to thank the Drug Controller of India for his constant encouragement and all the pediatricians who participated in this survey. The study was supported by a grant from the Drug Controller of India and ADR Monitoring Project of the Government of India, under the Union Ministry of Health and Family Welfare.

**REFERENCES**

1. Kshirsagar NA, Karnade SC, Potkar CN. ADR Monitoring in India. *In:* Selected Topics in Clinical Pharmacology Kshirsagar NA, Gupta KC. Eds Bombay, Akshar Pratiroop, 1990, pp 60-64.
2. Khadilkar VV, Khubchandani RP, Amdekar YK, Mehta KP, Anand RK. Drug resistant typhoid fever—an emerging problem. Indian Pediatr 1990, 27: 1227-1228.
3. Schluter G. Ciprofloxacin: Review of potential toxicologic effects. Am J Med 1987, 82 (Suppl 4A): S91-S93.
4. Keusch GT. Antimicrobial therapy for enteric infections and typhoid fever: State of the art. Rev Infect Dis 1988, 10 (Suppl 1): S199-S205.
5. Guerrant R. Salmonella infections. *In:* Harrison's Principles of Internal medicine, 11th edn. Eds Braunwald E. Isselbacher KJ, Petersdorf RD, Wilson JD, Martin JB, Fauci AS. New York, McGraw Hill Book Co, 1987, pp 592-599.
6. Wang F, Gu XJ, Zhang MF, Tai TY. Treatment of typhoid fever with ofloxacin. J Antimicrob Chemother 1989, 23: 785-788.
7. Stahlmann R. Fluoroginolones—a new class of antimicrobial agents. Drugs Today 1988, 24: 529-536.
8. Fass RJ. Ciprofloxacin. Best use of this new broad spectrum antibiotic. Postgrad Med 1990, 87: 117-131.
9. Adam D. Use of quinolones in pediatric patients. Rev Infect Dis 1989, 11 (Suppl 5): S113-S116.
10. Schacht P, Arcieri G, Hullmann R. Safety of oral ciprofloxacin. An update based on clinical trial results. Am J Med 1989, 87 (Suppl 5A): S98-S102.
11. Arcieri G, Griffith E, Gruenwaldt G, *et al*.. Ciprofloxacin: An update on clinical experience. Am J Med 1987, 82 (Suppl 4A): S381-S386.
12. Reiter C, Pfeiffer M, Hullman RN. Brief reports: Safety of ciprofloxacin based on Phase IV studies ("Anwendungsbeobachtung") in the Federal Republic of Germany. Am J Med 1989, 87 (Suppl 5A: S103-S106.
13. Schaad UB. Wedgwood-Krucko J. Nalidixic acid in children: Retrospective matched controlled study for cartilage toxicity. Infection 1987, 15: 165-168.
14. Schluter G. Ciprofloxacin: Toxicologic evaluation of additional safety data. Am J Med 1989, 87 (Suppl 5A): S37-S39.
15. Mc Ewan SR, Davey PG. Ciprofloxacin and tenosynovitis. Lancet 1988, 2: 900.
16. Stutman HR. Summary of a workshop on ciprofloxacin use in patients with cystic fibrosis. Pediatric Infect Dis J 1987, 6: 932-935.
17. Alfaham M, Holt ME, Goodchild MC. Arthropathy in a patient with cystic fibrosis taking ciprofloxacin. Br Med J 1987, 295: 699.

18. Rahm V, Schacht P. Safety of ciprofloxacin: A review. Scand J Infect Dis 1989, 60 (Suppl): S120-S128.
19. Davis H, MC Goodwin E, Reed TG. Anaphylactoid reactions reported after treatment with ciprofloxacin. Ann Intern Med 1989, 111: 1041-1043.
20. Schwartz J, Jaurequi L, Lettieri J, Backmann K. Impact of ciprofloxacin on theophylline clearance and steady state concentrations in serum. J Antimicrob Chemother 1988, 32: 75-77.
21. Neu HC. New oral and parenteral quinolones: A summary Am J Med 989, 87 (Suppl 5A): S283-S287.
22. Paulsen O. The antibacterial activity, pharmacology and therapeutic application of ciprofloxacin. Drugs Today 1988, 24: 361-401.
23. Bannon MJ, Stutchfield PR, Weindling AM, Damjanoic V. Ciprofloxacin in neonatal *Enterobacter cloacae* septicemia. Arch Dis Child 1989, 64: 1388-1391.

## NOTES AND NEWS

### CENTRE FOR DEVELOPMENTAL BIOLOGY

The Sanjay Gandhi Post Graduate Institute of Medical Sciences in the next phase has decided to establish a Centre for Developmental Biology, the components of which are:

(*a*) Basic Development Biology,

(*b*) Clinical Developmental Biology

(*i*) High Risk Obstetrics–Perinatology and Early Childhood,

(*ii*) Growth–Developmental and Clinical Psychology, and

(*iii*) Nutrition Division.

The members are requested to give their views and suggestions regarding this development to the Director, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Post Box No. 37, Lucknow 226 001.