Original Articles

CIPROFLOXACIN USE: ACUTE ARTHROPATHY AND LONG-TERM FOLLOW UP

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Objective: *To assess whether children treated with ciprofloxacin in 1990 had developed any permanent joint damage.* ***Design:*** *Retrospective questionnaire-based follow-up study.* ***Setting:*** *Adverse Drug Reaction (ADR) Monitoring Center in Mumbai.* ***Subjects:*** *3341 children treated with ciprofloxacin in 1990, including 7 who had developed a ciprofloxacin-related acute arthropathy.* ***Methods:*** *A questionnaire was sent in January 1995 to 147 pediatricians who had reported to us children in whom ciprofloxacin was prescribed in 1990. The information sought for included the number of children who had followed-up beyond 2 years and details of any joint-related complaints noted in them on long-term follow-up.* ***Results:*** *Long-term follow-up was reported in 582 of these 3341 children. No joint-related complaints had developed in 581 children, either as an acute ADR in 1990 or as a delayed ADR during a minimum follow-up period of 2 years. Long-term follow-up was available in only 1 of the 7 children in whom a ciprofloxacin-related acute arthropathy had developed in 1990, and this child was now asymptomatic. New information was received about 13 children treated with ciprofloxacin during 1991-1994 who had developed a ciprofloxacin-related acute arthropathy. In the total 20 children, aged 2-12 years, reported to us for acute ADR, the arthropathy (joint pains, restriction of joint movements and/or swelling of joint) had developed on day 1 to 8 of ciprofloxacin therapy, and in 18 the acute arthropathy had resolved within 1 day to 4 weeks of either discontinuing or completing ciprofloxacin therapy. Outcome in the remaining 2 children was not available.* ***Conclusions:*** *Ciprofloxacin use can cause an acute reversible arthropathy, but in this study there is no evidence that its use can cause a delayed arthropathy or any permanent joint damage.*

Key words: *Ciprofloxacin, Arthropathy, Adverse drug reaction reporting systems, adverse effects.*

THE advent of multi-drug resistant typhoid fever has led to widespread use of ciprofloxacin in Indian children(l-3). Ciprofloxacin, a fluoroquinolone, is not recommended for routine use in children. In juvenile animals, ciprofloxacin use leads to an arthropathy which presents as a joint swelling within days to weeks and is characterized by an irreversible erosion of joint cartilage(4). Till date it is not clearly known whether parallels can be drawn between animal findings and outcome in growing children.

In 1990 we had conducted a study to detect acute adverse drug reactions (ADRs) to ciprofloxacin in pediatric practice(5). One hundred and forty-seven pediatricians had given information about 3341 children treated with ciprofloxacin. Six pediatricians had reported ciprofloxacin-related arthropathy, as an acute ADR

in 7 (0.2%) children. The present study was conducted with the aim to assess whether children treated with ciprofloxacin in 1990 had developed any permanent joint damage.

Subjects and Methods

We sent a questionnaire in January 1995 to 147 pediatricians. The information sought for included: *(a)* number of children treated with ciprofloxacin in 1990 who were followed up beyond 2 years; *(b)* number of children, of these, in whom joint-related complaints were noted; (c) further details of patients who had developed ADR were requested, namely, age and sex of child, description and severity of the joint complaint, *i.e.,* joint pains (with no objective findings), restriction of joint movements, and/or swelling of joint(s). Also, time period for the joint-related ADR to occur after starting ciprofloxacin, and duration of the ADR, were asked for.

While responding to our 1995 questionnaire, 7 pediatricians, on their own, reported ciprofloxacin-related arthropathy as an acute ADR in 13 new children treated by them between 1991 to 1994. None of these 7 pediatricians had reported any children with such complaints during our 1990 survey. To these 7 pediatricians we sent a second detailed questionnaire (as in 1990, to the earlier 6 pediatricians) to seek further information, namely: *(a)* indication, dosage and duration of ciprofloxacin use; *(b)* joint(s) involved; *(c)* if any medication was necessary to treat the ADR; *(d)* if any joint aspiration or radiological studies were done; *(e)* whether the intensity of the joint complaints required ciprofloxacin to be discontinued; *(f)* whether ciprofloxacin was re-administered at any time after the ADR had appeared and abated; *(g)* if ciprofloxacin was re-administered, had the ADR reappeared; *(h)* whether the joint symptoms could be explained by the disease being treated itself *(e.g.,* typhoid fever), or by any other co-existing illness, *e.g.,* rheumatic fever, rheumatoid arthritis, tuberculosis, *etc.; (i)* whether there was a past history of joint pains or drug allergy; and *(j)* whether any associated tenosynovitis or subsequent tendon rupture was noticed.

Results

Forty-four pediatricians had followed-up 582 children for more than 2 years, and 581 had not developed any joint-related complaints during ciprofloxacin therapy in 1990, nor on long-term follow up. Of the 7 children who had developed ciprofloxacin-related arthropathy as an acute ADR in 1990, long-term follow up was achieved in only 1 child *(Table I).* There were no subsequent joint complaints in this 8 year old girl once the acute arthropathy had resolved within 2 weeks. Since she is totally asymptomatic, no MRI studies have been done. Also follow-up data is available in only 1 out of the 13 new cases reported *(Table IT).* This 11 year old girl has remained asymptomatic for more than a year after the acute arthropathy had resolved within a week.

Collectively, we are thus reporting 20 children, aged 2 to 12 years, with ciprofloxacin-related acute arthropathy *(Tables I & IT).* The joint-related acute ADR started on day 1-8 of ciprofloxacin therapy. Paracetamol, aspirin or similar analgesic was given for the joint pain as symptomatic treatment. Joint aspiration was not done in any child. X-rays of the affected joint(s) were done during the acute ADR in 5 children and were normal. In 9 children ciprofloxacin was discontinued as the joint pains were moderate to severe. In no child could the ADR be classified as certain, as re-challenge with ciprofloxacin was not attempted. In the 18 children who were followed up, the acute arthropathy resolved

TABLE I–*Details of Children with Typhoid Fever who Developed Ciprofloxacin Related Acute Arthropathy in 1990.*

Age in years (City/town)	Sex	Tretment with Ciprofloxacin (days)	Type of ADR noticed (Joint(s) involved)	ADR day of onset (Duration of ADR)	Relation to Ciprofloxacin	Intensity	Countermeasure	Outcome
8 (Mumbai)	F	5	a + b (knees)	5 (<2 weeks)	Highly probable	Moderate	Drug discontinued	Resolved. Follow-up till 1995.
10 (Pune)	M	10	a (N.A.)	3-5 (<2 weeks)	Probable	Mild	None	Resolved.
6 ½ (Pune)	M	7	a (knees)	7 (<2 weeks)	Probable	Moderate	None	Resolved.
11 (Karad)	M	7	a (shoulder)	3-4 (<2 weeks)	Probable	Moderate	None	Resolved.
10 (Karad)	F	7	a (shoulder)	3-4 (<2 weeks)	Probable	Mild	None	Resolved.
2 (Mumbai)	M	4	a + b (hip)	3-4 (N.A.)	Possible	Moderate	Drug discontinued	(N.A.)
12 (Nagpur)	F	10	a (N.A.)	3-4 (N.A.)	Possible	Mild	None	(N.A.)

Abbreviations used: a = Joint pains (no objective findings); b = Restriction of joint movements; c = Swelling of joint(s); Highly probable = ADR disappeared on discontinuing drug, but rechallenge not done; Probable = ADR disappeared after completing ciprofloxacin course and rechallenge not done; Possible = Outcome of ADR not known as follow-up was inadequate; (N.A.) = Information not available.

TABLE II–*Details of Children with Typhoid Fever who Developed Ciprofloxacin Related Acute Arthropathy in 1991-1994.*

Age in years (City/town)	Sex	Treatment with Ciprofloxacin (days)	Type of ADR noticed (Joint(s) involved)	ADR day of onset (Duration of ADR)	Relation to Ciprofloxacin	Intensity	Countermeasure	Outcome
6 (Pune)	(N.A.)	10	a (shoulder)	4 (1 week)	Higly probable	Moderate	Drug discontinued Paracetemol	Resolved.
10 (Pune)	(N.A.)	10	a (shoulder)	5 (5 days)	Probable	Mild	Paracetemol	Resolved.
4 (Pune)	(N.A.)	10	a + b (knee)	7 (5 days)	Probable	Mild	Paracetemol	Resolved.
11 (Pune)	(N.A.)	10	a + b + c (knee)	4 (6 days)	Probable	Mild	Paracetemol	Resolved.
7 (Pune)	(N.A.)	10	a + b (elbow)	3 (7 days)	Probable	Mild	Paracetemol	Resolved.
8 (Mumbai)	(N.A.)	One dose	a (knees)	Within 15 mins. of intravenous dose (1 day)	Highly probable	Severe	Drug discontinued Analgesics Ceftriaxone added	Resolved.
10 (Yavatmal)	F	10	a + b (knees)	6-8 (<1 month)	Probable	Moderate	(N.A.)	Resolved.
8 (Sangammer)	M	5	a (knees)	3 (<1 week)	Highly probable	Moderate	Drug discontinued	Resolved.
11 (Parbhani)	F	6	a + b + c (ankle)	4 (1 week)	Highly probable	Moderate	Drug discontinued	Resolved. Follow-up of >1 year

(Contd II...)

TABLE II (Contd.)–*Details of Children with Typhoid Fever who Developed Ciprofloxacin Related Acute Arthropathy in 1991-1994.*

Age in years (City/town)	Sex	Treatment with Ciprofloxacin (days)	Type of ADR noticed (Joint(s) involved)	ADR day of onset (Duration of ADR)	Relation to Ciprofloxacin	Intensity	Countermeasure	Outcome
4 (Pune)	M	7	a (knees + ankles)	7 (5 days)	Highly probable	Moderate	Drug discontinued	Resolved.
11 (Pune)	F	7	a + b (knees)	5-6 (7 days)	Probable	Moderate	Aspirin	Resolved.
4 (Yavatmal)	M	5	a + b (knee)	5 (<1 week)	Highly probable	Moderate	Drug discontinued	Resolved.
6 (Yavatmal)	M	7	a + b (knee + ankle)	7 (<1 week)	Highly probable	Moderate	Drug discontinued Analgesics	Resolved.

Abbreviations used: a = Joint pains (no objective findings); b = Restriction of joint movements; c = Swelling of joint(s); Highly probable = ADR disappeared on discontinuing drug, but rechallenge not done; Probable = ADR disappeared after completing ciprofloxacin course and rechallenge not done; Possible = Outcome of ADR not known as follow-up was inadequate; (N.A.) = Information not available.

within 1 day to 4 weeks of either omitting or completing ciprofloxacin therapy. In no child could any co-existing illness explain the joint complaints. No child had a past history of joint pains or drug allergy, nor was any associated tenosynovitis or tendon rupture noticed.

Discussion

No joint-related ADR developed either acutely during ciprofloxacin therapy or as a delayed effect in 581 children treated with ciprofloxacin in 1990. In 20 children ciprofloxacin-related acute arthropathy developed within 1-8 days of starting ciprofloxacin. Ciprofloxacin was used to treat typhoid fever in the recommended dose of 7.5 to 15 mg/kg/day orally or 5 to 10 mg/kg/day intravenously in twice daily doses(6). The acute arthropathy was always reversible on follow up, and usually within 2 weeks of either omitting or completing ciprofloxacin therapy. The reporting pediatricians clinically ruled out septic arthritis as a cause of the joint findings. Also, in 8 cases wherein the arthropathy necessitated discontinuing ciprofloxacin, the ADR resolved without any further anti-bacterial therapy. In only 1 child (8 years old, reported from Mumbai, *Table II),* in whom ciprofloxacin was omitted after the first intravenous dose, and ceftriaxone therapy substituted, the possibility of septic arthritis could not be ruled out.

In the West, ciprofloxacin has been used mostly in children and adolescents with cystic fibrosis who develop acute chest infections, at a much higher dose (upto 40 mg/kg/day) and for a longer duration (upto many weeks). Chysky *et al*.(7) reviewed data on 634 children and adolescents treated with ciprofloxacin, and reported acute arthralgia in 8 (1.3%) cases who were suffering from cystic fibrosis. The arthralgia had started on day 1-23 of ciprofloxacin therapy, and in 2 ciprofloxacin was discontinued as joint pain was moderate. In 7 the acute arthralgia resolved within 5-18 days, and in 1 no follow-up was available. Kubin(8) found that acute- reversible arthralgia occured in 36 (3.2%) out of 1113 patients with cystic fibrosis on ciprofloxacin, and the arthralgia disappeared in many cases while the patient was still on ciprofloxacin. In no case could cartilage damage be demonstrated by radiographic procedures. It is worth noting that arthropathy can occur in 7 to 8% of cystic fibrosis patients due to the disease itself(9). This fact complicates analysis of ciprofloxacin-related arthropathy data in cystic fibrosis patients. But ciprofloxacin-related acute arthropathy has been reported even in adults as bilateral knee arthropathy(10,ll), tenosynovitis(12) and tendinopathy with possible partial rupture of the Achilles tendon(13).

In conclusion, our study suggests a probable association between ciprofloxacin use and an acute arthropathy (joint pains, restriction of joint movements and/or swelling of joint), which is totally reversible. Long-term follow up in 581 children who had no symptoms of acute arthropathy when treated with ciprofloxacin in 1990, and 2 children who developed a ciprofloxacin-related acute arthropathy, did not reveal any permanent joint damage. We still recommend cautious use of ciprofloxacin in children till long-term follow-up studies from various centers are completed.

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NOTES AND NEWS

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