Fluoroquinolone Safety in Pediatric Patients: A Prospective, Multicenter, Comparative Cohort Study in France

Martin Chalumeau, MD*‡; Sylvie Tonnelier, PharmD*; Philippe d'Athis, PhD*; Jean-Marc Tréluyer, MD, PhD*; Dominique Gendrel, MD§; Gérard Bréart, MD‡; Gérard Pons, MD, PhD*; and the Pediatric Fluoroquinolone Safety Study Investigators

ABSTRACT. *Objective.* **To evaluate the safety of fluoroquinolones (FQ) in comparison with other antibiotics in pediatric patients.**

Methods. **A multicenter, observational, comparative cohort study was conducted between 1998 and 2000 in French pediatric departments. Patients who were receiving systemic FQ were included and matched to control patients who were receiving other antibiotics. Antibiotic-associated potential adverse events (PAEs) were recorded prospectively in both groups, and their rates were compared using univariate and multivariate analyses.**

Results. **Patients were recruited from 73 centers: 276 patients were exposed to FQ, and 249 composed the control group. Among patients who were exposed to FQ, 23% were younger than 2 years, 33% had cystic fibrosis, and PAEs occurred in 52 patients, leading to withdrawal for 11. The odds ratio for PAE in the FQ group was 3.7 (95% confidence interval: 1.9–7.5) and was not significantly modified after adjustment for potential confounders. Musculoskeletal PAEs also occurred more frequently in the FQ group (3.8%) than in controls (0.4%); they were recorded in 10 patients who were receiving standard FQ doses and were of moderate intensity and transient.**

Conclusion. **The rates of PAEs and musculoskeletal PAEs were higher for the FQ group than the control group. This observation supports the American Academy of Pediatrics statement restricting off-label FQ use in pediatric patients to second-line treatment in a limited number of situations.** *Pediatrics* **2003;111:e714–e719. URL: http://www.pediatrics.org/cgi/content/full/111/6/e714; *antibiotics, pharmacoepidemiology, drug toxicity, joints, children.***

ABBREVIATIONS. FQ, fluoroquinolone; PAE, potential adverse event; CF, cystic fibrosis; CI, confidence interval; PO, per os; OR, odds ratio.

Fluoroquinolones (FQs) are licensed and widely indicated for use in adults, owing to the agents' broad-spectrum antibacterial activity, their extensive tissue and intracellular penetration, and their suitability for oral administration.[1] These characteristics could also have led to numerous indications and wide use in pediatric patients but did not.[2–4] Indeed, FQ use in pediatric patients has been contraindicated by regulatory authorities in the United States and the European Union, given the cartilage damage that they cause in juvenile animal models.[5–7] FQ use has been expanded off-label to pediatric patients with conditions for which no alternative treatment was possible because of bacterial resistance or because other active antibiotics could not be given orally. Unfortunately, this use was not evaluated prospectively for safety with well-designed studies. Case reports of musculoskeletal potential adverse events (PAEs) during FQ use in pediatric patients appeared rapidly.[8–15]

Taking into account the potential benefits and risks of FQs in pediatric patients, different experts[2,3,16–18] and the American Academy of Pediatrics[19] have recommended prescribing FQs as a second-line antibiotic and restricting their use to a few specific situations, including *Pseudomonas aeruginosa* infections in patients with cystic fibrosis (CF), prophylaxis and treatment of bacterial infections in immunocompromised patients, life-threatening multiresistant bacterial infections in newborns and infants, and *Salmonella* or *Shigella* gastrointestinal tract infections. However, those guidelines were not evidence-based because of the lack of pharmacoepidemiologic surveys on FQ adverse events in pediatric patients. Indeed, interpretation of the results of cohort surveys on FQ use and adverse events in pediatric patients was limited by their retrospective design,[20–25] the lack of control groups,[20–24,26–31] and/or the small number of patients included.[29,32–36]

Nonetheless, FQ use in pediatric patients has increased as shown in the United States, where 8.4 million prescriptions for ciprofloxacin were written for patients 18 years and younger in 1996.[37] First-line therapy with FQ for invasive diarrhea has been reported.[33] Nelson and McCracken[37] and others[38,39] have called for clear safety data in this population. We report the results of a large, multicenter, prospective, controlled study describing FQ use in pediatric patients and evaluating antibiotic-associated PAE rates in comparison with controls.

From the *Perinatal and Pediatric Pharmacology Unit, Université René-Descartes, Hôpital Saint-Vincent-de-Paul (AP–HP), Paris, France; ‡INSERM U149, Paris, France; and §Department of Pediatrics, Hôpital Saint-Vincent-de-Paul, Paris, France.

Received for publication Oct 23, 2002; accepted Jan 14, 2003.

Reprint requests to (G.P.) Pharmacologie Périnatale et Pédiatrique, Hôpital Saint-Vincent-de-Paul, 75674 Paris Cedex 14, France. E-mail: gerard.pons@svp.ap-hop-paris.fr

METHODS

Study Design

A multicenter, observational, comparative, cohort study was conducted between May 1998 and September 2000. All French pediatric departments (n = 382) and CF centers (n = 68) were contacted up to 3 times by letter to participate in the study; 145 accepted. All consecutive pediatric patients (age <19 years) who were receiving FQ were included in each participating center. Descriptive data concerning patients' characteristics (age, medical history of CF, previous exposure to FQ within the last 5 years), the present FQ regimen (drug, dose, indication and bacteriologic findings, justification for use, concomitant drugs), and PAEs were collected prospectively. PAE rates were compared between patients who were receiving FQ and control patients who were given antibiotics other than FQs. The study protocol was approved by the local ethics committee, which concluded that a written consent from the patients and/or their parents was not necessary for this kind of observational research.

Exposure and Controls

Exposure was defined as systemic FQ use, regardless of the regimen prescribed. Exposed patients were allowed to receive other antibiotics or any other drug during FQ therapy. A control, defined as the next consecutive eligible individual after each exposed subject recruited in the same ward, was a pediatric patient who received at least 1 antibiotic other than FQ and who had not received FQ during the 15 days before inclusion. Control and exposed patients could have taken systemic FQ previously. Controls and exposed patients were matched, as much as possible, for age (<2 years, ≥2 and <6 years, ≥6 years to puberty onset, and after puberty onset) and medical history of CF or not. A patient could be recruited only once. When it was necessary to prescribe an FQ to a control patient during the study, she or he was transferred into the FQ group.

PAE Definition

For each patient included, the observation period started on day 1 of antibiotic administration and ended 15 days after the last dose. PAEs were recorded prospectively by the investigators and defined as any undesirable event potentially linked to FQs or another antibiotic. Investigators were asked to declare all PAEs in both study groups. Special emphasis was placed on data collection and the causality assessment (with Naranjo algorithm[40] and the French method[41]) for all patients in whom musculoskeletal events occurred (arthralgia, isolated joint swelling, myalgia, tendinopathy).

Statistical Analysis

Statistical analyses were performed using Epi Info software (Centers for Disease Control and Prevention, Atlanta, GA) and BMDP software (BMDP Statistical Software Inc, Los Angeles, CA). A first analysis was conducted to identify, within the FQ group, risk factors for PAEs and musculoskeletal PAEs. A second analysis was undertaken to compare PAE incidences in the FQ and control groups using the 2-tailed Fisher exact test and the Cornfield 95% confidence interval (CI). The Breslow-Day test assessed potential interactions with age, medical history of CF, previous exposure to FQ within the last 5 years, or number of concomitant drugs. Logistic regression multivariate analysis was performed to take into consideration these 4 potential confounders that were forced into the model. $P < .05$ was considered statistically significant.

RESULTS

Recruitment

Among the 145 participating centers, only 73 recruited at least 1 patient: 53 pediatric departments and 20 CF centers. Participating centers recruited 276 pediatric patients who were receiving FQ but only 249 control patients because of matching difficulties. Patients mainly originated from general pediatric wards or CF centers (62%), cancer units (18%), and intensive care units (9%).

FQ Use

Among the 276 pediatric patients who were receiving FQs, 23% were younger than 2 years, 16% were ≥2 and <6 years old, 31% ≥6 years to puberty onset, and 29% had started puberty. Among them, 233 (84%) had an underlying condition, with the most frequent being CF (33%), followed by malignancy (27%), immunosuppression (9%), neurologic disorders (8%), or urologic problems (6%). Thirty-two percent of the patients had previously received FQ a least once within the past 5 years.

The indications for FQ prescription to patients with CF (n = 90) were active bronchopulmonary infections (93%), bronchopulmonary infections prophylaxis (4%), and sinusitis (2%). Among patients without CF (n = 186), the main indications were bronchopulmonary infections (22%); urinary tract infections (18%); febrile neutropenia (13%); septicemia (12%); *Salmonella* or *Shigella* gastrointestinal tract infections (12%); ear, nose, and throat infections (6%); bone or joint infections (6%); and meningitis (5%). Bacteria were isolated from 96% of the patients with CF and 65% of the patients without CF. The main reasons given for using FQs were bacterial resistance to other antibiotics (51%), the possibility of administering the drug per os (PO; 17%), and allergy to other antibiotics (3%). When FQ was started, the number of other drugs that each patient was receiving was 5.2 ± 3.8 (mean ± standard deviation). Nine patients who were critically ill before FQ administration died before the end of the 15-day observation period. Six percent of the patients without CF and 64% of the patients with CF received FQs as outpatients. The FQs prescribed were ciprofloxacin (87%), ofloxacin (9%), and pefloxacin (4%). FQ regimens for each route of administration, PO or intravenous, are reported in Table 1.

PAEs in the FQ Group

The analysis was performed on 264 (96%) of the 276 patients included in the FQ group because 12 patients were lost to follow-up before the end of the 15-day observation period. They experienced 52 PAEs (an overall PAE rate of 19.7%; 95% CI: 14.9–24.5) for the population treated with FQ. These events mainly involved the gastrointestinal tract (n = 15), the musculoskeletal system (n = 10), the skin (n = 7), the kidneys (n = 5), and the central nervous system (n = 3). FQs were stopped for 11 children because of PAEs; for 2 of them, rechallenge during the 15-day observation period was negative.

Ten musculoskeletal PAEs were observed in 10 patients, including 2 patients with CF (Table 2). All of these patients were older than 6 years, 80% were female, and 8 had received ciprofloxacin and 2 had received pefloxacin. Musculoskeletal events tended to be more frequent with pefloxacin (18.2%) than ciprofloxacin (3.3%; P = .06). The FQ doses received and their durations were within the same range as those of patients without musculoskeletal events (Tables 1 and 2). The 10 musculoskeletal events were arthralgias of large joints or myalgias; no tendinopathy was observed. They occurred during the first

TABLE 1. FQ Regimens in Patients With CF ($n = 90$) and Without ($n = 186$)

FQ	n	Dose (mg/kg/d)*				Duration (d)*			
		Minimum	Maximum	Median	Mean (SD)	Minimum	Maximum	Median	Mean (SD)
Patients without CF									
Ciprofloxacin IV	75	6	40	16	16 (7)	1	45	10	13 (9)
Ciprofloxacin PO	79	7	53	20	21 (7)	1	43	10	12 (8)
Ofloxacin IV	7	5	30	8	12 (9)	2	31	8	12 (10)
Ofloxacin PO	14	6	21	12	13 (5)	6	301	10	50 (96)
Pefloxacin IV	3	5	13	12	10 (4)	1	10	9	7 (5)
Pefloxacin PO	8	7	36	19	20 (10)	5	15	8	9 (4)
Patients with CF									
Ciprofloxacin IV	11	11	30	16	18 (7)	14	30	16	19 (5)
Ciprofloxacin PO	76	4	52	29	29 (9)	2	327	16	27 (40)
Ofloxacin PO	3	10	14	10	11 (2)	7	17	11	12 (5)

SD indicates standard deviation.
* Data missing for 3 patients with and 3 patients without CF

($n = 8$) or second week ($n = 2$) after FQ introduction, and all were transient (maximum 20 days). They were of moderate intensity in 7 patients but led to transient or definitive discontinuation of FQs in 3 patients. Three patients were reexposed to FQ after the 15-day observation period; 1 rechallenge was positive. According to the Naranjo algorithm,[40] the FQ causality in these 10 events would have been considered possible in 9 patients and probable in 1. According to the French method,[41] the FQ causality would have been considered plausible in all 10 events.

Risk Factors for PAE

Among FQ recipients, the number of concomitant drugs ($<$ or ≥ 8) was significantly associated with PAE (odds ratio [OR]: 2.6; 95% CI: 1.3–5.2; $P = .004$). No significant associations with PAE were found with gender, age ($<$ or ≥ 6 years), medical history of CF, or previous exposure to FQ within the past 5 years. However, musculoskeletal PAEs were significantly associated with female gender ($P < .05$) and age ≥ 6 years ($P = .01$).

Control Group

Among the 249 control patients, the age distribution and the percentage of patients with CF did not differ significantly from the FQ group, as expected by the matching process. The most frequent underlying conditions were similar to those of the FQ group. However, significantly fewer patients had previously received FQ at least once within the last 5 years than in the FQ group (9% vs 32%; $P < .001$).

The main antibiotics used among controls were amoxicillin + clavulanic acid (12%), ceftriaxone (11%), cefotaxime (10%), amoxicillin (9%), oxacillin (6%), piperacillin + tazobactam (6%), ceftazidime (6%), and vancomycin (4%). The indications for antibiotics among control patients with CF were similar to those of the FQ group. Among control patients without CF, the indications for antibiotics were similar except for more frequent febrile neutropenia (22%; $P = .03$) and less frequent *Salmonella* or *Shigella* gastrointestinal tract infections (5%; $P = .01$), septicemia (4%; $P = .003$), or meningitis (0%; $P < .001$) than in the FQ group. Bacteria were isolated less often among control patients with CF (77%; $P < .001$) and without CF (38%, $P < .001$) than from patients who were receiving FQ. Each control patient was receiving significantly fewer drugs other than the antibiotic (mean ± standard deviation, 3.5 ± 2.9) compared with the FQ group ($P < .001$). Unlike the FQ group, only 1 control, who was critically ill before antibiotic administration, died before the end of the 15-day observation period ($P = .02$).

Relative Risk of PAEs

The following univariate and multivariate analyses included data from 237 (95%) of the 249 patients in the control group; 12 patients were lost to follow-up before the end of the 15-day observation period. Forty-seven (18%) FQ recipients experienced at least 1 PAE compared with 13 (5%) control patients, giving an OR for PAEs for the FQ group of 3.7 (95% CI: 1.9–7.5; $P < .0001$). Among patients with CF, 12 (13%) FQ recipients experienced at least 1 PAE compared with 1 (2%) control patient, giving an OR for PAE in the FQ group of 8.3 (95% CI: 1.1–176; $P = .001$). Among patients without CF, 35 (20%) FQ recipients experienced at least 1 PAE compared with 12 (7%) control patients, giving an OR for PAE in the FQ group of 3.6 (95% CI: 1.7–7.6; $P = .0001$).

Concerning the relationship between the present exposure to FQ and the occurrence of PAEs, no significant interaction was found for the underlying condition (CF or not; $P = .79$), age ($P = .73$), previous exposure to FQ within the past 5 years ($P = .86$), or number of concomitant drugs ($P = .43$). Logistic regression analysis was based on the data obtained from only 484 (97%) of the 501 patients who were not lost to follow-up, because of missing data for adjustment criteria. The treatment group (FQ or control) and the following potential confounders were entered into the model: age, underlying condition (CF or not), previous exposure to FQ within the past 5 years, and number of concomitant drugs ($<$ or ≥ 8). The adjusted OR for PAE in the FQ group was 3.0 (95% CI: 1.5–5.9; $P = .002$).

In the control group, only 1 musculoskeletal PAE was recorded, and it occurred in a patient with CF. The crude OR for musculoskeletal PAE in the FQ group was 9.3 (95% CI: 1.2–195; $P = .02$). Among patients with CF, the OR for musculoskeletal PAEs in the FQ group was 1.2 (95% CI: 0.1–35; $P = .99$).

TABLE 2. Description of Musculoskeletal PAE, in 10 Patients Exposed to FQs

Age (Years)	Gender (M/F)	Medical History	Previous FQ Course	Indication	FQ Regimen				PAES			
					Drug	Route	Dose (mg/kg/d)	Duration	Occurrence (Days)*	Duration (Days)	Clinical Description	Counter Measure	Late Rechallenge
7	M	None	No	Urinary tract infection	Pefloxacin	PO	16	10	5	2	Myalgia (thigh)	None	No
8	F	None	No	Salmonella diarrhea	Ciprofloxacin	IV	19	1	2	5	Arthralgias (knee, ankles)	None	No
						PO	24	13					
9	F	None	No	Yersinia diarrhea	Ciprofloxacin	PO	10	7	6	2	Diffuse myalgia	None	No
9	F	CF	Yes†	Bronchopulmonary infection	Ciprofloxacin	PO	17	15	6	1	Arthralgias (elbow, knees)	None	Positive
10	F	Acute leukemia	No	Pneumonia	Ciprofloxacin	IV	10	23	12	17	Arthralgia (shoulder)	FQ transiently stopped	Negative
11	F	Acute leukemia	No	Febrile neutropenia	Ciprofloxacin	IV	10	10	3	11	Arthralgias (shoulder, knees)	FQ stopped	No
13	F	Cholecystectomy	No	Cholangitis	Ciprofloxacin	IV	20	6	1	20	Arthralgias (knees)	FQ stopped	No
14	F	None	No	Urinary tract infection	Pefloxacin	PO	18	7	14	5	Arthralgias (wrist, knees)	None	No
17	M	Congenital immunodepression	Yes†	Infections prophylaxis	Ciprofloxacin	IV	7	10	1	10	Diffuse myalgia, arthralgia (knees)	None	No
18	F	CF	Yes	Bronchopulmonary infection	Ciprofloxacin	PO	19	21	6	14	Diffuse arthralgias	None	Negative

* From the onset of the FQ therapy.
† Previous exposures were also associated with similar musculoskeletal PAEs.

DISCUSSION

The pediatric centers that participated in this study prescribed FQ mainly for patients with severe chronic underlying conditions (eg, CF, malignancies, immunosuppression) for severe infections, most of which involved documented resistant bacteria. Thus, usage seems to be in good agreement with current recommendations.[2,3,16–19] The increase in the prescription patterns observed in the United States[37] does not seem to have occurred in France >10 years after FQs were first marketed. It may reflect the efforts to regulate the use of FQs in pediatric patients in France. However, our findings cannot be directly extrapolated to all pediatric and CF wards in France. Center participation was voluntary. This design may have introduced a selection bias concerning the FQ use in these centers. Indeed, centers where FQs are used according to recommendations may have been more likely to participate. Prescription patterns may also have changed as a consequence of this prospective study (Hawthorne effect). These 2 biases might have modified the results obtained in terms of FQ use but could not change those concerning the relative risk of PAEs.

Among patients who were exposed to FQs, the overall PAE rate (18% of the patients) and the safety profile observed in the present study were similar to those reported previously.[20–23,28] This safety profile also closely resembles that for adults, except for musculoskeletal events.[42] The incidence of musculoskeletal PAEs was low (3.8% of the patients), as described previously,[20,21,28,30] but was much higher than in adults (0.01%–0.2%).[27,42] In agreement with published data, musculoskeletal events that we observed involved mainly female patients[8,10,21,26,28,33,43] and teenagers.[8–10,13,21,24,26,28,43] In addition, their clinical characteristics conformed to previous descriptions: they appeared within 2 weeks of starting the FQ[10,13,28,33,43] and mainly presented as large-joint arthralgias (knees, shoulders, wrists).[8,9,13,23,24,26,29,30,33,43] The outcome was favorable in all cases, as noted by others.[8,9,13,21,22,24,26,28–30,33,44] No relationship could be established with FQ dose and duration. This is in contrast with findings in juvenile animals[5–7] but consistent with previous reports on pediatric patients.[21,24,28] The nonrandomized open-label design of our study offers the opportunity to anticipate PAE rates that might be expected in day-to-day practice in other settings. However, our results concern only the 3 FQs studied (ciprofloxacin, ofloxacin, and pefloxacin) and the short 15-day observation period chosen.

The PAE rate that we observed was significantly higher in the FQ group for both patients with and without CF. The rate of musculoskeletal PAEs was also significantly higher for the FQ recipients without CF. The failure to establish a significant relationship between exposure to FQ and the occurrence of musculoskeletal PAEs in patients with CF might be attributable to a lower statistical power in this subgroup or might confirm the particularly good musculoskeletal tolerance of FQ in patients with CF.[45] Musculoskeletal PAEs were much more frequent

with pefloxacin (18.2%) than ciprofloxacin (3.3%), and this difference tended toward statistical significance ($P = .06$). These results are consistent with several previously reported clinical findings[3,19] and may be related to a better musculoskeletal safety of ciprofloxacin versus pefloxacin in children. Several biases may have occurred in the evaluation of the relative risk of FQs versus other antibiotics in this nonrandomized, open-label study. An overestimation of the PAE rate in the FQ group may have resulted from the open-label design and produced a differential misclassification bias (ie, investigators might have reported more events in the FQ group because FQ use in pediatric patients is generally considered "at risk"). This bias was more likely for musculoskeletal events. We tried to limit this bias by asking the investigators to report systematically all PAEs in both groups and by reviewing nurses' notes. Confounding by indication may have resulted from the nonrandomized design. The presence of this bias is supported by the different frequencies of positive bacterial findings, the distributions of identified species, and the mortality rates of FQ and control groups. We tried to limit this bias by matching patients, but FQs were obviously prescribed to patients who had more severe conditions and were also receiving more concomitant drugs. Therefore, FQ recipients might have experienced more events, resulting from their conditions or their concomitant drugs, which might have led to an overestimation of the PAE crude risk for this group. However, after adjustment for the number of concomitant drugs, the relationship between FQs and PAEs was not significantly modified.

An unexpected finding of the present study was that 23% of FQ prescriptions were given for patients younger than 2 years. This rate is much higher than those previously reported[21–23,28] but is close to preliminary findings in the United States.[37] According to our data, this population was at lower risk of musculoskeletal PAEs, but they may have been underdiagnosed. Little is known about FQ safety in newborns and infants.[46,47] However, laboratory findings in juvenile animals indicated that younger animals were at higher risk of cartilage damage.[5–7] Therefore, future studies perhaps should focus on this age group with long-term follow-up.

CONCLUSIONS

FQ use in the centers that participated in this study was in good agreement with the current recommendations. Short-term PAEs and musculoskeletal PAEs occurred more frequently in association with FQs than other antibiotics, when compared in an observational, nonblinded manner. All of these PAEs were of moderate intensity and transient. In this prospective study of 276 pediatric patients who were exposed to relatively high FQ doses for long durations, no severe or persistent musculoskeletal lesion was observed.

Thus, the status quo recommended by the American Academy of Pediatrics[19]—justifying but restricting the off-label use of FQs in pediatric patients to a limited number of precise clinical situations—is supported by our findings. Any extension of the indications of off-label FQ prescription in pediatric patients should be accompanied by large, long-term cohort studies on their PAEs, particularly in newborns and infants.

ACKNOWLEDGMENTS

This work was presented in part at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, September 2002.

This work was financed by a grant from the Agence Française de Sécurité Sanitaire des Produits de Santé, Saint Denis, France, and by a grant from Bayer Pharma, Puteaux, France. Financial support was received from the Association des Juniors en Pédiatrie and Laboratoires Gallia to prepare the manuscript.

Pediatric Fluoroquinolone Safety Study main investigators: Christine Chretiennot, Franck Iserin (Hôpital Necker), Anne-France Ray-Lunven, Yves Reguerre (Hôpital Saint-Louis), Anne Auvrignon, Guy Leverger, Annick Tamalet (Hôpital Trousseau), Michel Larchet (Centre Hospitalier de Montbéliard), Paris and Montbéliard, France.

We thank all of the investigators who recruited patients. We are indebted to Françoise Bavoux, Françoise Haramburu, Marie-Claude Marchand, and Christiane du Mazaubrun for advice.

REFERENCES

1. Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. *N Engl J Med*. 1991;324:384–394
2. Schaad UB. Role of the new quinolones in pediatric practice. *Pediatr Infect Dis J*. 1992;11:1043–1046
3. Dagan R. Fluoroquinolones in paediatrics–1995. *Drugs*. 1995;49:92–99
4. Gendrel D, Moulin F. Fluoroquinolones in paediatrics. *Paediatr Drugs*. 2001;3:365–377
5. Maggiolo F, Caprioli S, Suter F. Risk/benefit analysis of quinolone use in children: the effect on diarthrodial joints. *J Antimicrob Chemother*. 1990;26:469–471
6. Schmidt M, Hoffmann K. The use of quinolones in children—toxicological aspects. *Adv Antimicrob Antineopl Chemother*. 1992;11–2s: 251–255
7. Schluter G. Ciprofloxacin: toxicologic evaluation of additional safety data. *Am J Med*. 1989;87:37S–39S
8. Jawad AS. Cystic fibrosis and drug-induced arthropathy. *Br J Rheumatol*. 1989;28:179–180
9. Alfaham M, Holt ME, Goodchild MC. Arthropathy in a patient with cystic fibrosis taking ciprofloxacin. *Br Med J (Clin Res Ed)*. 1987;295:699 (letter)
10. Chaslerie A, Bannwarth B, Fillol M, Joussein M, Laborde-Laulhe AM, Begaud B. Polyarthropathy in an adolescent treated with pefloxacin. *Therapie*. 1992;47:80 (letter)
11. Kesseler A, Lacassie A, Hugot JP, Talon P, Thomas D, Astier L. Arthropathies following the administration of pefloxacin to an adolescent with mucoviscidosis. *Ann Pediatr (Paris)*. 1989;36:275–278
12. Seigneuric C, Plantavid M, Bouygues D, Cassou M, Amar J, Cascarigny F. Joint manifestations of pefloxacin in adolescents. *Presse Med*. 1990;19: 428 (letter)
13. Touzet P, Thibaud D. Hydrarthrosis complicating a treatment with pefloxacine in a 14-year-old adolescent. *Arch Fr Pediatr*. 1991;48:151–152
14. Chevalier X, Albengres E, Voisin MC, Tillement JP, Larget-Piet B. A case of destructive polyarthropathy in a 17-year-old youth following pefloxacin treatment. *Drug Saf*. 1992;7:310–314
15. Chang H, Chung MH, Kim JH. Pefloxacin-induced arthropathy in an adolescent with brain abscess. *Scand J Infect Dis*. 1996;28:641–643
16. Schaad UB. Pediatric use of quinolones. *Pediatr Infect Dis J*. 1999;18: 469–470
17. Aradottir E, Yogev R. The use of fluoroquinolones in pediatrics—a reassessment. *Semin Pediatr Infect Dis*. 1999;10:31–37
18. Schaad UB, abdus Salam M, Aujard Y, et al. Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. *Pediatr Infect Dis J*. 1995;14:1–9
19. American Academy of Pediatrics. Antimicrobial agents and related therapy. Fluoroquinolones. In: Pickering LK, ed. *2000 Red Book: Report of the Committee on Infectious Diseases*. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2000:645–646
20. Pariente-Khayat A, Vauzelle-Kervroedan F, d'Athis P, et al. Retrospective survey of fluoroquinolone use in children. *Arch Pediatr*. 1998;5: 484–488

21. Black A, Redmond AO, Steen HJ, Oborska IT. Tolerance and safety of ciprofloxacin in paediatric patients. *J Antimicrob Chemother.* 1990;26: 25–29
22. Kuhn R, Palmejar A, Kanga J. Tolerability of ciprofloxacin in pediatric patients with cystic fibrosis. *Adv Antimicrob Antineopl Chemother.* 1992; 11–2s:269–271
23. Dab I, Desmyttere S, Malfroot A. Repeated use of ciprofloxacin in a pediatric cystic fibrosis population. *Adv Antimicrob Antineopl Chemother.* 1992;11–2s:143–146
24. Pertuiset E, Lenoir G, Jehanne M, Douchain F, Guillot M, Menkes CJ. Joint tolerance of pefloxacin and ofloxacin in children and adolescents with cystic fibrosis. *Rev Rhum Mal Osteoartic.* 1989;56:735–740
25. Yee CL, Duffy C, Gerbino PG, Stryker S, Noel GJ. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. *Pediatr Infect Dis J.* 2002;21:525–529
26. Rubio TT. Ciprofloxacin in the treatment of Pseudomonas infection in children with cystic fibrosis. *Diagn Microbiol Infect Dis.* 1990;13:153–155
27. Rahm V, Schacht P. Safety of ciprofloxacin. A review. *Scand J Infect Dis Suppl.* 1989;60:120–128
28. Chysky V, Kapila K, Hullmann R, Arcieri G, Schacht P, Echols R. Safety of ciprofloxacin in children: worldwide clinical experience based on compassionate use. Emphasis on joint evaluation. *Infection.* 1991;19: 289–296
29. Schaad UB, Stoupis C, Wedgwood J, Tschaeppeler H, Vock P. Clinical, radiologic and magnetic resonance monitoring for skeletal toxicity in pediatric patients with cystic fibrosis receiving a three-month course of ciprofloxacin. *Pediatr Infect Dis J.* 1991;10:723–729
30. Cheesbrough JS, Mwema FI, Green SD, Tillotson GS. Quinolones in children with invasive salmonellosis. *Lancet.* 1991;338:127 (letter)
31. Singh UK, Sinha RK, Prasad B, Chakrabarti B, Sharma SK. Ciprofloxacin in children: is arthropathy a limitation? *Indian J Pediatr.* 2000;67:386–387
32. Pradhan KM, Arora NK, Jena A, Susheela AK, Bhan MK. Safety of ciprofloxacin therapy in children: magnetic resonance images, body fluid levels of fluoride and linear growth. *Acta Paediatr.* 1995;84:555–560
33. Leibovitz E, Janco J, Piglansky L, et al. Oral ciprofloxacin vs. intramuscular ceftriaxone as empiric treatment of acute invasive diarrhea in children. *Pediatr Infect Dis J.* 2000;19:1060–1067
34. Petrilli AS, Dantas LS, Campos MC, Tanaka C, Ginani VC, Seber A. Oral ciprofloxacin vs. intravenous ceftriaxone administered in an outpatient setting for fever and neutropenia in low-risk pediatric oncology patients: randomized prospective trial. *Med Pediatr Oncol.* 2000;34:87–91
35. Doherty CP, Saha SK, Cutting WA. Typhoid fever, ciprofloxacin and growth in young children. *Ann Trop Paediatr.* 2000;20:297–303
36. Richard DA, Nousia-Arvanitakis S, Sollich V, Hampel BJ, Sommerauer B, Schaad UB. Oral ciprofloxacin vs. intravenous ceftazidime plus tobramycin in pediatric cystic fibrosis patients: comparison of antipseudomonas efficacy and assessment of safety with ultrasonography and magnetic resonance imaging. Cystic Fibrosis Study Group. *Pediatr Infect Dis J.* 1997;16:572–578
37. Nelson JD, McCracken GH. The Pediatric Infectious Disease Journal Newsletter. Fluoroquinolones in pediatrics. *Pediatr Infect Dis J.* 1998;17 Newsletter (yellow pages)
38. Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. *Clin Infect Dis.* 1997;25:1196–1204
39. Kubin R. Safety and efficacy of ciprofloxacin in paediatric patients—review. *Infection.* 1993;21:413–421
40. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30: 239–245
41. Begaud B. Standardized assessment of adverse drug reactions: the method used in France. Special workshop—clinical. *Drug Inf J.* 1984;18: 275–281
42. Ball P, Tillotson G. Tolerability of fluoroquinolone antibiotics. Past, present and future. *Drug Saf.* 1995;13:343–358
43. Le Loet X, Fessard C, Noblet C, Ait Sait L, Moore N. Severe polyarthropathy in an adolescent treated with pefloxacin. *J Rheumatol.* 1991; 18:1941–1942
44. Karande S, Kshirsagar NA. Ciprofloxacin use: acute arthropathy and long-term follow up. *Indian Pediatr.* 1996;33:910–916
45. Warren RW. Rheumatologic aspects of pediatric cystic fibrosis patients treated with fluoroquinolones. *Pediatr Infect Dis J.* 1997;16:118–122; discussion 123–126
46. Wlazlowski J, Krzyzanska-Oberbek A, Sikora JP, Chlebna-Sokol D. Use of the quinolones in treatment of severe bacterial infections in premature infants. *Acta Pol Pharm.* 2000;57:28–31
47. Martell M, de Ben S, Weinberger M, Beltrami G. Growth and development in preterm infants receiving fluoroquinolones. *J Perinat Med.* 1996; 24:287–291

Fluoroquinolone Safety in Pediatric Patients: A Prospective, Multicenter, Comparative Cohort Study in France

Martin Chalumeau, Sylvie Tonnelier, Philippe d'Athis, Jean-Marc Tréluyer, Dominique Gendrel, Gérard Bréart and Gérard Pons

Pediatrics 2003;111;e714
DOI: 10.1542/peds.111.6.e714

Fluoroquinolone Safety in Pediatric Patients: A Prospective, Multicenter, Comparative Cohort Study in France

Martin Chalumeau, Sylvie Tonnelier, Philippe d'Athis, Jean-Marc Tréluyer, Dominique Gendrel, Gérard Bréart and Gérard Pons

Pediatrics 2003;111;e714
DOI: 10.1542/peds.111.6.e714