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Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin

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Background. **Fluoroquinolones (FQs) have been infrequently used in children, largely because of concern that these agents can cause lesions of the cartilage in juvenile animals. However, the relevance of this laboratory observation to children treated with FQs is unknown. A retrospective, observational study was conducted to assess the incidence and relative risk of tendon or joint disorders (TJDs) that occur after use of selected FQs compared with azithromycin (AZ), a drug with no known effect on cartilage or tendons in humans or animals.**

Methods. **An automated database was searched to identify patients younger than 19 years who had been prescribed ofloxacin (OFX), levofloxacin, ciprofloxacin (CPX), or AZ. Potential cases of TJD occurring within 60 days of a prescription of one of the study drugs were identified based on assignment of a claims diagnosis consistent with a TJD within this period. Verified cases were identified by a blinded review of abstracts of medical records from subjects identified as potential cases.**

Results. **The incidence of verified TJD was 0.82% for OFX (13 of 1593) and CPX (37 of 4531) and was 0.78% for AZ (118 of 15 073). The relative risk of TJD for OFX and CPX compared with AZ was 1.04 (95% confidence interval, 0.55 to 1.84) and 1.04 (95% confidence interval, 0.72 to 1.51), respectively. The distributions of claims diagnoses and time to onset of TJD were comparable for all groups. The most frequently reported category of TJD involved the joint followed by tendon, cartilage and gait disorder.**

Conclusions. **In this observational study involving more than 6000 FQ-treated children, the incidence of TJD associated with selected FQ use in children was <1% and was comparable with that of the reference group, children treated with AZ.**

INTRODUCTION

Soon after the first quinolone antimicrobial, nalidixic acid, was introduced more than 30 years ago, animal experimentation revealed the potential for these agents to cause damage to cartilage in the weight-bearing joints of juvenile animals.[1, 2] Largely because of this observation, fluoroquinolones (FQs) have not been recommended for use in children. FQs, particularly those introduced into clinical practice in the last decade, have been used widely and effectively to treat adults with serious bacterial infections caused by multidrug-resistant bacteria. As these infections have become more important in children, it is apparent that

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the risk-benefit analysis for using FQs in children with these infections must be defined better.

Reviews of the published clinical experience and prospective studies, primarily in FQ-treated children with cystic fibrosis, have consistently concluded that the risk for arthropathy in children appears to be low.[3–7] On the basis of a review of the experience of >7000 children, Burkhardt et al. [7] estimated the incidence of definitive quinolone arthropathy to be zero. This observation has been difficult to understand considering that these lesions can be produced in juvenile dogs with doses comparable with those used in humans and can be induced in immature animals of a variety of species with these agents.[8, 9]

Given that the incidence of quinolone-associated arthropathy is likely to be low, assessing the risk for this event will require a very large sample of children exposed to these drugs. Retrospective analyses of a large population have been performed to assess the association of fluoroquinolones and tendon disorders in adults.[10] This large observational study with a focus on children was conducted to determine the incidence and relative risk of new onset tendon or joint disorders (TJDs) after treatment with one of three FQs, ofloxacin, levofloxacin (the L isomer of ofloxacin) and ciprofloxacin or a non-FQ agent, azithromycin.

METHODS

Study design. A retrospective cohort observational study was conducted utilizing the linked claims and pharmacy records of the United HealthCare Research Data. Data were obtained from the United Health Care Research Database, a validated research database containing 13 affiliated health plans across the United States with >3 million members (1997 enrollment). Approximately 95% of the members have a pharmacy benefit. This database contains member demographic data, medical claims data for health care services and pharmacy claims data for prescriptions.

Study population. All pharmacy claims for azithromycin (AZ) and the three selected fluoroquinolones, ofloxacin (OFX), levofloxacin (LFX) and ciprofloxacin (CPX) dispensed during the study period (January 1, 1992, to June 30, 1998) were identified. The member and claims data linked to these pharmacy claims were extracted from the research database. The earliest date for a prescription (index date) during the study period was determined for each of the four antibiotics. Subjects were included whose age was <19 years as of the index date and who had at least 90 days of continuous enrollment in their health plan, 30 days before and 60 days after the fill date of the index prescription.

All FQ-exposed children were selected as members of the study cohort based on the antimicrobial prescribed. Because of a large number of patients exposed to AZ, a sampling of this group was selected for the comparator cohort. Because both exposure to antibiotics and the occurrence of TJD may have been related to age and gender, the sampling was based on specific age and gender strata to achieve a 4:1 loading of AZ-exposed to FQ-exposed for all age groups <17 years. Because of the larger number of older subjects exposed to FQs, a 1:1 ratio of sampling was selected for patients 17 to 18 years old.

Claims diagnosis. Within the United Health Care system, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9cm) was used to code patient complaints, concomitant diseases and indications for submitting health claims. A list of ICD-9cm claims diagnoses was selected prospectively as screening diagnoses for potential TJD. These codes were further categorized as belonging to one of four groups: joint-related; cartilage-related; tendon-related; or gait-related.

Case identification. The primary objective of this study was to define the incidence and relative risk for TJD based on claims diagnosis for selected FQs and the non-FQ comparator, AZ. To maximize the sensitivity and specificity of identifying cases of TJD with onset after antibiotic exposure, a two phased approach was followed. In Phase I potential cases of TJD were identified by screening the research database for all subjects with a first time claims diagnosis of TJD after the index prescription. In Phase II the potential TJD cases were verified by an independent review of the medical record. Medical records of all potential cases of TJD were requested, and relevant medical data related to the onset, clinical presentation, diagnostic work-up, clinical diagnosis, clinical course and outcome of the TJD were abstracted with a standardized form. A pediatric rheumatologist and an orthopedic surgeon who were blinded to the identity of the antibiotic exposure independently reviewed the chart abstractions. The primary objective of this review was to verify TJD cases and confirm that the onset of the TJD occurred during the 1- to 60-day study period. Physicians also reviewed medical abstracts to assess whether there was adequate information to assess the relatedness of drug to the TJD. If there was disagreement between the two reviewers, consensus was sought by review of the case with a third expert (another pediatric rheumatologist) who was also blinded to the identity of the antibiotic exposure.

Characterization of TJD cases associated with each of the agents based on the distribution of TJDs related to age and gender, the anatomic location of TJDs and the time to onset of TJDs was a secondary objective of this study. Assessing differences in the character of TJDs among the cohorts was performed to determine whether TJDs associated with FQ treatment were qualitatively different from those associated with the comparator, AZ. Additional planned analyses aimed at

assessing the effect of drug dose, of indication for drug prescription and of comorbid conditions on TJDs and of attributing drug use as a cause of TJD were considered limited. The information needed to complete these analyses was not consistently identifiable.

Statistical methods. Analyses were performed using SAS Release 6.12 and 8.00 and STATA 6.0. An alpha level of 0.05 was selected to indicate statistical significance. Cumulative incidence and risk ratios are the primary calculated estimators of effect. Control for confounding, predominantly for age and gender, was accomplished via stratification by the confounding variables. Stratified analyses used Mantel-Haenszel estimators and *P* values with associated 95% confidence intervals. The appropriateness of using the summary Mantel-Haenszel risk ratio was assessed using the Breslow-Day statistic for heterogeneity. To provide an appropriate denominator for calculations with various case definitions, exclusion criteria were applied uniformly to the entire cohort. As potential cases failed to meet applied definitions, they were excluded from the cohort; consequently they were not counted in the denominator for exposure in subsequent calculations of incidence.

RESULTS

Incidence of TJDs. Search of the database identified 7897 children who had been prescribed 1 of the 3 fluoroquinolones during the study period. A large number of children (>20 000) were identified who had been prescribed AZ during the study period. Among these children 576 potential cases of TJDs were identified based on ICD-9cm claims diagnosis. The crude incidence of having an ICD-9 claims diagnosis consistent with a TJD recorded within 60 days of having been prescribed an antimicrobial was comparable for the 4 agents (Table 1). The incidence was 2.0% for AZ, 1.7% for ofloxacin, 2.6% for LFX and 2.2% for CPX.

To verify the TJD diagnosis, medical records of the potential cases were abstracted for medical review. Medical records were available for 11 of the 13 health plans; therefore 443 of the 576 potential cases of TJD were available for medical abstraction. For these 11 participating health plans, the crude incidences for potential TJD were again comparable and ranged from 2.2% for CPX to 1.9% for OFX (Table 1). The rates of availability of medical records for abstraction were comparable for each of the agents (Table 1). The slightly higher rate in the ofloxacin cohort (65% *vs.* 61 and 57%) was a result of the greater number of children in this cohort who belonged to health plans that allowed access to records. Of the 335 potential TJD cases with completed medical record abstraction, 78 were excluded because the TJD identified was a preexisting condition with onset before antibiotic exposure.

Of the 257 record abstractions reviewed, the physicians verified the TJD diagnosis in 168 cases. No verified cases of TJD were identified in the 16 subjects who received LFX. The incidences of verified TJDs associated with prescription of AZ, OFX and CPX were 0.78, 0.82 and 0.82%, respectively. Additional analysis that was aimed at assessing the relatedness of the prescribed drug to the TJD was dependent on the presence of an alternative nondrug etiology. However, this information was not consistently available from the chart abstractions. In the absence of being able to identify cases that were clearly drug-related, all verified cases of TJD were used in defining the incidence and relative risk for TJD.

Risk of TJD. The risk ratios for both potential and verified cases among children prescribed FQs compared with AZ approximated unity (Table 2).

Characterization of cases. Fluoroquinolone cartilage toxicity occurs largely in developing animals. Because there are differences in the timing of normal musculoskeletal development in girls and boys, the effect of both age and gender on the incidence of TJD was assessed. Seventy-seven children <2 years (62 CPX, 15 OFX), 239 children 2 to 5 years old (175 CPX, 64 OFX) and 403 children 6 to 9 years old (325 CPX, 78 OFX) were prescribed fluoroquinolones. These agents were prescribed most frequently in 17- to 18-year-old girls (1200 CPX, 592 OFX, 6 LFX). Crude and age-sex-adjusted stratified risk ratios for the potential TJD cases and the verified TJD cases were close to unity and similar (Table 2).

TABLE 1. Incidence of potential tendon-joint disorders based on claims diagnosis and verified tendon or joint disorders based on review of medical records in children within 60 days of antimicrobial prescription

Antimicrobial Prescribed	A. Total Exposure (13 Health Plans)	B. Potential Tendon or Joint Disorders (13 Health Plans)	Incidence (%) of Potential Disorders from 13 Health Plans (B/A)	C. Adjusted Total Exposure (11 Health Plans)	D. Adjusted Potential Tendon or Joint Disorders (11 Health Plans)	Incidence (%) of Potential Disorders from 11 Health Plans (D/C)	Potential Tendon or Joint Disorder Cases with Completed Medical Record Abstraction	No. of Verified Tendon-Joint Disorder Cases Based on M.D. Review of Record Abstract	Incidence (%) of Verified Disorders Based on Review of Medical Records
Azithromycin	20 283	413	2.0	15 265	310	2.0	235 (57)*	118	0.78
Ofloxacin	1905	34	1.7	1610	30	1.9	22 (65)	13	0.82
Levofloxacin	38	1	2.6	16	0	0	0	0	0.8
Ciprofloxacin	5904	128	2.2	4597	103	2.2	78 (61)	37	0.82

* Numbers in parentheses, percent of potential cases.

TABLE 2. Risk ratios compared with azithromycin for potential tendon-joint disorders based on claims diagnoses and verified tendon or joint disorders based on physician review of medical record abstracts

Fluoroquinolone Prescribed	Crude Risk for Potential Tendon or Joint Disorder	Crude Risk for Verified Tendon or Joint Disorder	Age-Sex-adjusted Stratified Risk for Verified Tendon or Joint Disorder	Age-Sex-adjusted Risk for Verified Lower Extremity Tendon or Joint Disorder
Ofloxacin	0.92 (0.63–1.33)*	1.04 (0.59–1.84)	1.13 (0.63–2.03)	1.20 (0.62–2.31)
Ciprofloxacin	1.10 (0.89–1.38)	1.04 (0.72–1.51)	1.08 (0.74–1.58)	1.18 (0.77–1.81)
Ofloxacin, levofloxacin or ciprofloxacin	1.05 (0.86–1.29)	1.04 (0.75–1.45)	1.08 (0.77–1.52)	1.18 (0.8–1.74)

* Numbers in parentheses, 95% CI.

Cases of TJD were characterized further based on the type and the anatomic location of the TJD. The distribution of claims code in potential cases was similar for each cohort with codes categorized as joint-related predominating and representing 69% (286 of 413), 62% (79 of 128) and 85% (29 of 34) of potential TJD cases respectively in the AZ, CPX and OFX cohorts. The frequency of claims codes in verified cases was similar to that for potential cases and accounted for 70% (83 of 118), 76% (28 of 37) and 69% (9 of 13) of cases, respectively, in the AZ, CPX and OFX cohorts. The location of the TJD was of particular interest because arthropathy occurs predominately in weight-bearing joints in juvenile animals treated with FQs. There was a predominance of lower extremity involvement in the TJD cases in all cohorts. No differences in the distribution of lower extremity TJD were apparent across the cohorts and the crude risk for involvement of the lower extremities compared with the AZ group was 1.18 for CPX and 1.20 for the OFX group (Table 2).

The time to onset of TJDs associated with antimicrobial use was assessed. In juvenile animals treated with fluoroquinolones, the toxicity to cartilage is clinically evident within days of the first dose of drug. Given this observation the distribution of time to onset of TJD associated with antimicrobial use may also provide evidence of an FQ-associated event. Time to onset of the 168 verified TJDs and the subset of verified TJDs involving the lower extremity are shown in Figure 1. For all cohorts the time to onset for these disorders was distributed evenly over the 60-day period of observation and did not suggest an FQ drug effect (*P* value log-rank test for equality = 0.9792 with chi square 3 df = 0.19).

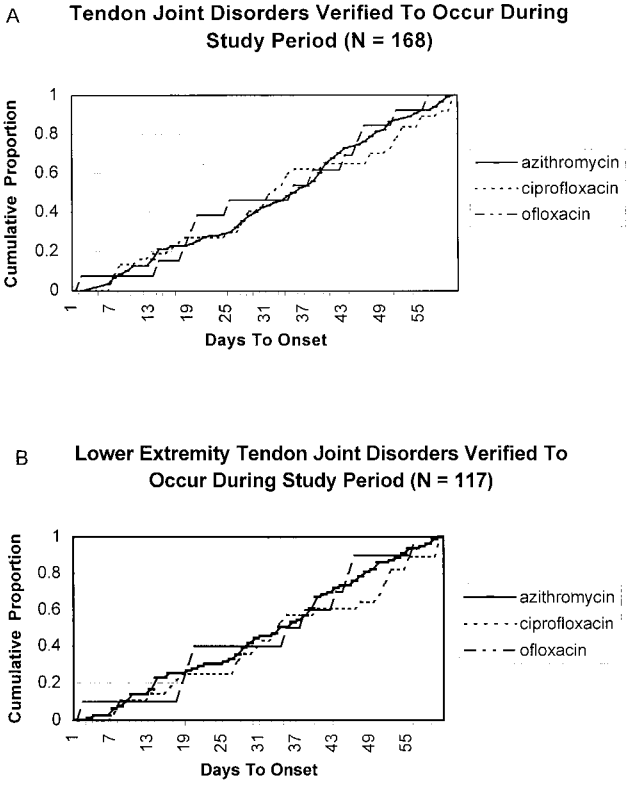

FIG. 1. Time to onset of verified tendon-joint disorders within 60 days of prescription of antimicrobial. *A,* time to onset of all tendon-joint disorders; *B,* time to onset of tendon-joint disorders involving a lower extremity.

DISCUSSION

This observational study involving >6000 FQ-treated and ~20 000 azithromycin-treated children identified the incidence of potential TJD for children treated with CPX, OFX or AZ to be ~2%. The incidence of verified TJD for each of these agents was <1%. Compared with AZ the relative risk for TJDs was 1.04 [95% confidence interval (95% CI), 0.72 to 1.51] for CPX and 1.04 (95% CI, 0.55 to 1.84) for OFX. Azithromycin has no known effect on cartilage, tendons or joints; therefore the incidence of TJDs estimated in this study for children prescribed AZ is likely to reflect the background incidence of these disorders in children. Levofloxacin was not used frequently enough to draw conclusions about this agent. However, levofloxacin, being the L isomer of ofloxacin, has the same potential for causing cartilage-related effects in laboratory animals. The experience with 1905 children using ofloxacin is likely to be highly representative of the experience with levofloxacin. Taken together these findings strongly suggest that TJDs occur rarely in children given FQs and that the frequency of these disorders occurring within 60 days of prescription of FQs is not different from that which occurs after prescription of AZ.

Although the calculated risk for a TJD in children

prescribed an FQ was not different from that risk associated with the use of AZ, this does not establish that use of FQs is associated with no increased risk for these disorders. Because a characteristic quinolone-associated arthropathy has not been defined in children, a broad range of ICD-9cm claims codes was used to identify potential episodes of TJDs. This approach maximized the sensitivity of detecting TJDs but likely overestimated the incidence. Even with review of medical record abstracts it was not possible to establish a causal relation between drug use and TJD. Hence the incidence and relative risk for TJD were calculated based on all verified TJDs. This may have resulted in an overestimation of the risk. Although the incidence of verified TJDs was low, it is possible that the risk of FQ use in causing TJDs is even lower and below the detection of this study. In addition this retrospective study involved off-labeled use of FQs and may largely reflect an experience using doses of FQs that are much lower than should have been used based on pharmacokinetic parameters associated with successful therapy in adults. Finally although no gender- or age-stratified risk was demonstrated, most of the children reviewed in this experience were >10 years of age. If the risk for fluoroquinolone-associated TJD is greater in young children, the distribution of children in this database may not have been adequate to demonstrate this phenomenon.

Precise definition of the risk for the cartilage toxicity associated with FQ use in children has not been possible despite large reviews and small, focused, prospective and retrospective studies. This shortcoming has made it difficult for clinicians to estimate the risk-benefit of using these agents in children. This large observational study provides further evidence that the risk for TJDs associated with these agents is low. The results reported here suggest that large prospective studies involving thousands of children may be needed to define the incidence and risks associated with these agents. Although a considerable challenge, the definition of this low risk remains critical to appropriate use of these highly effective drugs.

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