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BRIEF REPORT

Fluoroquinolone Use and Risk of Carpal Tunnel Syndrome: A Pharmacoepidemiologic Study

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Fluoroquinolone-induced peripheral neuropathies and tendinopathies are well documented, but there are no epidemiologic studies on the risk of carpal tunnel syndrome (CTS). We conducted a case-control study of >6 million patients. Fluoroquinolone use is associated with increased risk of CTS (rate ratio, 1.34 [95% confidence interval, 1.31–1.37]).

Keywords. fluoroquinolones; carpal tunnel; case-control study.

Fluoroquinolones (FQs) are a popular class of antibiotics. In 2013, the Food and Drug Administration issued a label requirement of association between use of FQs and neurologic conditions such as peripheral neuropathy [1] and musculoskeletal conditions such as tendinopathies [2]. One neurologic condition that might be affected by FQ use is carpal tunnel syndrome (CTS). Only 1 case report of CTS resulting from ciprofloxacin-induced tendinitis has been published to date [3]. CTS is a disease of significant societal burden with a prevalence of 5% and incidence of up to 2.3 per 1000 person-years [4, 5]. CTS causes loss of function and decreased quality of life for individual patients, and also comprises a large cumulative drain on healthcare and socioeconomic resources from loss of productivity and worker's compensation claims [6]. One study of 4443 CTS claimants in Washington State estimated a cumulative socioeconomic cost of US$197–$382 million over 6 years for this cohort alone [6]. Given that FQs are widely prescribed in North America, a potential risk of these drugs inducing CTS should be examined in a large epidemiologic study.

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METHODS

Data Sources

We conducted a case-control study within a large health claims database (LifeLink, IMS) from the United States. The description of the data has been published previously [7]. In short, we had access to a random sample of approximately 6 million male and female patients in the United States between the ages of 15 and 60. All subjects were followed from 2006 to 2014 and documented under the LifeLink health claims database, which included information on demographics, physician visits and procedures, hospitalizations, and prescription drugs. Within the random sample, we conducted a nested case-control study.

Case and Control Section

In the primary analysis, cases were defined as individuals with newly diagnosed idiopathic CTS with at least 2 *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes within 60 days of each other. As a sensitivity analysis, we also defined CTS in patients if they received an additional nerve conduction procedure code within 90 days of the first *ICD-9-CM* code. For both definitions, the index date was defined as the date of the first *ICD-9-CM* code. For each case, we selected 10 controls in the following fashion: each case was assigned with a pool of control subjects out of the cohort who (1) entered the cohort within the same year; (2) did not receive any CTS code; (3) were ±1 year of age and had the same sex as the case; and (4) received the same number of years of follow-up as the case. From this pool, we randomly selected 10 controls and matched them to the cases.

Statistical Analysis

We used descriptive statistics to examine data demographics. The onset of CTS with FQs is expected to be acute based on the 1 published case report and other FQ-related neurologic conditions [7]. Thus, we first identified the 1-year period prior to the index date as the risk period with FQ use. We further stratified the 1-year risk period into the following risk periods: 0–30 days (current use), 31–90 days (recent use), and 91–365 days (past use) prior to the index date. All rate ratios (RRs) were compared to nonusers of FQs. A conditional logistic regression model was used to compute crude and adjusted RRs. In the adjusted model, concurrent diabetes, obesity, hypothyroidism, rheumatoid arthritis, and lupus in the year prior to index date were included as confounding variables that could influence CTS risk.

RESULTS

We identified 75 895 cases and 758 950 controls under our regular inclusion criteria and 48 533 cases and 485 330 controls under

Table 1. Characteristics of Cases and Their Matched Controls

Characteristic	Primary Analysis[a]		Sensitivity Analysis[b]	
	Cases	Controls	Cases	Controls
No.	75 895	758 950	48 533	485 330
Age, y, mean ± SD	48.0 ± 10.3	47.9 ± 10.3	48.2 ± 10.1	48.2 ± 10.1
Follow-up, y, mean ± SD	2.1 ± 1.8	2.1 ± 1.8	2.2 ± 1.8	2.2 ± 1.8
Sex, female, %	67.5	67.5	66.3	66.3
Comorbidities (the year before index), %				
Diabetes mellitus	16.0	11.1	16.4	11.4
Obesity	7.9	5.0	8.0	5.0
Hypothyroidism	30.9	23.1	31.6	23.4
Rheumatoid arthritis	3.2	1.6	3.2	1.6
Lupus	0.18	0.15	0.19	0.15

Abbreviation: SD, standard deviation.

[a]Primary analysis: 2 codes within 60 days.

[b]Sensitivity analysis: 2 codes within 60 days AND nerve conduction procedure within 90 days after first code.

our inclusion criteria with additional sensitivity analysis (Tables 1 and 2). There were slightly higher incidences of comorbidities of diabetes mellitus, obesity, hypothyroidism, rheumatoid arthritis, and lupus in cases compared to controls (Table 1). The RR of CTS with any FQ in the year prior to the index date was 1.34 (95% confidence interval [CI], 1.31–1.37) (Table 2). There was a slight increase in RR with sensitivity analysis of added nerve conduction procedure inclusion criteria (RR, 1.36 [95% CI, 1.32–1.40]) (Table 2). Any use of FQ within the year prior to CTS diagnosis was associated with a 34% and 36% increased risk of CTS in the primary and sensitivity analyses, respectively (Table 2). There was an incremental increase in CTS risk in both primary and sensitivity analysis with past use, with RR of 1.19 for current use (95% CI, 1.12–1.26), 1.32 for recent use (95% CI, 1.27–1.38), and 1.37 for past use (95% CI, 1.34–1.41) in primary analysis and RR of 1.20 for current use (95% CI, 1.12–1.29), 1.32 for recent use (95% CI, 1.25–1.39), and 1.41 for past use (95% CI, 1.36–1.45) in sensitivity analysis (Table 2). This may suggest a possible delayed response with FQ use.

DISCUSSION

The results of our study are consistent with an increase in the risk of CTS with FQs. The risk was consistent among all risk periods with a slight increase among past users, which may be due to the longer period elapsed for CTS to manifest itself. FQ-related neurotoxicity can persist cumulatively in relation to exposure levels [8, 9]. The exact mechanism by which this occurs is unknown [9], but proposed models include direct nerve inflammation and ischemia from toxic metabolite and free radical formation [10], and FQ-induced tendonitis/tendinopathy causing mechanical compression upon the adjacent nerves (eg, median nerve) that share the carpal tunnel [11]. Reports of nerve biopsy studies on patients who have experienced FQ adverse events have revealed significantly reduced nerve fiber density consistent with small fiber neuropathy, which may be a potential mechanism of CTS [12]. Although neurotoxicity is the second most commonly reported adverse event, with several studies documenting FQ association with central and peripheral nerve damage [8, 9], this is the first large-scale study exploring the relationship between FQs and CTS. One case reported ciprofloxacin-induced flexor tendinitis precipitating into CTS, which persisted for 3 months until bilateral release procedure was performed [3].

Our study is unique for the large sample size, rigorous inclusion/exclusion criteria, and added sensitivity analysis with nerve conduction data for increased specificity in establishing CTS diagnosis. As with all pharmacoepidemiologic studies that use health claims data, we only had information on prescription dispensing and not necessarily drug intake. However, we can be relatively confident that most patients who require FQ therapy for an infection would be compliant with their medication. Moreover, we did not have direct access to diagnostic information on CTS. However, our results were validated through sensitivity analysis with added procedure codes for nerve conduction studies that improve the specificity of the CTS diagnosis.

Our study results demonstrate an increase in the risk of CTS with FQ use. Patients taking these drugs should be aware of the warning of adverse side effects. Those who experience pain,

Table 2. Rate Ratios of Carpal Tunnel Syndrome With Stratified Periods of Fluoroquinolone Use

Period of Use	Primary Analysis[a]					Sensitivity Analysis[b]				
				Adjusted					Adjusted	
	Cases	Controls	Crude RR	RR	(95% CI)	Cases	Controls	Crude RR	RR	(95% CI)
No.	75 895	758 950	…	…	…	48 533	485 330	…	…	…
No FQ use in the past year, %	85.04	88.63	1.00	…	Ref	84.71	88.57	1.00	…	Ref
Any FQ use in the past year, %	14.96	11.37	1.38	1.34	(1.31–1.37)	15.29	11.43	1.41	1.36	(1.32–1.40)
Current FQ use (days 0–30 in the past year), %	1.84	1.56	1.23	1.19	(1.12–1.26)	1.82	1.53	1.24	1.20	(1.12–1.29)
Recent FQ use (days 31–90 in the past year), %	3.27	2.50	1.37	1.32	(1.27–1.38)	3.29	2.52	1.37	1.32	(1.25–1.39)
Past FQ use (days 91–365 in the past year), %	9.86	7.31	1.42	1.37	(1.34–1.41)	10.19	7.38	1.46	1.41	(1.36–1.45)

Abbreviations: CI, confidence interval; FQ, fluoroquinolone; RR, rate ratio; SD, standard deviation.

[a]Primary analysis: 2 codes within 60 days.

[b]Sensitivity analysis: 2 codes within 60 days AND nerve conduction procedure within 90 days after first code.

numbness, tingling, and burning along median and ulnar digits may be at risk of developing CTS and should discuss their symptoms with their primary care physician.

Notes

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