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Article

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Oral fluoroquinolone use and risk of peripheral neuropathy

A pharmacoepidemiologic study

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ABSTRACT

Objective: To quantify the risk of peripheral neuropathy (PN) with oral fluoroquinolone (FQ) use.

Methods: We conducted a case-control study within a cohort of men aged 45 to 80 years in the United States followed from 2001 to 2011. Cases were defined as those with the first physician visit diagnosis of PN, polyneuropathy, or drug-induced polyneuropathy. Four controls were matched to each case by age, follow-up, and calendar time using density-based sampling. As a sensitivity analysis, we also quantified the risk of PN with finasteride use, a drug that is not expected to increase the risk of PN. Rate ratios (RRs) for current users of FQs were computed using conditional logistic regression, which was adjusted for chronic renal failure, chronic liver disease, hypothyroidism, postherpetic neuralgia, and the use of nitrofurantoin and metronidazole.

Results: We identified 6,226 cases and 24,904 controls. Current users of FQs were at a higher risk of developing PN (RR = 1.83, 95% confidence interval [CI] 1.49–2.27). Current new users had the highest risk (RR = 2.07, 95% CI 1.56–2.74). No risk was observed for current users of finasteride (RR = 1.21, 95% CI 0.97–1.51).

Conclusions: Current users, especially new users of FQs, are at a higher risk of developing PN. Despite the increase in the use of FQs, clinicians should weigh the benefits against the risk of adverse events when prescribing these drugs to their patients.

GLOSSARY

CI = confidence interval; **FDA** = Food and Drug Administration; **FQ** = fluoroquinolone; ***ICD-9*** = *International Classification of Diseases, ninth revision*; **PN** = peripheral neuropathy; **RR** = rate ratio

Oral fluoroquinolones (FQs) are a potent class of antibiotics and one of the most prescribed in the United States. In 2013, the Food and Drug Administration (FDA) issued a communiqué requiring a label change that specifically addressed the risk of peripheral neuropathy (PN) for all oral FQs.[1] This label change was prompted mainly from published case reports,[2,3] and reports sent to the FDA through the FDA's Adverse Event Reporting System[1] in the absence of evidence from large epidemiologic studies. Evidence from case reports alone cannot show a causal link between FQ use and PN. For example, FQs are routinely prescribed to patients with diabetes-related infections who may be at a higher risk of developing PN. Thus, we undertook the first pharmacoepidemiologic study to quantify the risk of FQs and PN in a cohort of older men.

METHODS

We conducted a case-control study within a cohort of men in the United States using the LifeLink health claims database. The data have been previously described in detail.[4] In brief, we had access to approximately 1 million men aged 40 to 85 randomly selected from LifeLink and followed from 2001 to 2011. For all subjects, we had information on hospitalizations, physician visits, demographics, and prescription drugs. We conducted a time-matched, case-control study, an ideal study design for time-varying interventions such as a prescription drug.[5]

Case and control definitions.

Cases were defined as those with the first physician visit for PN in accordance with *ICD-9* diagnosis code 356. Prevalent cases were excluded. The first date of the first visit for PN was deemed the index date. Because *ICD-9* 356 may also include hereditary PN, we restricted our analysis to only idiopathic polyneuropathy, PN, or drug-induced polyneuropathy (*ICD-9* 356.4, 356.8, 357.6, respectively). For each case, we created a pool of all subjects who had (1) not received a PN code, (2) were the same age as the case (±1 year), and (3) had the same follow-up as the case. Diabetes was an exclusion criterion for both cases and controls. Because antibiotic prescribing may vary over time, we also ensured that cases and controls were matched by calendar time (cases and controls were matched by the year of entry into the cohort). From the potential pool of controls, we selected 4 controls at random and matched them to a case. Controls were allowed to become future cases and could be selected more than once. This manner of control selection, referred to as density sampling, allows for the computation of the rate ratio (RR) similar to a cohort study.[5] We tested the hypothesis that FQ users are not at a higher risk of PN than non-FQ users (RR = 1) at a 5% significance level.

We identified all oral FQ prescriptions in the year before the index date. *Any use* of an FQ was defined as having received at least one prescription of FQ in the year before the index date. Because the onset to PN with FQ use has been shown to be acute,[1] we defined *current users* as those who had used an FQ prescription within 14 days of the index date. Current *new users* were current users who had received only one prescription, whereas those who had received more than one prescription were categorized as *prevalent users*. We also examined the risk of PN among finasteride users, a negative control drug that is not expected to increase the risk of PN. RRs were compared with nonuse of FQs in the year before the index date. We adjusted for the following confounding variables in the conditional logistic regression model: chronic renal failure, chronic liver disease, hypothyroidism, postherpetic neuralgia, and the use of nitrofurantoin and metronidazole. All RRs were compared with those of nonusers of FQs.

Standard protocol approvals, registrations, and patient consents.

The study was approved by the University of British Columbia's Behavioral Ethics Board.

RESULTS

We identified 6,226 cases and 24,904 controls in our cohort. We found that current users of FQs were at a high risk of developing PN (RR = 1.83, 95% confidence interval [CI] 1.49–2.27). Both crude and adjusted RRs for FQ users showed an increased risk of PN than nonusers of FQs. Current new users had the highest risk of PN (RR = 2.07, 95% CI 1.56–2.74). When we stratified our analysis by the type of oral FQs, the RRs for the more frequently prescribed FQs, ciprofloxacin, levofloxacin, and moxifloxacin, were similar (RR = 1.93, 95% CI 1.32–2.82; RR = 2.06, 95% CI 1.24–3.40; RR = 2.61, 95% CI 1.12–6.07, respectively). No risk was observed for current users of finasteride (RR = 1.21, 95% CI 0.97–1.51) (tables 1 and 2).

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TABLE 1

Characteristics of cases with peripheral neuropathy and their matched controls

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TABLE 2

Rate ratios for FQ and finasteride use and peripheral neuropathy

DISCUSSION

The results of our study demonstrate an increase in the risk of PN with the use of FQs. The strength of our study is the large sample size and the ability to exclude nondrug-related cases of PN, such as hereditary PN, to increase specificity. We were also able to exclude patients with diabetes, a potential confounding variable. Finally, as expected, finasteride users were not at a high risk of developing PN. Although the risk of PN was highest for current new users of FQ, any use of an FQ was still consistent with a 30% increase in the risk of PN (table 2). This means that the risk of PN with FQ use still persisted among those who may have been diagnosed late with this condition.

CNS effects are the second most common reported adverse events with FQs.[2,6,7] FQs have shown to be neurotoxic possibly through the inhibition of γ-aminobutyric acid receptors.[7] Oral FQs have also been associated with reported cases of psychosis and seizures,[7,8] which similar to PN, have been shown to be acute events occurring within days of FQ use. A recent analysis of all cases of antibiotic-induced PN reported to the FDA from 1997 to 2012 has shown a substantially higher number of PN cases with ciprofloxacin and levofloxacin compared with other non-FQ antibiotics.[3]

Our study, as with all epidemiologic studies that use health claims data, is subject to limitations. Although the results of our study are only directly generalizable to older men, nearly half of the reported cases of PN secondary to FQ use have been reported in this demographic.[2] Moreover, we do not believe that the mechanism of PN secondary to FQ differs in women.

The results of our study are consistent with an increase in the risk of PN with oral FQ use. In light of strong evidence of unnecessary prescribing of oral FQs in the United States,[9] clinicians must weigh the risk of PN against the benefits of FQs when prescribing these drugs to their patients.

AUTHOR CONTRIBUTIONS

Mahyar Etminan: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision. James M. Brophy: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Ali Samii: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, study supervision.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

FOOTNOTES

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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RESPONSES TO THIS ARTICLE

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