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Oral fluoroquinolones and the incidence of rhegmatogenous retinal detachment and symptomatic retinal breaks: a population-based study

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Abstract

Objective—To examine whether oral fluoroquinolone antibiotics are associated with an increase in subsequent rhegmatogenous retinal detachment and symptomatic retinal breaks in a large, population-based cohort.

Design—Population-based cohort study

Participants and Controls—Adult residents of Olmsted County, Minnesota who were prescribed oral fluoroquinolone medications from 1/01/03 – 6/30/11. Comparison cohorts consisted of patients prescribed oral macrolide and β-lactam antibiotics during the study period.

Methods—Procedure codes were used to identify retinal detachment repair and prophylaxis procedures occurring within 1 year of prescription dates. Travel clinic, pro re nata, and self-treatment prescriptions were excluded. Patients with tractional retinal detachment, previous retinal detachment repair, endophthalmitis, and necrotizing retinitis were excluded, as were those with intraocular surgery or severe head/eye trauma ≤ 90 days prior to the procedure.

Main Outcome Measures—Rates of retinal detachment repair and prophylaxis procedures within 7, 30, 90, and 365 days of the first prescription were calculated and compared between antibiotic prescription cohorts using Chi-square tests. Retinal detachment repair rates were also compared to the expected Olmsted County, Minnesota rates using the one-sample log rank test.

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This population-based cohort study suggests that oral fluoroquinolones do not confer an increased risk of rhegmatogenous retinal detachment or symptomatic retinal breaks.

The authors have no financial interests related to the content of this report. Andrew J. Barkmeier, MD had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The funding organizations had no role in the design or conduct of this research.

Results—Oral fluoroquinolones were prescribed for 38,046 patients (macrolide n=48,074, β-lactam n=69,079) during the study period. Retinal detachment repair procedures were performed within 365 days of the first prescription in 0.03% (95% confidence interval [CI] 0.01–0.06%) of the fluoroquinolone, 0.02% (95% CI 0.01–0.03%) of the macrolide, and 0.03% (95% CI 0.02–0.05%) of the β-lactam cohorts (p>0.05). Retinal detachment prophylaxis procedures for symptomatic retinal breaks were performed within 365 days of the first prescription in 0.01% (95% CI 0.00–0.03%) of the fluoroquinolone, 0.02% (95% CI 0.01–0.04%) of the macrolide, and 0.02% (95% CI 0.01–0.04%) of the β-lactam cohorts (p>0.05). Similar comparisons of treatment rates within 7, 30, and 90 days of the first prescription were all non-significant between cohorts. Post-fluoroquinolone retinal detachment repair rates were similar to expected rates (36.8 per 100,000/year vs 28.8 per 100,000/year for age- and sex-matched historical rates, p = 0.35).

Conclusions—Oral fluoroquinolone use was not associated with an increased risk of rhegmatogenous retinal detachment or symptomatic retinal breaks in this population-based study.

Introduction

Fluoroquinolone antibiotics are routinely prescribed for a wide range of clinical indications, offering broad-spectrum antimicrobial activity and excellent oral bioavailability. In the United States alone, fluoroquinolones account for over 32 million outpatient prescriptions each year.[1] Although these medications are generally well tolerated, potentially serious adverse effects include cardiac arrhythmia and QT interval prolongation, tendinopathy, and liver failure.[2–5] Several adverse ocular effects have also been reported in association with systemic fluoroquinolone use including diplopia, iris transillumination, pigment dispersion, uveitis, glaucoma, optic neuropathy, retinal hemorrhage, serous macular detachment, and retinal detachment.[6–15]

The potential association between fluoroquinolones and rhegmatogenous retinal detachment, previously noted in a single ciprofloxacin adverse reaction report,[14] has garnered significant attention following a pharmacoepidemiologic nested case-control study that reported an increased risk of retinal detachment with current use of oral fluoroquinolones (adjusted rate ratio 4.5 [3.56–5.70]).[15–17] Although neither “recent” (≤ 7 days since prescription completion) nor “past” use (8–365 days since prescription completion) were associated with an increased risk of retinal detachment, the calculated number needed to harm for any oral fluoroquinolone use was 2,500 and the authors speculated that 1,440 retinal detachments per year in the United States may be attributed to oral fluoroquinolone exposure.[15] Given the widespread use of fluoroquinolones and the sight-threatening nature of rhegmatogenous retinal detachment, such an association would have significant clinical implications.

Rhegmatogenous retinal detachment may occur when vitreous synchysis (liquefaction with formation of fluid-filled spaces) leads to posterior vitreous detachment and the development of retinal breaks, or rhegmas.[18–23] Accelerated degradation of the vitreous humor’s extracellular matrix, composed primarily of hyaluronan and collagen types II, V/XI, and IX,[18] would be a plausible pathophysiologic mechanism for acute fluoroquinolone-associated retinal detachment given that clinically evident tendinopathy and tendon rupture have been documented as early as the first day of exposure (median 8 days), with rapid

collagen and connective tissue degradation resulting from matrix metalloprotein up-regulation and other local biochemical changes.[3,4] Regardless of the specific pathophysiologic mechanism, any exogenous risk factor for acute rhegmatogenous retinal detachment would also likely increase the rate of symptomatic retinal breaks, as causative break-related symptoms commonly precede detachment and urgent treatment of these lesions reduces the risk of retinal detachment from approximately 50% to less than 5%.[20] Therefore, to investigate this hypothesis, we conducted a population-based cohort study to investigate whether oral fluoroquinolone prescriptions were associated with an increased risk of rhegmatogenous retinal detachment and symptomatic retinal tears.

Methods

Study Design and Data Collection

This research was compliant with the Health Insurance Portability and Accountability Act (HIPAA) and institutional review board (IRB) approval was obtained from both Mayo Clinic and the Olmsted Medical Center.

We used the resources of the Rochester Epidemiology Project (REP) to identify all residents of Olmsted County, MN, 18 years of age or older, who were prescribed oral fluoroquinolones from 1/01/2003 to 6/30/2011. We used the same resources to identify comparison cohorts of patients prescribed β-lactam and macrolide antibiotics during the same time frame. The REP has been extensively described; briefly, the REP is a medical record linkage system designed to capture data on virtually all patient-physician encounters for residents living in Olmsted County, Minnesota.[24] This population-based data resource allows comprehensive access to original medical records of identified patients to allow for case validation and extraction of clinical details from both paper and electronic components of inpatient, outpatient, medical, and surgical charts. More recently, the REP has added drug prescription data to this infrastructure, making it possible to identify cohorts of Olmsted County residents who have received a particular prescription since 2003.[25]

For this study, a medication class search was performed for fluoroquinolone, macrolide, and β-lactam antibiotic prescriptions, along with an individual medication search for past and present generic and trade names of medications in these classes. All non-oral route prescriptions were excluded, as were prescriptions with pro re nata (PRN) and self-treatment indications due to unpredictable utilization and timing of use for these medications. For example, fluoroquinolones and macrolides are both commonly prescribed for PRN self-treatment of traveler’s diarrhea and other travel-related infections. For this reason, prescriptions associated with commonly used Mayo Clinic Travel and Tropical Medicine Clinic International Classification of Diseases (ICD) V codes (V70.3 and V65.49) were excluded unless another treatment indication was specifically noted. Medication data was recorded including prescription date(s), dose, schedule, and duration.

Antibiotic prescription lists were crossed with current procedural terminology (CPT) codes for treatment of rhegmatogenous retinal detachment (67101, 67105, 67107, 67108, 67110, 67112, 67113) and retinal breaks (67141, 67145) within one year of the first prescription date for each individual patient. Clinical data for identified cases was recorded including

patient age, sex, pertinent past ocular history, as well as any history of severe trauma within the preceding 90 days. Timing of clinical diagnosis and treatment were noted to verify that no significant treatment delay had occurred. Prophylaxis procedures for asymptomatic retinal breaks discovered during routine follow-up were excluded due to unknown chronicity and the dissimilar risk profile. Patients with a history of endophthalmitis, necrotizing retinitis, ipsilateral intraocular surgery or severe ocular/head trauma within 90 days of the retinal detachment procedure were excluded, as were those treated for serous/exudative retinal detachment or diabetic retinopathy-related tractional retinal detachment. A second retina specialist blinded to the medication group adjudicated all exclusions and discrepancies between coding and chart data.

The Olmsted County, Minnesota population-based retinal detachment rate from a previous REP study (1976 –1995)[26] was used to calculate the expected retinal detachment rate in our fluoroquinolone prescription cohort. Traumatic retinal detachments were categorized separately in the previous study and were excluded from this comparison. Patients having undergone ipsilateral intraocular surgery within the past 90 days (except for retinal detachment re-operations) were included for this comparison, as post-operative detachments had not been excluded from the previous REP study.

Statistical Analysis

The incidence of rhegmatogenous retinal detachment repair and symptomatic retinal break prophylaxis procedures were calculated as a percentage and 95% confidence interval (CI) for specific time periods (within 7, 30, 90, and 365 days) following the first prescription in each medication cohort. The initial prescription from each cohort was chosen for the primary analysis in order to maintain true independent variables and to avoid issues associated with overlapping time periods. Given that all of these patients were local, the study assumed complete follow-up at 1 year for all groups. Comparisons of retinal detachment repair and prophylaxis rates between groups were performed using the Chi-square test for independence. Potential risk factor evaluations and adjustments for these risk factors were performed using logistic regression models. Odds ratios and 95% confidence intervals for those ratios were used to summarize these relationships. After applying the aforementioned patient exclusions, the age- and sex- specific population-based expected rate of retinal detachment in Olmsted County[26] was compared to the fluoroquinolone prescription cohort retinal detachment repair rate using a one-sample log-rank test.[27]

Results

Overall, 92,130 oral fluoroquinolone prescriptions were issued to 38,046 unique patients during the study period with over 95% of those being for ciprofloxacin or levofloxacin (54% ciprofloxacin, 42% levofloxacin, 4% moxifloxacin, <1% others). There were 107,086 macrolide prescriptions for 48,074 patients and 178,352 β-lactam prescriptions for 69,079 patients. Patients who received fluoroquinolones were older than patients who received macrolides or beta-lactams, and there were fewer women in the beta-lactam group compared to the fluoroquinolone group (table 1). The preponderance of Caucasian patients in all groups reflects the demographics of Olmsted County, Minnesota.[28]

Retinal detachment repair procedures were performed within 365 days in 0.03% (95% CI 0.01–0.06%) of the fluoroquinolone, 0.02% (95% CI 0.01–0.03%) of the macrolide, and 0.03% (95% CI 0.02–0.05%) of the β-lactam cohorts (table 2), with p values non-significant for all comparisons. Retinal detachment prophylaxis procedures were performed within 365 days in 0.01% (95% CI 0.00–0.03%) of the fluoroquinolone, 0.02% (95% CI 0.01–0.04%) of the macrolide, and 0.02% (95% CI 0.01–0.04%) of the β-lactam cohorts (see table 2), with p values non-significant for all comparisons. Similar comparisons for retinal detachment repair and prophylaxis procedures within 7, 30, and 90 days of the first prescription were all non-significant between cohorts (see table 2).

The mean fluoroquinolone exposure during the first 7 days of the initial prescription (dose [mg] x frequency [doses per day] x duration [number of days, maximum 7]) was 5668 +/− 4516 mg. A logistic regression analysis of retinal detachment procedure incidence found no relationship to increasing initial medication dosage exposure (p=0.18). The mean number of study period prescriptions in the fluoroquinolone cohort was 2.3 +/− 2.5 and logistic regression analysis revealed no increased incidence of retinal detachment with increasing number of prescriptions (p=0.18, see Table 3). A further cumulative dosage analysis comparing retinal detachment incidence following the first vs. the last fluoroquinolone prescription for each patient over previously identified time intervals was also non-significant for all comparisons (0, 1, 2, and 9 repair procedures at 7, 30, 90, and 365 days after the last prescription [n=38,046], respectively). For all 92,130 fluoroquinolone prescriptions (including those ≤365 days from previous prescription), there was 1 retinal detachment repair within 7 days, 2 repairs within 30 days, 8 within 90 days, and 37 within 365 days, although several repair procedures were counted multiple times due to overlapping time intervals (22 total retinal detachment repairs counted 37 times).

The Olmsted County, Minnesota population-based retinal detachment rate from a previous REP study (1976–1995)[26] was age- and sex- adjusted to the demographics of the fluoroquinolone prescription cohort. After adjusting for exclusion criteria differences between studies (excluding traumatic retinal detachments from the previous study and including immediate post-operative retinal detachment repairs from this study), a one-sample log-rank test was calculated. There was no significant difference between these rates (14 events in this study vs. 11 events per 38,046 patient years, or 36.8 per 100,000/year vs. 28.8 per 100,000/year, p = 0.35).[26,27]

Discussion

This population-based study found no differences in either the rate of rhegmatogenous retinal detachment requiring surgical repair or in the rate of symptomatic retinal break prophylaxis following prescriptions for oral fluoroquinolones compared to prescriptions for macrolide or β-lactam antibiotics. Our results corroborate the long term findings of Etminan, et al., who identified no increased 7- or 365-day risk of retinal detachment following the completion of a fluoroquinolone treatment course.[15] The critical finding of their study was a significantly increased risk of acute retinal detachment with “current use” of fluoroquinolones in a cohort of nearly 1 million British Columbian patients who had visited an ophthalmologist during a specified time period (number needed to harm = 2,500). [15] In

contrast, we identified no retinal detachment diagnoses or treatments during the first fluoroquinolone treatment course for 38,046 unique patients during the study period, and only one retinal detachment associated with “current use” out of 92,031 fluoroquinolone prescription courses overall (1/92,130, 0.001% [95% CI 0–0.01%]).

Given the natural histories of posterior vitreous detachment and rhegmatogenous retinal detachment, one would expect that the majority of adverse events occurring over this clinical spectrum would be diagnosed and likely treated within 30 days’ time. The upper bound of the 95% confidence interval for retinal detachment repairs within 7 and 30 days of the first fluoroquinolone prescription in this study was 0.01%, and an identical 0.01% upper bound at those time points was found for all 92,031 study period fluoroquinolone prescriptions. Although no increased risk was identified in this study, we cannot exclude a very small increased 7- and 30-day risk of less than 1 acute retinal detachment per 10,000 prescriptions (0.01% of prescriptions). We also cannot completely exclude the possibility that the retinal detachment rate at 365 days in the exposed group was greater than 0.03%. However, our study sample sizes were large and the confidence intervals around our estimates are very narrow (upper limit of 0.06% in the fluoroquinolone group). This suggests that the true detachment rate in the fluoroquinolone group is quite small and not significantly different from the rates observed in either patients treated with other antibiotics or in the general population.

Rochester Epidemiology Project resources offer the ability to calculate true population-based incidence rates as well as to critically review the medical records of all patients identified by procedure coding queries, both of which are strengths of this study. The chart review minimized limitations related to coding data that, in the case of retinal detachment repair surgery, would not differentiate between rhegmatogenous, tractional, and serous/exudative retinal detachment. In addition to excluding several patients who underwent tractional retinal detachment repair, we identified and excluded several patients with retinal detachment following fluoroquinolone prescriptions for endophthalmitis and for complications of severe eye and head trauma. These patients carried a significantly elevated risk for acute retinal detachment related to the conditions for which fluoroquinolones were prescribed. Our chart review also permitted the isolation of prophylaxis procedures for acutely symptomatic retinal breaks, thereby enabling examination and ultimately exclusion of any significant acute fluoroquinolone effect on another aspect of the rhegmatogenous retinal detachment clinical spectrum.

There are limitations to this study related to its retrospective nature and study design. As with any retrospective pharmacoepidemiologic study, there is limited data on actual medication compliance, though we would anticipate that usage would be similar across medication classes once PRN and self-treatment indications were excluded. The predominance of Caucasian subjects may preclude extrapolation to other populations.[28] Comparison with historical controls is complicated by changes in ophthalmologic care over the past several decades, with the >7x increased incidence of cataract extraction potentially being most significant.[29] Although immediate post-cataract extraction retinal detachments were excluded for the purposes of this study, a 4x increased risk of retinal detachment persists over the first 20 years post-operatively, and the risk is higher yet for younger

patients in their 6th and 7th decades.[30] One might expect that this cataract surgical practice evolution would increase the rate of retinal detachment in the more contemporary fluoroquinolone cohort; however, the overall effect of other differences between the contemporary and historical Olmsted County, Minnesota cohorts remains unclear.

Posterior vitreous detachment occurs spontaneously in the majority of individuals by age 70. Although premature posterior vitreous detachment caused by an enzymatic process (or any other etiology) could theoretically be more hazardous than spontaneous posterior vitreous detachment,[18] it is possible that many acute complications of any inducing factor would have eventually occurred with natural history. If a significant medication-related effect were present, one might have anticipated an increased incidence of bilateral complications in susceptible patients, as seen with the nearly 50% incidence of bilateral Achilles tendon involvement in fluoroquinolone-associated tendinopathy.[3,4] In this series, however, there were no cases of bilateral treatment for retinal detachment and/or symptomatic retinal breaks during the study period.

When considering complications across the clinical spectrum of rhegmatogenous retinal detachment, any increased risk would need to be clear and significant in order to classify systemic fluoroquinolone exposure as a true modifiable risk factor. Given the limitation of any undetected 30-day risk increase to less than 1 acute retinal detachment per 10,000 exposures (based on study power calculations herein), and the corroboration of no increased 365-day post-prescription risk, currently available data would not support alteration of oral fluoroquinolone prescription patterns for the general population on the basis of retinal detachment risk.

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Table 1

Characteristics of the study cohorts

	Fluoroquinolone	Macrolide	β-Lactam	p-value
Total patients (N)	38,046	48,074	69,079	
Total prescriptions (N)	92,130	107,086	178,352	
Female (%)	61.0%	61.4%	56.8%	<0.001
Mean patient age (years +/− std dev)	50.6 +/− 19.6	43.1 +/− 17.7	42.8 +/− 18.6	<0.001[a]
Caucasian (%)	88.6%	86.7%	86.2%	<0.001

[a]Analysis of variance (ANOVA) p-value

Table 2

Retinal detachment procedures following first prescription

	Fluoroquinolone (n=38,046)		Macrolide (n=48,074)		β-lactam (n=69,079)		
Repair	**n**	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**	**p-value[a]**
≤ 7 days	0	0% (0–0.01%)	1	0.002% (0–0.01%)	0	0% (0–0.01%)	0.33
≤ 30 days	1	0.002% (0–0.01%)	1	0.002% (0–0.01%)	1	0.001% (0–0.01%)	0.91
≤ 90 days	3	0.008% (0–0.02%)	2	0.004% (0–0.02%)	5	0.007% (0–0.02%)	0.75
≤ 365 days	12	0.03% (0.01–0.06%)	8	0.02% (0.01–0.03%)	24	0.03% (0.02–0.05%)	0.17
Prophylaxis							
≤ 7 days	1	0.002% (0–0.01%)	0	0% (0–0.01%)	0	0% (0–0.01%)	0.21
≤ 30 days	1	0.002% (0–0.01%)	3	0.006% (0–0.02%)	1	0.001% (0–0.01%)	0.35
≤ 90 days	1	0.002% (0–0.01%)	3	0.006% (0–0.02%)	7	0.01% (0–0.02%)	0.36
≤ 365 days	5	0.01% (0–0.03%)	10	0.02% (0.01–0.04%)	17	0.02% (0.01–0.04%)	0.46

CI = confidence interval

[a] unadjusted p-value

Table 3

Fluoroquinolone prescription data

Dosage (mg 1st 7 days)	Odds Ratio (OR)	95% CI	P for trend
Continuous measure (1000 mg change)	1.03	0.98–1.08	0.18
Quartiles			
Q1 (0–3000mg)	1 (referent)		
Q2 (3000–5000mg)	1.9	0.37–9.78	0.44
Q3 (5000–7000mg)	1.09	0.10–12.0	0.95
Q4 (>7000mg)	2.91	0.53–15.91	0.22
# of prescriptions			
Continuous measure (per 1 Rx increase)	1.09	0.96–1.23	0.18
1	1 (referent)		
2	1.9	0.42–8.51	0.40
3	2.73	0.50–14.90	0.25
4+	2.4	0.54,10.73	0.25

CI = confidence interval