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Risk of acute kidney injury associated with the use of fluoroquinolones

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Abstract

Background: Case reports indicate that the use of fluoroquinolones may lead to acute kidney injury. We studied the association between the use of oral fluoroquinolones and acute kidney injury, and we examined interaction with renin–angiotensin-system blockers.

Methods: We formed a nested cohort of men aged 40–85 enrolled in the United States IMS LifeLink Health Plan Claims Database between 2001 and 2011. We defined cases as men admitted to hospital for acute kidney injury, and controls were admitted to hospital with a different presenting diagnosis. Using risk-set sampling, we matched 10 controls to each case based on hospital admission, calendar time (within 6 wk), cohort entrance (within 6 wk) and age (within 5 yr). We used conditional logistic regression to assess the rate ratio (RR) for acute kidney injury with current, recent and past use of fluoroquinolones, adjusted by potential confounding variables. We repeated this analysis with amoxicillin and azithromycin as controls. We used a case-time–control design for our secondary analysis.

Results: We identified 1292 cases and 12 651 matched controls. Current fluoroquinolone use had a 2.18-fold (95% confidence interval [CI] 1.74–2.73) higher adjusted RR of acute kidney injury compared with no use. There was no association between acute kidney injury and recent (adjusted RR 0.87, 95% CI 0.66–1.16) or past (RR 0.86, 95% CI 0.66–1.12) use. The absolute increase in acute kidney injury was 6.5 events per 10 000 person-years. We observed 1 additional case per 1529 patients given fluoroquinolones or per 3287 prescriptions dispensed. The dual use of fluoroquinolones and renin–angiotensin-system blockers had an RR of 4.46 (95% CI 2.84–6.99) for acute kidney injury. Our case-time–control analysis confirmed an increased risk of acute kidney injury with fluoroquinolone use (RR 2.16, 95% CI 1.52–3.18). The use of amoxicillin or azithromycin was not associated with acute kidney injury.

Interpretation: We found a small, but significant, increased risk of acute kidney injury among men with the use of oral fluoroquinolones, as well as a significant interaction between the concomitant use of fluoroquinolones and renin–angiotensin-system blockers.

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Fluoroquinolones are commonly prescribed broad-spectrum antibiotics.[1] Although highly effective, they are known to cause cardiac arrhythmia, hypersensitivity reactions and central nervous system effects including agitation and insomnia.[2,3] Recent reports of tendon rupture[4] and retinal detachment[5] suggest that these drugs may damage collagen and connective tissue. Case reports of acute kidney injury with the use of fluoroquinolones have been published,[6] and the product label includes renal failure in a list of potential, but uncommon, adverse reactions.[2] In clinical practice, when oral fluoroquinolones are prescribed, the potential for acute kidney injury is generally not a clinical consideration. We aimed to quantify the risk of acute kidney injury with the use of oral fluoroquinolones among men. This study population was limited to men because the cohort we studied was formed to investigate health issues that affect older men.

Methods

Data source

The IMS LifeLink Health Plan Claims Database contains paid claims from US health care plans. Compared with the US Census, the database captures 17% of men aged 45–54 years, 13% of men aged 55–64 years and 8% of men aged over 65 years. Data for men over 65 years are cap-

tured through Medicare Advantage programs. These privatized health care plans combine medical and prescription services, providing more inclusive health care data.[7]

The IMS LifeLink database contains fully adjudicated medical and pharmacy claims for over 68 million patients, including inpatient and outpatient diagnoses (via International Classification of Diseases, 9th revision, clinical modification [ICD-9-CM], codes) in addition to retail and mail-order prescriptions. The data are representative of US residents with private health care in terms of geography, age and sex. The IMS LifeLink database is subject to quality checks to ensure data quality and minimize errors,[7] and it has been used in previous pharmacoepidemiologic studies.[8–10]

This study was approved by the University of Florida's Institutional Review Board. All coding used in this study can be found in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj. 121730/-/DC1).

Cohort formation

We used a nested case–control design for our primary analysis. Our cohort was formed to study health issues that affect older men. This population is at the greatest risk of acute kidney injury and is commonly prescribed fluoroquinolones. We extracted data for 2 million men from the IMS LifeLink database who had both prescription and medical coverage. We included men aged 40–85 years who met the inclusion criteria between Jan. 1, 2001, and June 30, 2011, and who had 365 days of enrolment with no acute kidney injury. We excluded men with a history of chronic kidney disease or dialysis because these men may be more prone to acute kidney injury. Censoring was performed at a study outcome, the end of enrollment and end of the study. The cohort was nested within inpatient hospital records, which were used to select cases and controls.

Cases and controls

Multiple studies have validated algorithms to determine acute kidney injury using ICD-9-CM coding. Several were not applicable because they were published only in abstract form,[11] included ICD-10-CM coding,[12] did not define acute kidney injury at hospital admission,[13] included cases before 1990,[14] assessed acute kidney injury that occurred after admission to hospital[15] or included unspecified (nonacute) renal failure (ICD-9-CM 586.x).[16] Two studies validated ICD-9-CM coding against a reference standard that required doubling of serum creatinine and found poor positive predictive values; however, this algorithm does not account for differences in baseline serum creatinine levels.[17,18] A second algorithm was developed that identified acute kidney injury based on baseline serum creatinine level: acute kidney injury was defined by a change in serum creatinine of 0.5 mg/dL (44.2 μmol/L) for a nadir serum creatinine of 1.0 mg/dL (88.4 μmol/L) or lower, a change in serum creatinine of 1.0 mg/dL for a nadir serum creatinine between 2.0–4.9 mg/dL (176.8–433.2 μmol/L), or a change in serum creatinine of 1.5 mg/dL (132.6 μmol/L) for a nadir serum creatinine of 5.0 mg/dl (44.2 μmol/L).[19] Two studies validated acute kidney injury using ICD-9-CM coding for all hospital discharges against this reference, finding positive predictive values of 80.2%[17] and 87.6%.[20]

We defined acute kidney injury as ICD-9-CM 584.0 (acute renal failure, unspecified), 584.5 (acute tubular necrosis), 584.6 (cortical acute renal failure), 584.7 (medullary acute renal failure), 584.8 (acute renal failure with other specified pathologic lesion) and 584.9 (acute renal failure, not otherwise specified). We further restricted cases to the primary hospital discharge diagnosis, a diagnostic code that identifies the main reason for hospital admission. This is known to increase the positive predictive values and identify the primary reason for admission. We excluded cases if they had been admitted to hospital during the 6 months before the admission for acute kidney injury. Previous hospital admissions could indicate a greater degree of morbidity (confounding by disease severity) and prevent us from measuring prescription use (immeasurable time bias).[21] We did not differentiate between subtypes of acute kidney injury because ICD-9-CM coding has not been validated to show this distinction.

We considered men who were admitted to hospital with a diagnosis other than acute kidney injury and who had not been admitted to hospital in the previous 6 months to be eligible for the control group. We used risk-set sampling to select the controls, whereby for each case, a pool of potential controls was formed that met the following criteria: were eligible for matching only on the day of hospital admission; were admitted to hospital within 6 weeks (calendar-time matching); entered the nested cohort no more than 6 weeks apart; and were within 5 years of age. From this risk set, 10 controls, who were still eligible to have an acute kidney injury, were randomly selected and matched for each case. This allows formation of an odds ratio equivalent to the rate ratio (RR).[22] Matching on hospital admissions (a strong proxy for health status) was done to provide controls of more similar comorbidity and to reduce residual confounding.

Drug exposure

We included exposure to oral fluoroquinolones: ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin and norfloxacin. We excluded ophthalmic and topical fluoroquinolones because they have minimal systemic absorption. We excluded intravenous fluoroquinolones because our focus was on outpatient-dispensed preparations. We excluded prescriptions dispensed on the day of hospital admission to prevent reverse causality bias.

We defined a current user as someone who had an active supply of fluoroquinolone at hospital admission or had stopped taking a fluoroquinolone (prescription termination; final day of drug supply) in the 1–7 days before admission. Recent users were those who had a prescription termination 8–60 days before admission and had no active supply within the 7 days before admission. We defined past users as those who had a prescription termination 61–180 days before admission and who had no active prescriptions during days 0–60.

We selected 2 common oral antibiotics (amoxicillin and azithromycin) as control drugs. Although both have been implicated in rare cases of interstitial nephritis,[23–26] we hypothesized that the burden of acute kidney injury with these drugs would be insufficient to produce a positive association.

Statistical analysis

Primary analysis: nested case–control

We used conditional logistic regression to determine the RR for acute kidney injury with fluoroquinolone use. The model was adjusted by fluoroquinolone indication (genitourinary, respiratory or gastrointestinal tract infection; skin infection; and joint or bone infection in the past 6 months), diseases associated with acute kidney injury (cancer, chronic obstructive pulmonary disease, congestive heart failure, diabetes mellitus, HIV and hypertension in the past year), potentially nephrotoxic drugs with high use (loop diuretics, nonsteroidal anti-inflammatory drugs and renin–angiotensin-system blockers at hospital admission) and markers of health care use (number of medications, billing codes and physician visits in the past 6 mo). We stratified the subsequent analyses by fluoroquinolone product (ciprofloxacin, levofloxacin and moxifloxacin).

We examined drug–drug interactions between fluoroquinolones (current use) and renin–angiotensin-system blockers (at admission) through the addition of an interaction term to our fully adjusted model. We defined renin–angiotensin-system blockers as angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers. We did not include aldosterone antagonists based on low use and concern for confounding based on the many indications for these medications. Although we hypothesized drug–drug interactions between fluoroquinolones and loop diuretics or nonsteroidal anti-inflammatory drugs, we did not have sufficient power for these analyses. We computed a number needed to harm (absolute risk increase × 100) in which the absolute risk increase equaled the estimated incidence among users (RR × incidence among nonusers) minus the incidence among nonusers.

Secondary analysis: case-time–control

A case-crossover design allows patients to serve as their own controls, using within-patient comparisons of drug exposure to assess the RR for the study outcome.[27] This technique has the advantage of having no residual confounding from time-invariant covariates. Two cardinal requirements for a case-crossover study are an acute outcome and a transient exposure. Acute kidney injury is an acute outcome, and fluoroquinolones are typically prescribed for 7–14 days,[2] meeting the assumption of transient exposure. Because most fluoroquinolone prescriptions are for 14 or fewer days, we chose the 14 days immediately before admission to hospital as the case-time. Four control-times were selected, each immediately following the previous 14 day window (days 15–28, 29–42, 43–56 and 57–71). We used conditional logistic regression to determine the RR for acute kidney injury with fluoroquinolone exposure. We sensitized the case-crossover by the distribution of fluoroquinolone use from these time windows in the 10 matched control patients from the main analysis. This analysis, referred to as a "case-time–control," adjusts for a potential trend toward increased use of all antibiotics before hospital admission.[28]

Sensitivity analysis

We were concerned that patients taking fluoroquinolones would be more likely to have a genitourinary infection (compared with patients taking one of the control medications), which could make them more likely to have acute kidney injury. We conducted a sensitivity analysis in which we removed patients who had experienced a genitourinary infection during the 6 months before admission, and we repeated the study analysis.

Because the sensitivity of excluding people with chronic kidney disease using ICD-9-CM coding is unknown, we repeated our analyses without excluding patients with previous claims

for chronic kidney disease; from this analysis, the changes in the study RRs can be used to assess whether residual confounding from unmeasured chronic kidney disease is a potential concern.

Results

Our nested cohort contained 767 209 patients (162 608 hospital admissions) eligible for matching. We identified 1292 cases with acute kidney injury and 12 651 matched controls. The characteristics of the cases and controls are shown in Table 1. Ciprofloxacin (44.5%) and levofloxacin (43.9%) were the most commonly used fluoroquinolones (Table 2); the most common indications were respiratory (45.6%) or genitourinary infections (27.0%) (Table 3).

We observed an increased risk of acute kidney injury with current use of fluoroquinolones (adjusted RR 2.18, 95% CI 1.74–2.73) and no change in risk with either recent (adjusted RR 0.87, 95% CI 0.66–1.16) or past (adjusted RR 0.86, 95% CI 0.66–1.12) use. There was no association between the use of amoxicillin or azithromycin and acute kidney injury (Table 4).

When we stratified our analysis by fluoroquinolone product, the largest RR was found for ciprofloxacin (RR 2.76, 95% CI 2.03–3.76), followed by moxifloxacin (RR 2.09, 95% CI 1.04–4.20) and levofloxacin (RR 1.69, 95% CI 1.20–2.39). When levofloxacin was used as a reference, ciprofloxacin had a significantly increased RR (RR 1.73, 95% CI 1.08–2.77), whereas moxifloxacin did not (RR 1.20, 95% CI 0.54–2.65).

The case-time–control analysis confirmed the results from the nested case–control study: we found an increased risk of acute kidney injury with fluoroquinolone use (RR 2.16, 95% CI 1.52–3.18) but not with amoxicillin (RR 0.65, 95% CI 0.38–

Table 1: Characteristics of cases and controls

Characteristic	Cases, *n* = 1292	Controls, *n* = 12 651	*p* value*
Age, median (IQR)	62 (54–72)	62 (54–72)	0.3
Disease state,† no. (%)			
Cancer	227 (17.6)	2183 (17.3)	0.8
Chronic obstructive pulmonary disease	121 (9.4)	1264 (10.0)	0.5
Congestive heart failure	198 (15.3)	1156 (9.1)	< 0.001
Diabetes mellitus	461 (35.7)	3068 (24.3)	< 0.001
HIV	8 (0.6)	34 (0.3)	0.053
Hypertension	567 (43.9)	4714 (37.3)	< 0.001
Medications,‡ no. (%)			
Loop diuretics	115 (8.9)	654 (5.2)	< 0.001
Nonsteroidal anti-inflammatory drugs	15 (1.2)	167 (1.3)	0.8
Renin–angiotensin-system blockers	228 (17.7)	1770 (14.0)	< 0.001
Health care use,§ median (IQR)			
Billing codes, no.	29 (11–62)	39 (18–69)	0.005
Drugs, no.	16 (4–31)	11 (3–22)	< 0.001
Physician visits, no.	4 (2–8)	4 (2–7)	0.2
Fluoroquinolone indications,§ no. (%)			
Joint or bone infection	17 (1.3)	143 (1.1)	0.8
Skin infection	430 (33.3)	4093 (32.4)	0.5
Tract infection			
Genitourinary	179 (13.9)	1287 (10.2)	< 0.001
Respiratory	490 (37.9)	5206 (41.2)	0.03
Gastrointestinal	309 (23.9)	3108 (24.6)	0.6

Note: IQR = interquartile range.
*Calculated using χ^2 test for categorical characteristics and Student *t* test for continuous characteristics.
†In the year before admission to hospital to maximize sensitivity.
‡Current medication use at the time of hospital admission was used to best assess use at the index date.
§In the 6 months before admission to hospital to reflect covariates during exposure ascertainment.

1.05) or azithromycin (RR 1.06, 95% CI 0.62–1.90) (Table 5). The absolute increase in the incidence of acute kidney injury was 6.5 events per 10 000 person-years with use of fluoroquinolones. We observed 1 additional case of acute kidney injury per 1529 patients who used fluoroquinolone or per 3287 prescriptions dispensed.

The addition of a drug–drug interaction to the "current use" models for study drugs found similar main effects. Although renin–angiotensin-system blockers can increase serum creatinine levels, we did not find an increased risk of acute kidney injury with renin–angiotensin-system blocker monotherapy (RR 1.00, 95% CI 0.84–1.18). We did find, however, an interaction between the combined use of fluoroquinolones and renin–angiotensin-system blockers (interaction RR 2.19, 95% CI 1.30–3.69). An interaction can be defined as the additional risk for acute kidney injury from the concomitant use of 2 drugs that is beyond the additive risk of each individual drug. This interaction resulted in a greater than fourfold increase in the RR for acute kidney injury (RR 4.46, 95% CI 2.84–6.99) with active use of both drugs. When we analyzed the data by drug class, a similar increased risk was found with the dual use of fluoroquinolones and either angiotensin-converting-enzyme inhibitors (RR 4.54, 95% CI 2.74–7.52) or angiotensin-receptor blockers (RR 3.80, 95% CI 1.72–8.41).

Adjustment for a genitourinary infection had a negligible effect on all point estimates for fluoroquinolone use and acute kidney injury (< 2% change). When we restricted the nested cohort to only patients with no history of genitourinary infection and repeated the nested case–control analysis, we found similar RRs as in the main analysis between fluoroquinolones and acute kidney injury (current use: RR 2.48, 95% CI 1.92–3.23; recent use: RR 0.95, 95% CI 0.65–1.37; past use: RR 0.98, 95% CI 0.75–1.29). When we included patients with a previous claim for chronic kidney disease, we found similar RRs for all user types (current use: RR 2.08, 95% CI 1.67–2.59; recent use RR 0.95, 95% CI 0.73–1.26; past use RR 0.88, 95% CI 0.67–1.13).

Table 2: Use of oral fluoroquinolones among cases and controls

Type of fluoroquinolone	Users, no. (%)
Ciprofloxacin	884 (44.5)
Gatifloxacin	10 (0.5)
Gemifloxacin	2 (0.1)
Levofloxacin	872 (43.9)
Moxifloxacin	218 (11.0)
Norfloxacin	2 (0.1)

Interpretation

We found a twofold increased risk of acute kidney injury with current use of fluoroquinolones. There were nonsignificant associations between fluoroquinolone use and acute kidney injury among recent and past users (point estimates less than 1.0). The twofold differential in risk between current and both recent and past fluoroquinolone use suggests that acute kidney injury is an acute adverse effect of fluoroquinolones. These results were replicated in the case-time–control analysis, which increases our confidence in these associations because of better control of time-invariant confounding.

Previous evidence of acute kidney injury with fluoroquinolone use comes from case reports. Most case reports result from an allergic or hypersensitivity reaction termed acute interstitial nephritis.[29,30] Fluoroquinolones have also been reported to cause granulomatous interstitial nephritis, characterized by infiltration of the renal tissue by histio-

Table 3: Indication for the use of antibiotics among cases and controls

	No. (%)		
Indication	Fluoroquinolone	Amoxicillin	Azithromycin
Joint or bone infection	49 (2.5)	68 (4.7)	61 (3.3)
Skin infection	135 (6.8)	150 (10.3)	135 (7.3)
Tract infection			
Gastrointestinal	185 (9.3)	138 (9.5)	154 (8.3)
Genitourinary*	536 (27.0)	144 (9.9)	198 (10.7)
Respiratory	909 (45.6)	780 (53.6)	1089 (58.7)
Other†	174 (8.8)	174 (12.0)	217 (11.7)

*Includes urethritis and cervicitis from sexually transmitted infections treated with azithromycin.
†Patients without physician billing codes for listed indications.

cytes and T lymphocytes, leading to the formation of granulomas.[31,32] Crystalluria has been reported to occur when urine pH is above 6.8,[33] and several cases of acute kidney injury from crystal formation secondary to fluoroquinolone use have been documented.[34,35] More severe cases of acute tubular necrosis have also been linked to fluoroquinolone use.[36,37]

Although most published case reports are of ciprofloxacin use,[6] this may be an artifact of its high use. Nephrotoxicity may not be entirely dependent on renal elimination,[6] and one patient with ciprofloxacin-induced nephrotoxicity did not experience a positive rechallenge after switching to ofloxacin.[38] We observed a larger risk of acute kidney injury with ciprofloxacin use, compared with the use of levofloxacin; however, this differential finding was not an a priori hypothesis and should be interpreted with caution until further investigation.

Although fluoroquinolones are thought to induce acute kidney injury through acute hypersensitivity reactions, renin–angiotensin-system blockers affect renal hemodynamics through dilation of the efferent arteriole, reducing intraglomerular pressure and increasing serum creatinine levels.[39] The risk of acute kidney injury with the use of renin–angiotensin-system blockers is thought to increase after a superimposed renal insult, such as that with dehydration or the use of other prescription medications.[5,6] Physician monitoring of serum creatinine levels, particularly after starting renin–angiotensin-system blocker therapy, and ascertainment of severe cases of acute kidney injury that require admission to hospital may explain the lack of a signal with renin–angiotensin-system blocker monotherapy.

Limitations

Because of the transient nature of fluoroquinolone use, we used 3 distinct and nonoverlapping definitions of drug exposure, allowing recent and past users to serve as negative controls. We found similar results after removing patients with genitourinary infections from the nested cohort analysis, thereby reducing concerns about confounding by indication.

We used admission to hospital to ascertain cases of severe acute kidney injury; however, we could not assess milder cases that resulted in mild or asymptomatic kidney injury. This could potentially result in an underestimation of the risk of acute kidney injury. We did not have information

Table 5: Case-time–control analysis of the risk of acute kidney injury with the use of fluoroquinolones or other antibiotics

Medication	Rate ratio (95% confidence interval)
Amoxicillin	0.65 (0.38–1.05)
Azithromycin	1.06 (0.62–1.90)
Fluoroquinolones	2.16 (1.52–3.18)

Table 4: Nested case–control analysis of the risk of acute kidney injury with the use of fluoroquinolones

Exposure; time frame*	No. (%)		Rate ratio (95% confidence interval)		
	Cases, *n* = 1292	Controls, *n* = 12 651	Crude	Adjusted†	Adjusted‡
No fluoroquinolone use	1059	10896	1.00 (ref)	1.00 (ref)	1.00 (ref)
Fluoroquinolone use					
Current	108 (8.4)	489 (3.9)	2.27 (1.83–2.82)	2.18 (1.74–2.73)	2.04 (1.55–2.69)
Recent	57 (4.4)	597 (4.7)	0.93 (0.71–1.23)	0.87 (0.66–1.16)	–
Past	68 (5.3)	669 (5.3)	1.00 (0.77–1.29)	0.86 (0.66–1.12)	–
Amoxicillin use					
Current	19 (1.5)	235 (1.9)	0.79 (0.49–1.26)	0.84 (0.52–1.35)	0.75 (0.41–1.38)
Recent	54 (4.2)	409 (3.2)	1.31 (0.98–1.75)	1.19 (0.89–1.60)	–
Past	73 (5.7)	664 (5.3)	1.08 (0.84–1.39)	0.96 (0.74–1.24)	–
Azithromycin use					
Current	22 (1.7)	203 (1.6)	1.06 (0.68–1.66)	1.08 (0.69–1.71)	1.14 (0.66–1.95)
Recent	32 (2.5)	420 (3.3)	0.74 (0.51–1.07)	0.71 (0.49–1.03)	–
Past	100 (7.7)	1077 (8.5)	0.90 (0.73–1.12)	0.82 (0.66–1.03)	–

Note: ref = reference
*Current use = 0–7 days before hospital admission; recent use = 8–60 days before admission; past use = 61–180 days before admission.
†Adjusted for all study covariates listed in Table 1.
‡Adjusted for all study covariates in addition to the interaction between fluoroquinolones and renin angiotensin system blockers.

about the severity of acute kidney injury, nor did we have sufficient power to assess the risk by dosage or duration of use.

Although we conducted a self-controlled analysis, which has implicit control for unmeasured time-invariant confounders, residual confounding, particularly by time-varying covariates, is always a potential concern in observational research.

There is no reason to think that the proposed mechanism for increased risk of acute kidney injury with fluoroquinolone use is specific only to middle-aged and elderly men; however, this limited population is a key limitation of this study. It is possible that these medications may have different associations in other populations, and verifying this will require further study.

Conclusion

We found a twofold increased risk of acute kidney injury requiring hospital admission with the use of fluoroquinolone antibiotics among adult men, using 2 analytic techniques. We did not find increased risk of acute kidney injury with other antibiotics, supporting the hypothesis that this potential adverse association of fluoroquinolones with acute kidney injury is not a class effect of all antibiotics. We found a strong interaction with concomitant use of fluoroquinolones and renin–angiotensin-system blockers, cautioning against the concomitant use of these 2 drug classes. Although it is clear that the risk of death due to serious infections outweighs the risks associated with the use of fluoroquinolones, the potential for acute kidney injury raises the importance of vigilant prescribing.

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