Fluoroquinolone therapy and idiosyncratic acute liver injury: a population-based study

J. Michael Paterson MSc, Muhammad M. Mamdani PharmD MPH, Michael Manno MSc, David N. Juurlink MD PhD; for the Canadian Drug Safety and Effectiveness Research Network

See related commentary by Hayashi and Chalasani on page 1555 and at www.cmaj.ca/lookup/doi/10.1503/cmaj.121270

Abstract

Background: Although fluoroquinolones are sometimes associated with mild, transient elevations in aminotransferase levels, serious acute liver injury is uncommon. Regulatory warnings have identified moxifloxacin as presenting a particular risk of hepatotoxicity. Thus, we examined the risk of idiosyncratic acute liver injury associated with the use of moxifloxacin relative to other selected antibiotic agents.

Methods: We conducted a population-based, nested, case–control study using health care data from Ontario for the period April 2002 to March 2011. We identified cases as outpatients aged 66 years or older with no history of liver disease, and who were admitted to hospital for acute liver injury within 30 days of receiving a prescription for 1 of 5 broad-spectrum antibiotic agents: moxifloxacin, levofloxacin, ciprofloxacin, cefuroxime axetil or clarithromycin. For each case, we selected up to 10 age- and sex-matched controls from among patients who had received a study antibiotic, but who were not admitted to hospital for acute liver injury. We calculated odds ratios (ORs) to determine the association between admission to hospital and previous exposure to an antibiotic agent, using clarithromycin as the reference.

Results: A total of 144 patients were admitted to hospital for acute liver injury within 30 days of receiving a prescription for one of the identified drugs. Of these patients, 88 (61.1%) died while in hospital. After multivariable adjustment, use of either moxifloxacin (adjusted OR 2.20, 95% confidence interval [CI] 1.21–3.98) or levofloxacin (adjusted OR 1.85, 95% CI 1.01–3.39) was associated with an increase in risk of acute liver injury relative to the use of clarithromycin. We saw no such risk associated with the use of either ciprofloxacin or cefuroxime axetil.

Interpretation: Among older outpatients with no evidence of liver disease, moxifloxacin and levofloxacin were associated with an increased risk of acute liver injury relative to clarithromycin.

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Correspondence to: David N. Juurlink, dnj@ices.on.ca

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Fluoroquinolones are among the most widely prescribed antibiotic agents in North America, and the use of broad-spectrum fluoroquinolones such as levofloxacin and moxifloxacin is increasing.[1,2] Despite their popularity, safety concerns have led to the restriction and, in some cases, withdrawal of several members of this class of drugs, including temafloxacin (owing to hemolysis, renal failure and hypoglycemia),[3] grepafloxacin (owing to QT interval prolongation),[4] trovafloxacin (owing to hepatotoxicity)[5] and, most recently, gatifloxacin (owing to dysglycemia).[6] The varied and unpredictable nature of these adverse reactions has led to the ongoing scrutiny of the entire class of drugs.

Although fluoroquinolones are occasionally associated with mild, transient elevations in aminotransferase levels, serious acute liver injury is uncommon (estimated at < 10 per million exposures).[7] Spontaneous reports and case–noncase analyses suggest wide variation in the risk of acute liver injury among individual fluoroquinolones, ranging from fewer than 1 per million prescriptions for levofloxacin and moxifloxacin to 6 per million prescriptions for trovafloxacin.[7] In a recent review of the safety of moxifloxacin, the European Medicines Agency raised concerns about potential hepatotoxicity, calling for both stronger warnings and restriction of its use in the treatment of community-acquired pneumonia.[8] Shortly thereafter, Health Canada issued a warning regarding the risk of moxifloxacin-associated liver injury.[9]

Despite the widespread use of fluoroquinolones, there are few published epidemiologic studies of their safety. Thus, we conducted a population-based, nested, case–control study to explore the association of fluoroquinolone use

with subsequent admission to hospital for acute hepatotoxicity. Because of recent regulatory warnings regarding moxifloxacin, we thought that admission to hospital for hepatotoxicity would be more likely following treatment with this agent than with other popular broad-spectrum antibiotic agents, including other commonly used fluoroquinolones.

Methods

Setting and design

We developed a case–control study to examine drug use and clinical outcomes in a cohort of Ontario outpatients aged 66 years or older who had received broad-spectrum antibiotic agents that are frequently used to treat respiratory tract infections. All of the patients have universal access to hospital care, physicians' services and prescription drugs. The study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre (Toronto, Ontario) and was performed at the Institute for Clinical Evaluative Sciences.

Sources of data

We identified prescription records using the Ontario Drug Benefit Database, which contains comprehensive records of outpatient prescription medications dispensed to residents of Ontario aged 65 years and older. We identified hospital visits using the Canadian Institute for Health Information Discharge Abstract Database, which contains detailed diagnostic and procedural information regarding all admissions to acute care hospitals in Ontario. We used the Ontario Health Insurance Plan (OHIP) Database to identify paid claims for inpatient and outpatient physician services. We obtained demographic information from the OHIP Registered Persons Database. Finally, we estimated socioeconomic status by linking each patient's residential postal code to the corresponding neighbourhood median household income according to Statistics Canada.[10] These datasets are linked in an anonymous fashion using encrypted health insurance numbers, they have little missing information,[11,12] and they are routinely used to study drug safety.[13–15]

Identification of cases and controls

We defined cases as admissions to hospital for acute liver injury between Apr. 1, 2002, and Mar. 31, 2011. We restricted our analysis to patients admitted within 30 days after receiving a prescription for 1 of 5 commonly used antibiotic agents: clarithromycin, cefuroxime, moxifloxacin, levofloxacin or ciprofloxacin. Hospital admissions for hepatotoxicity were identified using the Canadian enhancement to the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10-CA) codes for primary and secondary preadmission diagnoses of toxic liver disease (with hepatitis [K71.2, K71.6], hepatic necrosis [K71.1] or unspecified [K71.9]) or acute/subacute or unspecified hepatic failure (K72.0, K72.9).[16] We selected these codes because previous work suggested they had a high positive predictive value (95%) for drug-induced hepatotoxicity.[17] The date of admission served as the index date for all analyses. For patients with multiple admissions, only the first was included.

For each case, we randomly selected up to 10 controls from the population of patients who received 1 of the 5 antibiotic agents, but who were not admitted to hospital for acute liver injury. We randomly assigned the controls' index dates and, after applying our exclusion criteria, matched them to cases according to age (within 1 yr) and sex, and to within 90 days of their corresponding case's index date. When fewer than 10 controls could be matched to a case, we used only the controls who could be matched and did not alter the matching algorithm. Cases could serve as controls before becoming a case, but controls could serve as controls only once.

We excluded patients during their first year of eligibility for prescription drug insurance (age 65 yr) to avoid incomplete medication records in our analysis. We also excluded patients who received multiple study antibiotics in the 30 days before the index date, as well as those admitted to hospital in the 90 days before the index date, to avoid the possible confounding effects of recent illness and misclassification of exposure status due to lack of prescription records for inpatients. Finally, to limit our analyses to patients with no history of liver disease, we excluded patients with any hospital admission, physician service claim or procedure related to liver disease in the preceding 5 years (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.111823/-/DC1).

Statistical analysis

Our primary analysis examined the association between exposure to moxifloxacin and subsequent admission to hospital for acute liver injury. To contextualize our results, we conducted similar analyses for levofloxacin, ciprofloxacin and the second-generation cephalosporin cefuroxime axetil. We used clarithromycin as the reference group for all analyses, because although it has similar clinical indications to fluoroquinolones, it is not generally implicated as a cause of idiosyncratic liver injury.

We used multivariable logistic regression conditioned on the matched sets to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between hospital treatment for hepatotoxicity and recent exposure to one of the antibiotic agents we were studying. Potential confounding factors, such as previous use of health services for alcohol dependence, diabetes mellitus, recent use of other hepatotoxic drugs (phenytoin, isoniazid, amoxicillin/clavulanate and valproic acid),[18,19] residence in a long-term care facility, number of visits to a physician as an outpatient during the preceding year, socioeconomic status and number of prescription drugs received in the preceding year (a validated index of comorbidity),[20] were entered into the model if differences between cases and controls on bivariate analysis exceeded p less than 0.1. To assess the potential for residual confounding, we performed a sensitivity analysis in which we excluded residents of long-term care facilities and, by extension, unmeasured factors associated with such care.

Finally, in a supplementary analysis, we estimated the crude incidence of acute liver injury during treatment with one of the antibiotic agents under study by identifying all residents of Ontario aged 66 years or older who received one of these agents during the study period, applying our exclusion criteria and determining the number of patients admitted to hospital with acute hepatotoxicity within 30 days after the drug was dispensed. For those who had multiple prescriptions for antibiotic agents during the study period, each course of treatment was considered separately.

All analyses used a 2-sided type I error rate of 0.05 as the threshold for statistical significance.

Results

During the study period, we identified 746 patients admitted to hospital for acute hepatotoxicity within 30 days after outpatient treatment with one of the study drugs. Of these patients, 30 (4.0%) received multiple study drugs during the 30-day window, 490 (65.7%) had a diagnosis or procedure related to liver disease in the preceding 5 years, and 82 (11.0%) had been admitted to hospital in the preceding 90 days. The remaining 144 patients were our cases and were matched to 1409 controls.

The mean age of patients in the case group was 77.4 (standard deviation [SD] 7.9) years, and the mean age for controls was 77.0 (SD 7.5) years (Table 1). Women accounted for 47.2% of cases and 47.9% of controls. Patients in the case group had a relatively higher number of visits to physicians and received more prescriptions for drugs in the preceding year, had lower socioeconomic status, were more likely to have diabetes, and were more likely to have been recently exposed to sulfamethoxazole, trimethoprim and drugs with known hepatotoxicity than patients in the control group (Table 1). Among cases, the median time from the dispensing of the antibiotic agent to admission to hospital for acute liver injury was 9 (interquartile range [IQR] 3–19) days, and the median length of stay in hospital was 8 (IQR 4–16) days (data not

Table 1: Characteristics of cases and controls

Characteristic	No. (%) of patients or mean ± SD		
	Cases n = 144	Controls n = 1409	p value*
Age, yr	77.4 ± 7.9	77.0 ± 7.5	0.6
66–75	65 (45.1)	654 (46.4)	0.9
76–85	54 (37.5)	534 (37.9)	
≥ 86	25 (17.4)	221 (15.7)	
Female sex	68 (47.2)	671 (47.6)	
Study antibiotic received during the 30-d period before admission			
Clarithromycin (reference)	27 (18.8)	431 (30.6)	0.03
Cefuroxime axetil	14 (9.7)	141 (10.0)	
Ciprofloxacin	54 (37.5)	483 (34.3)	
Levofloxacin	23 (16.0)	180 (12.8)	
Moxifloxacin	26 (18.1)	174 (12.3)	
Any study antibiotic received 31–365 d before admission	70 (48.6)	655 (46.5)	0.6
Neighbourhood income quintile			
1 (lowest)	21 (14.6)	285 (20.2)	0.06
2	42 (29.2)	303 (21.5)	
3	36 (25.0)	280 (19.8)	
4	24 (16.6)	288 (20.4)	
5 (highest)	20 (13.9)	246 (17.5)	
Resident in a nursing home	20 (13.9)	162 (11.5)	0.4
No. of prescription drugs received in the preceding year	14.1 ± 6.7	12.0 ± 6.1	< 0.001
No. of outpatient visits to a physician in the preceding year	15.7 ± 11.0	13.4 ± 9.9	0.009
Diabetes mellitus	53 (36.8)	405 (28.7)	0.04
Alcohol dependence	6 (4.2)	30 (2.1)	0.1
Receipt of sulfamethoxazole–trimethoprim in the 90-d period before admission	9 (6.3)	42 (3.0)	0.04
Receipt of allopurinol in the 90-d period before admission	9 (6.3)	52 (3.7)	0.1
Receipt of a hepatotoxic drug in the 90-d period before admission†	8 (5.6)	40 (2.8)	0.07

Note: SD = standard deviation.
*χ^2 or t test, as appropriate.
†Isoniazid, phenytoin, amoxicillin–clavulanate, valproate.

shown). Eighty-eight patients (61.1%) died during their index admission to hospital (data not shown).

Compared with clarithromycin, moxifloxacin was associated with a more than 2-fold increased risk of admission to hospital for acute liver injury (adjusted OR 2.20, 95% CI 1.21–3.98) (Table 2). Levofloxacin was associated with a statistically significant but lower risk of hepatotoxicity than we saw with moxifloxacin (adjusted OR 1.85, 95% CI 1.01–3.39). In contrast, we saw lower risks with ciprofloxacin and cefuroxime axetil, which did not differ significantly from clarithromycin (Table 2). After we adjusted for other potential confounders, only lower median household income (quintiles 2 and 3) was independently associated with increased risk of acute liver injury (data not shown).

To test the robustness of our conclusions, we excluded residents of long-term care facilities, because these patients were older and systematically different from the rest of our cohort. In this analysis, we found a marginally stronger association between the risk of acute liver injury and exposure to moxifloxacin (adjusted OR 2.74, 95% CI 1.42–5.29) and levofloxacin (adjusted OR 2.29, 95% CI 1.17–4.46].

In total, about 2.86 million courses of antibiotic therapy were associated with 172 admissions to hospital for acute liver injury (some of the 144 cases were admitted more than once), or about 6 admissions per 100 000 exposures (data not shown). Consistent with the results of our case–control analysis, the crude incidences for admission to hospital with acute liver injury for moxifloxacin (7.98 per 100 000 exposures) and levofloxacin (8.62 per 100 000 exposures) were about double that associated with clarithromycin (3.95 per 100 000 exposures) (Table 3).

Table 2: Association between admission to hospital for acute liver injury and recent use of antibiotic agents

Antibiotic agent	Crude OR (95% CI)	Adjusted OR* (95% CI)	*p* value†
Clarithromycin (reference)	1.00	1.00	
Cefuroxime axetil	1.65 (0.84–3.24)	1.43 (0.72–2.83)	0.3
Ciprofloxacin	1.83 (1.12–2.98)	1.56 (0.95–2.58)	0.08
Levofloxacin	2.06 (1.14–3.73)	1.85 (1.01–3.39)	0.046
Moxifloxacin	2.44 (1.37–4.36)	2.20 (1.21–3.98)	0.009

Note: CI = confidence interval, OR = odds ratio
*Model includes neighbourhood income quintile, number of prescription drugs received in the preceding year, number of outpatient visits to a physician in the preceding year, diabetes mellitus, receipt of sulfamethoxazole and trimethoprim in the 90 days before admission, and receipt of isoniazid, phenytoin, amoxicillin/clavulanate or valproate in the 90 days before admission.
†Wald χ^2.

Table 3: Crude incidence of admission to hospital for acute liver injury within 30 days of exposure to an antibiotic agent

Antibiotic agent	No. of exposures	Admission to hospital for acute liver injury within 30 d of dispensing	Rate per 100 000 exposures
Clarithromycin (reference)	910 817	36	3.95
Cefuroxime axetil	248 458	16	6.44
Ciprofloxacin	1 051 959	67	6.37
Levofloxacin	324 660	28	8.62
Moxifloxacin	325 920	26	7.98

Interpretation

Using the administrative health records of more than 1.5 million older residents of Ontario, we found that, relative to clarithromycin, both moxifloxacin and levofloxacin were associated with almost twice the risk of admission to hospital for acute liver injury among patients with no history of liver disease. Despite recent regulatory warnings regarding the hepatic safety of moxifloxacin,[8,9] there is a lack of controlled studies supporting the notion that moxifloxacin presents a particular risk relative to other broad-spectrum antibiotic agents and, in particular, to other fluoroquinolones.[7–9,21,22] Our findings make an important contribution to an evidence base that is currently limited to case reports and registries of drug-induced liver injury.[19,23–26]

Almost two-thirds of the patients in our case group filled their prescriptions in the 2 weeks before they were admitted to hospital, which is consistent with the rapid onset of liver injury reported in most published cases of fluoroquinolone-associated hepatotoxicity.[23–26] Although the precise mechanism of injury is unknown in our patients' cases, the latency period is consistent with many hypersensitivity reactions to drugs.[25,27] In our study, more than one-third of patients in the case group were admitted to hospital within 4 days of receiving a prescription for an antibiotic agent. The relatively high case fatality in our study (61.1% during the index admission to hospital) may be due to our requirement that cases be admitted to hospital. However, given the sources of our data, we cannot be certain that fulminant liver failure was the cause of death for these patients.

Whether chronic liver disease increases a patient's risk for drug-induced liver injury is unknown. However, preexisting liver disease is thought to put patients at risk for a more complicated course and poorer outcomes after such

injuries.[28–30] In previous studies, factors such as female sex, diabetes mellitus, chronic alcohol dependence and HIV infection have shown inconsistent associations with drug-induced liver injury.[30] The American Drug-Induced Liver Injury Network has included 4 hepatotoxic medications in its registry: isoniazid, phenytoin, amoxicillin/clavulanate and valproate.[18] In our secondary analysis, none of these frequently cited risk factors were associated with acute hepatotoxicity. These results are important, because few previous studies of drug-induced liver injury have included controls or adjusted for potential confounders.

Our overall crude incidence rate of 6 admissions to hospital for acute liver injury per 100 000 antibiotic exposures is considerably higher than previously published rates, which are about 1 per 100 000 exposures.[7] Among other factors, our results may be due to differences in definitions of outcomes, incomplete reporting of adverse events in previous studies or the older age of our study's participants placing them at higher risk.[30]

Limitations

We used administrative data and had no information regarding liver function, actual medication consumption, use of nonprescription drugs or cause of death. Infection itself may predispose a person to liver disease, and our findings could be due to the use of moxifloxacin in patients who are particularly ill. However, confounding by indication is unlikely to fully explain our results. Both moxifloxacin and levofloxacin were associated with a similar risk of acute liver injury, and both drugs are used for indications similar to those for clarithromycin, our drug of reference. Furthermore, excluding residents of long-term care facilities increased the relative risk of liver injury associated with both moxifloxacin and levofloxacin, suggesting that residual confounding is unlikely to fully explain the increased risk.

We excluded patients with evidence of preexisting liver disease and attempted to control for the most frequently cited nongenetic risk factors for drug-induced liver injury, such as diabetes, alcohol dependence and use of hepatotoxic drugs. Although we were unable to control for genetic susceptibility, this is an incompletely understood issue for most drugs — any predisposition would be equally distributed among the drugs we studied. Finally, although the accuracy of hospital discharge coding for acute hepatotoxicity is not well characterized in our particular setting, the ICD10-CA codes we used did well in a study of acetaminophen-induced hepatotoxicity.[17] In addition, these limitations apply equally to all of the antibiotic agents we studied.

Although our study period largely predates regulatory warnings regarding the hepatic safety of moxifloxacin, some clinicians may have been aware of the earliest warnings, which could theoretically bias outcome determination. Differential outcome determination among patients given moxifloxacin is unlikely to affect our results, however, because liver biochemistry is routinely measured in older patients who present to hospital. Moreover, such a bias would not explain the elevated risk of acute liver injury associated with levofloxacin, for which regulatory warnings were not issued.

Our analysis focused only on patients admitted to hospital, excluding less severe cases of hepatotoxicity managed in emergency departments and other ambulatory care settings. Consequently, we may have underestimated the broader clinical consequences of this rare but important adverse reaction.

Finally, our results derive from data from patients aged 66 years or older. Their experiences may not reflect those of younger patients who may be more prone to purely idiosyncratic drug-induced liver injury.[30]

Conclusion

Relative to the use of clarithromycin, the use of moxifloxacin and levofloxacin was associated with an increase (about 2-fold) in the risk of admission to hospital for acute liver injury among the patients in our cohort. Similar risks were not seen with the use of ciprofloxacin or cefuroxime axetil. Although our results require confirmation in other settings, they suggest that both moxifloxacin and levofloxacin be considered for regulatory warnings regarding acute liver injury.

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Affiliations: From the Institute for Clinical Evaluative Sciences (Paterson, Mamdani, Manno, Juurlink), Toronto, Ont.; The Sunnybrook Research Institute (Juurlink), Toronto, Ont.; the Departments of Medicine (Juurlink) and Health Policy, Management, and Evaluation (Paterson), and the Leslie Dan Faculty of Pharmacy (Mamdani), University of Toronto, Toronto, Ont.; Keenan Research Centre of the Li Ka Shing Knowledge Institute (Mamdani), St. Michael's Hospital, Toronto, Ont.; and the Department of Family Medicine (Paterson), McMaster University, Hamilton, Ont.

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