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Clinical paper

Fluoroquinolone use and serious arrhythmias: A nationwide case-crossover study

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Abstract

Aim: Fluoroquinolones have been associated with life-threatening ventricular arrhythmias and even sudden cardiac death. We aimed to assess the temporal relationship of fluoroquinolone use and serious arrhythmias via a case-crossover analysis of a large cohort of serious arrhythmias patients.

Methods: In a national administrative database, we compare the distributions of fluoroquinolone exposure for the same patient across a 30-day period before the serious arrhythmia event and 5 randomly selected 30-day periods before the serious arrhythmia event. Odds ratios (ORs) and 95% Confidence Intervals (CIs) were estimated using conditional logistic regression analysis.

Results: From a total of 2 million participants, 7657 patients with serious arrhythmias were identified. Use of fluoroquinolones within the 30-day period before the event was significantly associated with increased risk for serious arrhythmia (OR:3.03, 95% CI:2.48, 3.71). The risk association was attenuated, but remained significant after adjustment for time-varying confounders (OR:1.48, 95% CI:1.18, 1.86). A consistent increase in risk of serious arrhythmia was observed for all time windows investigated (7 days, 14 days, 30 days, 60 days and 90 days).

Conclusions: Exposure to fluoroquinolones was substantially associated with serious arrhythmic events, independent of the temporal proximity of fluoroquinolone prescription.

Keywords: Fluoroquinolone, Serious arrhythmias, Case-crossover study

Introduction

Fluoroquinolones are one of the most commonly prescribed antibiotics with more than 7.8 billion pills dispensed worldwide every year.[1] These antimicrobial agents, due to their broad-spectrum antibacterial coverage and favorable pharmacokinetic profiles, have been approved for treating an extensive range of infections such as respiratory, genitourinary, abdominal, ocular, and soft tissue infections.[2]

Although fluoroquinolones are generally well tolerated, these antibiotics have been associated with life-threatening ventricular arrhythmias and even sudden cardiac death.[3,4] In particular, two fluoroquinolones (grepafloxacin and sparfloxacin) have been withdrawn from the market due to the aforementioned associations. Experimental animal studies related the induced arrhythmias to fluoroquinolones' ability to block the hERG cardiac potassium channel[5] and consequently prolong the QT interval, thus increasing the incidence of torsade de pointes.[6]

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Despite the findings of experimental studies, the clinical association between fluoroquinolones and ventricular arrhythmias remains controversial. In fact, several case-control or cohort studies reported a one- to three-fold increased risk of fluoroquinolone-induced serious arrhythmias, while a recent binational cohort study reported no significant association.[7–11] These conflicting data may be attributed to the small sample size (<2000 cases in all published studies) and differences in the selection of reference/control groups. The right reference group of study participants is crucial, as between-person confounding has been shown to change the effect estimate drastically. In fact, one study showed that using the same database and inclusion/exclusion criteria, macrolide use was associated with a significant increased risk of ventricular arrhythmias in a case-control design, but not in a case-crossover design, demonstrating the effect of between person confounding.[8] The case-crossover design is an adaptation of the case-control design, in which cases serve as their own controls, and avoids the issue of control selection. However, this approach can only give unbiased estimates for transient exposures and acute outcome events.[12] To assess whether the use of fluoroquinolones (usually used transiently during infections) was associated with an increased risk of serious arrhythmias in a large database, we opted for a case-cross over design. Moreover, it is still unclear whether the risk of fluoroquinolone-induced arrhythmias remains constant over time. Thus, we also aimed to estimate the risk of serious fluoroquinolone-induced arrhythmias in different hazard periods (from 7 to 90 days).

Methods

Data source

With approval from the institutional review board of National Taiwan University Hospital, we conducted a case-cross over study using a subset of the National Health Insurance Research Database (NHIRD) from Taiwan. The subset used in this study contains the information of two-million participants randomly selected from the entire beneficiaries (24 millions) of Taiwan's National Health Insurance (NHI), and has been verified to be representative of the overall population of beneficiaries in terms of age, sex, healthcare costs and geographical distribution. This database is maintained by the Collaboration Center of Health Information Application, which is supervised by the Department of Statistics, Ministry of Health and Welfare.

Patient's consent was not required for this study as all personal identifiers are encrypted, and data can be analyzed anonymously. The claims history includes patient demographics, outpatient and inpatient electronic claims records, individual diagnoses, operations, prescribed medications, and mortality. Survival status and cause of death for each patient was verified by a linked national death certificate database. Detailed information on brand/generic name of the prescribed drugs, route of administration, quantity, and number of days of supply are available in the NHIRD database. The Taiwanese government routinely inspects the claims record, and physicians who violate the standards of clinical practice are subject to financial penalties.[13]

Study population

Cases of serious arrhythmia, defined as ventricular arrhythmia or sudden cardiac death, were identified from the NHIRD subset from January 2008 to December 2013. Patients with severe ventricular arrhythmia were defined by both inpatient and emergency department diagnosis of ventricular arrhythmia (427.1, 427.4, 427.5, 798.1, 798.2, 798.9, V12.53) and if they received either one of the following treatments: defibrillation procedure, cardiopulmonary resuscitation procedure, or intravenous anti-arrhythmic agent prescriptions (amiodarone, lidocaine, magnesium sulfate, or sotalol). Three types of sudden cardiac death were identified by previously validated methods. First, the death certificate of the patients had to show a terminal diagnosis code consistent with sudden cardiac death. Second, patients with a one-day hospitalization or emergency department visit had to have a primary diagnosis code consistent with sudden cardiac death. Third, patients with a one-day hospitalization or emergency department visit needed to receive either one of the treatments: defibrillation procedure, cardiopulmonary resuscitation procedure, or intravenous anti-arrhythmic agent prescriptions.

Case-crossover design

The case-crossover design was based on the method initially proposed by Maclure, where each case serves as his own control.[14] In our study, each case contributed one case window, one wash period and ten control windows as depicted in supplementary Fig. 1. In all the analyses, all the windows were 30 days in total length. The only exception in the length of window was in the sensitivity analysis, where the length of the window was changed to 7, 14, 30 or 60 days (supplementary Fig. 2).

Time-variant confounding factors

Factors that could potentially change across the case and control periods were identified and analyzed in Table 1. These included both infectious complications and the prescriptions of concomitant medications potentially related to serious arrhythmia.

Exposure assessment and definition

Use of fluoroquinolone was defined as having a prescription for more than 3 days during the case or control period. Fluoroquinolones are drugs that contain any of the following active compounds: ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, norfloxacin, lomefloxacin, moxifloxacin, gemifloxacin, enoxacin, or pefloxacin. We defined users of other specific medication (β adrenergic antagonists, calcium channel blocker, statins, anti-histamines, antipsychotics and NSAIDs) as having a drug prescription record ≧ 7 days in the predefined risk period.

Statistical analysis

Participants' baseline characteristics were presented as means with standard deviations for continuous variables, and frequencies and percentages for categorical variables (Table 1). We used the Charlson index to quantify each individual's burden of comorbidity.[15] Supplementary Table 1 compares intra-individual variations in infectious complications and use of specific medications within case and control

Table 1 – Baseline characteristics of patients with serious arrhythmia.

Characteristic	Serious arrhythmia (n = 7567) mean (SD)
Demographics	
Age, years, median (IQR)	77 (63–84)
Male, sex, %	4463 (59.0)
Charlson score, n (%)	
0	5532 (73.1)
1	1338 (17.7)
≥2	697 (9.2)
Insurance premiums, n (%)	
Dependent	1524 (20.2)
<666 USD	3047 (40.4)
666–1331 USD	2391 (31.7)
≥1331 USD	578 (7.7)
Medical history, n (%)	
Diabetes	597 (7.9)
Hypertension	657 (8.7)
Lipid disorder	152 (2.0)
Ischemic heart disease	303 (4.0)
Chronic kidney disease	34 (0.5)
Asthma	55 (0.7)
Conduction disorder	14 (0.2)
Atrial fibrillation	166 (2.2)
Heart failure	376 (5.0)
Health Care Utilization in previous year, n (SD)	
Number of OPD visits	2.35 (2.6)
Number of emergency department visits	0.30 (0.6)
Number of hospitalizations	0.40 (0.6)
Indication of FQ prescription, n (%)	
Cardiovascular infection	12 (0.2)
Lower respiratory infection	1246 (16.5)
Intra-abdominal and biliary tract infection	66 (0.9)
Genitourinary tract infection	768 (10.2)
Prescription drug use in case period, n (%)	
β adrenergic antagonists	610 (8.1)
Calcium Channel Blockers	1237 (16.4)
Statins	290 (3.8)
Anti-histamines	677 (9.0)
Antipsychotics	83 (1.1)
NSAIDs	996 (13.2)

Note. n, number of participants; IQR, interquartile range; USD, United States dollar; SD, standard deviation; OPD, outpatient department; FQ, fluoroquinolone; NSAIDs, nonsteroidal antiinflammatory drugs.

period by the use of chi-square test. A two-tailed P-value of less than 0.05 was considered statistically significant.

Conditional logistic regression was used to estimate the association between use of fluoroquinolone and risk of sudden death or ventricular arrhythmia. In the main analysis, we calculated the crude odds ratio (OR) by comparing the odds of fluoroquinolone exposure between the case period and the 5 randomly selected control periods (Table 2 and Supplementary Fig. 1). The adjusted OR was calculated by controlling for potential time-varying confounding variables (cardiovascular infection, lower respiratory infection, intra-abdominal infection and biliary tract infection, genitourinary tract infection, and use of specific medications).

To verify the robustness of the primary results, we tested the effects of different exposure windows (7, 14, 30 or 60 days), which are shown in Table 3. In the sensitivity analysis using different exposure window, we calculated the OR by comparing the odds of fluoroquinolone exposure between the case period and the control period using 1:1 ratio (Supplementary Fig. 2). All analyses were carried out using SAS 9.3 for Windows (SAS Institute Inc., Cary, NC, USA), and the data were reported in accordance with STROBE guidelines.

Table 2 – Unadjusted and adjusted odds ratio between use of fluoroquinolone and development of serious.

Antibiotic	Used in the case window n (%)	Used in the control window n (%)	Odd ratio (95% CI)	Adjusted odd ratio (95% CI)
Fluoroquinolone	161 (2.13)	285 (0.75)	3.03 (2.48, 3.71)*	1.48 (1.18, 1.86)*

* $P < 0.005$.

Table 3 – Sensitivity analysis by different risk period windows (1:1, composite sudden death and ventricular arrhythmias).

Hazard period	Exposed cases in hazard periods (N = 7567)	Exposed cases in control periods (N = 7567)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
7 days	55 (0.73)	29 (0.38)	1.95 (1.23, 3.09)**	1.95 (1.15, 3.29)**
14 days	99 (1.31)	29 (0.38)	3.48 (2.29, 5.28)***	1.98 (1.26, 3.11)*
30 days	161 (2.13)	68 (0.90)	2.46 (1.84, 3.30)***	2.41 (1.65, 3.50)***
60 days	251 (3.32)	96 (1.27)	2.76 (2.16, 3.52)***	1.57 (1.16, 2.14)**
90 days	323 (4.27)	136 (1.80)	2.51 (2.04, 3.09)***	1.54 (1.17, 2.03)**

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Results

From a total of 2 million participants, 7657 patients with serious arrhythmias were identified (Fig. 1).

The baseline characteristics of patients were summarized in Table 1. Patients with serious arrhythmias were generally older, male and had a Charlson score of 0 (73%).[15] Patients were observed to have a low prevalence of comorbidities, with hypertension (8.68%) and diabetes (7.89%) as the two highest recorded comorbidities.

Supplementary Table 1 compares intra-individual variation in infectious complications and use of specific medications within case and the control period. As expected, more infectious complications were found during the case period than the control period. In addition, use of specific medications (β adrenergic antagonists, antihistamines and NSAIDs) to relive symptoms of infections were also more commonly observed during the case period.

Table 2 shows that the use of fluoroquinolones within the 30-day period before the event was significantly associated with an increased risk for serious arrhythmias (OR: 3.03, 95% CI: 2.48, 3.71). The risk association was attenuated, but remained significant after adjustment for time-varying confounders (OR: 1.48, 95% CI: 1.18, 1.86).

Table 3 compares the relationship between the temporal proximity of fluoroquinolone prescription and odds of serious arrhythmias, by changing the length of time window. A consistent increase in the risk of serious arrhythmias was observed for all the different time windows investigated (7 days, 14 days, 30days, 60 days and 90 days).

Discussion

Using a comprehensive national medical database including a dataset of two million randomly sampled individuals with serious arrhythmia, our population-based case-crossover study provides new evidence that the

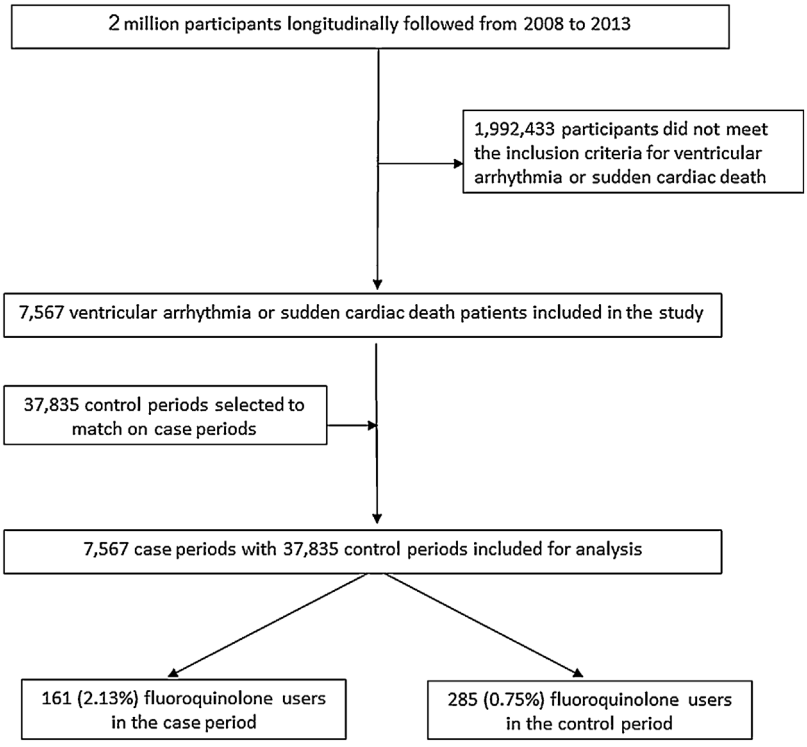

Fig. 1 – Flow of the study cohort.

use of fluoroquinolone is associated with an increased risk of serious arrhythmias. The risk is independent of the temporal proximity of fluoroquinolone prescription and remains significant after adjustment for potential time varying confounders. It should be taken into consideration the fact that to perform this type of research and, thus, to avoid the issue of control selection, cases served as their own controls. Inevitably, to do so, the case period would occur after the control periods, by an average of half a year. This might introduce confoundings or selection biases, depending on time trends in the exposure or/and outcome. Nonetheless, the conditional exchangeability could still be achieved by modelling, stratifying or matching on temporal variation.[16] Furthermore, even though, the role of aging in cardiac arrhythmias has been demonstrated, the possible bias due to a comparison between cases and "slightly younger" controls seem negligible.[17,18] In fact, not only a linear correlation between age and ventricular arrhythmias has never been fully studied, but the same correlation has not been demonstrated between age and sudden cardiac death.[19]

Current clinical information regarding the relationship between fluoroquinolone and serious arrhythmias are mainly based on randomized controlled trials (RCTs) and pharmacovigilance data. While RCTs detected a significant QT prolongation in only patients taking moxifloxacin,[20–23] pharmacovigilance analyses showed an excess of torsades de pointes among patients also taking gatifloxacin, levofloxacin and ciprofloxacin.[3,24] Due to the rarity of serious arrhythmia events and the exclusion of subjects with significant comorbidities, RCTs provide only limited data on the actual use of such medications, especially on a fragile population. Post-marketing surveillance, such as pharmacovigilance data, would be the preferred way to detect such events, although it could have been limited by selective reporting. Thus, observational studies, such as the one we conducted, are needed to confirm these findings.[25]

There are several possible biological explanations for the higher aforementioned risk in patients taking fluoroquinolones. In fact, these antibiotics are able to prolong the cardiac QT interval by interfering with the potassium channels, which play a significant role in the regulation of the action potentials of the cardiac cells. Thus, creating the setting for the start of arrhythmogenic activity, such as torsades de pointes, which might be followed by ventricular fibrillation, cardiac arrest, and sudden death.[26] Especially, the effect of the specific type of fluoroquinolone could be dependent upon the degree of the inhibition of the potassium channels.[27] Additionally, fluoroquinolones increase the heterogeneity of cardiac repolarization, thus, creating a substrate for a re-entrant mechanism, which is responsible for the maintenance of the arrhythmia.[28]

Our overall findings are consistent with both previous biological and experimental studies investigating the association between fluoroquinolone use and serious arrhythmias' adverse events. In fact, a recent meta-analysis by Liu et al. demonstrated that fluoroquinolones increase the risk of both cardiovascular death (RR:1.60, 95% CI:1.17–2.20) and serious arrhythmias (RR:2.29, 95% CI:1.20–4.36), but not the risk of all-cause mortality (1.02, 95% CI:0.76–1.37).[29] Moreover, in their study, moxifloxacin and levofloxacin were associated with a higher risk of serious arrhythmias. Treatment with fluoroquinolones was associated with an absolute risk increase of 160 additional sudden cardiovascular deaths or serious ventricular arrhythmias, and 43 additional cardiovascular deaths per 1 million treatment courses.[8,10,20,29]

Most of the previous studies did not take into account the infectious episode, which might be the cause of both short- and long-term increase in the risk of ventricular arrhythmia, heart failure, hemorrhagic stroke, myocardial infarction and cardiac arrest, especially among patients with a history of cardiovascular disease.[30–32] In fact, we found that the risk of serious arrhythmias decreased substantially after adjustment for time varying confounders, such as common infections. However, the infection could not totally explain the risk of serious arrhythmias in users of fluoroquinolones, as past users of fluoroquinolones also showed an increased risk of serious arrhythmias. Our analyses also found a consistent increase in the risk of serious arrhythmias, extending the hazard period. Recently, a study by Inghammar et al. failed to demonstrate any association between fluoroquinolones and the risk of serious arrhythmias using users of penicillin V as a reference group.[7] We believe there are several reasons why the study failed to detect an increased risk of fluoroquinolone associated arrhythmias. First, the risk of fluoroquinolone associated arrhythmias may be diminished after accounting for infection, thus a larger sample size would be required to detect a difference in the risk of arrhythmia. In the Inghammar et al. study, they only identified 66 current users of fluoroquinolones compared to our 161. Second, their population was mainly composed of younger patients, whom, as they reported, have lower risk to develop arrhythmias. This could have severely affected the results. In fact, several studies have shown different risks, after the exposure to a cardiovascular risk factor, depending on both age and sex.[17,33,34] Given the low incidence of serious arrhythmias, this controversy regarding patient population might require further analyses using meta-regression of published literature.

Results of our study should be interpreted considering both strengths and weaknesses. A major strength of our study is the case-crossover design, which allowed us to avoid the issue of control selection and, thus, between-person confounding. Another strength is the large comprehensive population, randomly selected from the entire beneficiaries of Taiwan's NHI, and verified to be representative of the overall population, despite frailty or co-pathologies. However, some limitations should be noted. First, misclassification of exposure could have been possible. In fact, the claim database in Taiwan provides accurate information on the drug dispensed, but it does not ensure patient compliance. It is likely, though, that such misclassification was random, thus, not biasing our result. Second, we did not conduct subgroup analyses on the specific types of fluoroquinolone. Given the limited sample size, this would not have been a fair comparison. Third, given the observational nature of this study, the association between fluoroquinolones and serious arrhythmias should theoretically be confirmed by an RCT. However, previous RCTs failed to demonstrate such an association probably because of biases in the study population and due to the rare incidence of serious arrhythmias. Furthermore, in consideration of the published data, it could be unethical to perform such RCTs, and it is unlikely that a large prospective trial will be available in the near future.

Due to their wide spectrum of antimicrobial activity and superior pharmacokinetic and bioavailability profiles, fluoroquinolones are one the most commonly prescribed antibiotics around the world. In fact, the global prescription of fluoroquinolones has rapidly increased, almost doubling from 4.75 billion to 7.81 billion doses in the last decade. With an estimated 25 million people prescribed fluoroquinolones in the US annually, which is expected to increase further, it is clear that fluoroquinolones may contribute substantially to the current and future burdens of serious arrhythmias. Given the biological plausibility of the association, the consistency between experimental and epidemiological findings, and the analogous findings of similar adverse events, clinicians should strongly consider

alternative antibiotic regimens in patients with high risk of serious arrhythmias.

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Contributors

All authors had access to the data. C-C L had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, concept and design, critical revision of the manuscript for important intellectual content, obtaining funding and supervision. LP was responsible for concept and design, drafting the manuscript, and critical revision of the manuscript. M-T L was responsible for drafting the manuscript, interpretation of the data, and obtaining funding. W-T H and T-Y Tsai responsible for critical revision of the manuscript and data analysis and writing the final draft, T-C H conducted the statistical analysis critically revised the manuscript.

Prior presentation

None.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.04.030.

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