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An investigation of the potential association between retinal detachment and oral fluoroquinolones: a self-controlled case series study

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Objectives: A study reported a significant association between oral fluoroquinolones and the development of retinal detachment among current users of oral fluoroquinolones (Etminan M, Forooghian F, Brophy JM *et al. JAMA* 2012; **307**: 1414–9). However, other published studies have discordant results. This study aimed to investigate this association and to estimate the absolute risk of developing retinal detachment in patients exposed to oral fluoroquinolones.

Methods: A self-controlled case series study was conducted with data retrieved from the Hong Kong Clinical Data Analysis and Reporting System database and the Taiwan National Health Insurance Research Database. Hong Kong and Taiwanese patients who had prescriptions for oral fluoroquinolones and a procedure for retinal detachment between 2001 and 2012 and between 2000 and 2010, respectively, were defined as cases and included in the analysis.

Results: A total of 9 events were found during the fluoroquinolone-exposed period and 1407 events were found during the non-exposed period. The adjusted incidence rate ratio in the combined model was 1.26 (0.65–2.47). The crude absolute risk of experiencing retinal detachment whilst on oral fluoroquinolones was ~1.3 per 200 000 prescriptions.

Conclusions: Our study does not support the association between the use of fluoroquinolones and the development of retinal detachment and our findings are strikingly similar to that of the study conducted in Denmark. Doubt is cast on the association between the use of fluoroquinolones and the development of retinal detachment. Therefore, the use of fluoroquinolones should not be precluded based on the current evidence on the risk of retinal detachment. The impact of different ethnicities on the response to fluoroquinolones should also be investigated.

Keywords: antimicrobials, Hong Kong, Taiwan, pharmacoepidemiology, adverse drug reactions

Introduction

Serious adverse effects[1,2] have been reported to be associated with the use of fluoroquinolones. Etminan *et al.*[3] reported that current users of oral fluoroquinolones were at a higher risk of developing retinal detachment (RD) compared with non-users. Other research groups have also investigated the association between fluoroquinolones and RD but the results are not concordant.[4,5] Therefore, this study aimed to investigate the acute effects of oral fluoroquinolones and the association with RD proposed by Etminan *et al.*[3] This study also aimed to estimate the crude absolute risk of developing RD in patients exposed to fluoroquinolones.

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Methods

Study design: self-controlled case series

The self-controlled case series relies on within-person comparisons in a population of individuals who have both the outcome and exposure of interest.[6] Incidence rate ratios (IRRs) are derived by comparing the rate of RD procedures (events) received by a patient during fluoroquinolone-exposed (risk periods) and non-exposed periods.

Data sources

Database in Hong Kong (HK)

The Clinical Data Analysis and Reporting System (CDARS) is a database managed by the HK Hospital Authority, a publicly funded primary, secondary and tertiary healthcare provider. Health services provided by the Hospital Authority are available to all residents (>7 000 000 million people).

Electronic patient records that contain patients' data, including demographic information, diagnoses, procedures, payment method, prescription information, laboratory tests and admission and discharge information, were entered by trained staff. Data are transferred to the CDARS for research and audit purposes. Patient records in the CDARS are completely de-identified to protect patient confidentiality. The CDARS has captured data since 1993 from all public hospitals, institutions and outpatient clinics under the Hospital Authority and has been used to conduct high-quality epidemiological studies.[7]

Taiwan database

The National Health Insurance Research Database (NHIRD) is a population-based electronic claims record database from Taiwan's National Health Insurance (NHI) administration. The NHI is a mandatory-enrolment, single-payment system created in 1995, now covering >98% of Taiwan's population.[8] The NHIRD comprises mainly demographic data on enrollees, information regarding healthcare professionals and facilities and service claims from inpatient, ambulatory care and contracted pharmacies for reimbursement purposes. A random sample of 3 000 000 patients were selected from the NHIRD for this study. The database has been used for pharmacoepidemiological research.[9]

Patient identification

Patients who received oral fluoroquinolones between 1 January 2001 and 31 December 2012 (HK) and between 1 January 2000 and 31 December 2010 (Taiwan) were identified. Cases were defined as patients who received fluoroquinolones and experienced an event(s) during the study period [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes are listed in Table S1 (available as Supplementary data at *JAC* Online)]. The index date was defined as the date of the event recorded in the database.

Exclusion criteria

Patients with unknown or incomplete demographics, previous RD diagnosis (Table S2, available as Supplementary data at *JAC* Online) and events (Table S1) within the screening period (2 years before the beginning of study period of each patient), history of head or eye trauma within 30 days before the first event or who had ever been diagnosed with endophthalmitis (Table S2) were excluded.

Statistical analysis

Age, history of diabetes and cataract surgery (Table S3, available as Supplementary data at *JAC* Online) were adjusted in the analysis. Adjusted IRR and the corresponding 95% CIs for RD were estimated using conditional Poisson regression. A significance level of 5% was used in all statistical analyses. Sensitivity analyses were conducted to address the potential issue of non-compliance, removal of recent and distant use of fluoroquinolones (up to 365 days) from the non-exposed period and to limit the duration of the non-exposed period. Based on the method of Musonda *et al*.,[10] 1300 cases were needed to detect an IRR of 2.5.

The crude absolute risk of experiencing RD with oral fluoroquinolone treatment was calculated as follows:

$$\text{crude absolute risk} = \frac{\begin{array}{c}[\text{number of patients who underwent}\\ \text{RD surgical repair while on oral fluoroquinolone treatment}]\end{array}}{\begin{array}{c}[\text{total number of oral fluoroquinolone prescriptions}\\ (\text{including those for patients without RD})]\end{array}}$$

The Wilson score interval[11] was used in calculating the 95% CI for crude absolute risk.

Microsoft Excel and Statistical Analysis System (SAS) v9.3 were used for data manipulation and analyses.

Ethics approval

The study protocol was approved by the Institutional Review Board of the Hospital Authority HK West Cluster (UW12-356) and the Taiwan National Cheng Kung University Hospital Institutional Review Board (B-ER-101-133).

Results

A total of 1 358 284 oral fluoroquinolone prescriptions were observed (Table S4, available as Supplementary data at *JAC* Online). The total number of patients exposed to fluoroquinolones was 150 417 in HK and 416 441 in Taiwan (Figure 1). We identified 469 patients (cases) in HK and 947 cases in Taiwan during the study period. Table 1 shows detailed characteristics of the cases. A total of nine events were identified during the risk period.

For comparisons within individuals adjusted for age, history of diabetes and cataract surgery, no statistically significant association was found between the oral fluoroquinolone and the risk of developing RD in HK, with an adjusted IRR of 0.82 (0.20–3.36), and in Taiwan, with an adjusted IRR of 1.45 (0.68–3.10). In the combined model there was also no significant association found, with an adjusted IRR of 1.26 (0.65–2.47) (Table 1). Sensitivity analyses of the combined model are shown in Table 1. The results from sensitivity analyses were consistent with the original analysis.

The absolute risk of experiencing RD whilst on fluoroquinolone treatment was ∼1.3 per 200 000 fluoroquinolone prescriptions.

Discussion

There were three large pharmacoepidemiological studies investigating the association between oral fluoroquinolones and the development of RD.[3–5] Etminan *et al*.[3] reported that oral fluoroquinolones are associated with a statistically significant risk of developing RD among current fluoroquinolone users [adjusted rate ratio 4.50 (3.56–5.70)]. Kuo *et al*.[4] also found an association with a 90 day follow-up period, but the median interval between use of oral fluoroquinolones and the onset of RD was 35.5 days. In contrast, Pasternak *et al*.[5] found an adjusted rate ratio of 1.29 (0.53–3.13) among current users (i.e. 1–10 days from the

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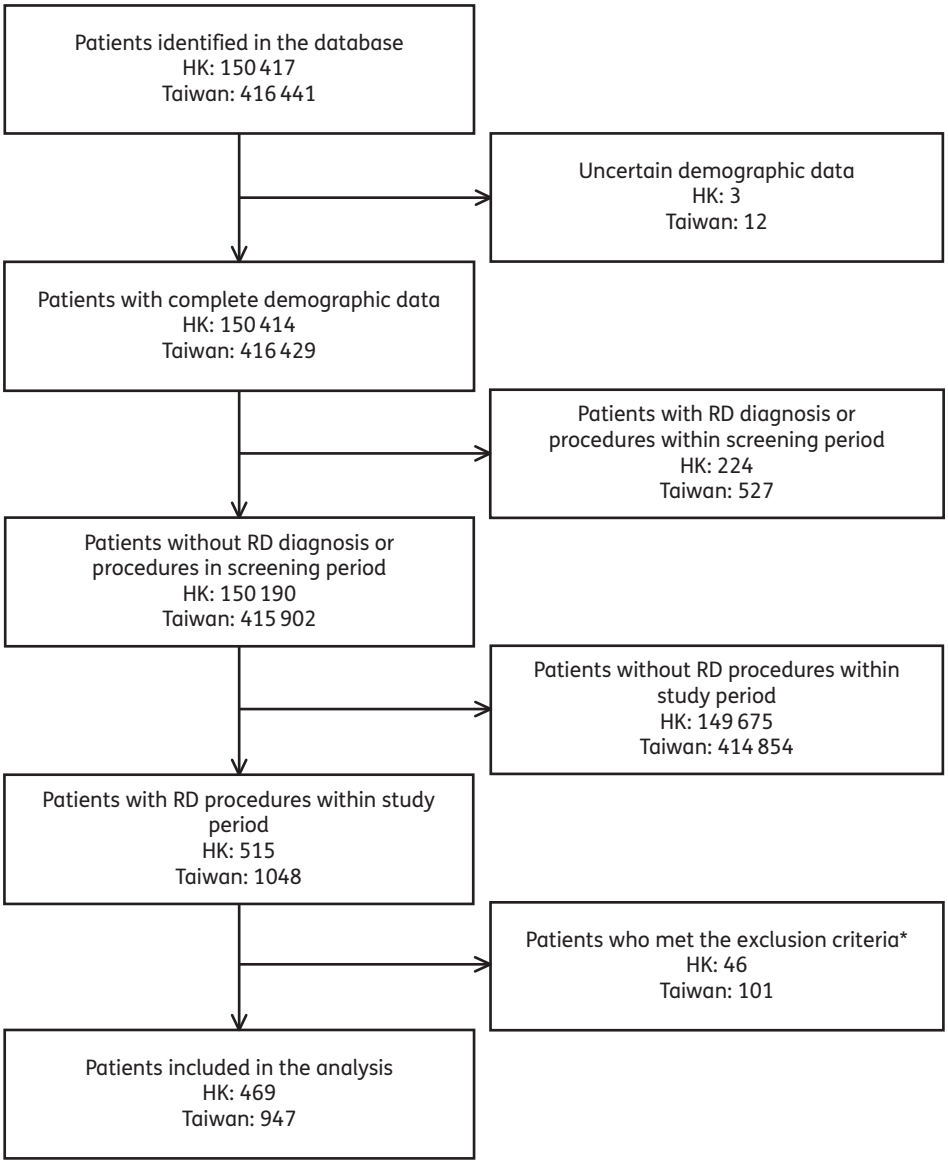

*Head or eye trauma 30 days before the RD procedures; history of endophthalmitis.

Figure 1. Illustration of the inclusion/exclusion of patients.

beginning of fluoroquinolone treatment), which is strikingly similar to the IRR in our study [1.26 (0.65–2.47)]. Both the findings of Pasternak *et al.*[5] and our findings do not support the association of oral fluoroquinolone use and the development of RD.

There are two potential explanations for the apparent difference in findings between our study and that of Etminan *et al.*[3] First, we used the self-controlled case series method, which could control time-invariant characteristics[12] because within-person comparison was performed. Although the study of Etminan *et al.*[3] controlled for the presence or absence of myopia, they did not control for the severity of myopia. Our study design could control for time-invariant intra-patient characteristics, and therefore to some degree we could control for the severity of myopia. Second, the majority of HK and Taiwan citizens are ethnically Chinese. Hence, our study population was genetically different from that of Etminan *et al.*[3] In view of the different incidences of RD among different ethnicities,[13] we are unable to exclude the possibility of genetic influences on the response to fluoroquinolones.

In our study, the ICD-9-CM codes used to identify a treatment procedure for RD were very specific; hence there was no need to use RD codes for validation, as applied by Etminan *et al.*[3] and Pasternak *et al.*[5] We estimated the absolute risk of experiencing RD whilst on fluoroquinolone treatment to be 1.3 per 200 000 prescriptions, whilst the absolute risk in the work of Pasternak *et al.*[5] was also 1.3 per 200 000 prescriptions. Pasternak *et al.*[5] indirectly validated our methods of RD identification.

The absolute increase reported by Etminan *et al.*[3] was 4 per 10 000 person-years with number needed to harm (NNH) 2500. They used person-years for the estimation of risk, which may be

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Table 1. Patient characteristics and model details of self-controlled case series on the association between oral fluoroquinolones and RD

Characteristics	HK ($n=469$)	Taiwan ($n=947$)	Overall ($n=1416$)	
Sex				
male	273	445	718	
female	196	502	698	
Age at baseline (years)				
mean	54.1	48.5	50.4	
SD	13.7	15.7	15.3	
Length of follow-up				
total (patient-years)	5089.6	10139.9	15229.4	
with oral fluoroquinolones	21.0	50.0	71.0	
without oral fluoroquinolones	5068.5	10089.9	15158.4	
Model details	IRR[a,b]	LCL[c]	UCL[d]	*P* value
Area				
HK	0.82	0.20	3.36	0.79
Taiwan	1.45	0.68	3.10	0.34
overall	1.26	0.65	2.47	0.49
Sensitivity analysis				
prescription period extended for 7 days[e]	1.07	0.62	1.87	0.80
prescription period extended for 14 days[e]	1.14	0.72	1.81	0.57
removal of recent and distant use of fluoroquinolones from the control period[f]	1.24	0.63	2.45	0.53
limit the non-exposed period to 365 days before and after the risk period[g]	1.09	0.55	2.18	0.80

[a]Current fluoroquinolone use.
[b]Adjusted IRR, adjusted for age, history of diabetes and cataract surgery.
[c]Lower 95% confidence limit of the IRR.
[d]Upper 95% confidence limit of the IRR.
[e]To address potential issue of non-compliance.
[f]By removing 365 days after the risk period to reduce the potential effects of recent and distant use of fluoroquinolones on the non-exposed period.
[g]By including 365 days before and after the risk period only as the non-exposed period.

difficult to interpret for acute treatments. Assuming that the average length of one fluoroquinolone course is 14 days, at the time based on the estimation of Etminan *et al.*[3] the absolute risk increase would be ∼1 per 65000 prescriptions. In addition, Pasternak *et al.*[5] reported an absolute risk increase of 1.5 per 1000000 treatment episodes (i.e. NNH 670000) for current users. Based on the findings of these studies, the risk of experiencing RD whilst on fluoroquinolone treatment is likely to be minimal.

Our study is subject to limitation. Like other research databases in the UK, such as the Clinical Practice Research Datalink, the CDARS does not contain data from private medical practitioners. Therefore, some patients who might have received an occasional oral fluoroquinolone prescription from a private clinic would not be recorded, and this could potentially lead to an underestimate of exposure time. However, as the NHIRD contains data from both public and private practitioners in Taiwan, this limitation is not applicable to the NHIRD data. The advantage of this study is that combined database analysis was used, which also enhances its generalizability.

In view of the results of this study, current practice for the use of fluoroquinolones should not be altered. We agree with Han and Szabo[14] that RD is not a life-threatening condition compared with uncontrolled infection and the use of fluoroquinolones should not be limited because of its current debatable association with RD.[15] Based on the available literature and the findings of this study, doubt is cast on the association between oral fluoroquinolones and the development of RD.

In conclusion, our study does not support the association between the use of fluoroquinolones and the development of RD. As a result of the findings of this study, together with the available literature, the association between the use of fluoroquinolones and the development of RD is doubtful. Therefore, the use of fluoroquinolones should not be precluded. The impact of different ethnicities on the response to fluoroquinolones should be investigated.

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Transparency declarations

None to declare.

Author contributions

C. S. L. C., K. K. C. M., Y.-H. Y. K. and I. C. K. W. had the original idea for this study and contributed to the development of the idea and the study design. C. S. L. C. reviewed the literature. K. K. C. M., C.-L. C., W. C. Y. L. and E. W. C. undertook the primary analysis. C. S. L. C., K. K. C. M., C.-L. C., E. W. C., W. C. Y. L., V. C. C. C., D. S. H. W., Y.-H. Y. K. and I. C. K. W. contributed to the interpretation of the analysis. C. S. L. C., K. K. C. M. and E. W. C. wrote the first draft of the paper. E. W. C., V. C. C. C., D. S. H. W., Y.-H. Y. K. and I. C. K. W. critically reviewed the paper. E. W. C. and I. C. K. W. provided oversight over all aspects of this project. C. S. L. C., K. K. C. M. and I. C. K. W. are the guarantors. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

Supplementary data

Tables S1 to S4 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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