Fluoroquinolones : quels risques pour l'aorte ?

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DRUGS SAFE R
Drugs Systematized Assessment in real-life Environment

Liens d’intérêt

- Industrie
  - lien d’intérêt indirect : père : consultance laboratoire Intercept
- Institutions
  - ANSM
    - Financement du Centre de Pharmaco-épidémiologie DRUGS-SAFE^{R} et collaborations
    - Financement du CRPV de Bordeaux
    - Expertise et membres de groupes et commissions
  - EMA
    - Expert indépendant pour le *Pharmacovigilance Risk Assessment Committee (2018-21)*

Contexte

- Action des fluoroquinolones sur l’activité des métalloprotéinases
- Augmentation du catabolisme des fibres élastiques
- Fragilisation possible des matrices conjonctives

Contexte

Mise en évidence après identification risque rupture tendineuse

CIPROFLOXACIN AND TENOSYNOVITIS

SIR,—A man aged 67 with a history of severe chronic obstructive airways disease and hypertension had an acute chest infection with a productive cough. At the time he was taking hydrochlorothiazide plus triamterene one tablet daily, nifedipine 20 mg twice daily, theophylline 450 mg twice daily, a salbutamol "spandet" once daily, and inhaled salbutamol, ipratropium, and beclomethasone. While the sputum culture result was awaited he was treated with amoxycillin 500 mg 8-hourly. Culture revealed *Pseudomonas aeruginosa* sensitive to netilmicin, ciprofloxacin, and piperacillin, and he was then put on ciprofloxacin 750 mg twice daily.

3 days after starting treatment with ciprofloxacin, an itch developed over both Achilles tendons. He had scratched the area, which had become excoriated. There was also some thickening and swelling of the Achilles tendons near their insertion. There was no erythema and no oedema of the dorsum of the foot. He had no history of joint conditions and had no oral or ocular symptoms. The pain increased over the next few days, making walking difficult and climbing stairs impossible. He completed 7 days' treatment with ciprofloxacin and his chest symptoms resolved. 2 weeks later the tendon swelling had not diminished and the pain was still affecting his mobility. He was prescribed naproxen and the pain and swelling subsided over the next 4 weeks, though morning stiffness persisted. Complete resolution was noted 6 weeks after ciprofloxacin was discontinued and there has been no recurrence in the 3 months since then.

In this patient the tenosynovitis and the ciprofloxacin therapy coincided. Rechallenge was thought unethical. Animal experiments have shown that quinolones are deposited in immature cartilage and erosive changes have been noted,[1] but a study of adults given nalidixic acid in childhood revealed no evidence of arthritis.[2] By November, 1987, fourteen instances of musculoskeletal disorders associated with ciprofloxacin had been reported to the Committee on Safety of Medicines (ten arthralgia, two arthopathy, one muscle cramps/spasm, one tendon rupture). Pefloxacin, another 4-quinolone, has been marketed in France since 1985 and a post-marketing survey from March, 1985, to March, 1987, revealed 63 spontaneous reports of "arthralgia, arthromyalgia, myalgia and tendinitis" from an estimated 71 428 cases treated (data courtesy of Dr B. L. Prieur, Rhone-Poulenc Santé).

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1. Schluter G. Ciprofloxacin: review of potential toxicologic effects. *Am J Med* 1987; **82** (suppl 4A). 91–93.
2. Schaad UB, Wedgwood-Krucko J. Nalidixic acid in children: Retrospective matched controlled study for cartilage toxicity. *Infection* 1987; **15**: 165–68.

Lancet 1988
2(8616):900

Contexte

Mise en évidence après identification risque rupture tendineuse

Case Reports › Rev Rhum Mal Osteoartic. 1992 Apr;59(4):297-8.

[Tendon rupture and fluoro-quinolones: an undesirable effect of drug selection]

[Article in French]

A Chaslerie, B Bannwarth, J M Landreau, L Yver, B Begaud

PMID: 1496284

Case Reports › Ann Med Interne (Paris). 1993;144(7):493-4.

[Tendinopathy caused by ciprofloxacin with possible partial rupture of Achilles tendon]

[Article in French]

I Boulay, D Farge, A Haddad, P Bourrier, B Chanu, J Rouffy

Contexte

Mise en évidence après identification risque rupture tendineuse

ARTHRITIS & RHEUMATISM
Vol. 46, No. 11, November 2002, pp 3034–3040
DOI 10.1002/art.10617

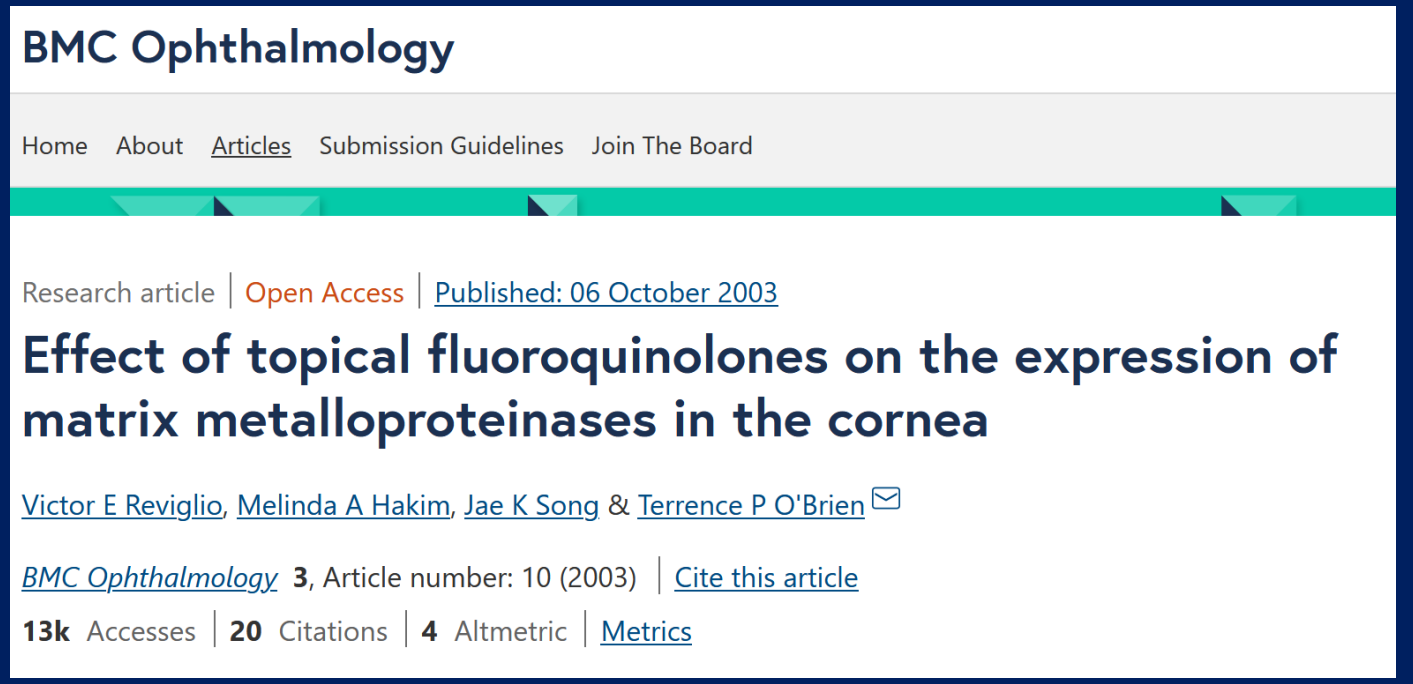
Ciprofloxacin Enhances the Stimulation of Matrix Metalloproteinase 3 Expression by Interleukin-1β in Human Tendon-Derived Cells

A Potential Mechanism of Fluoroquinolone-Induced Tendinopathy

Anthony N. Corps,[1] Rebecca L. Harrall,[1] Valerie A. Curry,[1] Steven A. Fenwick,[2] Brian L. Hazleman,[1] and Graham P. Riley[1]

Contexte

- Mise en évidence après identification risque rupture tendineuse
- Et extension de la problématique



BMC Ophthalmology

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Research article | Open Access | Published: 06 October 2003

Effect of topical fluoroquinolones on the expression of matrix metalloproteinases in the cornea

Victor E Reviglio, Melinda A Hakim, Jae K Song & Terrence P O'Brien

BMC Ophthalmology **3**, Article number: 10 (2003) | Cite this article

13k Accesses | **20** Citations | **4** Altmetric | Metrics

Contexte

Si ce n’est pas que tendineux

Case Reports > Bull Soc Ophtalmol Fr. Aug-Sep 1983;83(8-9):1019-21.

[Serous macular detachment and treatment with flumequine (Apurone = urinary antibacterial). Apropos of 2 cases]

[Article in French]

D Sirbat, E Saudax, B Hurault de Ligny, E Hachet, P Abellan, J L George

Oral Fluoroquinolones and the Risk of Retinal Detachment

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Farzin Forooghian, MD, MSc, FRCSC
James M. Brophy, MD, PhD, FRCPC
Steven T. Bird, PharmD
David Maberley, MD, MSc, FRCSC

FLUOROQUINOLONES ARE ONE OF the most commonly prescribed classes of antibiotics. Their broad-spectrum antibacterial coverage and high-tissue distribution provide potency for a wide variety of community-acquired infections. Although fluoroquinolones are generally well tolerated, they have been associated with a wide array of adverse events such as dysglycemia,[1] cardiac arrhythmia,[2] and neuropsychiatric events.[3] Fluoroquinolones also have been linked to several forms of ocular toxicity such as corneal perforations,[4] optic neuropathy,[5] and retinal hemorrhages.[6] In 2011, the label for gemifloxacin was updated to include hemorrhage,[6] which includes retinal hemorrhage that was reported during postmarketing surveillance. A class-

Context Fluoroquinolones are commonly prescribed classes of antibiotics. Despite numerous case reports of ocular toxicity, a pharmacoepidemiological study of their ocular safety, particularly retinal detachment, has not been performed.

Objective To examine the association between use of oral fluoroquinolones and the risk of developing a retinal detachment.

Design, Setting, and Patients Nested case-control study of a cohort of patients in British Columbia, Canada, who had visited an ophthalmologist between January 2000 and December 2007. Retinal detachment cases were defined as a procedure code for retinal repair surgery within 14 days of a physician service code. Ten controls were selected for each case using risk-set sampling, matching on age and the month and year of cohort entry.

Main Outcome Measure The association between retinal detachment and current, recent, or past use of an oral fluoroquinolone.

Results From a cohort of 989 591 patients, 4384 cases of retinal detachment and 43 840 controls were identified. Current use of fluoroquinolones was associated with a higher risk of developing a retinal detachment (3.3% of cases vs 0.6% of controls; adjusted rate ratio [ARR], 4.50 [95% CI, 3.56-5.70]). Neither recent use (0.3% of cases vs 0.2% of controls; ARR, 0.92 [95% CI, 0.45-1.87]) nor past use (6.6% of cases vs 6.1% of controls; ARR, 1.03 [95% CI, 0.89-1.19]) was associated with a retinal detachment. The absolute increase in the risk of a retinal detachment was 4 per 10 000 person-years (number needed to harm=2500 computed for any use of fluoroquinolones). There was no evidence of an association between development of a retinal detachment and β-lactam antibiotics (ARR, 0.74 [95% CI, 0.35-1.57]) or short-acting β-agonists (ARR, 0.95 [95% CI, 0.68-1.33]).

Conclusion Patients taking oral fluoroquinolones were at a higher risk of developing a retinal detachment compared with nonusers, although the absolute risk for this condition was small.

JAMA. 2012;307(13):1414-1419 www.jama.com

Contexte

Mais pas totalement concordant

Association Between Oral Fluoroquinolone Use and Retinal Detachment

Fanny Raguideau, PharmD; Magali Lemaitre, PhD; Rosemary Dray-Spira, MD, PhD; Mahmoud Zureik, MD, PhD

DESIGN, SETTING, AND PARTICIPANTS This case-crossover study included 27 540 adults with RD from French health care databases from July 1, 2010, through December 31, 2013. Patients with a history of RD or retinal break, endophthalmitis, intravitreal injection, choroidal retinal vitreal biopsy, and human immunodeficiency virus infection or those hospitalized within 6 months of RD were excluded. The risk period of primary interest was current use, defined as exposure to fluoroquinolones within 10 days immediately before RD surgery, according to previous findings. Oral fluoroquinolone use was assumed to start on the day the prescription was dispensed.

MAIN OUTCOMES AND MEASURES Exposure to fluoroquinolones during the risk period (1-10 days) compared with the control period (61-180 days). The association was also assessed regarding use in the recent (11-30 days) and past (31-60 days) intermediate risk period, type of fluoroquinolone, and type of RD.

RESULTS Of the 27 540 eligible patients (57% men; mean [SD] age, 61.5 [13.6] years), 663 patients with RD were exposed to fluoroquinolones during the observation period, corresponding to 80 cases exposed during the 10-day risk period (≤10 days before RD) and 583 cases exposed during the control period (61-180 days). We found a significant increased risk for RD during the 10-day period after the dispensing of oral fluoroquinolones, with an adjusted odds ratio of 1.46 (95% CI, 1.15-1.87). The risk was significantly increased for rhegmatogenous and exudative RD, with adjusted odds ratios of 1.41 (95% CI, 1.04-1.92) and 2.57 (95% CI, 1.46-4.53), respectively. Recent and past use of fluoroquinolones were not associated with a higher risk for RD, with adjusted odds ratios of 0.94 (95% CI, 0.78-1.14) and 1.06 (95% CI, 0.91-1.24), respectively.

CONCLUSIONS AND RELEVANCE Current oral fluoroquinolone use was associated with an increased risk for RD, including the rhegmatogenous and exudative types. These findings, along with the available literature, suggest an association between fluoroquinolone use and the risk for RD. The nature of this association should be further investigated in future studies.

Association Between Oral Fluoroquinolone Use and Retinal Detachment

Björn Pasternak, MD, PhD; Henrik Svanström, MSc; Mads Melbye, MD, DrMedSci; Anders Hviid, MSc, DrMedSci

DESIGN, SETTING, AND PARTICIPANTS A nationwide, register-based cohort study in Denmark from 1997 through 2011, using linked data on participant characteristics, filled prescriptions, and cases of retinal detachment with surgical treatment (scleral buckling, vitrectomy, or pneumatic retinopexy). The cohort included 748 792 episodes of fluoroquinolone use (660 572 [88%] ciprofloxacin) and 5 520 446 control episodes of nonuse.

MAIN OUTCOMES AND MEASURES Poisson regression was used to estimate rate ratios (RRs) for incident retinal detachment, adjusting for a propensity score that included a total of 21 variables. The risk windows were classified as current use (days 1-10 from start of treatment), recent use (days 11-30), past use (days 31-60), and distant use (days 61-180).

RESULTS A total of 566 cases of retinal detachment occurred, of which 465 (82%) were rhegmatogenous detachments; 72 in fluoroquinolone users and 494 in control nonusers. The crude incidence rate was 25.3 cases per 100 000 person-years in current users, 18.9 in recent users, 26.8 in past users, and 24.8 in distant users compared with 19.0 in nonusers. Compared with nonuse, fluoroquinolone use was not associated with a significantly increased risk of retinal detachment: the adjusted RRs were 1.29 (95% CI, 0.53 to 3.13) for current use; 0.97 (95% CI, 0.46 to 2.05) for recent use; 1.37 (95% CI, 0.80 to 2.35) for past use; and 1.27 (95% CI, 0.93 to 1.75) for distant use. The absolute risk difference, estimated as the adjusted number of retinal detachment cases per 1 000 000 treatment episodes, was 1.5 (95% CI, −2.4 to 11.1) for current use.

CONCLUSIONS AND RELEVANCE In this cohort study based on the general Danish population, oral fluoroquinolone use was not associated with increased risk of retinal detachment. Given its limited power, this study can only rule out more than a 3-fold increase in the relative risk associated with current fluoroquinolone use; however, any differences in absolute risk are likely to be of minor, if any, clinical significance.

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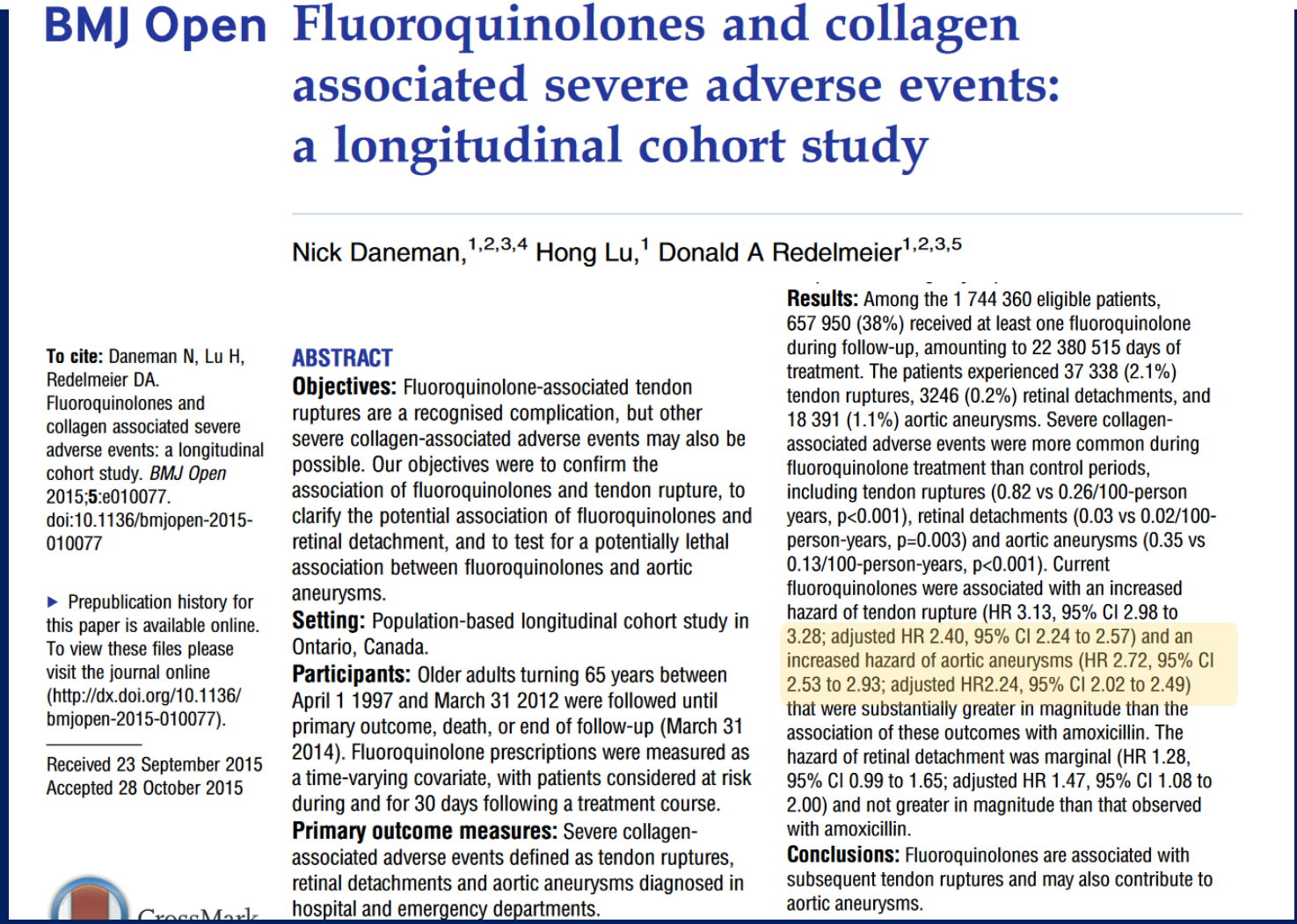
Contexte

Des approches plus larges



BMJ Open

Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study

Nick Daneman,[1,2,3,4] Hong Lu,[1] Donald A Redelmeier[1,2,3,5]

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► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2015-010077).

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Accepted 28 October 2015

ABSTRACT

Objectives: Fluoroquinolone-associated tendon ruptures are a recognised complication, but other severe collagen-associated adverse events may also be possible. Our objectives were to confirm the association of fluoroquinolones and tendon rupture, to clarify the potential association of fluoroquinolones and retinal detachment, and to test for a potentially lethal association between fluoroquinolones and aortic aneurysms.

Setting: Population-based longitudinal cohort study in Ontario, Canada.

Participants: Older adults turning 65 years between April 1 1997 and March 31 2012 were followed until primary outcome, death, or end of follow-up (March 31 2014). Fluoroquinolone prescriptions were measured as a time-varying covariate, with patients considered at risk during and for 30 days following a treatment course.

Primary outcome measures: Severe collagen-associated adverse events defined as tendon ruptures, retinal detachments and aortic aneurysms diagnosed in hospital and emergency departments.

Results: Among the 1 744 360 eligible patients, 657 950 (38%) received at least one fluoroquinolone during follow-up, amounting to 22 380 515 days of treatment. The patients experienced 37 338 (2.1%) tendon ruptures, 3246 (0.2%) retinal detachments, and 18 391 (1.1%) aortic aneurysms. Severe collagen-associated adverse events were more common during fluoroquinolone treatment than control periods, including tendon ruptures (0.82 vs 0.26/100-person years, p<0.001), retinal detachments (0.03 vs 0.02/100-person-years, p=0.003) and aortic aneurysms (0.35 vs 0.13/100-person-years, p<0.001). Current fluoroquinolones were associated with an increased hazard of tendon rupture (HR 3.13, 95% CI 2.98 to 3.28; adjusted HR 2.40, 95% CI 2.24 to 2.57) and an increased hazard of aortic aneurysms (HR 2.72, 95% CI 2.53 to 2.93; adjusted HR2.24, 95% CI 2.02 to 2.49) that were substantially greater in magnitude than the association of these outcomes with amoxicillin. The hazard of retinal detachment was marginal (HR 1.28, 95% CI 0.99 to 1.65; adjusted HR 1.47, 95% CI 1.08 to 2.00) and not greater in magnitude than that observed with amoxicillin.

Conclusions: Fluoroquinolones are associated with subsequent tendon ruptures and may also contribute to aortic aneurysms.

Fluoroquinolones et risque aortique

2018

FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients

FDA Drug Safety Communication

This information is an update to the FDA announcement issued on May 10, 2017

Safety Announcement

[12-20-2018] A U.S. Food and Drug Administration (FDA) review found that fluoroquinolone antibiotics can increase the occurrence of rare but serious events of ruptures or tears in the main artery of the body, called the aorta. These tears, called aortic dissections, or ruptures of an aortic aneurysm can lead to dangerous bleeding or even death. They can occur with fluoroquinolones for systemic use given by mouth or through an injection.

2018

We reviewed cases reported to FDA* and four published observational studies[1,2,3,4] that showed an increased risk of aortic aneurysm or dissection associated with fluoroquinolone use (see Data Summary). How some of the studies were designed or carried out, and the ways the data were analyzed could affect the study findings; however, taken together, the results of all four studies provide consistent evidence of an association between fluoroquinolone use and aortic aneurysm or dissection. The underlying mechanism for this risk cannot be determined from these studies, and the background risk of aortic aneurysm can vary depending on the population. The background risk has been estimated from nine aortic aneurysm events per 100,000 people per year in the general population to 300 aortic aneurysm events per 100,000 people per year in individuals at highest risk. Because multiple studies showed higher rates of about twice the risk of aortic aneurysm rupture and dissection in those taking fluoroquinolones, FDA determined the warnings were warranted to alert health care professionals and patients.

We communicated safety information associated with fluoroquinolones in July 2018 (significant decreases in blood sugar and certain mental health side effects), July 2016 (disabling side effects of the tendons, muscles, joints, nerves, and central nervous system), May 2016 (restricting use for certain uncomplicated infections), August 2013 (peripheral neuropathy), and July 2008 (tendinitis and tendon rupture).

2015-2018

- *Four published observational studies*

1. Daneman et al.; Lee et al.; Pasternak et al.; Lee et al. (2)

Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone

Chien-Chang Lee, MD, ScD; Meng-tse Gabriel Lee, PhD; Yueh-Sheng Chen, MD; Shih-Hao Lee, MA; Yih-Sharng Chen, MD, PhD; Shyr-Chyr Chen, MD, MBA; Shan-Chwen Chang, MD, PhD

DESIGN, SETTING, AND PARTICIPANTS We conducted a nested case-control analysis of 1477 case patients and 147 700 matched control cases from Taiwan's National Health Insurance Research Database (NHIRD) from among 1 million individuals longitudinally observed from January 2000 through December 2011. Cases patients were defined as those hospitalized for aortic aneurysm or dissection. One hundred control patients were matched for each case based on age and sex.

EXPOSURES Current, past, or any prior-year use of fluoroquinolone. Current use was defined as a filled fluoroquinolone prescription within 60 days of the aortic aneurysm or dissection; past use refers to a filled fluoroquinolone prescription between 61 and 365 days prior to the aortic aneurysm; and any prior-year use refers to having a fluoroquinolone prescription filled for 3 or more days any time during the 1-year period before the aortic aneurysm or dissection.

MAIN OUTCOMES AND MEASURES Risk of developing aortic aneurysm or dissection.

RESULTS A total of 1477 individuals who experienced aortic aneurysm or dissection were matched to 147 700 controls. After propensity score adjustment, current use of fluoroquinolones was found to be associated with increased risk for aortic aneurysm or dissection (rate ratio [RR], 2.43; 95% CI, 1.83-3.22), as was past use, although this risk was attenuated (RR, 1.48; 95% CI, 1.18-1.86). Sensitivity analysis focusing on aortic aneurysm and dissection requiring surgery also demonstrated an increased risk associated with current fluoroquinolone use, but the increase was not statistically significant (propensity score–adjusted RR, 2.15; 95% CI, 0.97-4.60).

CONCLUSIONS AND RELEVANCE Use of fluoroquinolones was associated with an increased risk of aortic aneurysm and dissection. While these were rare events, physicians should be aware of this possible drug safety risk associated with fluoroquinolone therapy.

Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study

Björn Pasternak,[1,2] Malin Inghammar,[2,3] Henrik Svanström[2]

ABSTRACT

OBJECTIVE
To investigate whether oral fluoroquinolone use is associated with an increased risk of aortic aneurysm or dissection.

DESIGN
Nationwide historical cohort study using linked register data on patient characteristics, filled prescriptions, and cases of aortic aneurysm or dissection.

SETTING
Sweden, July 2006 to December 2013.

PARTICIPANTS
360 088 treatment episodes of fluoroquinolone use (78%ciprofloxacin) and propensity score matched comparator episodes of amoxicillin use (n=360 088).

MAIN OUTCOME MEASURES
Cox regression was used to estimate hazard ratios for a first diagnosis of aortic aneurysm or dissection, defined as admission to hospital or emergency department for, or death due to, aortic aneurysm or dissection, within 60 days from start of treatment.

RESULTS
Within the 60 day risk period, the rate of aortic aneurysm or dissection was 1.2 cases per 1000 person years among fluoroquinolone users and 0.7 cases per 1000 person years among amoxicillin users. Fluoroquinolone use was associated with an increased risk of aortic aneurysm or dissection (hazard ratio 1.66 (95% confidence interval 1.12 to 2.46)), with an estimated absolute difference of 82 (95% confidence interval 15 to 181) cases of aortic aneurysm or dissection by 60 days per 1 million treatment episodes. In a secondary analysis, the hazard ratio for the association with fluoroquinolone use was 1.90 (1.22 to 2.96) for aortic aneurysm and 0.93 (0.38 to 2.29) for aortic dissection.

CONCLUSIONS
In a propensity score matched cohort, fluoroquinolone use was associated with an increased risk of aortic aneurysm or dissection. This association appeared to be largely driven by aortic aneurysm.

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Oral Fluoroquinolone and the Risk of Aortic Dissection

Chien-Chang Lee, MD, ScD,[a] Meng-tse Gabriel Lee, PhD,[a] Ronan Hsieh, MD,[b] Lorenzo Porta, MD,[c] Wan-Chien Lee, MS,[a] Si-Huei Lee, MD,[d,e] Shy-Shin Chang, MD, PhD[f]

ABSTRACT

BACKGROUND Previous studies raised safety concerns on the association between fluoroquinolone treatment and serious collagen disorders, aortic aneurysm and dissection (AA/AD).

OBJECTIVES This study sought to evaluate this association via a case-crossover analysis in a large national administrative database.

METHODS A case-crossover design was used to compare the distributions of fluoroquinolone exposure for the same patient across a 60-day period before the AA/AD event (hazard period) and 1 randomly selected 60-day period (referent period) between 60 to 180 days before the AA/AD events. In the sensitivity analysis, the authors repeated the main analysis using a 1:5 ratio of hazard period to referent period, to adjust for the effect of time-variant confounders. A disease-risk score-matched time control analysis was performed to investigate the potential time-trend bias. The risks were calculated by a conditional logistic regression model.

RESULTS A total of 1,213 hospitalized AA/AD patients were identified between 2001 and 2011. In the main case-crossover analysis, exposure to fluoroquinolone was more frequent during the hazard periods than during the referent periods (1.6% vs. 0.6%; odds ratio [OR]: 2.71; 95% confidence interval [CI]: 1.14 to 6.46). In the sensitivity analysis, after adjustment for infections and co-medications, the risk remains significant (OR: 2.05; 95% CI: 1.13 to 3.71). An increased risk of AA/AD was observed for prolonged exposure to fluoroquinolones (OR: 2.41 for 3- to 14-day exposure; OR: 2.83 for >14-day exposure). Susceptible period analysis revealed that the use of fluoroquinolone within 60 days was associated with the highest risk of AA/AD. In the case-time-control analysis, there was no evidence that the observed association is due to temporal changes in fluoroquinolone exposure.

CONCLUSIONS Exposure to fluoroquinolone was substantially associated with AA/AD. This risk was modified by the duration of fluoroquinolone use and the length of the hazard period. (J Am Coll Cardiol 2018;72:1369-78)

Interrogations

- Plausibilité biologique : OUI
- Cohérence de la littérature : OUI

Interrogations

- Plausibilité biologique : OUI
- Cohérence de la littérature : OUI
- MAIS études observationnelles
  - Biais potentiels : d'indication ? de confusion ?
  - Peut-on vraiment avoir confiance dans la *real-world evidence*
- Paradoxe des décisions régulatoires
  - Crédibilité limitée accordée aux études observationnelles
  - Mais majorité des décisions de retrait encore basées sur des séries de cas
- Et toujours : « peut-on attribuer au médicament quand les patients présentaient d'autres facteurs de risque ? »

Depuis 2018

Depuis 2018

Ciprofloxacin accelerates aortic enlargement and promotes dissection and rupture in Marfan mice

Scott A. LeMaire, MD,[a,b,c] Lin Zhang, MS,[a,b] Nicholas S. Zhang,[a] Wei Luo, MD,[a,b] James P. Barrish, BS, MBA,[d] Qianzi Zhang, MPH,[e] Joseph S. Coselli, MD,[a,b,c] and Ying H. Shen, MD, PhD[a,b,c]

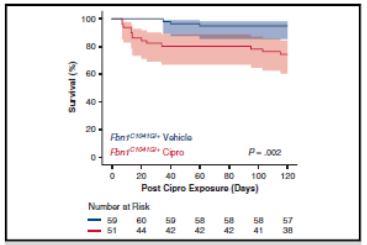
ABSTRACT

Objective: Aortic aneurysm and dissection are major life-threatening complications of Marfan syndrome. Avoiding factors that promote aortic damage is critical in managing the care of these patients. Findings from clinical and animal studies raise concerns regarding fluoroquinolone use in patients at risk for aortic aneurysm and dissection. Therefore, we examined the effects of ciprofloxacin on aortic aneurysm and dissection development in Marfan mice.

Methods: Eight-week-old Marfan mice ($Fbn1^{C1041G/+}$) were given ciprofloxacin (100 mg/kg/d; n = 51) or vehicle (n = 59) for 4 weeks. Mice were monitored for 16 weeks. Aortic diameters were measured by using ultrasonography, and aortic structure was examined by using histopathologic and immunostaining analyses.

Results: Vehicle-treated $Fbn1^{C1041G/+}$ mice showed progressive aortic enlargement, with aortic rupture occurring in 5% of these mice. Compared with vehicle-treated $Fbn1^{C1041G/+}$ mice, ciprofloxacin-treated $Fbn1^{C1041G/+}$ mice showed accelerated aortic enlargement ($P = .01$) and increased incidences of aortic dissection (25% vs 47%, $P = .03$) and rupture (5% vs 25%, $P = .005$). Furthermore, ciprofloxacin-treated $Fbn1^{C1041G/+}$ mice had higher levels of elastic fiber fragmentation, matrix metalloproteinase expression, and apoptosis than did vehicle-treated $Fbn1^{C1041G/+}$ mice.

Conclusions: Ciprofloxacin accelerates aortic root enlargement and increases the incidence of aortic dissection and rupture in Marfan mice, partially by suppressing lysyl oxidase expression and further compromising the inherited defect in aortic elastic fibers. Our findings substantiate that ciprofloxacin should be avoided in patients with Marfan syndrome. (J Thorac Cardiovasc Surg 2020;■:1-12)



Significantly increased premature death in Marfan mice that received ciprofloxacin.

CENTRAL MESSAGE

Ciprofloxacin accelerates aortic root enlargement and aortic dissection and rupture in Marfan mice. These findings suggest that ciprofloxacin should be avoided in patients with Marfan syndrome.

PERSPECTIVE

Aortic aneurysm and dissection are major life-threatening manifestations of Marfan syndrome

Effect of Ciprofloxacin on Susceptibility to Aortic Dissection and Rupture in Mice

Scott A. LeMaire, MD[1,2,3]; Lin Zhang, MS[1,2]; Wei Luo, MD[1,2]; et al

» Author Affiliations | Article Information

JAMA Surg. 2018;153(9):e181804. doi:10.1001/jamasurg.2018.1804

mice. Compared with aortic tissues from challenged control mice, those from challenged mice that received ciprofloxacin showed decreased expression of lysyl oxidase, an enzyme that is critical in the assembly and stabilization of elastic fibers and collagen. These aortas also showed increased matrix metalloproteinase levels and activity, elastic fiber fragmentation, and aortic cell injury. In cultured smooth muscle cells, ciprofloxacin treatment significantly reduced lysyl oxidase expression and activity, increased matrix metalloproteinase expression and activity, suppressed cell proliferation, and induced cell death. Furthermore, ciprofloxacin—a DNA topoisomerase inhibitor—caused nuclear and mitochondrial DNA damage and the release of DNA into the cytosol, subsequently inducing mitochondrial dysfunction, reactive oxygen species production, and activation of the cytosolic DNA sensor STING, which we further showed was involved in the suppression of lysyl oxidase expression and induction of matrix metalloproteinase expression.

Conclusions and Relevance Ciprofloxacin increases susceptibility to aortic dissection and rupture in a mouse model of moderate, sporadic AAD. Ciprofloxacin should be used with caution in patients with aortic dilatation, as well as in those at high risk for AAD.

Depuis 2018

BMC Pediatrics

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Research article | Open Access | Published: 11 February 2020

The incidence of collagen-associated adverse events in pediatric population with the use of fluoroquinolones: a nationwide cohort study in Taiwan

Pei-Han Yu, Chih-Fen Hu, Jen-Wei Liu, Chi-Hsiang Chung, Yong-Chen Chen, Chien-An Sun & Wu-Chien Chien

Pas d'augmentation de risque

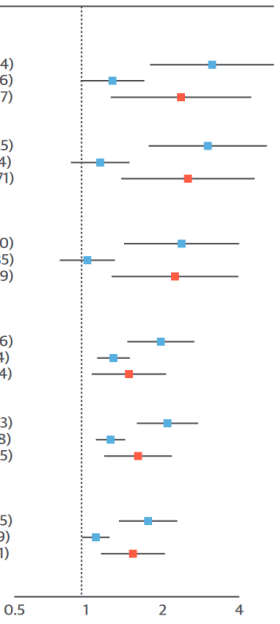
BMC Pediatrics **20**, Article number: 64 (2020) | Cite this article

Depuis 2018

Short-Term Risk of Aortoiliac Aneurysm or Dissection Associated With Fluoroquinolone Use

Sandy Maumus-Robert PharmD, PhD, Xavier Bérard MD, PhD, Yohann Mansiaux PhD, Pascale Tubert-Bitter PhD, Stéphanie Debette MD, PhD, Antoine Pariente MD, PhD

	Subjects	Cases	Exposed Cases Risk Window	Exposed Cases Control Window	Odds Ratio 95% CI
Ruptured Aneurysm or Dissection					
30-Day Risk Window					
CTC Fluoroquinolone	946	86	36	23	3.23 (1.85-5.64)
CTC Amoxicillin	3,476	316	82	161	1.32 (0.99-1.76)
Ratio					2.44 (1.31-4.57)
60-Day Risk Window					
CTC Fluoroquinolone	946	86	48	23	3.08 (1.81-5.25)
CTC Amoxicillin	3,476	316	132	161	1.18 (0.91-1.54)
Ratio					2.60 (1.44-4.71)
90-Day Risk Window					
CTC Fluoroquinolone	946	86	65	23	2.45 (1.46-4.10)
CTC Amoxicillin	3,476	316	180	161	1.06 (0.83-1.35)
Ratio					2.32 (1.31-4.09)
Ruptured or Unruptured Aneurysm or Dissection					
30-Day Risk Window					
CTC Fluoroquinolone	3,245	295	92	101	2.04 (1.51-2.76)
CTC Amoxicillin	13,750	1,250	311	620	1.33 (1.15-1.54)
Ratio					1.53 (1.09-2.14)
60-Day Risk Window					
CTC Fluoroquinolone	3,245	295	153	101	2.15 (1.64-2.83)
CTC Amoxicillin	13,750	1,250	532	620	1.29 (1.14-1.48)
Ratio					1.66 (1.23-2.25)
90-Day Risk Window					
CTC Fluoroquinolone	3,245	295	202	101	1.81 (1.40-2.35)
CTC Amoxicillin	13,750	1,250	722	620	1.14 (1.01-1.29)
Ratio					1.59 (1.19-2.11)



Odds ratio (OR) for fluoroquinolone use (and for amoxicillin use) in the 30 days prior to outcome occurrence, and ratio of OR for fluoroquinolones to OR for amoxicillin. CI = confidence interval; CTC = case-time-control.

PDS Pharmacoepidemiology & Drug Safety
ispe Official Journal of the International Society for Pharmacoepidemiology

BRIEF REPORT

A quantitative bias analysis of the confounding effects due to smoking on the association between fluoroquinolones and risk of aortic aneurysm

Mingfeng Zhang, Monique Falconer, Lockwood Taylor

Results

For an apparent relative risk of 2, the *E*-value is 3.41, suggesting that smoking needs to be associated with both FQ and AA with a minimal magnitude of 3.41 to explain away the observed twofold FQ-AA association. The array approach found that the prevalence of smoking among FQ users would need to be at least 2.9 times higher (43%) than the nonusers (15%), assuming smoking increases the risk of AA by 7.6-fold. A numerical comparison demonstrated that the results from the rule-out approach are similar to that of the *E*-value approach when there is a lack of prior data on bias parameters.

Conclusions

Using three different approaches, we demonstrate that the strengths of association between smoking and both FQ and AA need to be unusually strong to fully account for the twofold increased risk between FQ and AA. Therefore, it is unlikely that smoking alone would explain away the association reported in the epidemiologic studies.

Depuis 2018

Association of Fluoroquinolones With the Risk of Aortic Aneurysm or Aortic Dissection

Chandrasekar Gopalakrishnan, MD, MPH[1]; Katsiaryna Bykov, PharmD, ScD[1]; Michael A. Fischer, MD, MS[1]; et al

» Author Affiliations | Article Information

YES, but not always

JAMA Intern Med. 2020;180(12):1596-1605. doi:10.1001/jamainternmed.2020.4199

Conclusions and Relevance The findings of this nationwide cohort study of adults with pneumonia or UTI suggest an increased relative rate of AA/AD associated with fluoroquinolones within the pneumonia cohort but not within the UTI cohort. In both cohorts, the absolute rate of AA/AD appeared to be low (<0.1%). The increased relative rate observed in the pneumonia cohort may be due to residual confounding or surveillance bias.

Association of Infections and Use of Fluoroquinolones With the Risk of Aortic Aneurysm or Aortic Dissection

Yaa-Hui Dong, PhD[1,2]; Chia-Hsuin Chang, MD, ScD[3,4,5]; Jiun-Ling Wang, MD[6,7]; et al

» Author Affiliations | Article Information

NO

JAMA Intern Med. 2020;180(12):1587-1595. doi:10.1001/jamainternmed.2020.4192

Results A total of 28 948 cases and 289 480 matched controls were included (71.37% male; mean [SD] age, 67.41 [15.03] years). Among these, the adjusted OR of AA/AD for any indicated infections was 1.73 (95% CI, 1.66-1.81). Septicemia (OR, 3.16; 95% CI, 2.63-3.78) and intra-abdominal infection (OR, 2.99; 95% CI, 2.45-3.65) had the highest increased risk. Fluoroquinolones were not associated with an increased AA/AD risk when compared with combined amoxicillin-clavulanate or combined ampicillin-sulbactam (OR, 1.01; 95% CI, 0.82-1.24) or with extended-spectrum cephalosporins (OR, 0.88; 95% CI, 0.70-1.11) among patients with indicated infections. The null findings for fluoroquinolone use remained robust in different subgroup and sensitivity analyses.

Conclusions and Relevance These results highlight the importance of accounting for coexisting infections while examining the safety of antibiotics using real-world data; the findings suggest that concerns about AA/AD risk should not deter fluoroquinolone use for patients with indicated infections.

Depuis 2018

Association of Fluoroquinolones With the Risk of Aortic Aneurysm or Aortic Dissection

Chandrasekar Gopalakrishnan, MD, MPH[1]; Katsiaryna Bykov, PharmD, ScD[1]; Michael A. Fischer, MD, MS[1]; et al

» Author Affiliations | Article Information

YES

JAMA Intern Med. 2020;180(12):1596-1605. doi:10.1001/jamainternmed.2020.4199

Conclusions and Relevance The findings of this nationwide cohort study of adults with pneumonia or UTI suggest an increased relative rate of AA/AD associated with fluoroquinolones within the pneumonia cohort but not within the UTI cohort. In both cohorts, the absolute rate of AA/AD appeared to be low (<0.1%). The increased relative rate observed in the pneumonia cohort may be due to residual confounding or surveillance bias.

Association of Infections and Use of Fluoroquinolones With the Risk of

Findings of Positive Control Outcomes

Fluoroquinolone use was associated with a numerically increased risk of Achilles tendon rupture vs amoxicillin-clavulanate or ampicillin-sulbactam (OR, 1.56; 95% CI, 0.56-4.36) or vs extended-spectrum cephalosporins (OR, 2.33; 95% CI, 0.60-9.07) in adult patients. The limited sample size precluded an analysis restricted to older patients. Fluoroquinolone use was also associated with a higher risk of any type of tendon rupture compared with either amoxicillin-clavulanate or ampicillin-sulbactam (OR, 1.13; 95% CI, 0.72-1.77) or extended-spectrum cephalosporins (OR, 2.04; 95% CI, 1.08-3.84) in elderly patients (eFigure 11 and eTable 20 in the **Supplement**).

ampicillin-sulbactam (OR, 1.01; 95% CI, 0.82-1.24) or with extended-spectrum cephalosporins (OR, 0.88; 95% CI, 0.70-1.11) among patients with indicated infections. The null findings for fluoroquinolone use remained robust in different subgroup and sensitivity analyses.

Conclusions and Relevance These results highlight the importance of accounting for coexisting infections while examining the safety of antibiotics using real-world data; the findings suggest that concerns about AA/AD risk should not deter fluoroquinolone use for patients with indicated infections.

Depuis 2018

Même force

Prise en compte de l'indication

Même faiblesse

Anévrysmes non rompus

Et résultat différent

JAMA Surg. 2021 Mar; 156(3): 264–272.
Published online 2021 Jan 6. doi: 10.1001/jamasurg.2020.6165: 10.1001/jamasurg.2020.6165

Association of Fluoroquinolone Use With Short-term Risk of Development of Aortic Aneurysm

Emily R. Newton, MD,[1] Adam W. Akerman, PhD,[1] Paula D. Strassle, PhD, MSPH,[1] and Melina R. Kibbe, MD[1,2,3]

Outpatient fill of an oral fluoroquinolone or comparator antibiotic (amoxicillin-clavulanate, azithromycin, cephalexin, clindamycin, and sulfamethoxazole-trimethoprim).

Main Outcomes and Measures

The 90-day incidence of aortic aneurysm and dissection. Inverse probability of treatment weighting in Cox regression was used to estimate the association between fluoroquinolone fill and 90-day aneurysm incidence. Interaction terms were used to assess the association of known risk factors (ie, sex, age, and comorbidities) with aneurysm after fluoroquinolone use. Data analysis was performed March 2019 to May 2020.

Results

Of 47 596 545 prescription fills, 9 053 961 (19%) were fluoroquinolones and 38 542 584 (81%) were comparator antibiotics. The median (interquartile range) age of adults with fluoroquinolone fills was 47 (36-57) years vs 43 (31-54) years with comparator antibiotic fills. Women comprised 61.3% of fluoroquinolone fills and 59.5% of comparator antibiotic fills. Before weighting, the 90-day incidence of newly diagnosed aneurysm was 7.5 cases per 10 000 fills (6752 of 9 053 961) after fluoroquinolones compared with 4.6 cases per 10 000 fills (17 627 of 38 542 584) after comparator antibiotics. After weighting for demographic characteristics and comorbidities, fluoroquinolone fills were associated with increased incidence of aneurysm formation (hazard ratio [HR], 1.20; 95% CI, 1.17-1.24). More specifically, compared with comparator antibiotics, fluoroquinolone fills were associated with increased 90-day incidence of abdominal aortic aneurysm (HR, 1.31; 95% CI, 1.25-1.37), iliac artery aneurysm (HR, 1.60; 95% CI, 1.33-1.91), and other abdominal aneurysm (HR, 1.58; 95% CI, 1.39-1.79), and adults were more likely to undergo aneurysm repair (HR, 1.88; 95% CI, 1.44-2.46). When stratified by age, all adults 35 years or older appeared at increased risk (18-34 years: HR, 0.99 [95% CI, 0.83-1.18]; 35-49 years: HR, 1.18 [95% CI, 1.09-1.28]; 50-64 years: HR, 1.24 [95% CI, 1.19-1.28]; $P = .04$).

Conclusions and Relevance

This study found that fluoroquinolones were associated with increased incidence of aortic aneurysm formation in US adults. This association was consistent across adults aged 35 years or older, sex, and comorbidities, suggesting fluoroquinolone use should be pursued with caution in all adults, not just in high-risk individuals.

Depuis 2018

Risk of aortic aneurysm and dissection following exposure to fluoroquinolones, common antibiotics, and febrile illness using a self-controlled case series study design: Retrospective analyses of three large healthcare databases in the US

Ajit A. Londhe[1¤], Chantal E. Holy[2*], James Weaver[1], Sergio Fonseca[1], Angelina Villasis[1], Daniel Fife[1]

1 Janssen Pharmaceutical Research and Development, LLC, Titusville, NJ, United States of America,
2 Johnson & Johnson, New Brunswick, NJ, United States of America

Design

Retrospective database analysis–SCCS.

Setting

Primary and Secondary Care.

Study population

51,898 patients across 3 US claims databases (IBM® MarketScan® commercial and Medicare databases, Optum Clinformatics).

Exposure

FQ or other common antibiotics or febrile illness.

Outcome

AAD.

Methods

We studied patients with exposures and AAD between 2012 and 2017 in 3 databases. Risk windows were defined as exposure period plus 30 days. Diagnostic analyses included p-value calibration to account for residual error using negative control exposures (NCE), and pre-exposure outcome analyses to evaluate exposure-outcome timing. The measure of association was the incidence rate ratio (IRR) comparing exposed and unexposed time.

Results

Most NCEs produced effect estimates greater than the hypothetical null, indicating positive residual error; calibrated p (Cp) values were therefore used. The IRR following FQ exposure ranged from 1.13 (95% CI: 1.04–1.22 –Cp: 0.503) to 1.63 (95% CI: 1.45–1.84 –Cp: 0.329). An AAD event peak was identified 60 days before first FQ exposure, with IRR increasing between the 60- to 30- and 29- to 1-day pre-exposure periods. It is uncertain how much this pre-exposure AAD event peak reflects confounding versus increased antibiotic use after a surgical correction of AADs.

Conclusion

This study does not confirm prior studies. Using Cp values to account for residual error, the observed FQ-AAD association cannot be interpreted as significant. Additionally, an AAD

Calibration of p values

To estimate residual error in each analysis, 38 exposures known to have no causal association with AAD were identified as negative controls [18]. These included: cyclobenzaprine, tramadol, benzonatate, pseudoephedrine, benzoyl peroxide, clobetasol, phenazopyridine, olopatadine, ascorbic acid, fluocinonide, antipyrine, dicyclomine, cefprozil, magnesium sulfate, terbinafine, terconazole, niacin, diphenoxylate, alendronate, permethrin, cetirizine, eszopiclone, oxybutynin, thiamine, phenobarbital, calcipotriene, sodium phosphate, acetic acid, pyrilamine, glucagon, exenatide, selenium sulfide, penciclovir, methylene blue, ciclesonide, clidinium, rifaximin, and loperamide. These negative control exposures were used to calibrate

Depuis 2018

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 77, NO. 15, 2021

PUBLISHED BY ELSEVIER

Effects of Fluoroquinolones on Outcomes of Patients With Aortic Dissection or Aneurysm

But yes…

Shao-Wei Chen, MD, PhD,[a,b] Yi-Hsin Chan, MD,[c] Victor Chien-Chia Wu, MD,[c] Yu-Ting Cheng, MD,[a] Dong-Yi Chen, MD,[c] Chia-Pin Lin, MD,[c] Kuo-Chun Hung, MD,[c] Shang-Hung Chang, MD, PhD,[b,c] Pao-Hsien Chu, MD,[c] An-Hsun Chou, MD, PhD[d]

BACKGROUND Recent population-based studies have revealed that the use of fluoroquinolones (FQs) is associated with an increased risk of aortic dissection (AD) and aneurysm (AA). However, no evidence is available on whether FQs increase adverse events in patients who had been diagnosed with AD or AA.

OBJECTIVES This study investigated whether the use of FQs increases the risk of aortic-related adverse events and death in this high-risk population.

METHODS A retrospective cohort study was conducted by using the Taiwan National Health Insurance Research Database. A total of 31,570 adult patients who survived after admission for AD or AA between 2001 and 2013 were identified. We divided each calendar year into 6 data units (2 months) for each patient and each year during follow-up. Covariates and exposure of interest (FQs) were reassessed every 2 months. We used another common antibiotic, amoxicillin, as a negative control exposure.

RESULTS Exposure to FQs was associated with a higher risk of all-cause death (adjusted hazard ratio: 1.61; 95% confidence interval: 1.50 to 1.73), aortic death (adjusted hazard ratio: 1.80; 95% confidence interval: 1.50 to 2.15), and later aortic surgery. However, amoxicillin exposure was not significantly associated with risk of any of the outcomes. A subgroup analysis revealed that the effect of FQs was not significantly different between the AD and AA groups.

CONCLUSIONS Relative to amoxicillin use, FQ exposure in patients with AD or AA was associated with a higher risk of adverse outcomes. FQs should not be used by high-risk patients unless no other treatment options are available.
(J Am Coll Cardiol 2021;77:1875–87)

Synthèse : 7 + ; 2 - ; 1 +/-

Auteur	Année	Pays	Schéma	Evénement	Comparateur actif	Indication / Infection	Conclusion
Daneman	2015	CAN	Cohorte 65 ans	Hosp. pour A/D Ao	NON	NON	HR=2,24
Lee	2016	TW	Cas-T nichée	Hosp. pour A/D Ao	NON	NON	OR=2,4
Pasternark	2018	SE	Cohorte*	Hosp. pour A/D Ao	OUI	NON	HR=1,7
Lee	2018	TW	Case Cross-over	Hosp. pour A/D Ao	NON	OUI	OR=2
Maumus-Robert	2019	FR	Case Time-Control	A rompu / D Ao	OUI	NON	ORR = 2,4
Gopala-krishnan	2020	US	Cohorte UTI / pneumonie 50a +	Hosp. pour A/D Ao	OUI	OUI	HR=2,6 vs. AZY dans pneumo HR=1 vs. TMP/SMX dans UTI
Dong	2020	TW	Cas-T nichée	Hosp. pour A/D Ao	OUI	OUI	OR=1
Chen	2021	TW	Cohorte AAD	DC Ao ou chir Ao	OUI	OUI	HR=1,6 chez AAD
Newton	2021	US	Cohorte*	A/D art par loc°	OUI	OUI	HR 1,2 à 1,9
Londhe	2021	US	SCCS	A/D Ao chir ou ER	OUI	NON	NS après correction

Conclusion

- Plausibilité biologique : OUI ; *Animal studies* : OUI
- Cohérence de la littérature : majorité OUI ;  choix de l'événement
- Risque mis en évidence chez sujets à risque

- Certitude du risque
  - mauvaise question : piège de lecture critique d'étude observationnelle
  - bonne question : quel est le plus vraisemblable : causal ou on causal ?

- Quelle serait aujourd'hui votre réponse à la question clinique ?

  Sauf si absolument indispensable, mettriez-vous des FQ chez des patients à risque ?

Conclusion : FDA 2018

"Although the risk of aortic aneurysm or dissection is low, we've observed that patients are twice as likely to experience an aortic aneurysm or dissection when prescribed a fluoroquinolone drug," FDA Commissioner Scott Gottlieb, MD, said in a statement. "For patients who have an aortic aneurysm or are known to be at risk of an aortic aneurysm, we do not believe the benefits outweigh this risk, and alternative treatment should be considered."

Back-up : not all arteries

Risk of Intracranial Aneurysm and Dissection and Fluoroquinolone Use
A Case-Time-Control Study

Pas d'augmentation de risque

Sandy Maumus-Robert, PharmD, PhD; Stéphanie Debette, MD, PhD; Xavier Bérard, MD, PhD; Yohann Mansiaux, PhD; Pascale Tubert-Bitter, PhD; Antoine Pariente, MD, PhD

Background and Purpose—Fluoroquinolone use is associated with an increased risk of aortic aneurysm and dissection. We investigated this risk of arterial wall injury on intracranial arteries, given the similar pathophysiological mechanisms for aneurysm and dissection in both types of arteries.

Methods—A case-time-control study was conducted using French National Insurance databases covering >60 million inhabitants. Cases were aged ≥18 years with first ruptured intracranial aneurysm and dissection between 2010 and 2015. For each case, fluoroquinolone use was compared between the exposure-risk window (day 30–day 1 before the outcome) and matched control windows (day 120–day 91, day 150–day 121, and day 180–day 151) and adjusted for time-varying confounders; potential time-trend for exposure was controlled using an age- and sex-matched reference group. Amoxicillin use was studied similarly for indication bias controlling. The potential excess of risk conveyed by fluoroquinolones was assessed by the ratio of OR for fluoroquinolones to that for amoxicillin.

Results—Of the 7443 identified cases, 75 had been exposed to fluoroquinolones in the prior 180 days, including 16 in the 30-day at-risk window (385/97 cases exposed to amoxicillin, respectively). The adjusted OR for fluoroquinolones was 1.26 (95%CI, 0.65–2.41) and that for amoxicillin of 1.36 (95% CI, 1.05–1.78). Ratio of OR for fluoroquinolones to that for amoxicillin was estimated at 0.92 (95% CI, 0.46–1.86). Result was similar when extending outcome definition to unruptured events (ratio of OR for fluoroquinolones to that for amoxicillin, 0.97 [95% CI, 0.61–1.53]).

Conclusions—This study did not evidence an excess of risk of intracranial aneurysm or dissection with fluoroquinolone use. **(*Stroke*. 2020;51:994-997. DOI: 10.1161/STROKEAHA.119.028490.)**

Confusion POTENTIELLE non mesurée

2. Les contrôles négatifs / Les variables de falsification

		IRR	95% CI LB	95%CI UB	p	C p
FQ	OPTUMEXTDOD	1.242	1.159	1.329	0.000	0.797
	IBMMDCR	1.127	1.043	1.215	0.002	0.503
	IBMCOM	1.632	1.446	1.836	0.000	0.329
	Pooled estimate: $I^2 = 0.92$		N/A			
Febrile illness not treated with antibiotics	OPTUMEXTDOD	4.291	3.137	5.757	0.000	0.000
	IBMMDCR	1.532	0.592	3.245	0.326	0.561
	IBMCOM	0.709	0.217	1.692	0.511	0.391
	Pooled estimate: $I^2 = 0.86$		N/A			
Amoxicillin	OPTUMEXTDOD	1.002	0.918	1.091	0.969	0.246
	IBMMDCR	0.919	0.833	1.012	0.089	0.001
	IBMCOM	1.163	1.058	1.276	0.002	0.859
	Pooled estimate: $I^2 = 0.84$		N/A			
Azithromycin	OPTUMEXTDOD	1.153	1.039	1.276	0.007	0.578
	IBMMDCR	0.983	0.869	1.108	0.785	0.031
	IBMCOM	1.320	1.156	1.501	0.000	0.762
	Pooled estimate: $I^2 = 0.81$		N/A			
Trimethoprim without Sulfamethoxazole	OPTUMEXTDOD	0.706	0.398	1.159	0.201	0.082
	IBMMDCR	0.326	0.137	0.650	0.005	0.001
	IBMCOM	0.629	0.191	1.518	0.381	0.296
	Pooled estimate: $I^2 = 0.24$		0.55 (95%CI: 0.19–1.55)			
Trimethoprim with Sulfamethoxazole	OPTUMEXTDOD	0.921	0.780	1.080	0.322	0.145
	IBMMDCR	1.067	0.906	1.247	0.428	0.317
	IBMCOM	1.065	0.874	1.287	0.521	0.720
	Pooled estimate: $I^2 = 0.00$		1.01 (95%CI: 0.82–1.25)			