FLUOROQUINOLONES ASSOCIATED WITH THE RISK OF SERIOUS ARRHYTHMIA

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Abstract

Objective: Fluoroquinolones are commonly used to treat infection. Most doctors prescribe this antibiotic without considering the history of cardiovascular diseases in patients. Several studies found that the risk of one of the cardiovascular diseases, arrhythmia, is apparently influenced by the use of fluoroquinolones. This review aims to describe the risk of arrhythmia associated with the use of fluoroquinolone antibiotics.

Method: We collected data from the Clinical Infectious Disease and British Medical Journal database. We used a descriptive review for the two studies whose design was a cohort study.

Result: Of the two studies reviewed, both reported that the use of fluoroquinolones was associated with an elevated risk of serious arrhythmia, with some differences among molecules. The Clinical Infectious Disease Research found 1838 cases identified in which the rate of serious arrhythmia was high with current fluoroquinolone use. Gatifloxacin use was associated with the highest rate. Meanwhile, the British Medical Journal Research found 144 cases of serious arrhythmia, but the risk of serious arrhythmia did not statistically significantly increase in any of the groups. The mechanism of fluoroquinolones includes their role as weak inhibitors of the cardiac potassium channels and as an antibiotic that may cause prolongation of QT interval. In studies with healthy individuals, fluoroquinolones prolong QTc intervals from 0 to 17.8 milliseconds. However, the use of these medications in high-risk patients results in cardiovascular mortalities.

Conclusion: The use of fluoroquinolones is associated with the risk of serious arrhythmia and could increase cardiovascular deaths. Yet, oral fluoroquinolone treatment is not associated with an increased risk of serious arrhythmia. The risk of serious arrhythmia depends on whether patients have a high risk.

Keywords: Antibiotics, Fluoroquinolones, Arrhythmia

INTRODUCTION

Fluoroquinolones have an effective bactericidal, broad-spectrum activity against many pathogens. These relatively new synthetic antibiotics are potent for such infections as gastrointestinal infections, urinary tract infections (UTI), sexually transmitted diseases (STD), respiratory tract infections (RTI), as well as skin infections. They are also useful for prostatitis, bone infections, bacterial enteric infections, and prophylaxis in the immunocompromised neutropenic host. These agents become an alternative therapy to bacteria, particularly in areas with penicillin resistant and macrolide resistant organism prevalence (Sharma, Jain, 2009).

Fluoroquinolones are primarily used to treat complicated urinary tract infections, pyelonephritis due to *Escherichia Coli,* a variety of illnesses, and infections caused by susceptible bacteria. These antibiotics include ciprofloxacin, gemifloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. More than 23 million patients received a prescription for one of them in 2011.

Table 1. Classification of fluoroquinolones (Sharma, Jain, 2009).

Generation	Drug	Drug Characteristics
First	Nalidixic acid	Active against some Gram-negative bacteria
	Oxolinic acid	Highly protein-bound drugs
	Pipemidic acid	Short half-life
Second	Norfloxacin	Protein binding (50%)
	Enoxacin	Longer half-life than previous agents
	Ofloxacin	Improved activity against Gram-negative bacteria
	Lomefloxacin	
Third	Temafloxacin	Active against Gram-negative bacteria
	Sparafloxacin	Also active against Gram-positive bacteria
	Grepafloxacin	

Fourth	Clinafloxacin	Show extended activity against both strains of bacteria
	Trovaloxacin	Active against anaerobes and atypical bacteria
	Moxifloxacin	
	Gatifloxacin	

Fluoroquinolone antibiotics are often associated with disabling and potentially permanent serious adverse effects that may occur together in the same patient. They should not be used to treat certain uncomplicated infections, such as severe bacterial sinusitis, acute worsening of bacterial chronic bronchitis, and uncomplicated urinary tract infections. Their adverse reactions include problems with the tendons, muscles, joints, nerves, and central nervous system, and these can occur within hours to weeks after the beginning of treatment using fluoroquinolones (FDA, 2016).

The side effects on the tendons, muscles, joints and nerves can include tendon inflammation and rupture, tingling or pricking sensation, arm or leg numbness, muscle pain and weakness, as well as joint pain and swelling. Serious side effects can also occur to central nervous system, including depression, hallucinations, suicidal thoughts, confusion, and anxiety. Other adverse reactions are abnormally rapid or irregular heartbeat, ringing or buzzing in the ears, vision problems, skin rash, sunlight-sensitive skin, headache, sleep trouble, and exhaustion (FDA, 2016). Since there were reports of a possible association with sudden cardiac death, fluoroquinolones (i.e. Sparafloxacin, Grepafloxacin) were withdrawn from the European and US market in 1999 and 2001 (Owen, 2005). In addition, a cohort study of Medicaid patients in Canada reported increased risk of ventricular tachyarrhythmia and CV death associated with moxifloxacin and levofloxacin (Inghammar, 2016).

METHOD

We systematically searched for the Clinical Infection Disease and British Medical Journal databases throughout 2012 for studies published in any languages using the following text and key words in combination, both as medical subject heading terms and text words: fluoroquinolones, adverse reaction/side effect, cardiac, cardiovascular, death, mortality, arrhythmia, and sudden cardiac death. Further manual retrieval was performed using

reference lists from the relevant original and review to identify other potentially relevant articles.

We selected the relevant papers to review and summarized them. The summary was in the form of narrative description and a table of comparison. We then compared the methods, participants, results, and conclusions of both studies followed by drawing our own conclusions.

RESULT

We found two papers relevant to the topic, which were "Fluoroquinolones and the Risk of Serious Arrhythmia: A Population-Based Study" by Francesco Lapi, Machelle W., Abbas Kezouh, Jacques, Pierre E., and Samy S. from the Clinical Infection Diseases Database (2012) and "Oral Fluoroquinolone Use and Serious Arrhythmia: Bi-national Cohort Study" by Malin Inghammar, Henrik S., Mads Melbye, Bjorn P., and Anders H. from the British Medical Journal (2016).

The two papers assessed and evaluated fluoroquinolone use associated with an increased risk of serious arrhythmia defined as ventricular arrhythmia or sudden/unattended death identified in hospital discharge diagnoses related to fluoroquinolones as a class as well as for each individual molecule. Both studies used the same method, which was the cohort study. The study by Lapi, et al. was conducted in Canada between 1990 and 2007, while the study by Inghammar, et al. was conducted in Denmark between 1997 and 2011 and Sweden in 2006-2013.

Lapi, et al. involved 605,127 participants receiving a prescription of respiratory drugs with 1838 of them experiencing serious arrhythmia cases. Inghammar, et al. involved 909,656 participants and differentiated arrhythmia cases based on the period of use and comparison of fluoroquinolone and penicillin V. There were 144 cases of serious arrhythmia occurring during the follow-up, 66 among current fluoroquinolone users, and 78 among current penicillin users.

The results of both studies are presented in the following table.

Table 2. Risks of serious arrhythmia

	Lapi, et al.	**Inghammar, et al.**
Rate ratio (95% CI)	• The rate of serious arrhythmia was elevated with current fluoroquinolone use RR = 1.76; 95% confidence interval [CI], 1.19–2.59) • in particular with new current use (RR = 2.23; 95% CI, 1.31–3.80) • Gatifloxacin use was associated with the highest rate (RR = 7.38; 95% CI, 2.30–23.70) • Moxifloxacin and ciprofloxacin were also associated with elevated rates of serious arrhythmia (RR = 3.30; 95% CI, 1.47–7.37 and RR = 2.15; 95% CI, 1.34–3.46, respectively).	The risk of serious arrhythmia with oral fluoroquinolone for drugs by period of use : • Current use (Days 0-7 after prescription) Incidence Rate 3.4 per 1000 person years ; RR 0.85 ;95% CI, 0.6-1.18) • Indeterminate use (Days 8-14 after prescription) Incidence Rate 2.5 per 1000 person years ; RR 1.13 ;95% CI, 0.71-1.78) • Past use (Days 15-44 after prescription) Incidence Rate 1.8 per 1000 person years ; RR 1.08 ;95% CI, 0.83-1.42)

From Table 2, we can see that Lapi, et al. found the use of fluoroquinolones associated with an elevated risk of serious arrhythmia with some differences among molecules. Given that the individual fluoroquinolones shared various indications, the relative risks of serious arrhythmia could inform the choice of different molecules in high-risk patients. This is different with the study by Inghammar, et al. in which the risk of serious arrhythmia did not statistically significantly increase in any of the subgroups, including analyses by fluoroquinolone types.

DISCUSSION

Lapi, et al. found that the recent clinical information related to fluoroquinolone-induced arrhythmias was mainly based on a few randomized clinical trials (RCTs) and pharmacovigilance data. The RCTs reporting the prolongation of QT interval as a proxy for arrhythmia found that such prolongation was rare in most of the subjects administered with levofloxacin or ciprofloxacin. Moxifloxacin was the only type associated with

a QT interval prolongation, which was potentially clinically significant. Meanwhile, the current pharmacovigilance analyses revealed an excess of torsades de pointes among users of moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin.

The research found that patients newly exposed to fluoroquinolones had a greater risk of developing a serious arrhythmia compared with nonusers. This effect was mainly due to the use of gatifloxacin, moxifloxacin, and ciprofloxacin. Levofloxacin did not seem to trigger the risk of serious arrhythmia.

Having studied the information about the increasing use of these antibiotics, particularly ciprofloxacin and levofloxacin, in the last decades, they found an increasing number of serious and unintended side effects. As long as the individual fluoroquinolones give different indications, the relative risks of serious arrhythmia could show the molecule choices in high-risk patients. It was suggested that since serious arrhythmias are uncommon, it would be advantageous if future studies could be conducted in larger patient population with these outcomes to obtain confirmation. Meanwhile, Inghammar, et al. did not find an increased risk of serious arrhythmia with treatments using fluoroquinolones although the drugs increased the risk of torsades de pointes, which became significantly lower in the younger-age group. The outcome of "serious arrhythmia" has not been formally validated, but previous studies of myocardial infarction, cardiac death, and atrial fibrillation showed that 86-97% of diagnoses from the register of patients and causes of death in Denmark were valid based on the original medical or autopsy files. This was similar in Sweden where validation studies showed that 90-100% of these diagnoses were correct.

Non-fatal ventricular arrhythmia was probably underdiagnosed and misclassification might be differential (higher certainty in fluoroquinolone users) due to a presumably increased risk of QT prolongation. If this bias were present, it would raise estimates, but the finding of no association would still be true.

The study also found that gatifloxacin, moxifloxacin, and levofloxacin increased the risk of serious arrhythmias but not ciprofloxacin. Similar to the findings, the recent mechanistic data that compared individual Fluoroquinolones also suggested that gatifloxacin, moxifloxacin, and levofloxacin had high potential of Ikr inhibition, leading to possibly higher QT prolongation and proarrhythmic properties. For instance, Abo-Salem et al. revealed that concentrations of moxifloxacin and levofloxacin serum for Ikr inhibition were 2 and 15 times higher than those of ciprofloxacin,

respectively. In addition, pharmacovigilance data showed that the prevalence of TdP incidence was higher in users of moxifloxacin and levofloxacin compared to those of ciprofloxacin. For example, the side-effect events reported to FDA from 2004 to 2008 revealed that the least-frequently reported antibacterial agent to induce TdP was ciprofloxacin. There were 230 TdP cases associated with the use of antibacterial agents, while only 35 cases were related to the administration of ciprofloxacin. Since there was no CV risk associated with ciprofloxacin, it was suggested that ciprofloxacin was relatively safe for the heart, which is in line with the recent opinion that ciprofloxacin has limited proarrhythmic liability.

Another factor confounding the association between Fluoroquinolones and CV risk was that the patients who took Fluoroquinolones probably had a more-serious disease or CV risk than those not taking antibiotics. Therefore, the increased CV risk in the study could be associated with the acute infection itself rather than with the use of Fluoroquinolones. However, similar risk of serious arrhythmias occurred in subjects with current or former use of Fluoroquinolones, indicating that baseline differences between the groups did not have a significant influence on the results. Additionally, another meta-analysis of 33 studies found that no increased risk of SCD was found in the subgroup of patients taking penicillin or amoxicillin compared with those not using antibiotics.

The U.S. Food and Drug Administration have revised the Boxed Warning to deal with Fluoroquinolone serious safety problems, including its CV risk. Considering the widespread Fluoroquinolone use, although the rate of fatal adverse cardiac incidents was low, the risks and benefits of antibacterial therapies should be further considered. The results suggested that moxifloxacin and levofloxacin but not ciprofloxacin increased the risk of serious arrhythmias. Doctors are suggested to avoid prescribing moxifloxacin and levofloxacin when other antibiotic choices remain available, and patients with preexisting risk factors that rise their vulnerability to deadly arrhythmia should be given better attention. Such patients include those with hyperlipidemia, severe heart disease, current use of another QT interval prolonging drug, a family history of long QT syndrome, and a history of drug-induced TdP. Patients with those risk factors may be given alternative drugs or additionally monitored when Fluoroquinolones need to be administered.

CONCLUSION

Our review found that fluoroquinolones could increase the risk of serious arrhythmias and CV death; however, fluoroquinolones do

not increase the risks of all-cause death. Moreover, moxifloxacin and levofloxacin are associated with a higher risk of serious arrhythmias. Yet, oral fluoroquinolone treatment is not associated with an increased risk of serious arrhythmia. The risk of serious arrhythmia depends on whether patients have a high risk.

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