Division of Public and Behavioral Health
Technical Bulletin

Date: January 2, 2019
Topic: FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients
Section/Program: Office of Public Health Informatics and Epidemiology
To: All State-Licensed Healthcare Facilities

Current Situation:
On December 20,2018 The U.S. Food and Drug Administration (FDA) issued a notice warning about the use of fluoroquinolone antibiotics in certain patients. An FDA review found that fluoroquinolones can increase the occurrence of rare, but serious events of ruptures or tears in the aorta. These aortic dissections, or ruptures of an aortic aneurysm can lead to dangerous bleeding and even death. Such serious complications can occur with the systemic oral or injectable use of fluoroquinolones.

According to the FDA, fluoroquinolones should not be used in high risk patients unless there are no other treatment options available. People at increased risk include those with a history of blockages or aortic aneurysms or other blood vessels, high blood pressure, certain genetic disorders that involve blood vessel changes, and the elderly. The FDA is requiring a new warning about this risk be added to the prescribing information and patient Medication Guide for all fluoroquinolones.

Recommendations:
FDA recommends that health care professionals should:

- Avoid prescribing fluoroquinolone antibiotics to patients who have an aortic aneurysm or are at risk for an aortic aneurysm, such as patients with atherosclerotic vascular diseases, hypertension, certain genetic conditions such as Marfan syndrome and Ehlers-Danlos syndrome, and elderly patients.
- Prescribe fluoroquinolones to such patients only when no other treatment options are available.
- Advise all patients to seek immediate medical care for any symptoms associated with aortic aneurysm.
- Stop fluoroquinolone treatment immediately if a patient reports side effects suggestive of aortic aneurysm or dissection.
- Please contact the FDA at https://www.fda.gov/AboutFDA/ContactFDA/default.htm to report any to report side effects involving fluoroquinolones or other medicines.

Educational Resources:

- Visit FDA website https://www.fda.gov/Drugs/DrugSafety/ucm628753.htm for more information on prescribing fluoroquinolone antibiotics.

Ihsan Azzam, Ph.D., M.D.
Chief Medical Officer

Julie Kotchevar, Ph.D.
Administrator, DPBH

U.S. Food and Drug Administration
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Drug Safety Communications

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

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

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.

Fluoroquinolones should not be used in patients at increased risk unless there are no other treatment options available. People at increased risk include those with a history of blockages or aneurysms (abnormal bulges) of the aorta or other blood vessels, high blood pressure, certain genetic disorders that involve blood vessel changes, and the elderly. We are requiring that a new warning about this risk be added to the prescribing information and patient Medication Guide for all fluoroquinolones.

Fluoroquinolone antibiotics are approved to treat certain bacterial infections and have been used for more than 30 years. They work by killing or stopping the growth of bacteria that can cause illness. Without treatment, some infections can spread and lead to serious health problems (see List of Currently Available FDA-Approved Systemic Fluoroquinolones).

Health care professionals should avoid prescribing fluoroquinolone antibiotics to patients who have an aortic aneurysm or are at risk for an aortic aneurysm, such as patients with peripheral atherosclerotic vascular diseases, hypertension, certain genetic conditions such as Marfan syndrome and Ehlers-Danlos syndrome, and elderly patients. Prescribe fluoroquinolones to these patients only when no other treatment options are available. Advise all patients to seek immediate medical treatment for any symptoms associated with aortic aneurysm. Stop fluoroquinolone treatment immediately if a patient reports side effects suggestive of aortic aneurysm or dissection.

Patients should seek medical attention immediately by going to an emergency room or calling 911 if you experience sudden, severe, and constant pain in the stomach, chest or back. Be aware that symptoms of an aortic aneurysm often do not show up until the aneurysm becomes large or bursts, so report any unusual side effects from taking fluoroquinolones to your health care professional immediately. Before starting an antibiotic prescription, inform your health care

professional if you have a history of aneurysms, blockages or hardening of the arteries, high blood pressure, or genetic conditions such as Marfan syndrome or Ehlers-Danlos syndrome. If you have been prescribed a fluoroquinolone to treat an infection, do not stop the antibiotic without first talking to your health care professional.

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).

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving fluoroquinolones or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS).

List of FDA-Approved Systemic Fluoroquinolones

Brand Name	Active Ingredient
Avelox	moxifloxacin[+]
Baxdela	delafloxacin
Cipro	ciprofloxacin[+]
Cipro extended-release[±]	ciprofloxacin extended-release
Factive	gemifloxacin[+]
Levaquin	levofloxacin[+]
Ofloxacin (generic brand)[±]	ofloxacin

+ available as brand and generic
± available only as generic

Facts about the Fluoroquinolone Class

- Fluoroquinolones are a class of antibiotics approved to treat or prevent certain bacterial infections.

- Fluoroquinolones work by killing or stopping the growth of bacteria that can cause illness. Like other antibiotics, fluoroquinolones do not treat viral infections such as colds, the flu or bronchitis in otherwise healthy persons.
- The benefits of fluoroquinolone medicines outweigh the risks for treatment of serious infections caused by fluoroquinolone-susceptible bacteria, such as pneumonia or intra-abdominal infections.
- Common side effects include nausea, diarrhea, headache, dizziness, lightheadedness or trouble sleeping.

Additional Information for Patients

- 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.
- People at risk for aortic aneurysms include those with a history of blockages or aneurysms of the aorta or other blood vessels, high blood pressure, certain genetic disorders that involve blood vessel changes such as Marfan syndrome and Ehlers-Danlos syndrome, and the elderly.
- FDA is requiring that a new warning about the rare but serious risk of aortic aneurysm be added to the prescribing information and patient Medication Guide of all fluoroquinolone antibiotics.
- Seek medical attention immediately by going to an emergency room or calling 911 if you experience sudden, severe, and constant stomach, chest or back pain.
- Imaging tests are used to diagnose an aortic aneurysm. If you have a history of aneurysms, routine checkups and treatment for an aortic aneurysm can help prevent growth and rupture.
- If you have an aneurysm, signs and symptoms of a growing aortic aneurysm depend on its location along the aorta blood vessel and can include:
    - A throbbing feeling in the stomach area
    - Deep pain in your back or the side of your stomach area
    - Steady, gnawing pain in your stomach area that lasts for hours or days
    - Pain in your jaw, neck, back or chest
    - Coughing or hoarseness
    - Shortness of breath, and trouble breathing or swallowing
- Contact your health care professional immediately if you experience any serious side effects while you are taking your fluoroquinolone antibiotic.
- Before starting a new fluoroquinolone antibiotic, inform your health care professional if you have previously experienced any serious side effects with another antibiotic.
- Lifestyle changes can help lower the risk of developing an aortic aneurysm. These include:
    - Stopping smoking. The health benefits of quitting smoking are immediate and substantial. Soon after quitting, circulation and blood pressure improve, the senses of taste and smell return, and it becomes easier to breathe. In the longer term, quitting smoking can decrease the chances of developing lung disease, heart

disease, and some cancers. More information about quitting smoking can be found on the National Cancer Institute's website and the Smokefree website.
    - Healthy diet. A healthy diet is low in saturated fat, trans fat, cholesterol, salt, and added sugar. More information about following a healthy diet can be found on the National Heart, Lung, and Blood Institute's website.
    - Controlling medical conditions such as high blood pressure and high blood cholesterol.
- Read the patient Medication Guide you receive with your fluoroquinolone antibiotic prescriptions, which explains the important things you need to know about the medicine. These include side effects, what the medicine is used for, how to take and store it properly, and other things to watch for when you're taking the medicine.
- Talk to your health care professional if you have questions or concerns about fluoroquinolone antibiotics.
- 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 (restrict use for certain uncomplicated infections), August 2013 (peripheral neuropathy), and July 2008 (tendinitis and tendon rupture).
- To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving fluoroquinolone antibiotics or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- The use of fluoroquinolone antibiotics has been associated with the rupture or dissection of aortic aneurysms.
- People at risk for aortic aneurysms include those with a history of peripheral atherosclerotic vascular diseases, hypertension, certain genetic disorders that involve blood vessel changes such as Marfan syndrome and Ehlers-Danlos syndrome, and the elderly.
- Prescribe fluoroquinolones to these patients only when no other treatment options are available.
- FDA is requiring that a new warning about the rare but serious risk of aortic aneurysm be added to the prescribing information and patient Medication Guide of all fluoroquinolone antibiotics.
- In patients with a history of aneurysms, routine checkups and treatment for an aortic aneurysm can help prevent growth and rupture.
- Counsel patients who have been diagnosed with an aneurysm to promptly seek medical attention if they experience any signs or symptoms of a growing aortic aneurysm, which can include:
    - A throbbing feeling in the stomach area
    - Deep pain in your back or the side of your stomach area
    - Steady, gnawing pain in your stomach area that lasts for hours or days
    - Pain in your jaw, neck, back or chest
    - Coughing or hoarseness

    - Shortness of breath, and trouble breathing or swallowing
- Counsel patients about lifestyle changes that can help lower the risk of developing an aortic aneurysm, which can include a plan to stop smoking, follow a healthy diet, and manage medical conditions such as high blood pressure and high blood cholesterol.
- Encourage patients to read the Medication Guide they receive with their fluoroquinolone antibiotic prescription.
- 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 (restrict use for certain uncomplicated infections), August 2013 (peripheral neuropathy), and July 2008 (tendinitis and tendon rupture).
- To help FDA track safety issues with medicines, report adverse events involving fluoroquinolone antibiotics or other medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.

Data Summary

We searched the FDA Adverse Event Reporting System (FAERS) database and reviewed four epidemiological studies[1,2,3,4] to investigate the association between fluoroquinolone antibacterial use and the risk of aortic aneurysm and dissection. The studies were published between 2015 and 2018. Although the findings from the epidemiological studies and the FAERS cases appear to provide evidence of an association between fluoroquinolone use and increased risk of aortic aneurysm or dissection, we cannot determine a definite causal association due to study limitations.

In 2015, we reviewed a single epidemiological study by Lee et al.[1] published on this safety issue, which described an increased risk of aortic aneurysm or dissection based on a rate ratio of 2.28 (95% confidence interval [CI]=1.67-3.13), after adjusting for individual confounders. Patients older than 70 years appeared to have a numerically higher risk; however, we found significant design and analytical limitations with the study. We also searched the FAERS database for cases submitted through December 15, 2015 and identified 15 cases of aortic aneurysm or dissection reported with fluoroquinolone use. However, all the patients had other risk factors for aortic aneurysm or dissection such as smoking, male gender, older age, hypertension, and atherosclerosis. Based on the limited information available at that time, we concluded that a causal association between aortic aneurysm or dissection with fluoroquinolones could not be determined.

Following our initial review, three additional epidemiological studies[2,3,4] were subsequently published between 2015 and 2018, each of which are described in greater detail below. All three studies found an increased risk of aortic aneurysm or dissection associated with fluoroquinolone use; however, there were study limitations such as confounding by indications and other factors, including small sample sizes. We conducted another search of the FAERS database from December 15, 2015, through April 30, 2018, and identified an additional 56 cases of aortic aneurysm or dissection reported during or after treatment with a fluoroquinolone. However, all patients had at least one risk factor for aortic aneurysm or dissection, and most cases were submitted by litigation attorneys between 2016 and 2017. Although the cause of these specific

events among patients taking fluoroquinolones cannot be determined, evidence on the association between fluoroquinolone use and aortic aneurysm or dissection appears to be consistent across multiple epidemiological studies showing an approximately two-fold increased risk over the baseline risk of aortic aneurysm or dissection in each study.

Pasternak et al.[2] conducted a retrospective cohort study that evaluated the risk of aortic aneurysm or dissection with oral fluoroquinolone use compared to amoxicillin use during the first 60 days after the start of treatment in patients aged 50 years or older. To investigate the timing of the association, the 60-day risk period was divided into 10-day intervals for separate assessment. In the first 60-day risk period, the fluoroquinolone group showed a 1.66-fold increased risk (95% CI=1.12-2.46) compared to the amoxicillin group. Secondary analysis by 10-day interval showed the increase in risk occurred mainly in the first 10 days. A secondary analysis investigated risk in days 61 to 120. There was no increased risk associated with fluoroquinolone use in the period from days 61-120 (hazard ratio [HR]=0.67; 95% CI=0.40-1.11).

Daneman et al.[3] conducted a retrospective cohort study that compared the risk of severe collagen-associated adverse events, including aortic aneurysm, during periods of fluoroquinolone use to periods of non-use in older patients turning 65 years old between April 1, 1997 and March 31, 2012. It was noted that patients who received a fluoroquinolone were more likely to have baseline comorbidities, including hypertension, diabetes, atherosclerosis, and infections compared to those who never received a prescription. After adjustment for baseline characteristics, the study found that the hazard of aortic aneurysm increased by 2.24-fold (95% CI=2.02-2.49) during a 30-day risk window following the treatment episode.

Lee et al.[4] conducted self-controlled analyses to evaluate the association between fluoroquinolone use and aortic aneurysm or dissection in elderly patients with a mean age of 71 years old. In this study design, each patient served as his/her own control to reduce or eliminate between-patient differences that could confound the results. The case interval was a 60-day period before the diagnosis date of aortic aneurysm or dissection, and the control interval was one randomly selected 60-day period between 60 to 180 days before the adverse event. This study found an increased risk of aortic aneurysm or dissection associated with exposure to fluoroquinolones (odds ratio [OR]=2.71; 95% CI=1.14-6.46). In addition, exposure to fluoroquinolones for longer than 14 days was associated with a higher risk of aortic aneurysm or dissection (for 3-14 days of exposure, OR=2.41, 95% CI=1.25-4.65; for >14 days of exposure, OR=2.83, 95% CI=1.06-7.57).

The background risk of aortic aneurysm and dissection varies widely depending on the population at risk. One epidemiological study gives an estimate of the annual risk for aortic aneurysm that ranges from nine aortic aneurysm events per 100,000 persons in a general population to 300 aortic aneurysm events per 100,000 persons at the highest risk (e.g., persons over the age of 85 years).[5]

References

1. Lee CC, Lee MG, Chen YS, et al. Risk of Aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. JAMA Int Med 2015;175(11):1839-1847.

2. Pasternak B, Inghammar M, Svanstrom H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ. 2018;360:k678.
3. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open. 2015;5(11):e010077.
4. Lee CC, Lee MG, Hsieh R, et al. Oral fluoroquinolone and the risk of aortic dissection. J Am Coll Cardiol. 2018;72(12):1369-1378.
5. Howard DPJ, Banerjee A, Fairchild JF, et al. Age-specific incidence, risk factors and outcome of acute abdominal aortic aneurysms in a defined population. BJS 2015;102:907-915.

Related Information

- Aneurysm
- Fluoroquinolone Antimicrobial Drugs Information
- Harms of Cigarette Smoking and Health Benefits of Quitting
- Where to Get Help When You Decide to Quit Smoking
- Want to Quit Smoking? FDA-Approved Products Can Help Here's what to know about these over-the-counter and prescription products
- Smokefree
- Centers for Disease Control and Prevention: Smoking and Tobacco Use
- Aim for a Healthy Weight
- High Blood Pressure
- High Blood Cholesterol
- The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective
- Think It Through: Managing the Benefits and Risks of Medicines