Risks associated with the use of fluoroquinolones

ABSTRACT

Fluoroquinolones are a widely used class of antibiotic that are effective in treating a wide variety of pathogens. Despite their popularity there is increasing concern regarding the potential complications associated with these agents. Patients who take a fluoroquinolone have an increased risk of developing tendinopathy, peripheral neuropathy, and aortic aneurysm or dissection. Providers should consider the risk of these potential complications before using these medications.

Fluoroquinolones are a widely used class of antibiotic that are effective in treating a wide variety of pathogens. Despite their popularity there is increasing concern regarding the potential complications associated with these agents. While the exact aetiology of these associated risks remains somewhat unclear, in certain patient populations these agents appear to pose a significant risk to both patients and potentially providers.

Why are these medications risky?

Over the past decade there have been increasing numbers of potential adverse events associated with the use of fluoroquinolones. While there may not be an abundance of evidence demonstrating the causative relationship between quinolones and these adverse events, the literature shows a clear association between the use of these medications and an increase in various complications. From a pathophysiological standpoint there are several potential explanations for the increase in adverse events that is seen when patients are taking quinolones.

Fluoroquinolones have a variety of non-antimicrobial effects on cells including modulating inflammatory mediators, limiting the expression of extracellular matrix proteins and inhibiting cell proliferation in isolated tendon cells (Corps et al, 2002). Experimental studies have shown that tendon cells upregulate matrix metalloproteinases when exposed to ciprofloxacin. These metalloproteinases have been shown to degrade various components of the extracellular matrix, a process which is thought to play a role in tendon injury as well as the development of aortic aneurysms (Kent, 2014). While there are limited data regarding the magnitude of these effects in humans, in theory these cellular manipulations could compromise the micro-integrity of tendons and collagen and increase the risk of injury and rupture (Kato et al, 1995). The potential mechanisms behind the increased risk of neuropathy and other neurological complications are even less well understood but may involve quinolone-induced antagonism of amino acid neurotransmitter receptors (De Sarro and De Sarro, 2001).

One of the most difficult aspects of evaluating potential adverse events is the overall low quality of the available evidence both in terms of the incidence of reported events and the reliability of the available reports. Reports of adverse events are largely subjective and can be influenced by a number of variables including baseline knowledge of potential complications and media attention. Reviews of the Food and Drug Administration's adverse event reporting system database show a peak in the rate of adverse event reporting ~2 years after the release of a drug, a phenomenon that has been termed the 'Weber effect' (Weber, 1984). Some differences in reporting may be based on geography and associated societal differences, as seen in early studies of levofloxacin which showed a 3x increase in the rate of reported adverse events between the United States and Japan (Davis and Bryson, 1994).

When available, the available database reports are often incomplete. When looking at serious complications such as the risk of inducing torsades de pointes in the setting of antibiotic use, Shaffer et al (2002) found that only ~30% of patients with this adverse outcome had documented electrocardiogram data. Additionally ~11% of reports lacked basic demographic information including age and gender (Shaffer et al, 2002). These evidentiary limitations are not unique to fluoroquinolone-associated complications and do not negate any of the particular risks discussed below, but must be acknowledged as they can make it difficult to calculate the exact risk to any particular patient.

In terms of formal warnings associated with the use of fluoroquinolones, the USA-based Food and Drug Administration has issued a series of warnings to providers over the past decade. Following an increasing number of case reports, in 2008 the Food and Drug Administration issued one of its 'black box' or most significant warnings to providers involving fluoroquinolone use and an increased risk of tendon rupture. In 2013 the Food and Drug Administration (2013) released another warning regarding the risk of peripheral neuropathy followed in 2016 by an enhanced warning purporting a broad risk of complications to 'tendons, muscles, joints, nerves, and

Dr Matthew C DeLaney, Associate Professor, Department of Emergency Medicine, University of Alabama at Birmingham, Birmingham, Alabama, 35209, United States (mdelaney@uabmc.edu)

central nervous system' (Food and Drug Administration, 2016). There is an increasing body of literature reporting cases of retinal detachment and aortic aneurysm; however, the most recent warnings do not include these outcomes in their most rigid black box warnings (Food and Drug Administration, 2016). In terms of particular agents or routes of administration, essentially all formulations of fluoroquinolones have a reported risk of complication and the data have yet to identify any drugs within this family of medications that are considered to be immune from these warnings. Outside the USA, in part as a result of differing medicolegal environments, there have been fewer formal warnings regarding the use of these agents; however, the available data strongly suggest that this potential risk to patients exists across a wide variety of practice settings.

Tendinopathy

Case reports suggesting an association between the use of fluoroquinolones and the development of tendinopathy or increased rates of tendon rupture started to emerge in the early 1980s (Bailey et al, 1983). Early reports focused on the risk of injury to the Achilles tendon, but as time progressed there were multiple reports of injury to a wide variety of tendons (Gültuna et al, 2009). In 2000, a World Health Organization survey performed in Australia reported an increase in tendon rupture in patients taking fluoroquinolones and found ciprofloxacin to be the culprit in ~90% of cases (Williams et al, 2000). The mean onset of tendon complications is 6 days after the first dose of medication with ~85% of cases occurring within 1 month of treatment. The risk of tendon injury does not necessarily decrease once the patient has completed the course of antibiotics as ~50% of cases occur after the patient has taken the final dose of medication (Royer et al, 1994; Akali and Niranjan, 2008). As a wider variety of fluoroquinolones has been released onto the market, reports of tendinopathy have been associated with almost all fluoroquinolones including otic and ophthalmic formulations of the medication. In 2008, the Food and Drug Administration issued a black box warning for all fluoroquinolone products which indicated an increased risk of tendon rupture in patients taking these agents (Food and Drug Administration, 2008).

Peripheral neuropathy

Starting in the early 2000s the Food and Drug Administration issued a warning regarding the risk of peripheral neuropathy associated with fluoroquinolone use (Hedenmalm and Spigset, 1996). Initial reports suggested that most associated peripheral neuropathies were transient; however, subsequent studies found that up to 58% of patients who reported having peripheral neuropathy associated with fluoroquinolone use were symptomatic 1 year after symptom onset. Symptoms typically start within the first few weeks of treatment, but there are scattered reports implicating fluoroquinolones in patients who had a delayed onset of peripheral neuropathy (Gold and Igra, 2003). In 2013, after reviewing several years of reports from the adverse events reporting system, this warning was enhanced (Food and Drug Administration, 2013). The current warning does not offer guidance in terms of patients who are at an increased risk of developing peripheral neuropathy, nor does it suggest that these medications should not be used in patients who have pre-existing peripheral neuropathy; rather it advises providers to stop these medications if the patient has any new or worsening symptoms of peripheral neuropathy.

Aortic aneurysm or dissection

In a recent cohort of ~360 000 treatment episodes of fluoroquinolone use Pasternak et al (2018) found an increase in the 60-day rate of a new diagnosis of aortic aneurysm or dissection compared to a similar cohort of patients who took amoxicillin. In the quinolone cohort the rate of aneurysm or dissection was 1.2 cases per 1000 person years compared to 0.7 case per 1000 patient years in the amoxicillin group. While the overall number of cases of dissection or aneurysm was low (64 in the quinolone group and 40 in the amoxicillin group) this increase resulted in an absolute difference of 82 cases of adverse events per 1 million treatment episodes over the 60-day period of monitoring (Pasternak et al, 2018).

On secondary analysis, the risk of aneurysm was higher than the risk of dissection with a hazard ratio of 1.9 (95% confidence interval 1.22–2.96) compared to 0.93 (0.38–2.29). In terms of timing the highest incidence of complications occurred early in the treatment period with ~41% of adverse events taking place during days 1–10. After day 60 there was no association between the use of fluoroquinolones and the risk of aneurysm or dissection.

While this study sheds light on what seems to be a significant association between the use of fluoroquinolones and the risk of dissection or aneurysm, it sheds little light in terms of patient risk factors that may result in an increased risk of complications. The rate of adverse events was similar between men and women and the risk was similar across various age groups. This study only included patients with a new diagnosis of aneurysm or dissection and therefore does not clarify the potential risk of using these medications in patients with a history of aortic pathology. As the risk to these patients is unclear, and increasing scrutiny is being placed on these medications, it would be prudent for providers to consider alternative antibiotic choices in patients with a history of aortic aneurysm or dissection.

Can we risk stratify the individual patient?

As discussed above, the data regarding associated complications come largely from patient and provider self-reporting and suffer from several issues in terms of quality. These limitations can make it difficult to precisely risk stratify patients who are taking fluoroquinolones. Despite these obstacles, given the large number of reports for conditions such as tendinopathy there are several broad

risk factors that seem to predict a higher chance of a patient having an adverse outcome.

When compared to the general population, patients taking fluoroquinolones have a 4.1-fold increased rate of Achilles tendon rupture. This risk is increased in:

- Men
- Those aged >60 years
- Patients with chronic renal disease
- Patients taking corticosteroids – there is a 46-fold increase in the rate of tendon rupture when compared to age-matched controls (Royer et al, 1994)
- Recipients of solid organ transplants.

The risk factors associated with fluoroquinolone use and peripheral neuropathy are still somewhat unclear. Patients have reported developing new neuropathy in addition to experiencing a worsening of underlying neuropathy. The time between exposure to fluoroquinolones with development of complications is somewhat unclear, as these have been reported to occur within a few days with a reported range of adverse events occurring within the first week or as long as several months after starting medications. Providers are advised to monitor all patients for any signs of nerve damage including pain, numbness, weakness, or changes in sensitivity to pain or temperature.

The most recent Food and Drug Administration (2016) warnings include a broad variety of side effects, including damage 'to the central nervous system', but give very little clarification terms of the actual risk to the patient. There are multiple case reports where patients report chronic or debilitating pain that started after taking fluoroquinolones. The overall quality of the data on this warning is low, and as such it is difficult to draw any clear risk factors from the available evidence.

While there appears to be an association between use of fluoroquinolones and the development of an aortic aneurysm or dissection, the available evidence does not reliably give us much in the way of clinical guidance. While we await inevitable further studies looking at this association, it would be reasonable to avoid these medications in patients who have a history of a previous aortic aneurysm or dissection.

The most recent Food and Drug Administration (2016) communication regarding the risk of fluoroquinolones and aortic dissection or aneurysm stopped short of issuing a formal warning, but this was written before the publication of the Pasternak et al (2018) study. Given the increasing concern about the associated risk of aortic pathology it is thought that there may be enhanced warnings involving these issues in the near future.

There are case reports alleging increased risk of retinal detachment in patients who are exposed to fluoroquinolones (Etminan et al, 2012). These cases are discussed in recent updates, but the Food and Drug Administration has stopped short of issuing a formal warning regarding these potential complications (Food and Drug Administration, 2016).

What is the risk to the provider?

Lawsuits related to complications from fluoroquinolones are increasing. In recent years, levofloxacin has come under particular scrutiny as its popularity has increased. In 2010 a jury awarded $1.8 million to an 82-year-old man who experienced bilateral calcaneal tendon ruptures after taking levofloxacin. As of 2011 in the USA there were over 2500 lawsuits pending with regards to tendon rupture in the setting of fluoroquinolone use (Klauer, 2011). As Food and Drug Administration warnings in regards to neuropathy are published, there will likely be a rise in related lawsuits.

Should we stop prescribing fluoroquinolones?

Fluoroquinolones remain an effective antibiotic that can be used to treat a wide variety of conditions. In patients with community-acquired pneumonia, there is growing resistance to macrolide therapy and several guidelines now recommend respiratory fluoroquinolones as the first-line agent of choice (Stahlmann and Lode, 2013). Additionally, fluoroquinolones are suitable for patients who are allergic to penicillin, and are also available in once daily dosing (Viasus et al, 2013). While the risk of complication from these antibiotics cannot be ignored, they are arguably the drug of choice to treat a variety of infections.

How to limit your risk

Provider risk is increased any time medications are used which carry significant Food and Drug Administration warnings. Despite this risk, in certain clinical situations the relatively minor risk of tendinopathy is vastly outweighed by the benefit offered by this class of antibiotics. When considering the potential risk of aortic complication this risk–benefit analysis may change, but the mere risk of complication does not necessarily mean the medication should not be used.

When using these medications there are several practical tips that may limit the risk of potential adverse events.

Identify those at higher risk

First providers should identify patients who have an increased baseline risk of complication. As above, patients taking corticosteroids or with a history of solid organ transplant have a significantly elevated risk of developing tendinopathy. Similarly patients with previous aortic pathology may have an increased risk of complication when exposed to fluoroquinolones.

Advise the patient about adverse events

The second step to using these medications is to offer common sense guidelines and return instructions. Given the vast number of potential complications patients should have a low threshold to seek medical care or notify their provider if they think they are experiencing an adverse event. Patients taking quinolones should avoid high impact activities and should immediately stop exerting themselves

if they develop any tendon or joint pain and seek medical care. Similarly patients who develop any symptoms concerning for aortic complication should be advised to seek immediate medical care.

Ensure the patient is involved in decision making

The final step is to have a discussion with the patient regarding potential risks and benefits and participate in shared medical decision making. This discussion should be concisely and clearly documented in the medical record. The example below shows an analysis of the risk–benefit ratio, provides appropriate warnings for the patient and documents the process of making a shared medical decision.

> **I am prescribing a fluoroquinolone for the patient to treat their pneumonia. I have discussed the risks associated with this medication including risk of tendon rupture and neuropathy. I have considered other classes of antibiotics and I think this is the most appropriate choice of medication. The patient has verbalized an understanding of these risks, has been advised to limit strenuous exercise while taking these medications, and will return immediately for any pain, swelling or if they develop any new or concerning symptoms.**

Conclusions

While focusing this level of attention on one class of antibiotics may seem excessive, given the high number of prescriptions for these agents and the increasing data surrounding their potential risks, the risks to both patient and provider are real. Rather than avoiding these medications completely ideally shared medical decision making when using fluoroquinolones can improve outcomes for all involved. **BJHM**

Conflict of interest: none.

KEY POINTS

- While commonly prescribed, fluoroquinolones are associated with an increased risk of various complications.
- Patients taking corticosteroids and fluoroquinolones have a significantly increased risk of developing tendonitis or rupture.
- An increased risk of developing peripheral neuropathy is seen in patients who have been exposed to fluoroquinolones.
- Patients who are exposed to fluoroquinolones have higher rates of aortic aneurysm and dissection compared to patients who are taking other antibiotics.
- Providers should consider the risks associated with fluoroquinolones and participate in shared medical decision making with patients who have an elevated risk of complication.

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