EDITORIAL

Should Urology Reconsider the Routine Use of Fluoroquinolones?

The fluoroquinolones have been a staple of urologic care since their first approval in 1986. Norfloxacin was first licensed in the United States for use in genitourinary infections followed soon after by ciprofloxacin in 1987. Their desirable features included high oral absorption, excellent tissue penetration in target organs such as the prostate and a broad spectrum against many urologic pathogens. Current FDA approved fluoroquinolone antibiotics include ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, and ofloxacin. Fluoroquinolone antibiotics are bactericidal and their mechanism of action is interference with the bacterial DNA synthesis via inhibition of the DNA gyrase or topoisomerase II. There has been a slow but steady increase in reports of serious safety concerns with this class of antibiotics. While believed to be uncommon they may in fact be underreported.[1] This spectrum of fluoroquinolone reported toxicity has not been seen with any other class of antibiotic.

The first "Black Box" warning relating to fluoroquinolones did not appear until 2008 and noted an increased risk of tendinitis and tendon rupture. It was followed by a 2011 black box addition of worsening symptoms among patients with myasthenia gravis and in 2013 the addition of irreversible peripheral neuropathy. In 2016 an FDA advisory updated labeling to warn against their use in patients with acute bacterial sinusitis, acute exacerbation of chronic bronchitis, and uncomplicated urinary tract infections unless there are no other options. That labeling update increased the adverse event warnings to include others such as, CNS effects, prolongation of the QT interval, torsades de pointes, and phototoxicity. Some of the effects noted can be seen even with short term use and after the exposure to the drug ends.

The FDA has recognized Fluoroquinolone-Associated Disability (FQAD) syndrome in otherwise healthy people who took fluoroquinolones for minor conditions and developed disabling side effects, some of which are permanent. The conditions associated with this syndrome include, disruption of tendons, joins, muscles, nerves, and a variety of nervous system disturbances (insomnia, restlessness, fatigue and less commonly, seizures, convulsions, and psychosis). The induction of type 2 diabetes, cardiotoxicity, hepatotoxicity and nephrotoxicity are also a concern. Patients at risk for fluoroquinolone toxicity appear to be middle age, females and patients who are also taking steroids. No effective screening strategy or treatment other than discontinuation has been identified. Many theories have been proposed to explain the toxicity of the fluoroquinolone class of antibiotics. The research focus is on oxidative stress with alterations in mitochondrial function, epigenetic effects, and changes in enzyme expression. No studies are conclusive.

The FDA recommends these agents be reserved for serious infections. Other regulatory agencies are beginning to also weigh in including Health Canada that generated fluoroquinolone advisories in 2017. In the summer of 2018 the European Medicines Agency conducted a public hearing on the safety of fluoroquinolones with their final report pending. This concern over fluoroquinolone safety has led to a new 2018 clinical trial entitled the "Fluoroquinolone Associated Disability" study (NCT03535558). It will track patients on a variety of antibiotic regimens including fluoroquinolones for conditions such as UTI who become eligible for disability insurance through a national claims system.

The AUA recognized the 2016 FDA advisory and noted that these agents can have serious side effects that outweigh the benefit in conditions such as uncomplicated UTI's where other agents may be effective. The AUA has also provided guidance on the use of antimicrobial prophylaxis for urologic procedures (http://www.auanet.org/guidelines/antimicrobial-prophylaxis). In those recommendations a fluoroquinolone and often an alternative medication such as trimethoprim/sulfamethoxazole or a cephalosporin are also listed as antimicrobials of choice. This listing provides urologists with the opportunity to limit fluoroquinolone use for procedures prophylaxis. The AUA notes that fluoroquinolone prophylaxis has evidence for use in prostate biopsy; however, it recommends not to prescribe more than 24 hours of the medication to reduce exposure.

Recent data has shown another concerning side of the fluoroquinolone use, the increasing resistance patterns to common agents such as ciprofloxacin. Fortunately, fluoroquinolone toxicity does not impact the majority of patients exposed to the drugs. With urology's long-standing reliance on fluoroquinolone agents such as ciprofloxacin and others, increased vigilance is needed as these toxicity issues become more widely analyzed and reported.

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1. Tennyson LE, Averch TD. An update on fluoroquinolones: the emergence of a multisystem toxicity syndrome. *Urol Pract* 2017;4(5):383-387.