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Platinum Opinion

In the Line of Fire: Should Urologists Stop Prescribing Fluoroquinolones as Default?

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Fluoroquinolones are widely used in urology, but despite their popularity, there is increasing concern regarding the potential severe side effects associated with this class of antibiotic. On October 5, 2018, the European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) recommended restriction of the use of fluoroquinolones and removal of some medicinal products from the market owing to the possibility of persistent adverse effects [1]. Over the past decade, the US Food and Drug Administration (FDA) has also issued a series of warnings to stress the serious and disabling adverse events associated with fluoroquinolone use. Furthermore, in 2018 the FDA required changes to the labelling of all systemic fluoroquinolone antibiotics to strengthen warnings about the risk of severe hypoglycaemia and mental health effects associated with their use. Does this mean it is time for a game change? Should we as urologists stop prescribing and using fluoroquinolones?

Since the discovery of nalidixic acid in 1960, a large number of synthetic compounds have been developed to form the quinolone and fluoroquinolone classes of antimicrobials [2]. Originally, quinolones were primarily used for the treatment of urinary tract infections (UTIs). However, the development of fluoroquinolones, which have a broader antimicrobial spectrum and better pharmacokinetic properties, resulted in a shift in prescribing practice, making fluoroquinolones one of the most commonly prescribed antimicrobial groups across all medical specialities. In 2002 fluoroquinolones became the most commonly prescribed class of antibiotics among adults in the USA [3]. In 2014, 31 500 000 fluoroquinolone prescriptions were issued to outpatients in the USA [4], and 3.1 million prescriptions for fluoroquinolones have been issued in Canada each year for the last 3 yr. Overall, in both countries this represents approximately one prescription per ten inhabitants.

However, fluoroquinolone use has been associated with serious side effects including diarrhoea and vomiting; effects on tendons, joints, muscles, and nerves; retinal detachment; aortic aneurysm; and a variety of central nervous system disturbances (insomnia, restlessness, fatigue, seizures, convulsion, and psychosis). More rarely, reactions such as haemolytic uremic syndrome and Stevens Johnson syndrome have also been reported [1]. A meta-analysis showed that fluoroquinolones are associated with more central nervous system and gastrointestinal-related adverse events compared to other types of antimicrobials [4]. The FDA has recently recognised a fluoroquinolone-associated disability syndrome in otherwise healthy patients. These patients had taken fluoroquinolones for minor conditions and developed disabling side effects, some of which are permanent. In the USA, 178 cases with persistent disabilities were reported between 1997 and 2015, representing approximately 10 cases per year and one case per 3 000 000 prescriptions. In Canada, there have been 115 cases involving persistent disabilities reported between 1986 (early marketing of fluoroquinolones) and 2017, representing approximately four cases per year and one case per 1 million prescriptions. Fortunately, the incidence of cases with persistent disabilities is low;

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however, these are only the worst cases and one should aim to decrease overall adverse reactions. From a statistical point of view, decreasing the number of prescriptions using a legislative tool to reduce the use of fluoroquinolones will decrease the number of adverse effects reported, but this is an extreme approach.

To address the issue of fluoroquinolone use, the starting point should be to improve the quality of prescriptions. Several studies have reported that fluoroquinolones were poorly prescribed, with four main aspects of misuse commonly encountered: (1) no indication for fluoroquinolone therapy (no bacterial infection or inappropriate coverage); (2) extended treatment duration without indication; (3) inappropriate dosage; and (4) inappropriate use for antimicrobial prophylaxis [5,6]. Inappropriate prescription of fluoroquinolones for uncomplicated UTIs represents a large fraction of poor prescriptions, and prescription of fluoroquinolones as first-line agents in this context can be as high as 41% [7]. For many urologists, extending treatment with fluoroquinolones is considered appropriate; however, this line of reasoning must be challenged in light of their associated adverse effects and the critical problem of emerging resistance [8].

Unfortunately, many prescribers ignore recommendations on the correct use of antimicrobials. According to a recent study, guidelines on clinical practice endorsed by the Centers for Disease Control and Prevention and UpToDate did not have a clinically relevant impact on the prescribing of antibiotics [7]. How can we improve the current situation? Critical approaches to address this question include the following:

- Active targeted education of young and established urologists to promote appropriate fluoroquinolone (and other antimicrobials);
- Consideration of suitable alternative non-antibiotic treatment modalities to avoid use of antimicrobials in the future; and
- The development of interactive tools to assist urologists to make more informed and evidence-based decisions when prescribing not just fluoroquinolones but all antimicrobials.

Increased microbiological education supported by institutional implementation of rapid microbiology identification and drug susceptibility tests should, overtime, lead to a decrease in incorrect antimicrobial prescribing practices.

So should urologists stop prescribing fluoroquinolones? The European Association of Urology (EAU) Guidelines Panel on Urological Infections and the EAU Section of Infections in Urology believe that the answer is “no”. Fluoroquinolones have unique pharmacokinetic and pharmacodynamic properties that are advantageous in the treatment of various infections, such as complicated UTIs and genital infections. High bactericidal activity, a high distribution volume, and high bioavailability characterise their pharmacological properties. For certain infections such as chronic bacterial prostatitis, they are the most appropriate agents for treatment. For oral treatment of uncomplicated pyelonephritis, comparator agents such as oral cephalosporins are associated with a high risk of underdosing, making fluoroquinolones the preferred option. Fluoroquinolones will therefore remain an effective antibiotic class in urology; however, it is critical that urologists strictly follow guidelines when prescribing fluoroquinolones owing to their serious potential adverse events.

Prescribing the right antibiotic at the right dose for the right duration and at the right time helps to optimise patient care and fight antimicrobial resistance. Urologists must stop prescribing fluoroquinolones for uncomplicated UTIs and for antimicrobial prophylaxis [9]. The decision to prescribe fluoroquinolones should always be based on a discernible benefit-to-harm ratio for the patient. Urologists should also be aware of the higher risks pointed out by significant PRAC and numerous FDA warnings. Lawsuits related to complications from fluoroquinolones have been increasing since 2011, with more than 2500 lawsuits pending with regard to tendon rupture in the setting of fluoroquinolone use in the USA. In order to ensure the best level of care for each individual patient, urologists should always consider the serious side effects associated with fluoroquinolones and participate in a shared-decision making process with each patient, clearly outlining the associated complication risks for them [10].

Conflicts of interest: Gernot Bonkat has nothing to disclose. Florian Wagenlehner is a company consultant for Astellas Pharma Europe, Rosen Pharma, Janssen-Cilag, Pierre Fabre, Bionorica, OM Pharma, Serag Wiessner, MSD, Achaogen, Pfizer, and Leo Pharma; has received speaker honoraria from Pierre Fabre, Strathmann, Bayer Vital, Cernelle, OM Pharma, and Leo Pharma; has participated in trials for CRM Pharma, Calixa Pharma, OM Pharma, Janssen-Cilag, Johnson and Johnson, Rosen Pharma, AstraZeneca, Bayer Vital, Zambon, Cubist, Aventis, Cerexa, and Astellas; has received honoraria/consultation fees from Bionorica, Leo Pharma, and Cubist; and has received grants/research support from Bionorica.

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