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Fluoroquinolone antibiotics – what we shouldn't forget two years after the restriction by the European Commission

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The use of fluoroquinolone and quinolone antibiotics was legally restricted by the European Commission (EC) on 11 March 2019.

Before this, fluoroquinolones were among the most popular antimicrobial drugs prescribed across all medical disciplines. Common indications included intra-abdominal infections, infections of bones and joints, acute exacerbation of chronic bronchitis and community-acquired pneumonia, acute bacterial or chronically exacerbating sinusitis and urinary tract infections (UTIs). Furthermore, fluoroquinolones have been used as antimicrobial prophylaxis prior to surgical interventions and long term prophylaxis of recurrent UTIs. Interestingly, fluoroquinolones have been given as prophylaxis or as postexposure prophylaxis to protect gulf war soldiers from anthrax. They were also widely used in animal fattening.

And even in cases where international guidelines no longer recommended their use in recent years because of rising antimicrobial resistance rates, they were still widely used in clinical practice [1]: a Swiss cross-sectional study on general practitioners' prescribing patterns between 2017 and 2018 reported that 13.8% of antibiotics prescribed inappropriately for UTI were fluoroquinolones [2]. A survey-based study among urologists in Germany, Austria and Switzerland in 2017 showed that fluoroquinolone use continued for antimicrobial prophylaxis in transurethral prostate surgery despite guideline recommendations [3].

Even in 2008, gradual warnings had been issued in the United States (US) due to the increasing number of significant and – sometimes – irreversible side effects [4]. Tendinopathy, with the most recognised adverse event tendon rupture, led to the first black box warning in the US. Fluoroquinolones exert a toxic effect not only on tendons but also on cartilage, bone and muscle. These musculoskeletal adverse events may be fulminant and can result in surgery, but they may also occur years after fluoroquinolone use and may – at first sight – not be associated with this medication because of their lack of specificity. Other adverse events include psychiatric complaints, hypoglycaemia and aortic aneurysms. Furthermore, a fatigue syndrome can develop. Fluoroquinolones work through inhibition of bacterial topoisomerases. However, this inhibition is not specific and consequently human topoisomerases might be inhibited as well and, in particular, human mitochondrial DNA is at risk of being altered. Consequently, the use of fluoroquinolones, even if months to years ago, should always be considered as a cause.

In the US, these warnings first appeared as so-called "black box warnings" on the package leaflet. These warnings were followed by restricted treatment recommendations by the Food and Drug Administration (FDA) in 2016 for acute bacterial sinusitis, acute bronchitis and uncomplicated UTIs in patients for whom other treatment options were available.

The review of fluoroquinolones in Europe was initiated in February 2017 at the request of the German Medicines Agency (BfArM). On 5 October 2018, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended the European Medicines Agency (EMA) to limit the use of fluoroquinolones and to withdraw some substances from the market because of possible long-lasting side effects. The Committee for Medicinal Products for Human Use (CHMP) agreed to these recommendations. Therefore, the EMA closed its review on the serious, debilitating and potentially permanent adverse events associated with the administration of quinolones and fluoroquinolones on 15 November 2018. This ultimately led to the legally binding decision of the EC in March 2019 to restrict the use of these antibiotics (a) for infections that might get better without treatment or are not severe, (b) for non-bacterial infections, (c) for prevention of traveler's diarrhoea or recurrent UTIs and (d) for the treatment of mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used. Furthermore, their use should be avoided in patients who had serious side effects with fluoroquinolones before and they should only be used with special caution in the elderly, patients with kidney disease or organ transplantation [5].

Depending on the country, this was implemented differently: in addition to adapting the drug information, Germany

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responded with a “Red Hand Letter”, which was sent to pharmacists and doctors to point out side effects and limitations of the indication of fluoroquinolones.

The drug information in Switzerland was updated analogously to the adaptation recommended by the PRAC. Swissmedic published a report specifying the safety profile and restricted first-line treatment of uncomplicated infections and infections of the genital organs [6]. Furthermore, a disclaimer was added to the beginning of the packet leaflet stating that the fluorochinoles only can be prescribed when other antibiotics are not suitable or have failed. If the drug is not prescribed according to this disclaimer, it would be considered as off-label use and the prescribing practitioner or specialist would be fully responsible for potential adverse events. Keeping in mind that the number of legal proceedings regarding complications after the use of fluoroquinolones have been increasing, physicians must adhere to clear recommendations: in Switzerland, physicians must carry out their work in accordance with Article (Art.) 40 Paragraph (Para.) A of the Medical Professions Act (MedBG) and exercise Art. 3 of the Therapeutic Products Act (HMG) with care and diligence. To justify the off-label use of drugs, the doctor must be able to rely on recommendations from professional associations or scientific articles in recognised medical journals and demonstrate an obvious benefit and successful use. Taking uncomplicated UTI as an example, both the guidelines of the European Association of Urology and articles in response to the EC decision against the use are available [1, 7], so that a prescribing doctor cannot refer to them. An off-label prescription should not only be justified, it should also be clearly explained to the patient and documented (Art. 40, Para. C MedBG). The prescribing physicians must also document the reasons for their decision and the treatments taken for the patient and their insurance. In view of the peculiarity of an off-label prescription, the doctor must ensure that they have sufficient coverage of their liability insurance for any damage to the patient (Art. 40, Para. H, MedBG) [8].

These restrictions sound like a big hurdle and therefore the question arises what consequence they had on the prescription of fluoroquinolones in clinical practice. It is not yet possible to make explicit statements about a change in prescribing pattern as a result of the EC restrictions. However, in general, prescriptions of fluoroquinolones seem to have decreased: according to the Swiss Antibiotic Resistance Report, the general consumption of fluoroquinolones in human medicine fell by 39% from 2010 to 2019 [9]. Fluoroquinolone non-susceptibility has steadily increased from 10.3% in 2004 to 20.5% in 2015, since it has stabilised between 18.6% and 20.5% (18.7% in 2019). Whether this was due to the promotion of fluoroquinolone-free antibiotic regimens for uncomplicated UTIs must be further analysed. In states of the European Union, a slight but significant increase in fluoroquinolone resistance from 24.8% to 25.3% was observed from 2015 to 2018 [9]. In France, the *Société de pathologie infectieuse de langue française* and the *Haute autorité de la santé* updated their guidelines on UTI management in December 2015 and now recommend a single dose of fosfomycin for acute uncomplicated UTI and stopped reimbursement of fluoroquinolones thereafter. Between 2014 and 2019 the dispensing of lomefloxacin and norfloxacin decreased by 80% and that of ciprofloxacin by 26% [10].

Another way to judge the impact of EC restrictions is to not only observe prescribing patterns and resistance rates, but to also look at reported adverse events. Analysis of the Eudra-Vigilance database of adverse events of fluoroquinolones revealed that reported total, musculoskeletal and connective tissue-related, and neurological adverse events were stable 21 month before and after the EC restriction [11]. The assessment of adverse events has several limitations as it is strongly dependent not only on the use of the medication but also on the awareness of adverse events or their extent. Since many adverse events of fluoroquinolones are rather non-specific, it is assumed that these symptoms were often not associated with the use of the drug and therefore tended to be underreported. However, EC restrictions have been reported both in the medical literature and in the general press, so that there is much greater awareness of musculoskeletal and neurological adverse events in particular. This increased awareness is also reflected in the fact that more self-help groups have been set up throughout Europe and in Switzerland. For example, the “Association for Education on the Side Effects of Fluoroquinolone Antibiotics” has developed as a part of Swissmedic's working group for patient/consumer organisations. Their main aim is to inform clinicians and patients about fluoroquinolone adverse events.

This increasing awareness of fluoroquinolone-associated adverse events underlines how important it is for clinicians to adhere to the EC restrictions and to strictly follow the recommendations in the case of off-label uses.

In conclusion, besides the development of resistance and the occurrence of adverse events, not only the choice of antibiotic substance but the indication for antibiotic therapy in general must be well evaluated. The decision to use antibiotic therapy should always be carefully considered and made only when clinically indicated.

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