УДК 615.33/.065 https://doi.org/10.37436/2308-5274-2020-4-13

# INTERNATIONAL SEVERE WARNING REQUIREMENTS AND SMART DECISIONS IN CHOICE TACTICS FOR FLUOROQUINOLONES

O. O. YAKOVLEVA, O. Yu. HOINA-KARDASEVICH

*National Pirogov Memorial Medical University, Vinnytsya, Ukraine*

**Fluoroquinolones occupy one of the leading places when using worldwide. However, the range of adverse reactions at post-marketing levels is expanding, that requires attention and restrictions. The specified list of adverse reactions in the instructions for the drugs is supplemented by a great attention to disorders of the nervous system, joints and the risk of rupture of aortic aneurysm. Additional indications comprise: elderly patients, previous history of reactions to fluoroquinolones, renal or joint dysfunction, interaction with glucocorticoids. These limitations must be taken into account by physicians in daily practice.**

*Key words: fluoroquinolones, adverse reactions, restrictions on indications, international recommendations.*



A feature of the use of antibiotics (AB) is the existing interaction between three components: human body, microbial pathogen and drug, each of which has its own multidirectional vectors. Therefore, the very for AB the frequency of inadequate prescriptions reaches a maximum among all pharmacological agents and reaches 50–70% of errors, according to the world statistics. For the group of fluoroquinolones (FQ), this situation also persists: without the need for a prescription of these antibiotics, 1 among 3 patients receives a prescription. At the same time, recently their indications have been re-thought due to the accumulation of information about their toxicity.

FQ application has prevailed after developments based on the achieved expansion of the range of effects on gram-positive flora, i.e. inclusion in the treatment protocols for community-based pneumonia and exacerbations of chronic obstructive bronchitis of respiratory FQ [1]. Thus, by the beginning of the 2000s, over the past decade, 250 million patients worldwide were levofloxacin treated. Then, in a review by Peter Ball (2003) [2], the authors believed that the new FQs «are the drugs of the future for these indications» as powerful, first-class alternative treatments, including atypical pathogens and even Legionella, with minimal pneumococcal resistance. Their effectiveness exceeded cephalosporins and reached 95–100% [2].

The emergence of individual negative reports about the side effects of FQ has constantly increased [3]. Initially, they were associated with damage to the articular system, i. e. tendinitis, tendon ruptures [4], neuropathies [5], photosensitization, cardiotoxicity.

However, the following years have refined the safety of FQ therapy, summarized as class effects. One of the first pieces of evidence in the field of FQ safety was the published data on the banning and removal of some of them out of the pharmaceutical market. In the first instructions for this class drugs, mainly adverse reactions of the gastrointestinal tract were mentioned, which did not interrupt the therapy. It is noteworthy that the toxic effects of FQ drugs were detected already in post-marketing observations, when they were implemented in millions of patients.

One of the early reviews on the safety of fluoroquinolones [6] provides the timing to prohibit the FQ use: June 1992 for temafloxacin [7], October 1999 for grepafloxacin [8], and limiting the indications for trovafloxacin only in case of serious infections. The «temafloxacin syndrome» was manifested by hemolytic anemia, renal failure, hepatotoxicity, hypoglycemia, and disseminated intravascular coagulation: an acute renal failure was found in two thirds of patients, in half of them there were observed hepatobiliary disorders, and coagulopathy was revealed in a third of them. For grepafloxacin withdrawn as early as 2 years after application, the cardiac arrhythmias and prolonged QTc time were typical [9]. Subsequently, it has been clarified that arrhythmias are possible for other FQs in some patients with risk factors, such as female sex, old age, bradycardia, cardiac pathology, electrolyte imbalance, interaction with other class I/ III antiarrhythmic agents.

Hepatic pathology, eosinophilia, and hypoglycemia have been reported as serious adverse reactions to trovafloxacin [10]. Phototoxicity was more often manifested in therapy with lomefloxacin, sparfloxacin, or clinofloxacin, owing to the putative mechanism of generation of free oxygen radicals [6].

Categorized adverse reactions are associated both with various structural modifications of FQ formulas, replacement of fragments around the nucleus, and with pathophysiological mechanisms of different points of application in pharmacodynamics [11].

Re-thinking the safety of pharmaceuticals is constantly being updated and refined, that contributes to a decrease in prescribed drugs: for example, in the USA since January 2014, their number has reduced by 37–40%.

Food and Drug Administration ((FDA), USA) is actively encouraging for stronger warnings, this

time sequence of restrictive recommendations is quite illustrative. The first black box warnings were presented in July 2008, following the observation of the Public Citizen group to recognize the risks of tendonitis and tendon rupture; this requirement was supplemented in 2013 by a greater risk in the patients with myasthenia gravis; in 2013, the FDA demanded the inclusion of the possibility of irreversible nerve damage in peripheral neuropathy in the information for the drug, and in 2016 the risks were also enhanced for persistent adverse reactions of the musculoskeletal and central nervous systems.

In June 2018, the FDA warned against the adverse effect of FQ on glucose homeostasis in diabetes mellitus (when taking hypoglycemic drugs) and in aged people.

The most unexpectedly the FDA reported on December 20, 2018 this was about an increased risk of ruptured aortic aneurysm. As the researchers (Nick Deineman's team) assessed themselves, «overwhelming» evidence of the assumption of possible collagen damage, both in the tendons and in the aorta, was obtained. We analyzed data from over 1.7 million citizens of Ontario aged over 65 (from April 1, 1997 to March 31, 2012), who were prescribed with one of the FQ in 38% of cases, and it was found that 2.1% of them had tendon rupture, and 1.1% did aortic aneurysm, i.e. the risk of tendon rupture tripled, and that of aortic aneurysm doubled [12–14]. These findings were met with disbelief, but the evidence was incontestable and attributed to serious adverse reactions. FQs activate metalloproteins of the cell matrix, this is accompanied by a decrease in the synthesis of collagen fibrils of types I and III, they are the main metabolites in the Achilles tendon and in aorta. The terms of the development of aortic aneurysm rupture in 41% of cases was observed in the first 10 days of treatment, and in 55% within 20 days, which excludes the danger of long-term therapy with FQ [14–16].

These data allow us to recommend a thorough assessment of both the diagnosis of aortic aneurysm and conditions predisposing to similar prognosis: Marfan or Ehlers-Danlos syndromes, Takayasu's arteritis, giant cell arteritis, Behcet's disease, atherosclerosis, hypertension, atherogenesis, especially in aged people.

Ehlers-Danlos syndrome (EDS) is hereditary mesenchial dysplasia, i.e. disorders and defects in the molecular structure of collagen — hyperelasticity of the skin. It is mentioned in 1682 (J. van Meekeron) and described in 1891 (Chernogubov A. N.), Edward Ellers (1901), Henry Danlos (1908). It is often found in population and has the following manifestations such as: hypermobility of joints and tongue, thin skin, vascular insufficiency, lesions of the eyes, teeth, kyphoscoliosis, hernias, varicose veins, mitral valve prolapse, arrhythmias, organ ptosis, vascular aneurysms, hemorrhages.

Clarifications for the control of mental health disorders were proposed by the FDA as a requirement to list these adverse reactions separately from others in the central nervous system: they are related to an impaired attention, arousal, hallucinations, nervousness, psychosis, disorientation, memory impairment or delusions, suicide [15–18].

Apparently a comprehensive assessment of the reviews and reports allows the FDA to update relevant warnings and safety requirements for this class of antibiotics, although they highlight that this is often not an easy task, especially in elderly patients with comorbidity.

To illustrate the above, the results of the latest studies published taking into account the well-known restrictive recommendations of the FDA until 2018 should be attributed. Thus, a study in Italy, published in April 2020, was based on spontaneous reports and national data from an online public reporting system in Campania (southern region of the country) from January 1, 2001 to March 31, 2019 [18]. The comparison was carried out depending on the FQ generations in terms of antimicrobial activity: the first group includes cinoxacin, pipemidic acid and nalidixic acid; the second comprised ciprofloxacin, enoxacin, lomefloxacin, norfloxacin, ofloxacin, rufloxacin; he third included gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, pefloxacin, sparfloxacin; the fourth consisted of prulifloxacin, clinafloxacin, gemifloxacin, trovafloxacin. Post-marketing observations revealed serious and dangerous adverse reactions (ADs), so some FQs were withdrawn from the market (grepa, temafloxacin). Following a public hearing in June 2018, the European Medicines Agency (EMA) has drawn attention and completed a review of the risk of serious and persistent adverse reactions that affect muscles, joints and the nervous system, with marketing authorization for cinoxacine, nalidixic and pipemidic acid to be suspended and for the rest of the FQ the restrictions were proposed.

Limitations of indications include as follows: infections that could have been cured without treatment or were not serious, non-bacterial infections, prevention of diarrhea, recurrent lower urinary tract infections [19], mild to moderate bacterial infections that can be treated with other antibacterial agents.

In spontaneous reports [18], the most frequent adverse reactions to FQ were established at the age of 18–65 years (47%) and after 66 years (43%). Among the frequent complications, the «guilty» drug was levofloxacin (49.3%), ciprofloxacin (37.3%), moxifloxacin (6.8%), for other FQs this was from 2 to 0.2%. More than half of FQ (57.6%) affected muscles, joints and the nervous system. Thus, among the diseases of the nervous system (47.7%) the following prevailed: tremor (25.4%), paresthesia (11.1%), headache (11.1%) [18]. The mechanisms of the stimulating effect of FQ on the CNS are associated with an affinity for the GABA receptor [20] or activation of N-methyl-D-aspartate (NMDA) or adenosine receptors.

Among the symptoms of damage to the musculoskeletal system are typical myalgia (20.0%), arthralgia (20.0%), tendonitis (17.8%), up to 34.1% in total [15]. They can persist for weeks or even

months, especially from pefloxacin, in combination with low serum magnesium levels [21].

Psychiatric disorders were manifested by insomnia (12.5%), hallucinations (12.5%), confusion (8.3%) [18]. Other authors draw attention to precautions taking into account an increased risk of mental disorders such as toxic psychosis, depression, nightmares, suicidal thoughts or complete suicide, especially since they can occur after the first dose, which requires an immediate treatment termination.

Risk factors of possible adverse responses were analyzed in detail in this Italian study: totally up to 59 were described, the most common was age over 60 years (69.5%), incorrect indications for treatment (16.9%), renal failure (5.1%), heart transplant (3.4%), corticosteroid use (3.4%), previous history of adverse reactions to FQ (1.7%). Among inadequate indications for treatment were found such as: tonsillitis, ovarian cyst, fever, cataracts, tracheitis, flu, toothache, renal colic, drug addiction.

Evaluating the results obtained, the authors note as follows: the nature of spontaneous reporting has limitations (incomplete information), which implies an underestimation of the real number of cases of these three groups of FQs, which are serious before disability; among 12,059 cases of FQs, they accounted for almost 20%, with the highest frequency for the third generation FQ. Moreover, assuming that the reports do not contain data on concomitant pathology, drug interactions, age of patients, such a frequency in these situations may be underestimated and is a subject of ongoing public concern [18].

Life-threatening infections in pregnant women remain a complicated medical problem [22–24]. Therefore, the previously recommended contraindications to the FQ prescribing in this situation should be clarified. The results of a recent meta-analysis in Israel [25] allow assessing the risks of complications in fetus during pregnancy using the fluoroquinolones. There were thoroughly analyzed 256 papers from several English-language databases, 13 of which met the criteria for inclusion in the study. The overall prevalence of fetal malformations reached 5%, this frequency was the same as in the control group of women (FQ during the first trimester or throughout pregnancy). The cumulative prevalence of preterm birth was 7.1%, with a similar lack of difference versus the control group. The overall prevalence of stillbirths was at the level of 0.2–0.5%, which was also the same in the control group, as well as among the frequency of miscarriages up to 11.2% (except for the data of the study by Loebstein et al. in 1998). However, the authors believe that without additional information and profound studies on the safety of fluoroquinolones in the first trimester of pregnancy, these antibiotics «should not be used as first-line therapy» during this period, even in the absence of negative prognosis for the development of fetal malformations [25].

For the safety of this class of antibiotics, careful assessments of risk factors and actions of medical professionals are obviously recommended, taking into account and based on the following provisions:

— systemic fluoroquinolones can cause a long-term (up to months or years) irreversible organ injury, contributing to disability;

— when threatening symptoms as follows: muscle pain, weakness, joint pain, peripheral neuropathy, disorders in the central nervous system appear one should immediately consult a physician about the decision to discontinue treatment, to assess the risk-benefit ratio for the patient;

— interaction of fluoroquinolones and corticosteroids should be avoided if there are any symptoms of tendinitis, since the negative risks exacerbate, especially in the patients over 60 years old.



References


1. *Dekker A. R. J., Verheij T. J. M., van der Velden A. W.* Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. 2015. Fam. Pract. 32. P. 401–407. doi: 10.1093/fampra/cmv019
2. *Ball P.* Efficacy and safety of levofloxacinin the context of other contemporary fluoroquinolones: A review // Current Therapeutic Research. 2003. Vol. 64, № 9.
3. *Golomb B. A., Koslik H. J., Redd A. J.* Fluoroquinolone-inducedserious, persistent, multi symptom adverse effects // BMJ CaseRep. 2015. bcr2015209821. doi: 10.1136/bcr-2015-209821
4. *Akali A. U., Niranjan N. S.* Management of bilateral Achilles tendon rupture associated with ciprofloxacin: a review and case presentation // J. Plast. Reconstr. Aesthet. 2008. Surg. 61. P. 830–834. doi: 10.1016/j.bjps.2006.08.005
5. *Popescu C.* Severe Acute Axonal Neuropathy Induced by Ciprofloxacin: A Case Report. 2018. CaseRep. Neurol. 10. P. 124–129. doi: 10.1159/000489303
6. *Mandell L., Tillotson G.* Safety of fluoroquinolones: An update // Can. J. InfectDis. 2002. № 13 (1). P. 54–61.
7. *Blum M. D., Graham D. J., McCloskey C. A.* Temafloxacin syndrome: A review of 95 cases // Clin. Infect. Dis. 1994. № 18. P. 946–950. doi: https://doi.org/10.1093/clinids/18.6.946
8. Pfizer relabels antibiotic Trovan for serious infections. Doctors Guide (e-mailedition), August 30, 1999. URL: http://www.pslgroup.com/dg/106B6.htm
9. *Ball P.* Quinolone-induced QT interval prolongation: A not-sounexpected class effect // J. Antimicrob. Chemother. 2000. Vol. 45. P. 557–559. doi: https://doi.org/10.1093/jac/45.5.557
10. *Chen J. L., MacLean J. A.* Trovafloxacin associated eosinophilic hepatitis // N Engl. J. Med. 2000. Vol. 342. P. 359–360.
11. *Childs S.* Safety of the fluoroquinolone antibiotics; focus on the molecular structure // Infect. Urol. 2000. Vol. 13. P. 3–10.

12. *Daneman N., Bronskill S. E., Gruneir A.* Variability in Antibiotic Use Across Nursing Homes and the Risk of Antibiotic-Related Adverse Outcomes for Individual Residents // JAMA Intern Med. 2015. Vol. 175 (8). P. 1331–1339. doi: 10.1001/jamainternmed.2015.2770
13. *Daneman N., Lu H., Redelmeier A.* Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study // BMJ Open. 2015. Vol. 5 (11). e010077. doi: https://doi.org/10.1136/bmjopen-2015-010077
14. *Pasternak B., Inghammar M., Svanstrom H.* Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study // BMJ. 2018. Vol. 360. k678. doi: https://doi.org/10.1136/bmj.k678
15. *Higdon E., Twilla J. D., Sands C.* Moxifloxacin-Induced Visual Hallucinations: A Case Report and Review of the Literature // J. Pharm. 2017. Pract. 30. P. 375–377. doi: 10.1177/0897190016637987
16. *Mattappalil A., Mergenhagen K. A.* Neurotoxicity with antimicrobials in the elderly: a review // Clin. Ther. 2014. Vol. 36. P. 1489–1511. doi: 10.1016/j.clinthera.2014.09.020
17. *Mazhar F., Akram S., Haider N.* Moxifloxacin-induced acute psychosis: A case report with literature review // J. Res. Pharm. 2016. Pract. 5. P. 294. doi: 10.4103/2279-042x.192457
18. *Scavone C., Mascolo A., Ruggiero R.* Quinolones-Induced Musculoskeletal, Neurological, and Psychiatric ADRs: A Pharmacovigilance Study Based on Data From the Italian Spontaneous Reporting System // Front Pharmacol. 2020. Vol. 11. P. 428. doi: https://doi.org/10.3389/fphar.2020.00428
19. European Association of Urology (2018). EAU Guidelines on Urological Infections. Availableat: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urological-Infections-2018-large-text.pdf [Accessed-February 12, 2020].
20. *Hori S., Shimada J., Saito A.* Comparison of the inhibitory effects of new quinolones on gamma-aminobutyric-acid receptor binding in the presence of anti-inflammatory drugs // Rev. Infect. Dis. 1989. Suppl. 5. P. 1397–1398.
21. Ultrastructure of Achilles tendon of rats treated with ofloxacin and fed a normal or magnesium deficient diet / M. Shakibaei et al. // Antimicrob. Agent. Chemother. 2000. Vol. 44. P. 261–266. doi: https://doi.org/10.1128/aac.44.2.261-266.2000
22. The safety of quinolones — a meta-analysis of pregnancy outcomes / B. Bar-Oz et al. // Eur. J. Obstet. Gynecol. Reprod. Biol. 2009. Vol. 143. P. 75–78.
23. The safety of quinolones in pregnancy / E. Yefet et al. // Obstet. Gynecol. Surv. 2014. Vol. 69. P. 681–694.
24. *Muanda F. T., Sheehy O., Berard A.* Use of antibiotics during pregnancy and risk of spontaneous abortion // CMAJ. 2017. Vol. 189. P. 625–633. doi: https://doi.org/10.1503/cmaj.161020
25. The safety of quinolones and fluoroquinolones in pregnancy: a meta-analysis / E. Yefet et al. // An International J. of Obstetrics and Gynaecology. 2017. doi: 10.1111/1471-0528.15119



## МІЖНАРОДНІ ВИМОГИ СЕРЙОЗНИХ ПОПЕРЕДЖЕНЬ І РОЗУМНИХ РІШЕНЬ У ТАКТИЦІ ВИБОРУ ФТОРХІНОЛОНІВ

О. О. ЯКОВЛЕВА, О. Ю. ГОЙНА-КАРДАСЕВІЧ

**Фторхінолони займають одне з перших місць із застосування у світі. Однак спектр побічних реакцій на їх вживання на постмаркетингових рівнях розширюється, що вимагає додаткової уваги та обмежень у їх застосуванні. Перелік побічних реакцій в інструкціях до препаратів доповнюється розладами нервової системи, суглобів і ризиками розриву аневризми аорти. Доповненнями до обмежень показань є літній вік пацієнтів, реакції на фторхінолони в анамнезі, порушення функцій нирок або суглобів, взаємодія з глюкокортикоїдами. Зазначені обмеження мають враховуватися у повсякденній практиці лікаря.**

*Ключові слова: фторхінолони, побічні реакції, обмеження показань, міжнародні рекомендації.*

## МЕЖДУНАРОДНЫЕ ТРЕБОВАНИЯ СЕРЬЕЗНЫХ ПРЕДУПРЕЖДЕНИЙ И РАЗУМНЫХ РЕШЕНИЙ В ТАКТИКЕ ВЫБОРА ФТОРХИНОЛОНОВ

О. А. ЯКОВЛЕВА, О. Ю. ГОЙНА-КАРДАСЕВИЧ

**Фторхинолоны занимают одно из ведущих мест по применению в мире. Однако спектр побочных реакций на их применение на постмаркетинговых уровнях расширяется, что требует дополнительного внимания и ограничений в их использовании. Перечень побочных реакций в инструкциях к препаратам дополняется расстройствами нервной системы, суставов и рисками разрыва аневризмы аорты. Дополнениями к ограничению показаний являются пожилой возраст пациентов, реакции на фторхинолоны в анамнезе, нарушения функций почек или суставов, взаимодействие с глюкокортикоидами. Данные ограничения должны учитываться в повседневной практике врача.**

*Ключевые слова: фторхинолоны, побочные реакции, ограничения показаний, международные рекомендации.*

Accepted in 26.08.2020