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Review

The safety profile of fluoroquinolones

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ABSTRACT

While they are very useful agents, fluoroquinolones (FQs) are associated with a number of serious adverse effects (AEs). The objective of this paper is to describe the characteristics of frequent serious AEs related to FQs along with their risk factors, their safety in specific populations, and the main drug-drug interactions that may occur. Serious AEs commonly associated with FQs include tendon disorders (particularly tendinopathy and tendon rupture), CNS toxicity (seizure and encephalopathy), peripheral neuropathy (including small fiber neuropathy), cardiovascular toxicity (QT interval prolongation, dissection, and aneurysm rupture), disrupted glucose metabolism, phototoxicity, C. difficile infections, acute renal failure, and hepatic toxicity. Most of these AEs are common to all FQs, but some, such as acute kidney failure on crystallization with ciprofloxacin or norfloxacin, are more specific. Unlike the AEs associated with most other antibiotics, some of these AEs (e.g. tendinopathy or neuropathy) may occur after FQ discontinuation, and others may subsequently progress (e.g. FQ-associated disability). The risk of serious AE is heightened by factors having to do with patient age and comorbidities, the characteristics of the FQ treatment (dose and/or duration) and associated drug intake. To conclude, FQs appear to be associated with a higher risk of serious AEs than most of the other antibiotics available for the same indications, however some AEs can be avoided by bearing in mind the predisposing risk factors.

1. Introduction

Even though the safety profiles of fluoroquinolones (FQs) are now relatively well-established, doubts persist about a possibly increased risk for certain rare adverse effects (AEs), one of them being retinal detachment [1]. Due to the infrequency of AEs, clinical trials often fail to detect them, and changes in FQ safety profile only gradually ensue, once post-authorization observational studies, *meta*-analyses of clinical trials, and pharmaco-epidemiological studies have become available. Indeed, once a new risk of an AE has been identified, these studies may not only confirm an association with exposure to an FQ, but also describe the AE and determine its characteristics and risk factors. The objective of this article is to detail the characteristics of common serious AEs associated with FQs including, where available, their risk factors, their safety in specific populations, and major drug-drug interactions.

2. Generalities

It is difficult to compare the safety profile of FQs to that of the other main antibiotics available for the same indications. However, FQs appear to be associated with a higher risk of AEs, especially of serious AEs. In a *meta*-analysis of 28 clinical trials that compared AEs due to FQs versus other antimicrobials prescribed in primary care, the incidence of treatment discontinuation due to AEs was higher for FQs (OR 1.19 [1.00–1.42]). FQs were associated with more central nervous system (CNS) (OR 1.40 [1.12–1.75]) and more gastro-intestinal (GI) (OR 1.20 [1.06–1.36])-related AEs compared with other types of antimicrobial (aside from the combination of amoxicillin/clavulanic acid for GI-related AE) [2]. The incidence of cutaneous AEs was significantly lower than with trimethoprim/sulfamethoxazole (OR 0.25 [0.10–0.63]). In addition, unlike most other antibiotics, some AEs attributable to FQs (such as tendinopathy or neuropathy) may occur after FQ discontinuation and others may subsequently progress (e.g. FQ-associated disability) [3]. Finally, some serious AEs can be avoided by keeping in mind the risk factors predisposing to FQ-related AEs.

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3. The main serious adverse effects reported during fluoroquinolone therapy

3.1. Musculoskeletal adverse effects

3.1.1. Tendon injury (tendinopathy and tendon rupture) [4–6]

FQs are associated with an increased risk of tendinitis and tendon rupture (preceded or not by tendinitis), including after short-term treatment. They particularly affect (about 90 % of cases) the Achilles tendon but can also affect the biceps, the quadriceps and the rotator cuff tendons. Involvement can be unilateral or bilateral. Although manifestations can begin within the first 48 h of treatment, median time to onset is about six days, and the risk persists for up to three months after FQ discontinuation (half of the cases occur after FQ is discontinued). The risk seems to be the same for the different FQs currently on the market. In addition to previous Achilles tendinopathy or tendon rupture, risk factors include: age (> 65 years), associated (especially systemic), corticosteroid therapy, impaired kidney function (acute or chronic renal failure), duration of treatment, high cumulative dose, and transplant reception. These effects are explained by degenerative damage to collagen and reduced synthesis of proteoglycans. More than a dozen published pharmacoepidemiologic studies have evaluated the risk of tendon damage and rupture, particularly Achilles tendon rupture [3,5,7,8]. All are consistent and the majority show an almost 3-fold risk increase (potentially less for 3rd-generation FQs, but in only one study). This increase could rise up to 20-fold in case of concomitant use of corticosteroids; it would then affect about 6 out of 10,000 treated patients.

3.1.2. FQ-associated disability [9]

A new toxicity, FQ-associated disability (FQAD), was described for the first time in 2015 [10]. Four patients with no previous history developed symptoms while on FQs, with progression that continued following discontinuation and evolved into a severe, disabling multisymptomatic profile involving tendinopathy, muscle weakness, peripheral neuropathy, autonomic dysfunction, sleep disorder, cognitive dysfunction and psychiatric disturbance, suggesting a link with the neuropsychiatric toxicity of FQs. Some authors have referred to delayed mitochondrial toxicity ("exposure-induced mitochondrial neurogastrointestinal encephalomyopathy") [10]. The number of reported cases of FQAD is very low [11,12]. However, the severity and very prolonged duration of the manifestations (several months or years), which are not always reversible, has led the health authorities (FDA, EMA, etc.) to inform health professionals of this risk and to restrict the indications of FQs [13].

3.1.3. Myasthenia gravis

Due to structural features similar to quinoline derivatives, which block neurotransmission and aggravate muscle weakness in individuals with myasthenia gravis, FQs may exacerbate the disease in these patients.

3.2. Neuropsychiatric adverse effects [14,15]

Neuropsychiatric AEs occur in 1–4.4 % of patients, second in frequency after gastrointestinal AEs. Although the most common disturbances are non-serious (irritability, insomnia,..), compared to other antibiotics such as macrolides or amoxicillin/clavulanic acid, FQs are associated with a higher risk of serious neuropsychiatric AEs, including peripheral neuropathy [16,17]. The phenotype of serious AEs is quite broad, with both CNS-related AEs (encephalopathy, convulsions, etc.), and peripheral effects such as neuropathy. Central neurotoxicity appears, at least in part, to be concentration-dependent [18], while peripheral neuropathies depend on cumulative dose and duration of treatment [17].

3.2.1. Central nervous system adverse effects

CNS-related AEs (seizures and encephalopathy) are explained by the structural similarity of FQs to GABA agonists (FQs can displace GABA from its receptors, decreasing GABAergic inhibition and leading to CNS stimulation) and by their N-methyl-D-aspartate (NMDA) agonist effect [18]. Risk factors include high dosage, history of seizures, older age, electrolyte disorder, associated drug lowering the seizure threshold, impaired kidney or liver function, and association with an NSAID. The risk of seizures and other CNS-related AEs may be heightened by increased CNS penetration and a particular structure of the FQ. While only levofloxacin and ofloxacin are contraindicated in patients with seizure, all FQs are listed as drugs that lower the seizure threshold [19]. After discontinuation, central disorders typically regress within a few days. Cases of benign intracranial hypertension have been reported, and in one study, a link is suggested [20]. Psychiatric AEs are most often benign (nervousness, agitation, insomnia, anxiety, nightmares, confusion), but (visual, auditory or tactile) hallucinations, psychomotor agitation, and even delirium have been reported. The incidence of delusional psychiatric disorders is particularly high in elderly patients, estimated at 3.7 % of those treated in a study of American veterans (median age 71 years) [21]. The identified risk factors were older age and neuroleptic treatment. However, as the effects are concentration-dependent, any other risk factor for overexposure (high dosage, non-adaptation to renal function, etc.) increases this risk. Lastly, a pharmacoepidemiologic study did not conclude that risk of suicide increased in patients treated with FQ.

3.2.2. Peripheral neuropathy

At least three pharmacoepidemiologic studies have investigated the risk of peripheral neuropathy associated with fluoroquinolone use [16,17,22]. All of them are consistent and conclude that the risk of neuropathy is increased by a factor of 1.5 to 2. As the baseline risk of this event is very low, AE incidence in patients treated with fluoroquinolones remains extremely limited. One study estimated that between 120,000 and 200,000 patients need to be treated for 10 days before observing an additional case of peripheral neuropathy. The risk of peripheral neuropathy (sensory or sensory-motor polyneuropathy) is increased by duration of treatment and cumulative dose [17], rising by 3 % for each additional day of exposure. After discontinuation, regression is slow, but neuropathy is not always reversible. Cases of acute small fiber neuropathy with delayed diagnosis due to the initial normality of the electromyogram have been reported [23].

3.3. Cardiovascular effects

3.3.1. Arrhythmias: QT interval prolongation and torsades de pointes

The main cardiovascular risk associated with FQ prescription is the risk of torsades de pointes in connection with a concentration-dependent QT interval prolongation. This type of cardiac toxicity is most often observed in two circumstances: high dosage (or overly rapid infusion); risk factors related to the patients (comorbidities) or to associated drugs [24]. A *meta*-analysis of clinical trials concluded that there was an increased risk of arrhythmia and cardiovascular mortality with FQs, with the risk of arrhythmia being particularly pronounced for moxifloxacin (risk doubled compared to ciprofloxacin and levofloxacin) [25]. Aside from moxifloxacin and in the absence of a risk factor, the absolute risk of torsades de pointes with FQs is low (about 160 sudden deaths or serious ventricular arrhythmias per 1,000,000 treatments) [26]. However, this risk increases in cases of hypokalemia, hypomagnesemia, concomitant use of QT-prolonging or bradycardic drugs, or in the presence of an underlying cardiac pathology. In addition, women are more affected than men [24]. FQs are classified into three groups according to potential QT interval prolongation. Moxifloxacin (group 1), has the highest risk, especially when delivered by the intravenous route. Its effect on the QT interval is virtually constant [27], which explains its contraindications. The risk is lower (group 2) for levofloxacin,

norfloxacin, ciprofloxacin and ofloxacin. Finally, data on delafloxacin remain insufficient to draw conclusions.

Moxifloxacin in patients with risk factors for torsade de pointes is contraindicated. In practice, they are patients treated with another torsadogenic drug (see ref [19] and § interactions), patients with congenital or acquired QT prolongation, hydro-electrolytic disorders (particularly hypokalemia or uncorrected hypomagnesemia), clinically significant bradycardia, heart failure with reduced ejection fraction, or a history of clinically significant arrhythmias. Aside from these situations, during treatment with moxifloxacin, hypokalemic or bradycardic drugs should be used cautiously. For injectable moxifloxacin, as the extent of QT prolongation rises with increasing plasma concentrations due to rapid intravenous infusion rate, infusion duration should not be less than recommended (60 min), and the intravenous dose of 400 mg once daily should not be exceeded. Use of ciprofloxacin, levofloxacin, norfloxacin, and ofloxacin with a torsadogenic drug is possible, but requires QT interval monitoring. As this is a concentration-dependent AE, ECG must be performed when the plasma concentration of the FQ is highest (Cmax). Ciprofloxacin, levofloxacin, norfloxacin, and ofloxacin should likewise be used cautiously in patients with known risk factors for QT interval prolongation (see above).

3.3.2. Aortic involvement: dissection, aneurysm and aneurysm rupture

More than ten studies on this topic have been published, with at least eight concluding that the risk of aortic dissection or aneurysm rupture is increased by 1.5 to 2.5. Most of the positive studies have been conducted by comparing the risk entailed by fluoroquinolone with that observed with amoxicillin (with or without clavulanic acid) [3,28–31]. Studies with negative results used various comparators or attempted to consider in depth the potential influence of the infectious site (particularly urinary tract infection vs. respiratory infection). Although there is currently no absolute consensus on the risk of aortic wall injury, the number of concordant studies and the existence of a strong pharmacodynamic rationale lead to recommending precaution in patients with known prior aortic frailty. The risk is recognized by several drug agencies (FDA, Health Canada, etc.). The exact mechanism has not been confirmed. However, ultrastructural similarity of the tendon and the aortic wall, as well as the effects of FQs on certain matrix metalloproteinases, could explain the association.

3.3.3. Aortic and mitral valve diseases

Four studies on the subject are identifiable, two of them positive (one is very small) concluding that there is a potential increase in the risk of valvular disorder, and the other two negative [32–34]. As it stands, the existing pharmacoepidemiologic studies do not demonstrate a potential risk of valvular injury, even if it cannot be fully ruled out.

3.4. Renal adverse effects [35]

Use of FQs can be complicated by kidney failure, but this type of side effect remains rare. In a case-control study in men aged 40 to 85 years, there was a small but significant increase in the risk of acute kidney injury with oral FQs (OR 2.18 [1.74–2.73] (i.e. one additional case per 1529 patients treated), whereas the risk was not increased with amoxicillin or azithromycin [35]. In concomitant treatment with renin-angiotensin system inhibitors, the risk of acute renal failure was quadrupled (OR 4.46 [2.84–7]) [35]. Several types of kidney damage have been reported. The most common is acute immuno-allergic tubulointerstitial nephropathy, which occurs at therapeutic doses (not concentration −dependent) and usually within the first three weeks of treatment, peaking within the first ten days. Asymptomatic or complicated by acute renal failure, crystalluria has been reported with norfloxacin and more often with ciprofloxacin, which are insoluble at neutral or alkaline urinary pH and crystallize in alkaline urine (pH > 6.8) [36]. In addition to urinary pH, the risk of crystalline nephropathy is heightened by high dose or non-adjusted dose in patients with declined kidney function, insufficient hydration, an associated nephrotoxic drug (NSAIDs, renin-angiotensin system inhibitor, diuretic, etc.) and older age. While it can occur at any time during treatment as long as the relevant risk factors are met, it is most often observed during the first 15 days and is reversible; unlike situations characterized by the occurrence of acute immuno-allergic interstitial nephritis, future use of FQs is not contraindicated. Finally, acute tubular necrosis (in the absence of crystalluria) has been reported, mainly in cases of high dosage.

3.5. Hypoglycemia and hyperglycemia

Patients treated with FQs present an increased risk of hypoglycemia or hyperglycemia compared to those treated with other antibiotics. At least four studies have been published regarding the risk of hypoglycemia, two of which explored the risk of dysglycemia and hyperglycemia [37–39]. All of them present consistent results and conclude that the risk of hypoglycemia and hyperglycemia is increased by a factor of 1.3 to 2. Estimated risks were found to be lower for levofloxacin or ciprofloxacin when the products were evaluated individually (two studies) [38,39]. Risk of dysglycemia seems to increase, especially in patients with diabetes mellitus [37], leading to recommendations of intensified glucose blood monitoring during FQ treatment periods. One suggested mechanism consists in an effect on the ATP-sensitive potassium channels of pancreatic islet cells allowing the entry of calcium and the release of insulin.

3.6. Hepatotoxicity [40,41]

While trovafloxacin has been withdrawn from the market due to its hepatotoxicity, some currently marketed FQs can cause serious liver damage; however, incidence has remained low. Small increases in liver enzymes occur in 1 % to 3 % of patients receiving ciprofloxacin, norfloxacin, or ofloxacin. In one study, the crude incidence of medically significant acute liver injury, estimated at 1/100,000 patients for FQs, was much lower than that associated with amoxicillin/clavulanic acid (20/100,000), which is the antibacterial agent most frequently implicated in liver damage, close to that of erythromycin (2/100,000), and higher than that of amoxicillin [42]. For other authors, it is likewise much lower than the incidence observed with amoxicillin/clavulanic acid, which has also been estimated at 1/2500 patients [43]. However, currently available FQs only rarely cause serious acute hepatocellular damage (hepatic necrosis and hepatic failure) by means of an immuno-allergic mechanism, and occurs one to four weeks after treatment initiation. The FQs most frequently associated with reported cases of liver damage are ciprofloxacin and levofloxacin however they are also the most widely prescribed. Given the functioning of the immuno-allergic mechanism, treatment resumption is contraindicated.

3.7. Skin and immuno-allergic adverse effects

The risk of severe cutaneous adverse reactions (SCAR) (i.e. Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS syndrome, etc.) is lower than that associated with other antibiotics. In a recent study on elderly patients (> 66 years) hospitalized for skin AE after antibiotic therapy, the risk of SCAR (compared to that of macrolides) was lower with FQs (aOR 1.3 [1.2–1.4]) and penicillin derivatives (aOR 1.4 [1.3–1.5]) than with sulfonamides (aOR 2.9 [2.7–3.1]) and cephalosporins (aOR 2.6 [2.5–2.8]) [44].

Immediate hypersensitivity reactions are rare. In the event of an anaphylactic reaction with a FQ, only until an allergology consultation is resumption of another FQ contraindicated; risk of recurrence with another fluoroquinolone is not constant (around 15 %) [45]. Risk of a phototoxic reaction is present with all FQs, with the probable exception of delafloxacin, but differs according to their respective chemical structures (lomefloxacin > ciprofloxacin ≫ enoxacin > levofloxacin > ofloxacin > norfloxacin > moxifloxacin). Patients should avoid

Table 1
Main risk factors for serious adverse reactions with fluoroquinolones.

Risk factors predisposing to FQ-related AE	Types of serious AEs for which the risk is increased
Patient characteristics and comorbidities	
–age > 60 years	–tendinopathy/tendon rupture –convulsions –psychiatric adverse reactions
–impaired renal function, acute or chronic renal failure, hemodialysis	–tendinopathy/tendon rupture –convulsions –QT interval prolongation
–solid organ transplant	–tendinopathy/tendon rupture
–diabetes	–hypo or hyperglycemia
–glucose-6-phosphate dehydrogenase deficiency	–hemolysis
–myasthenia gravis	–myasthenia gravis flare-up
–history of seizures	–seizures **levofloxacin or ofloxacin are contraindicated**
–psychiatric history	–psychiatric adverse reactions
–history of clinically significant arrhythmias	–QT interval prolongation, torsades de pointes **moxifloxacin is contraindicated**
–uncorrected electrolyte disorder (hypokalemia, hypomagnesemia, hyponatremia)	–QT interval prolongation, torsades de pointes (if hypokalemia or hypomagnesemia not corrected); **moxifloxacin is contraindicated** –convulsions (if hyponatremia)
–dehydration	–for ciprofloxacin or norfloxacin: acute renal failure (urine crystallization)
–congenital/acquired QT prolongation, significant bradycardia, heart failure (clinically significant reduction in left ventricular ejection fraction)	–QT interval prolongation, torsades de pointes **moxifloxacin is contraindicated**
–aortic aneurysm, history of aortic dissection, family history of aneurysm, connective tissue disorders (Marfan, Ehlers-Danlos, Turner, rheumatoid arthritis), vascular disorders (high blood pressure, known atherosclerosis), vasculitis (Behçet, Takayasu, giant cell arteritis, Sjögren's)	–aneurysm rupture and aortic dissection
–heart valve disease, confirmed family history of congenital heart valve disease, infective endocarditis	– possible aortic or mitral valve involvement
–alkaline urinary pH	–for ciprofloxacin and norfloxacin = acute renal failure (renal crystallization)
Treatment features	
–high dosage or not adapted to kidney function	–convulsions –psychiatric adverse effects –QT interval prolongation, torsades de pointes (major for moxifloxacin)
–long duration of treatment or high cumulative dose	–tendinopathy/tendon rupture –neuropathy
–overly rapid infusion (moxifloxacin)	–QT interval prolongation, torsades de pointe
Drug-drug interactions (also see Table II interactions)	
–corticosteroid therapy (especially if systemic or prolonged)	–tendinopathy/tendon rupture (risk x 20) –aneurysm rupture, aortic dissection, possible aortic or mitral valve involvement
–torsadogenic drugs (see Table II interactions)	QT interval prolongation, torsades de pointe
– drugs lowering the seizure threshold (see Table II interactions)	–seizures
–nephrotoxic drugs: NSAIDs, renin-angiotensin system inhibitors, diuretics, …	–for ciprofloxacin and norfloxacin acute renal failure (renal crystallization)
–nonsteroidal anti-inflammatory drugs	–seizures

significant direct exposure to sunlight or UV radiation during treatment and, as regards levofloxacin, for 48 h after discontinuation.

3.8. *Clostridioides difficile-associated disease*

C. difficile infection is one of the most commonly reported AEs with FQs, which were nevertheless initially associated with a lower risk than other antibiotics. Ciprofloxacin and moxifloxacin are actively eliminated by the biliary route and reach high concentrations in the feces, and theoretically have the greatest impact on the gut microbiota, especially moxifloxacin (due to its activity against anaerobes). Stool-to-plasma concentration ratios are highest for ciprofloxacin and norfloxacin (approximately 100-fold) [46]. This ratio is in the range of 10 to 15 for levofloxacin, moxifloxacin and ofloxacin. In addition, very high concentrations of ciprofloxacin (around 1 g/g of stool) have been found in healthy volunteers up to seven days after a single dose.

3.9. *Ocular effects*

At least five pharmacoepidemiologic studies regarding the risk of retinal detachment have been published [1]. The results present major discrepancies, with half of the studies concluding the risk is increased and the other half that it remains unchanged. Pharmacoepidemiologic evidence fails to provide adequate safety assessment, and information from other sources (preclinical, pharmacovigilance) is likewise limited. The underlying hypothesis is premised on the ability of FQs to interfere with synthesis of the different types of collagen that attach the retina to the choroid.

As for the risk of uveitis, three pharmacoepidemiologic studies have been published; only one concludes that there is an increased risk [47]. As of now, limited available pharmacoepidemiologic evidence does not confirm the existence of this risk.

4. Risk factors predisposing to FQ-related AEs

The risk of serious AEs is heightened by risk factors related to patient characteristics and comorbidities, the characteristics of FQ treatment (dose and/or duration) and associated drugs. Risk factors predisposing to FQ-related AEs are summarized in Table 1. Most are common to all FQs, but some are more specific to ciprofloxacin and norfloxacin (risk of acute kidney failure on crystallization) and to moxifloxacin (QT prolongation).

5. Special populations

5.1. *Elderly subjects [48]*

It is not so much age *per se* that alters the safety profile of FQs, but rather comorbidities, physiological changes in kidney function, and associated treatments that favoring certain adverse effects.

Older people have a higher risk of tendon damage (see § 3.1.1. Tendon injury), including rupture. The consequences of tendon rupture in the elderly make it essential to systematically check for other risk factors and to inform the patient on the first symptoms of tendinitis. The risk of neuropsychiatric disorders, particularly seizures, also increases, especially in the over 80 s. They are more common when neurological pathologies predispose to seizure (previous seizure, recent stroke, etc.) or if the dosage of FQ is too high and non-adjusted to renal function. In one study, elderly patients with advanced chronic kidney disease treated with FQs at a dose higher than recommended were significantly more often hospitalized for neurological or psychiatric adverse events [49].

The risk of arrhythmia related to QT interval prolongation is also higher, due to risk factors such as hydro-electrolytic disorders (hypokalemia, hypomagnesemia), and bradycardia induced by antiarrhythmic drugs (quinidine, procainamide, amiodarone, sotalol, etc.). Similarly, cardiovascular risk factors more specific to elderly subjects

(aortic aneurysm, heart valve disease, vascular pathologies, etc.) favor an increased risk of aneurysm, aortic dissection and valve regurgitation.

One study also reported an increased risk of acute kidney injury in patients over 65 years of age, likely related to known risk factors for crystallization of ciprofloxacin and norfloxacin (insufficient hydration, drugs associated with nephrotoxicity) [50]. Some studies also report an increased risk of C. difficile infection in elderly patients. Lastly, renal function declines steadily with age and when clinically relevant reduction in creatinine clearance occurs, dosage of renally excreted FQs should be adjusted.

5.2. Patients with renal or hepatic impairment

5.2.1. Renal impairment

The FQs other than moxifloxacin are often eliminated by the renal route in unchanged form (40–90 % according to FQ) [51,52]. That is why, in patients with impaired renal function, dosage of these FQs must be reduced using Cockroft-Gault formula, the objective being to reduce the risk of concentration-dependent AEs.

– ciprofloxacin: dosage should be adjusted as soon as creatinine clearance is less than 60 ml/min

– levofloxacin and ofloxacin: dosage should be adjusted as soon as creatinine clearance is less than 50 ml/min

– norfloxacin, delafloxacin and lomefloxacin: dosage should be adjusted as soon as creatinine clearance is less than 30 ml/min; for intravenous delafloxacin, there is a risk of accumulation of sodium sulfobutyl betadex ether sodium, the intravenous delivery route, in patients with moderate to severe renal impairment, necessitating a switch to the tablet form.

– moxifloxacin: no adaptation

5.2.2. Hepatic impairment

Based on limited clinical data on hepatic elimination in this population, moxifloxacin is contraindicated in patients with severe hepatic impairment (Child-Pugh C) and in those with transaminase values 5-fold higher than normal. For ofloxacin, it is recommended, due to potentially decreased excretion in patients with hepatic impairment, that the maximum daily dose of 400 mg not be exceeded. For other FQs, there is no need to change the dosage.

5.3. Pediatric patients

In some very specific severe infections, ciprofloxacin and ofloxacin may be used in children and adolescents, whereas due to reported cases of severe arthropathies selectively affecting the large joints, the other FQs are contraindicated until the end of the growth period. This risk of joint damage has been demonstrated in animals and cases have been reported in pediatrics [53]. However, the affected children were being treated for cystic fibrosis pulmonary superinfection, which can lead to arthropathies, and most of the severe cases occurred with pefloxacin, which entailed greater joint toxicity than other FQs [54].

A *meta*-analysis of 51 studies (mostly with ciprofloxacin) showed that the risk of musculoskeletal AEs was approximately doubled in children treated with FQ [55]. The FDA's analysis of the safety data for ciprofloxacin and levofloxacin collected in pediatric clinical studies concluded that there was a slightly increased risk of musculoskeletal AEs in children receiving fluoroquinolones compared to other antibacterials [56]. Regarding the risk of Achilles tendon rupture, two pharmacoepidemiologic studies focused more specifically on the pediatric population and did not find any association, and with an extremely reduced number of AEs in both fluoroquinolone users and non-users, attesting to the low risk of Achilles tendon rupture in this population; moreover, these musculoskeletal disorders are most often moderate and reversible. As for severe joint damage, which is very rare, the size of clinical studies is insufficient to highlight this specific risk. Indeed, the period of maximum risk of arthropathy represented by the growth period in animals, the high concentration of certain FQs in the cartilage, and their effect on the differentiation of certain chondrocytes are arguments suggesting a specific effect of FQs on growth cartilage, even if the link has not been formally demonstrated [57,58]. To summarize, use of FQs in pediatrics must remain exceptional and be initiated by prescribers experienced in the management of severe childhood infections or cystic fibrosis.

5.4. Pregnancy [59]

Levofloxacin and moxifloxacin are contraindicated during pregnancy and other FQs are not recommended or should be avoided due to their toxicity to developing cartilage, which has been observed in experimental studies: alteration of immature joint cartilages of weight-bearing joints in young dogs, proportional to dose and duration of treatment. As this risk has also been identified in young children, the question of joint toxicity after exposure during the fetal period remains unanswered, even if no case of cartilage damage secondary to treatment during pregnancy has been described to date. Regarding malformation risks (specific to 1st trimester exposure), *meta*-analysis of eight cohort studies and two case-control studies did not show a significant increase in the rates of major malformations with FQ treatment (RR, 0.89 [0.70–1.14]) during the 1st trimester of pregnancy, particularly with ciprofloxacin (RR, 0.72 [0.43–1.19]) [60]. These results were confirmed in a recent cohort study [61]. In some very specific situations; use of a FQ, generally ciprofloxacin, during pregnancy is therefore possible, but only as a second-line treatment in the absence of any other alternative.

5.5. Breast-feeding [62,63]

According to their SmPC, FQs are contraindicated during breast-feeding because of their passage into the milk, entailing the joint risk for the breastfed newborn. However, rare studies in a small number of patients show that despite the excretion of some FQs in milk, the exposure of the breastfed child is low, which could be explained by complexation of FQ with calcium, which would limit its absorption. As for ciprofloxacin, it has been estimated that the newborn receives 3.5 % of the pediatric therapeutic dose via milk [64]. No adverse effects have been noted in children. Ciprofloxacin can therefore be used in a nursing mother, avoiding breastfeeding within three to four hours of taking it, and monitoring for the risk of diarrhea or candidiasis.

5.6. Overweight patients

With the exception of levofloxacin, which has an intermediate lipophilic character, the fluoroquinolones are hydrophilic drugs. Data on the dosage adjustment of FQs aside from ciprofloxacin and levofloxacin in overweight patients are limited, and those on ciprofloxacin are discrepant. Some authors recommend the administration of higher doses, using the adjusted weight formula with a correction factor of 0.45 (adjusted weight = ideal weight + 0.45*(actual weight measured – ideal weight)) without exceeding 800 mg/12 h. Others have not found any pharmacokinetic changes and do not recommend adjustment, but they recognize that higher doses may be called for in difficult-to-reach infections. For levofloxacin, studies have not shown increased clearance in overweight patients, although dosage adjustment is suggested based on creatinine clearance (estimated by Cockcroft and Gault) and ideal weight [65]. Some case series have suggested a need for higher doses (1000 mg every 12 h) in obese patients in order to achieve therapeutic goals [66]. Very limited pharmacokinetic data for moxifloxacin and delafloxacin suggest that adjustment is not necessary.

6. Drug-drug interactions [19,67–69]

The risk of drug interaction with FQs is twofold: pharmacokinetics, when the FQ modifies the concentration of the associated drug (or

Table 2
Main drug-drug interactions with fluoroquinolones [19,67].

Pharmacokinetic interactions		
– All FQs	Vitamin K antagonists: increased INR	Control INR
	Digestive topicals, sucralfate, calcium, iron salt, didanosine: decreased absorption of FQs	delay intake by 2 h
	Mycophenolate: decreased residual concentration of mycophenolate at the beginning of treatment	
– Ciprofloxacin	– Tizanidine: increased concentration of tizanidine	**Contraindicated**
	– Methotrexate, zolpidem, agomelatine: increased concentration of methotrexate, zolpidem or agomelatine	Not recommended association
	–Cyclosporin, phenytoin, sildenafil, duloxetine, ropinirole, clozapine, olanzapine, theophylline, lidocaine: increase in their concentration	Possible association but with reduced dosage of the associated drug and special monitoring
	–Probenecid: increased concentration of ciprofloxacin	
– Levofloxacin	– Methotrexate, cyclosporin: increased concentration of methotrexate or cyclosporin	Possible combination but with dosage adaptation and special monitoring
– Norfloxacin	–Theophylline (caffeine): increased concentration of caffeine	Possible combination but with dosage adaptation and special monitoring
– Ofloxacin	– Methotrexate, glibenclamide, furosemide, probenecid, cimetidine: increase in their concentration	Possible combination but with dosage adaptation and special monitoring
Pharmacodynamic Interactions		
–Risk of QT interval prolongation		
–Moxifloxacin	– Drugs known to prolong QT: class IA or III antiarrhythmics, antipsychotics, tricyclic antidepressants, certain antimicrobials (saquinavir, sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine), some antihistamines (hydroxyzine, astemizole, mizolastine)	**Contraindicated**
	–Drugs that can cause hypokalemia (loop or thiazide diuretics, amphotericin B, laxatives and enemas (in high doses), corticosteroids,…)	Used with caution: serum potassium level and heart rate should be monitoring
	–Drugs that can induce clinically significant bradycardia (anticholinesterases, beta-blockers, diltiazem, digoxin, fingolimod, pilocarpine, sofosbuvir, thalidomide, crizotinib, nilotinib, trametinib, etc.).	
Ciprofloxacin, levofloxacin, norfloxacin, ofloxacin	–Drugs known to prolong QT: class IA or III antiarrhythmics, antipsychotics, tricyclic antidepressants, certain antimicrobials (saquinavir, sparfloxacin, IV erythromycin, pentamidine, antimalarials including halofantrine), some antihistamines (hydroxyzine, astemizole, mizolastine)	Possible association, but QT interval should be monitoring
	–Drugs that can cause hypokalemia (loop or thiazide diuretics, amphotericin B, laxatives and enemas (in high doses), corticosteroids,)	Used with caution: monitoring of serum potassium level and heart rate
	–Drugs that can induce clinically significant bradycardia (anticholinesterases, beta-blockers, diltiazem, digoxin, fingolimod, pilocarpine, sofosbuvir, thalidomide, crizotinib, nilotinib, trametinib, etc.)..	
–Risk of seizure		
– All FQs	–Drugs lowering the seizure threshold: tramadol, antidepressants (imipraminics, SRIs), neuroleptics (phenothiazines and butyrophenones), mefloquine, chloroquine, bupropion.	Possible association but risk of seizure should be carefully considered
–Risk of tendinopathy and tendon rupture		
– All FQs	–Glucocorticoids (aside from hydrocortisone), especially systemic administration (or prolonged treatment) by oral route, increases the risk of tendinopathy and rupture, especially in prolonged corticosteroid therapy	Possible association but risk of tendinopathy should be carefully considered

conversely); and pharmacodynamics, when AEs due to FQs are amplified in incidence or intensity by combination with another drug. Specific pharmacokinetic interactions occur almost exclusively with ciprofloxacin, which inhibits cytochrome P450 1A2 and OAT1/3 tubular transporters, and will therefore increase the concentrations of the substrate drugs. Major pharmacodynamic interactions concern the risk of QT interval prolongation, seizures and tendinopathy/tendon rupture. The main drug-drug interactions with FQs are summarized in Table 2.

7. Patient information

The EMA, the ANSM and the SmPC recommend systematic patient information to facilitate rapid management of certain serious and/or disabling adverse effects and to limit their consequences [70].

The key messages are:

– "If you experience the following side effects, stop the treatment and contact your doctor (the prescriber or your general practitioner) immediately: pain or swelling of the tendons, especially in the ankle or calf; muscle pain, numbness, tingling, swelling, or weakness in different parts of the body, often starting in the hands or feet, which gets worse over time; severe fatigue, depression, poor memory, or severe sleep problems; changes in vision, hearing, taste, and smell; swelling of the shoulders, arms, or legs, or joint pain.

– "Seek help from a healthcare professionals or emergency services if you experience sudden abdominal, thoracic or back pain, acute dyspnea, new heart palpitations, or the development of edema of the abdomen or lower extremities."

8. Recommendations for the management of certain adverse reactions

– At the first sign of tendinitis (e.g. painful swelling, inflammation), FQ should be discontinued, and an alternative treatment should be considered.

– If symptoms suggestive of neuropathy develop (e.g., pain, burning, tingling, numbness, weakness, abnormality in sensitivity), FQ should be discontinued so as to prevent irreversible damage.

– If C. difficile-associated diarrhea is suspected or confirmed, FQ

should be discontinued immediately and appropriate treatment should be initiated without delay. Drugs that inhibit peristalsis are contraindicated.

Finally, remember to report AEs related to FQs to your Regional Pharmacovigilance Centre, especially when they are serious (hospitalization or prolonged hospitalization, sequelae, life-threatening prognosis or death).

CRediT authorship contribution statement

Annie-Pierre Jonville-Béra: Conceptualization, Supervision, Writing – original draft. **Bérenger Largeau:** Writing – review & editing. **Ferderico di Meglio:** Conceptualization, Writing – original draft. **Antoine Pariente:** Conceptualization, Writing – original draft.

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