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Safety of fluoroquinolones

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ABSTRACT

Fluoroquinolones (FQs) are one of the most commonly prescribed classes of antibiotics. Although they were initially well tolerated in randomized clinical trials, subsequent epidemiological studies have reported an increased risk of threatening, severe, long-lasting, disabling and irreversible adverse effects (AEs), related to neurotoxicity and collagen degradation, such as tendonitis, Achilles tendon rupture, aortic aneurysm, and retinal detachment. This article reviews the main potentially threatening AEs, the alarms issued by regulatory agencies and therapeutic alternatives.

Keywords: Fluoroquinolones, adverse effects, neuropathy, tendon rupture, aortic aneurism, dysglycemia

Seguridad de las fluoroquinolonas

RESUMEN

Las fluoroquinolonas son una de las clases de antibióticos más prescritas. Aunque inicialmente fueron bien toleradas en ensayos clínicos aleatorizados, estudios epidemiológicos posteriores han informado de un mayor riesgo de efectos adversos efectos adversos amenazantes, graves, duraderos, incapacitantes e irreversibles, relacionados con la neurotoxicidad y la degradación del colágeno, como tendinitis, rotura del tendón de Aquiles, aneurisma aórtico y desprendimiento de retina. Este artículo repasa los principales efectos adversos potencialmente amenazadores, las alarmas emitidas por las agencias reguladoras y las alternativas terapéuticas.

Palabras clave: Fluoroquinolonas, efectos adversos, neuropatía, rotura de tendón, aneurisma de aorta, disglucemia

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INTRODUCTION

Quinolones are a synthetic class of antibiotics. The first quinolone (nalidixic acid) was discovered by George Lesher in the early 1960s as a secondary product in the synthesis of chloroquine. Afterwards, new compounds with at least one fluorine atom in their chemical structure, fluoroquinolones (FQs), were synthesized. Since their introduction in the 1990s, they have become one of the most prescribed antibiotics because of their exceptional pharmacokinetic (PK) and pharmacodynamic (PD) profile, broad-spectrum antibacterial action, and satisfactory tolerance [1]. In the last decade, two new systemic FQs, finafloxacin and delafloxacin, have been approved by the FDA or EMA, that present a broad antibacterial spectrum, including anaerobic bacteria, and activity in acidic pH environments. However, the emergence of resistance, particularly in Gram-negative bacteria, and the association with severe adverse effects (AEs) have conditioned their current clinical use [2]. The aim of this article is to review the main AEs induced by CFs, the alarms issued by the main regulatory agencies and the therapeutic alternatives.

In the historical development process of FQs, many promising compounds, such as sparfloxacin, temafloxacin, grepafloxacin, gemifloxacin, trovafloxacin, and clinafloxacin, were withdrawn from the market because of serious AEs [3]. In randomized controlled trials (RCTs), considered the gold standard in clinical research, the currently approved FQs (ofloxacin, ciprofloxacin, levofloxacin and moxifloxacin) had been shown to be fairly well tolerated with mild to moderate and reversible AEs. However, some of them had not been detected due to their low frequency. Most of these RCTs have reported AEs of FQs on the hepatic system, central nervous system, gastrointestinal tract, skin, and musculoskeletal system. Observational studies in comparison with RCTs explore rare events among a larger number of patients in the real-life setting with longer follow-up time. In addition, large databases provide an important platform for the undertaking of observational studies to

generate safety of drugs, including incidence and prevalence of rare (between ≥1/10 000 and <1/1000) to very rare (<1/10 000) events [4]. Several systematic reviews and meta-analyses of observational studies and case-control studies addressing the emerging safety concerns associated with FQs have been recently published, especially in the last years [5,6]. On the other hand, several regulatory agencies, such as US Food and Drug Administration (FDA), European Medicine Agency (EMA), Canada Health and the Therapeutic Goods Administration in Australia, have reported unusual and serious AEs that can also help to measure the real incidence of these events [7].

FQs are associated with a higher risk of central nervous system and gastrointestinal-related AEs compared to other types of antimicrobials [5]. AEs by FQs can occur within 48 hours from administration, but can also cause delayed damage after several months from drug discontinuation. AEs are mainly located in: gastrointestinal tract (nausea, vomiting, abdominal discomfort and pain, anorexia, and in some cases, diarrhea), muscles (neuromuscular blocking activity), tendons (tendonitis, tendon rupture, particularly to the Achilles tendon), joints (arthralgia), nervous system (headache, dizziness, confusion, seizures, depression, and insomnia), and cardiovascular system (QTc prolongation and arrhythmias). Other less frequent adverse effects include: phototoxicity, dysglycemia, hepatotoxicity, acute renal failure, allergic reactions, genotoxicity, hematological and immunological side-effects, aortic aneurysm (AA) and aortic dissection (AD), retinal detachment, and CYP 450 inhibition [8].

FQs kill bacteria by interfering with DNA synthesis and inhibiting their replication pathway. They exert their action through the inhibition of the bacterial topoisomerase II type enzymes, DNA gyrase and DNA topoisomerase IV. Although there is similarity in the sequence of human topoisomerase type II, FQs have been shown not to affect the action of human enzymes. This fact can be explained because the A and B subunits of human enzymes fused together during evolution and nowadays they function as homodimers. Despite this strong affinity of FQs for prokaryotic topoisomerases compared to eukaryotic topoisomerases, they are not free of clinically relevant adverse effects [8]. Some of the fluoroquinolone AEs are related to structure abnormalities, based on constituents found at specific sites on the quinolone nucleus, but here are other AEs mechanisms [2]. FQs have an excellent penetration into almost all tissues and intercellular compartments. The volumes of distribution in some molecules are so high that exceed the volume of total body water, indicating its accumulation in some tissues. Moreover, in certain sites they exceed serum concentrations. This pharmacokinetic profile is the main responsible for these drugs success against infections [9].

POTENTIALLY LIFE-THREATENING AND DISABLING ADVERSE EFFECTS

Tendinopathy and tendon rupture. Tendinopathy is one of the first reported AEs related to the use of FQs, mainly ciprofloxacin. They have been associated with an increased risk of tendonitis and rupture particularly of the Achilles tendon (90% of all cases). Treatment time and cumulative dose of FQs, concomitant use of corticosteroids and other drugs, older age and comorbidity, seem to be additional risk factors for tendinopathy [10-14]. The time of symptoms onset is variable, with a median latency period of between 6–14 days. However, other reports have indicated tendinopathy symptoms and Achilles tendon rupture occurring weeks to months after cessation of treatment. These clinical findings suggest a certain incapability to return to normal tendon homeostasis and a prolonged period of elevated risk of FQ-associated tendinopathy after discontinuation of FQ therapy. FQ-associated tendinopathy is associated with collagen disruption and degeneration, and a proteoglycan synthesis reduction, partially attributable to downregulation of matrix metalloproteinase (MMP)-degrading enzymes [13,15].

Central and peripheral neuropathy. FQs are associated with a higher risk of central and peripheral nervous-related AEs compared to other types of antimicrobials [4,16,17]. In addition, third-generation FQs (levofloxacin and moxifloxacin) have been associated with an increased likelihood of neurological and psychiatric AEs compared to second-generation FQs (ofloxacin, norfloxacin and ciprofloxacin) [18]. The frequency of peripheral neuropathy is poorly quantified and may occur after the first FQs doses have been administered and may be permanent [2]. FQs AEs related to central nervous system (CNS) are the second most frequent after gastrointestinal-related AEs. They are estimated to occur in 1–4.4% patients and range from mild (confusion, irritability, and insomnia) to severe (encephalopathy, seizures, suicidal depression, catatonia, psychosis, and mania) [19,20]. FQs have been associated with neurotoxicity through the inhibition of GABA (gamma-aminobutyric acid) and NMDA (N-methyl-D-aspartate) receptors. In addition, FQs derivatives with unsubstituted heterocycles in position C7 seem more associated with CNS side-effects [2,20]. The similar chemical structures of certain substituents at position 7 (piperazine in ciprofloxacin and norfloxacin) of the quinolone nucleus and the chemical structure of GABA allows these FQs to compete and displace GABA from its receptor sites, possibly leading to overstimulation. However, substituted compounds containing 7-pyrollidinyl (levofloxacin) are associated with reduced seizure-causing potential [21]. The FQs may also induce exacerbations of myasthenia gravis due to structural characteristics similar to quinolone derivatives that block neurotransmission [22].

Cardiovascular system. There is a significant association between the use of FQs and an increased risk of arrhythmia and cardiovascular mortality, that is higher with moxifloxacin than levofloxacin and ciprofloxacin. Women are more affected than men [6,23-26]. In some patients with coronary artery disease and electrolyte disturbances, QT prolongation may be followed by sudden onset of torsade de pointes and death. QT prolongation is mainly based on the increased repolarization duration through the blockade of the cardiac K+ channel [23].

In recent years, several observational and case-control studies, systematic reviews and meta-analysis have suggested

a positive association between the use of FQs and an increased risk of aortic aneurysm (AA) and aortic dissection (AD) [27-42]. FQs intake within 60 days was associated with the highest risk of AA/AD [27-30,32,35]. However, recent results show that FQs were associated with increased 90-day incidence, and in addition there is a consistent association across adults aged 35 years or older [42]. Furthermore, compared with intravenous administration of FQs, oral FQs were more likely to be implicated in the increased risk of AA/AD [43,44]. The exact mechanism of FQ-induced AA/AD remains unknown. But, the ultrastructural similarity of tendon and aortic wall, together with FQ-induced MMP overactivity, may well explain the emerging association between these antibiotics and AA/AD [29,45-48].

Retinal Detachment. Many large cohort studies have showed conflicting results concerning the association between retinal detachment and FQs use. Further studies with additional information disclose the necessity of complementary studies to clarify these data [49,50].

The mechanism by which FQs therapy could be associated with certainty of retinal detachment is not yet fully elucidated. However, FQs may interfere with the synthesis of the different types of collagen that attach the retina to the choroid, just as it does in AA. In addition, CF may also alter the collagen that forms part of the retina [51,52].

Dysglycemia/hypoglycemia and hyperglycemia. Observational studies have reported that FQs users (diabetics and non-diabetics) are at an increased risk of serious disglycemia compared with other antibiotic users and appears to be more common with moxifloxacin and levofloxacin [53-56].

The mechanisms by which FQs cause dysglycemia are unknown. It is thought to be due to sulfonylurea-like effects on the ATP-sensitive potassium channels of pancreatic islet cells that allow the entry of calcium and the release of insulin. FQs can also inhibit the activity of P450 isoenzymes, which are responsible for several anti-diabetic drugs metabolism [55,57].

Hepatotoxicity. In the past, some FQs were withdrawn as a result of serious side-effects, including hepatotoxicity (e.g., trovafloxacin), However, the usual FQs are rarely associated with severe liver damage concerning increased transaminase levels. Ciprofloxacin is the most hepatotoxic FQ [58-61]. Liver damage includes hepatocellular necroses, cholestasis, and immune allergic reactions and appears to start from the first week to four weeks of treatment [59,62].

***Clostridiodes difficile* Infection.** *C. difficile* infection is currently one of the most frequent reported AEs with FQs, although they were initially associated with a low risk compared with other antibiotics. Additionally, several reports have established a link between the administration of common FQs and the *C. difficile* infection. FQs, as broad-spectrum antibiotics, may cause alterations in the colon flora [63,64]. Ciprofloxacin and moxifloxacin are actively eliminated via the biliary route and reach high concentrations in the faeces, and therefore, theoretically have the greatest impact on the gut microbiota, particularly moxifloxacin due to its activity against anaerobes [65].

AEs of delafloxacin. Delafloxacin has a proven safety profile. Clinical studies have only reported gastrointestinal, skin and subcutaneous AEs, sporadic cases of peripheral neuropathy and *C. difficile* infection, but not the occurrence of severe aortic aneurysms, aortic dissection, treatment-related tendinitis, tendon rupture, or myopathy, retinal detachment, neuropsychiatric toxicity and others [2]. But we have to wait for further clinical experience to confirm these data.

MANAGEMENT AND SAFETY WARNINGS CONCERNING EMERGING LIFE-THREATENING AND DISABLING ADVERSE EFFECTS

Based on the serious AEs reported in several studies, numerous cautions regarding the use of FQs have been issued. In addition, the FDA received 210,705 adverse event reports for marketed FQs between November 1, 1997 and July 28, 2015. The most commonly reported toxicities were neurologic (30% and 26%), tendon damage (8% and 6%), and psychiatric (10% and 2%). A new toxicity, FQ-associated disability (FQAD), was first described in detail at FDA Advisory Committee meetings in April 2013 and November 2015 [65,66]. Since 2008 and 2018, several warnings on the use of FQs have been issued by the FDA and EMA, respectively. Currently, FDA and EMA have restricted the use of FQs in treating mild and uncomplicated infections, non-bacterial infections, preventing traveler's diarrhea, and recurring lower UTI, unless other recommended antibacterial agents cannot be used. Additionally, the FDA and EMA recommend that FQs should not be used as first-line therapies in treating acute sinusitis, bacterial infections among patients with chronic obstructive pulmonary disease (COPD), or UTIs, as the risks outweigh the benefits [7,67-69]. Instead, FQs should be used to treat infections when other antibiotics are ineffective [70]. FQs should also be contraindicated in patients who have already experienced substantial AEs from a previous regimen of FQs, and should be used with extreme caution in elderly patients. Moreover, the combination of FQs and corticosteroids increases the risk of tendon rupture and should be avoided [69]. But these FQs regulatory measures seem to have had only a modest impact on FQs prescribing, especially in Spain. Just a few months ago, the EMA published a study based on data on electronic prescribing of oral FQs in different European countries. Compared to the rest of the countries, Spain has the highest oral FQs consumption, particularly in the age group over 75 years old and the one with the highest risk of suffering adverse effects. It is also noteworthy that 94% of levofloxacin prescriptions are for respiratory infections and 99% of these prescriptions are off label according to the AEMPS (Agencia Española de Medicamentos y Productos Sanitarios) [71,72]. In mild and moderate respiratory infections, the use of oral FQs is restricted to isolated cases, when other antibiotics recommended by clinical guidelines, such as amoxicillin, amoxicillin-clavulanate and cefditoren, cannot be used [72,73].

Cefditoren, in particular, has an intrinsic activity superior to FQs against the most frequent causative pathogens of respiratory infections with a narrower spectrum exerting less collateral damage on the microbiota [74].

Management of the AEs associated with FQs' administration depend on the type and severity of the AEs. The measures include discontinuation of the therapy and avoiding FQs therapy in patients with risk of severe, long-lasting, disabling and potentially irreversible adverse reactions. We must apply the well-known *primun non nocere* [2,75].

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CONFLICT OF INTEREST

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