Antimicrobial Stewardship News

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Here We Go Again! FDA Updates Drug Safety Communication for Fluoroquinolones

Introduction

Fluoroquinolones were first introduced in 1962 with the accidental discovery of nalidixic acid as a by-product of chloroquine synthesis and have been a mainstay of antibacterial therapy for decades.[1] The high oral bioavailability and broad-spectrum of activity place them in a unique position among antimicrobials. As such, their use has become increasingly widespread for common infections including community-acquired pneumonia, urinary tract infection, sinusitis, and even in syndromes not caused by bacterial infections such as bronchitis.

Since their development, fluoroquinolones have had multiple updates to drug safety labeling. The first update in July 2008 included the addition of the "black box warning" related to the risk of tendinitis and tendon rupture. In August 2013, the risk of peripheral neuropathy was described. In July 2016, the Food and Drug Administration (FDA) changed the labeling for fluoroquinolones to enhance warnings about already known, disabling musculoskeletal and central nervous system (CNS) side effects including joint pain, tendinitis and tendon rupture, anxiety, depression, and altered mental status. The FDA recommended limited use in common, uncomplicated bacterial infections, including acute bacterial sinusitis, acute exacerbations of chronic bronchitis, and uncomplicated urinary tract infections.[2] This newsletter will review the most recent safety labeling update released by the FDA in July 2018 to the fluoroquinolone class of antibiotics.

July 10, 2018 FDA Label Update

On July 10, 2018 the FDA issued an updated Drug Safety Communication that encompassed all fluoroquinolones approved by the FDA for systemic use (Table 1).[3] The update focused on review of post-marketing adverse event data that highlighted hypoglycemic episodes and adverse psychiatric effects. Delafloxacin, approved in June of 2017, was not part of the data review. As these are presumed class effects, however, the safety labeling changes were also applied to delafloxacin.

Table 1: List of FDA-Approved Fluoroquinolones for Systemic Use[3]

Brand Name	Active Ingredient
Avelox	moxifloxacin+
Baxdela	delafloxacin
Cipro	ciprofloxacin+
Cipro XR±	ciprofloxacin extended-release
Factive	gemifloxacin+
Levaquin	levofloxacin+
Ofloxacin (generic brand)±	ofloxacin

+ available as brand and generic
± available only as generic

Hypoglycemic Coma

Both hypo- and hyperglycemic events have been described during use of fluoroquinolones for years. Park-Wyllie et al. described dysglycemia in relation to outpatient gatifloxacin therapy in 2006, which led to the removal of gatifloxacin from the market later that year.[4] Aspinall et al. also described hypo- and hyperglycemia among patients receiving gatifloxacin, levofloxacin, or ciprofloxacin.[5] More recently, Chou et al. described episodes of 30-day adverse dysglycemic events in 78,433 Taiwanese patients receiving levofloxacin, ciprofloxacin, moxifloxacin, or macrolides.[6] The adjusted odds-ratio (OR) for each antibiotic is summarized in **Table 2**. Of note, moxifloxacin-associated dysglycemic events were the most common with an event rate more than two-fold higher than macrolides. While these studies recognized hypoglycemia and hyperglycemia associated with fluoroquinolone use in various settings, they did not fully examine severe hypoglycemic events such as hypoglycemic coma.

The FDA further investigated severe hypoglycemic events by using the FDA Adverse Event Reporting System (FAERS). Fifty-six reports of hypoglycemic coma associated with fluoroquinolones occurred between October 1987 and April 2017. A literature search yielded eleven additional cases. Notably, forty-seven of these patients were diabetic and forty-one of those were taking oral hypoglycemic agents (most of which were an oral sulfonylurea, n=35). Thirteen deaths occurred and nine patients had permanent disability. Based on these additional data, the FDA added hypoglycemic coma to fluoroquinolone labels and strengthened the warnings about blood sugar disturbances.

Table 2: Risk of Hyperglycemia and Hypoglycemia Associated with Macrolides and Fluoroquinolones[6]

Antibiotic	Absolute Risk/ 1000 Persons	Adjusted OR (95% CI)
Hyperglycemia		
macrolides	1.62	1.00
moxifloxacin	6.87	2.48 (1.5-4.12)
levofloxacin	3.91	1.75 (1.12-2.73)
ciprofloxacin	3.98	1.87 (1.2-2.93)
Hypoglycemia		
macrolides	3.72	1.00
moxifloxacin	9.95	2.13 (1.44-3.14)
levofloxacin	9.26	1.79 (1.33-2.42)
ciprofloxacin	7.88	1.46 (1.07-2.00)

Abbreviation: OR, Odds Ratio; CI, confidence interval

Psychiatric Adverse Reactions

Psychiatric adverse reactions related to fluoroquinolone use have also been described in detail over the last decade. In a comprehensive 2010 literature review, Tome and Filipe identified 111 case reports related to psychiatric adverse events.[7] Of those, the most prevalent symptoms were mania (n=38), insomnia (n=10), acute psychosis (n=8), and delirium (n=8). Ciprofloxacin, ofloxacin, and pefloxacin were most highly associated with psychiatric events. The authors noted that the observed association with ciprofloxacin may have been affected by its relatively high utilization in comparison to other agents.

In light of these data, the FDA restructured the drug labeling for fluoroquinolones regarding psychiatric events. Previously, individual fluoroquinolones labels listed psychiatric adverse reactions specific to each agent, such as hallucinations, psychoses, depression, etc. Based on a review of the FAERS and medical literature, the FDA adjusted labeling to be uniform across the antibiotic class for six psychiatric adverse reactions: disturbance in attention, memory impairment, delirium, nervousness, agitation, and disorientation. These adverse events were noted to occur even after a limited number of doses. Delafloxacin was again exempt from the review but received the same class labeling.

The exact mechanism of central nervous system side effects is unknown; however, they are possibly driven by the structural similarity to GABA agonists and interaction with neurotransmitters **(Figure 1).**

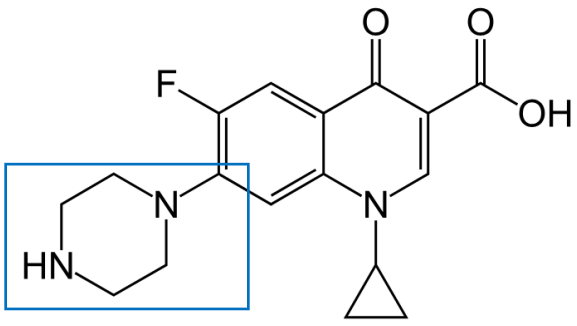

Figure 1. Ciprofloxacin molecule with 7-position side chain highlighted. The 7-position side chain modulates the affinity of the fluoroquinolones for GABA receptors.

Table 3: List of Serious Adverse Effects [3]

MSK and PNS*	CNS*	Other
Tendinitis	Agitation	Worsening of MG
Tendon rupture	Delirium	Skin Rash
Numbness/tingling	Nervousness	Severe Diarrhea
Muscle weakness/pain	Memory Impairment	Abnormal heart beat
Joint pain	Disorientation	Dysglycemia
Joint Swelling	Attention	Hypoglycemic Coma

*MSK, musculoskeletal; PNS, peripheral nervous system; CNS, central nervous system

Implications for Clinical Practice

A major goal of antimicrobial stewardship programs is to reduce unintended consequences related to antibiotic use, which includes adverse safety events and toxicities. The updated FDA advisory warning for fluoroquinolones highlights the dysglycemic and psychiatric adverse events in addition to the other known serious adverse events previously included in safety labeling. Although relatively uncommon, these serious reactions have likely been unmasked due to massive utilization (or over-utilization) of this class. As the list of possible serious risks increases, it is very clear that fluoroquinolones should be avoided in uncomplicated bacterial infections because the risks outweigh the benefits when more appropriate alternatives are available. We agree with the FDA statement that fluoroquinolones should not be first-line therapy for acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, or uncomplicated urinary tract infections. For these and other indications, clinicians should use safer and more tolerable alternatives whenever possible. Most DASON hospitals have already introduced fluoroquinolone-sparing institutional guidelines and order sets. As a result, fluoroquinolone use has declined across the network.

As one of the few classes of highly bioavailable, broad-spectrum oral antibiotics, however, we believe that some lower level of "appropriate" use of fluoroquinolones will remain for specific clinical scenarios (e.g., oral transition for Gram-negative bacteremia, osteomyelitis, or in the setting of severe beta-lactam allergy). In these situations, antimicrobial stewardship programs can assist clinicians by promoting shorter durations of therapy, prospectively monitoring for adverse events, and intervening when necessary. In addition, stewards can provide guidance and materials to help clinicians best advise and educate patients and families of the known risks when these high-risk drugs must be used.

Take Home Points:

1. Fluoroquinolones are broad spectrum, highly oral bioavailable antibiotics that have been used for a variety of community acquired infections.
2. Recognized adverse reactions associated with fluoroquinolones have been evolving over the past decade. The newest additions to safety labeling include warnings of severe hypoglycemic events and psychiatric side effects.
3. Hypoglycemic events are most commonly precipitated by fluoroquinolone use in elderly patients taking concomitant oral hypoglycemics.
4. The recognized adverse reactions are thought to be class effects, and thus also apply to the newly developed fluoroquinolone, delafloxacin.
5. Fluoroquinolones should be avoided when safer, more tolerable alternatives exist.

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