THE OREGON STATE DRUG REVIEW©

AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter

January 2019 Volume 9, Issue 1

2017-18 Year in Review: Important Safety Updates

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The United States Food and Drug Administration (FDA) issues drug alerts and safety recommendations to inform patients and health care practitioners of urgent precautions which improve patient care. Drugs are often approved by the FDA after evaluating safety and efficacy in short-term trials. Once these medications are marketed, post-surveillance monitoring continues to further evaluate safety. As new drugs are used in the general population, important safety signals become apparent. The purpose of this newsletter is to provide an update on relevant safety alerts published from 2017 through 2018.

Sodium-glucose-cotransporter-2 (SGLT2) Inhibitors

Fournier's Gangrene: In 2018, the FDA warned of rare but serious cases of genital and perigenital infections with the use of sodium-glucose cotransporter-2 (SGTL2) inhibitors. In the last five years, 12 cases of Fournier's gangrene (also known as necrotizing fasciitis) were reported in patients taking a SGTL2 inhibitor.[1] This effect has been reported with several drugs within this class, and is considered a class-wide effect resulting in labeling changes for all SGLT2 inhibitors. Fournier's gangrene severity should not be underestimated as mortality rates are high, ranging from 20% to 40%.[2] Potential risk factors for Fournier's gangrene are thought to be uncontrolled diabetes, obesity, smoking, urinary catherization, operative procedures, and recurrent fungal infections.[3]

Risk of amputation: In 2017, the FDA found an increased risk of leg and foot amputations with canagliflozin.[4] Results of the CANVAS trial showed leg and foot amputations occurred approximately twice as often in patients treated with canagliflozin compared to patients treated with placebo.[5] The risk of amputation was 5.9 out of every 1000 patients taking canagliflozin and 2.8 out of every 1000 patients treated with placebo per year, with a number needed to harm (NNH) of 323.[5] During the CANVAS-R 3-year follow up study, the amputation risk was found to be even higher, equivalent to 7.5 out of every 1,000 patients treated with canagliflozin and 4.2 out of every 1,000 patients treated with placebo with a NNH of 270 and a hazard ratio (HR) of 1.97 (95% CI, 1.41-2.75).[5] While only canagliflozin has a black-boxed warning for this risk, other SGTL2 inhibitors are being monitored to determine if this is a class effect.[6]

The drivers for amputation in patients with diabetes mellitus are complex and multi-factorial. A nationwide register based cohort study determined lower limb amputation to be a class wide effect, showing a hazard ratio of 2.32 for number of events per 1000 patient years with SGLT2 inhibitors compared to glucagon-like peptide-1 (GLP-1) receptor agonists.[7] In contrast, a large outcomes trial titled DECLARE-TIMI 58 evaluating the cardiovascular outcomes of dapagliflozin showed a non-significant risk of amputation.[8] Similarly, the EMPA-REG OUTCOME trial showed risk of lower limb amputation was similar between empagliflozin and placebo.[9] Determining whether drugs within a class exhibit similar or different therapeutic and safety profiles can be challenging in the absence of large randomized controlled trials (RCTs) with head-to-head comparisons.

Fluoroquinolone Safety

In July 2018, the FDA issued a warning about the possibility of life-threatening hypoglycemia and adverse psychiatric effects associated with fluoroquinolone antibiotics resulting in changes to prescribing information and patient medication guides. These findings were derived from post-marketing adverse event data including 56 reports in the FDA Adverse Event Reporting System (FAERS) from October 1987 through April 2017, and 11 additional cases in reported in the medical literature. The newest fluoroquinolone, delafloxacin, was not included in the FDA's review, but similar warnings are anticipated to be applied to this medication in the future.[10] More recently in December of 2018, another warning was added for increased occurrence of aortic aneurysm or dissection, leading to bleeding or death. This warning originated from case reports and four published observational studies.[11]

Risk of Hypoglycemia: Three of the fluoroquinolones (levofloxacin, ciprofloxacin, and ofloxacin) have a labeled warning about the risk of hypoglycemia when co-administered with sulfonylurea agents. Moxifloxacin also has a warning about possible dysglycemia in elderly patients receiving insulin or an oral hypoglycemic agent.[10] These warnings were strengthened to include risk of hypoglycemia leading to coma in July 2018 for the entire fluoroquinolone class; however, it is unclear if dysglycemia is a class effect, or specific to certain fluoroquinolones.

There are several proposed mechanisms for hypoglycemia due to exposure to fluoroquinolones. These hypotheses include pancreatic beta cell calcium release, blockade of ATP-sensitive potassium channels, magnesium deficiency leading to insulin resistance, or blockade of a gene that enhances insulin secretion.[12-15] The evidence related to dysglycemia has primarily been published in observational case reports and retrospective studies in patients with and without anti-diabetic agents or a diagnosis of diabetes. A retrospective cohort found an increased risk of dysglycemia with gatifloxacin and levofloxacin, but not ciprofloxacin, as shown in Table 1.[16]

Table 1: Risk of Dysglycemia with Fluoroquinolones[16]

Antibiotic	Hypoglycemia OR (95% CI)	Hyperglycemia OR (95% CI)
Patients with diabetes		
Levofloxacin	2.1 (1.4-3.3)*	1.8 (1.2-2.7)*
Ciprofloxacin	1.1 (0.6-2.0)	1.0 (0.6-1.8)
Patients without diabetes		
Levofloxacin	1.6 (0.4-6.6)	0.7 (0.3-1.7)
Ciprofloxacin	0.7 (0.1-6.9)	0.9 (0.3-2.6)
Key: * Statistically significant (P<0.05) Abbreviations: CI – confidence interval; OR – odds ratio		

A large cohort study (n=78,433) conducted in diabetic patients based in Taiwan concluded fluoroquinolones were associated with a higher, statistically significant risk of hypoglycemia compared with macrolides or cephalosporins (Table 2).[17]

Table 2: Hypoglycemia Associated with Selected Antibiotics[17]

Antibiotics	Incidence (%) per 1000 persons	Time to event, days mean ± SD	Adjusted OR (95% CI)
Macrolides (reference group)	1.62	6.32 +6.81	1.00
Moxifloxacin	9.95	7.02 + 9.51	2.13 (1.44-3.14)*
Levofloxacin	9.26	7.12 +8.48	1.79 (1.33-2.42)*
Ciprofloxacin	7.88	9.16 + 9.40	1.46 (1.07-2.0)*

Key: * Statistically significant (P<0.05)
Abbreviations: CI – confidence interval; OR – odds ratio; SD – standard deviation

In an analysis of the incidence of hypoglycemic coma submitted to the FDA, there were 67 identified case reports, mainly in older patients with renal insufficiency and concomitant use of anti-glycemic agents. Patients were treated with levofloxacin (n=44), ciprofloxacin (n=12), moxifloxacin (n=9), and ofloxacin (n=2).[10] Of the 67 total patients, 47 had diabetes (70%), with 41 (62%) reportedly taking at least one oral hypoglycemic drug and 35 (52%) taking a sulfonylurea specifically.[10] Twenty patients did not have a diabetes diagnosis (30%), and some patients were only being treated for uncomplicated infections. A total of 13 deaths occurred (19%), and 14 patients had disability or neurological injury (21%).[10] Although evidence is insufficient to determine which fluoroquinolone has the highest incidence of dysglycemia, there should be awareness surrounding the risk of hypoglycemic coma with fluoroquinolones.

Psychiatric Adverse Effects: The FDA recently updated the warnings and precautions section of the fluoroquinolone drug label concerning mental health side effects: disturbances in attention, disorientation, agitation, nervousness, memory impairment, and delirium.[10] The mechanism behind fluoroquinolone-associated delirium or psychosis is unknown, but is hypothesized to involve n-methyl-d-aspartate (NMDA) agonistic activity, and gamma-aminobutyric acid A (GABA) antagonism.[18-20] A retrospective, single center study conducted at a Veteran Affairs hospital between 2005 and 2014 found a 3.7% incidence of intravenous or oral fluoroquinolone-associated delirium/psychosis in the inpatient veteran population. This finding is higher than the current estimate of <1% from post marketing surveillance reported by the manufacturer.[21] Interestingly, all patients experienced hyperactive delirium, and there were no differences noted between the type of pre-existing psychiatric condition and manifestation of delirium/psychosis.[22] A review of 206 articles for fluoroquinolone-associated neurological and psychiatric adverse reactions found ciprofloxacin to be associated with the highest number of neurological and psychiatric adverse events compared to other fluoroquinolones.[23] Investigators concluded the psychiatric adverse effects are dose-dependent and in majority of cases, activated without presence of predisposing conditions. They noted that although the events were serious, they resolved upon discontinuation of the medication.[23]

Risk of Aortic Aneurysm: The use of fluoroquinolones has been associated with rupture or dissection of aortic aneurysms based on numerous epidemiological studies and case reports.[11] Many patients in these studies were found to have risk factors for aortic aneurysm which include peripheral atherosclerotic vascular diseases, hypertension, genetic blood vessel disorders and old age, making the event more likely.[24] Based on severity of the data findings, the FDA advises prescribing of fluoroquinolones to patients with or at risk for an aortic aneurysm only when no other treatment options are available. A summary of the evidence is highlighted in Table 3.

Table 3: Risk of aortic aneurysm or dissection[25-28]

Study type	Results (95% CI)	Time of Fluoroquinolone Use	Patient Age (yrs.)
Epidemiological[26]	RR 2.28 (1.67-3.13)*	Current or use in the prior year	≥70
Retrospective cohort[28]	HR 1.66 (1.2-2.46)*	First 60 days	≥50
	HR 0.67 (0.4-1.11)	Day 61-120	
Retrospective cohort[25]	HR 2.24 (2.02-2.49)	30-day risk window	≥65
Self-controlled analyses[27]	OR 2.41 (1.14-6.46)*	60 days	Mean of 71
	OR 2.41 (1.25-4.65)*	3-14 days of exposure	
	OR 2.83 (1.06-7.57)*	>14 days of exposure	

Key: * Statistically significant (P<0.05)
Abbreviations: CI – confidence interval; HR – hazard ratio; OR – odds ratio; RR – rate ratio

Other Updates and Ongoing Safety Investigations:

Clarithromycin

The FDA communicated an update this year regarding a previous safety issue issued in 2015 associated with prescribing clarithromycin for patients with heart disease.[29] This warning was based on a 10-year follow up study[30] to the CLARICOR trial[31] which showed a potential increase in risk of heart problems or death in patients with coronary heart disease occurring years after prescribing of a 2-week course of clarithromycin.[30] The hazard ratio for cardiovascular mortality was 1.42 (95% CI, 1.09-1.84; p=0.008), 1.24 (95% CI, 0.96-1.60; p=0.06), and 0.91 (95% CI 0.74-1.13: P=0.39) within 0-3 years, 3-6 years and 6-10 years, respectively. There is insufficient evidence to determine if this warning can be applied to patients without heart disease. This warning will continue to be monitored closely with post-marketing MedWatch submissions.

Loperamide

Another FDA drug safety warning addresses the safe use of over-the-counter (OTC) anti-diarrhea drug loperamide.[32] Loperamide blocks the *mu*-opioid receptors in the intestinal muscles to slow the movement in the intestines and decrease the number of bowel movements.[33] Recent reports have described the use of loperamide by consumers to treat the symptoms of opioid withdrawal at doses 40-100 times the recommended dose.[34] At these high doses, loperamide has caused QTc prolongation leading to Torsades de Pointes.[35] There is insufficient evidence to define the correlation between loperamide abuse and cardiac toxicity. In the 39 years since loperamide was approved, the FDA has received 48 cases of serious heart problems, most of which were reported after 2010. This is most likely due to the growing abuse or misuse of the product by patients to achieve a feeling of euphoria.[36] Due to this dangerous effect, health professionals are advised to recommend only the maximum approved daily dose for adults at 8 mg per day over the counter (OTC) dose and 16 mg per day for prescription use.[32]

- SGLT2 inhibitor safety alerts include Fournier's gangrene
- Evidence has demonstrated amputations with canagliflozin – it is unknown if this is a SGLT2 class effect
- Fluoroquinolone safety alerts include hypoglycemia, psychiatric events, and risk of aortic aneurysm/dissection
- Loperamide at high doses may cause QTc prolongation
- Clarithromycin use in existing heart disease causes

Conclusion

These safety warnings have brought attention to the possible harm related to use of the associated medications. The fluoroquinolone risk of hypoglycemia and psychiatric events have been added to the drug labels, as well as the risk of necrotizing fasciitis for SGLT2 inhibitors. The risk of aortic aneurysm with fluoroquinolones will be added to the prescribing information and medication guides, as required by the FDA. Ongoing safety assessments are still being conducted for risk of amputation in SGLT2 inhibitors and heart complications with clarithromycin. A higher level of evidence using randomized controlled trials is needed to confirm a clear association. Pharmacists and prescribing providers should be aware of the evolving evidence of safety for drugs after FDA approval.

Peer Reviewed by: Andrew Gibler, Pharm D, Director of Pharmacy Legacy Mount Hood Medical Center

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