October 2019
Issue 39

ToxUpdate

Regional Poison Control Center, Birmingham, AL
www.childrensal.org/rpcc 1-800-222-1222

FDA Warnings Regarding Fluoroquinolones

By Katherine Cory, Samford University PharmD Candidate

The fluoroquinolone class of antibiotics include agents that variably cover gram positive aerobes, gram negative aerobes, anaerobes and atypicals. These bacteriocidal agents include levofloxacin, ciprofloxacin, moxifloxacin and gemifloxacin. This class works by inhibiting an essential enzyme, DNA gyrase, that maintains the bacteria's structure and replication process. Despite their effective spectrum of activity and variable roles in therapy, they do not go without negative adverse effects. Serious adverse reactions of the class include phototoxicity, QT interval prolongation, changes in liver enzymes, and cartilage and tendon abnormalities.

As studies are conducted and adverse reports are gathered, the Food and Drug Administration (FDA) continues to alert health care professionals and patients of new significant adverse effects that are pertinent to know of when prescribing, dispensing and taking the medication. In December of 2018, the FDA warned of the increased risk of tears or ruptures in the aorta blood vessel in high risk patients such as those with peripheral atherosclerotic vascular diseases, a history of blockages or aneurysms of the aorta, hypertension or in the elderly. Studies estimated 300 of 100,000 individuals in the high-risk population developed an aortic aneurysm while taking a fluoroquinolone compared to the general population of having nine of 100,000 individuals. While it is important for patients to recognize early signs of this concerning effect, it is important for prescribers to be aware of the patient's medical history before initiating therapy.

In July of 2018, the FDA communicated a safety warning regarding the quinolone's significant class effects in blood glucose. The alert cautioned the public of serious clinical effects of hypoglycemia episodes that can potentially result in coma. The mechanism is unclear. Between the time of October 1987 and April 2017, FDA Adverse Event Reporting System received 56 reports of hypoglycemic coma related to fluoroquinolones and 11 reports from literature with most patients having risk factors for hypoglycemic episodes. Thirteen deaths resulted from this group. This will most frequently be seen in individuals

(Continued on page 3)

POISON Help® 1-800-222-1222

Special Interest Articles

- Fluoroquinolones
- Baqsimi
- E-cigarette Concerns

Did you know?

Effective November 18, 2019, the Alabama State Committee of Public Health voted to change gabapentin to a Schedule V medication. Refills will be limited to five and prescriptions will expire within six months.

Baqsimi™: First FDA Approved Needle-Free Glucagon Therapy for the Emergency Treatment of Severe Hypoglycemia

By Jihyun Kim, Auburn University PharmD Candidate

"Unlike glucagon injections, Baqsimi does not require training and it does not require mixing or preparation."

The U.S Food and Drug Administration has approved Baqsimi, the first nasal administered glucagon, on July 24,2019. Baqsimi is a needle-free treatment for severe hypoglycemia in emergency settings for ages 4 years and above. Glucagon stimulates adenylate cyclase to increase the production of cyclic AMP (cAMP). Increased production of cAMP promotes hepatic glycogenolysis and gluconeogenesis, resulting in an antihypoglycemic effect. Patients with Type 1 Diabetes Mellitus (T1DM) or Type 2 Diabetes (T2DM) with insulin or glucose-lowering medications such as sulfonylureas are at great risk of severe hypoglycemia. Baqsimi is passively absorbed in the nose so it can be used with patients who are unconscious. Baqsimi can be administered intranasally 3mg (one actuation) into either nostril, and it can be repeated with a new device in 15minutes if no response after the first dose. Unlike glucagon injections, Baqsimi does not require training and it does not require mixing or preparation. Baqsimi can be stored at room temperature (≤30^{o}C).

Efficacy of Baqsimi in adult patients was evaluated in two randomized, multi-center, open-label, 2-period, cross over studies. A single 3mg dose of Baqsimi was compared to a 1mg dose of intramuscular glucagon (IMG). Study 1 included 70 T1DM patients with a mean age of 41.7 years. Study 2 included 83 T1DM or T2DM patients aged 18 to <65 years. The primary outcome was to measure the proportion of patients achieving treatment success. Treatment success was defined as either an increase in blood glucose to ≥70mg/dL or a ≥20mg/dL glucose increase from the lowest glucose level within 30 minutes after receiving the study glucagon. Baqsimi demonstrated non-inferiority to IMG in both studies in reversing insulin-induced hypoglycemia. Similar results were reported in a study with 48 pediatric patients aged ≥4 years old with T1DM.

Side effects of Baqsimi are similar to injectable glucagons, such as nausea, vomiting, headache, and upper respiratory tract irritation. Additionally, Baqsimi may cause nasal and eye-related symptoms including watery eyes and nasal congestion, due to its route of administration. Baqsimi is contraindicated in patients with pheochromocytoma, insulinoma, or any known hypersensitivity to glucagon or any of the excipients in Baqsimi. In the setting of glucagon overdose, treatment consists of symptomatic and supportive care. Rebound hypoglycemia may appear in the setting of acute toxicity of glucagon, and IV dextrose and carbohydrates may be used. Severe glucagon toxicity is not anticipated in most cases due to its short half-life.

References

1. BAQSIMI™ [Prescribing Information]. Eli Lilly and Company. Indianapolis, IN. July 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210134s000lbl.pdf (Accessed September 15, 2019).
2. BAQSIMI™(Glucagon). Lexi-Comp® (electronic version). Wolters Kluwer Clinical Drug Information. Hudson, Ohio, USA. https://online.lexi.com. (Accessed September 16, 2019).
3. BAQSIMI™(Glucagon). Micromedex® (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. http://www.micromedexsolution.com. (Accessed September 16, 2019).
4. FDA approves first treatment for severe hypoglycemia that can be administered without an injection [press release]. Silver Spring, MD: FDA. July 24, 2019. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-severe-hypoglycemia-can-be-administered-without-injection (Accessed September 13, 2019).

Fluoroquinolones (continued)

who are elderly or diabetic, already on anti-hyperglycemic medication or insulin; however, studies have proven that this effect can occur in the non-diabetic healthy population as well.

In addition to the hypoglycemic effects, the newly found psychiatric adverse reactions include disturbance in attention, memory impairment and delirium. The FDA performed a class review on CNS effects in order to create harmony among all agents due to the differing labels between individual agents.

Because these effects can occur in a single dose, new additions and changes in labeling for all fluoroquinolones were required. The new label updates now clearly state the risk of hypoglycemic coma under the "Blood Glucose Disturbance" subsection. To address the mental health effect labeling issue, the FDA required in the Central Nervous System Effects of the "Warnings and Precautions" section that all fluoroquinolone agents include the six reactions they found to be consistent within the class. Through these alerts and label changes, the FDA has created awareness of the dangers within the quinolone antibiotic class to health care professionals prescribing and patients receiving these medications.

References

1. US Food and Drug Administration. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics. Updated December 21, 2018. Accessed September 8th, 2019.
2. US Food and Drug Administration. FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions. https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics-risks-mental-health-and-low-blood-sugar-adverse. Updated July 10, 2018. Accessed September 8th, 2019.
3. Kelesidis, Theodoros et al. Quinolone-induced Hypoglycemia: A Life-threatening but Potentially Reversible Side Effect. The American Journal of Medicine, Volume 123, Issue 2, e5 - e6.
4. US Food and Drug Administration. FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. Drug Safety Communications. https://www.fda.gov/media/114192/download. Updated July 10, 2018. Accessed September 10th, 2019.

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

+ available as brand and generic
± available only as generic

FDA Drug Safety Communication

PharmD students, Jihyun Kim from Auburn University and Katherine Cory from Samford University, visited Centerpoint Senior Center on September 17, 2019 to teach them about Medication Safety.

CDC Recommends the Public Contact Poison Control Centers for E-Cigarette Concerns

By Laura Read, RPh, CSPI, Regional Poison Control Center, Children's of AL

The Centers for Disease Control and Prevention issued an Investigation Notice on October 1, 2019 warning the public of lung illness associated with E-cigarette Products. There are 1,080 cases of lung illness possibly linked to e-cigarette products that have been reported from 48 states and one United States territory. Eighteen deaths have been confirmed and these numbers are increasing every day. The public is being urged to contact their local poison control center for questions and recommendations regarding vape exposures. Calling will also help with tracking illness as this is an ongoing investigation.

A report was published in the New England Journal of Medicine from Illinois and Wisconsin Departments of Health of 53 cases of severely ill patients that had vaped and presented with acute, severe respiratory distress. Two letters followed, reporting a 6-case patient cluster from Utah and imaging of Vaping-Associated Lung disease. The cases noted a diverse collection of pneumonitis patterns including acute respiratory distress syndrome (ARDS), eosinophilic pneumonia, and lipoid pneumonia. About 80% of the people that have vaped and become ill reported using both nicotine products and tetrahydrocannabinol (THC) and cannabidiol (CBD) products.

The early symptoms of e-cigarette related illness include lethargy, nausea, vomiting, coughing and fever that escalates to dyspnea. On lung scans, the illness looks like bacterial or viral pneumonia, but no evidence of infectious disease has been identified.

One theory to explain the new patient cases is that new chemicals have been introduced in the current vaping products. E-cigarette fluids have been shown to contain at least six groups of potentially toxic compounds: nicotine, carbonyls, volatile organic compounds (such as benzene and toluene), trace metal elements according to flavor, and bacterial endotoxins and fungal glucans. Two flavorants, diacetyl and 2,3-pentanediol, have been shown to disturb gene expression. The effect of adding ingredients such as THC or CBD to this mix is being investigated. The Food and Drug Administration has found a vitamin E-derived oil in THC products but are unable to confirm at this point if this is the cause.

Regional Poison Control Center in Birmingham, AL, has received 556 (16 information) calls regarding e-cigarettes since 2010 with 117 (1 information) of those calls coming in 2019. Alabama health officials confirm that nineteen cases are under investigation in Alabama. As of October 1, Alabama reports one death. One study showed that more than half of American adult e-cigarette users are under 35 years old. In Alabama, the Campaign for Tobacco-Free Kids reports that 24.5 percent of high school students use e-cigarettes, as compared to 20.8 percent nationwide. Long-term consequences of using e-cigarettes is unclear and vaping-related illness continues to be on the rise.

References

1. Centers for Disease Control and Prevention. Outbreak of Lung Disease Associated with E-cigarette Use, or Vaping. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. September 12, 2019. (Accessed September 13, 2019).
2. The New England Journal of Medicine. Vaping-Induced Lung Injury. https://www.nejm.org/doi/full/10.1056/NEJMe1912032?query=recirc_curatedRelated_article. September 6, 2019. (Accessed September 13, 2019).
3. Richtel, M and Grady, D. What You Need to Know About Vaping-Related Lung Illness. https://www.nytimes.com/2019/09/07/health/vaping-lung-illness.html. September 7, 2019. (Accessed September 14, 2019).
4. Layden, J. et al. The New England Journal of Medicine. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin – Preliminary Report. https://www.nejm.org/doi/full/10.1056/NEJMoa1911614?query=recirc_curatedRelated_article . (Accessed September 14, 2019).
5. Christiani David C. (2019) Vaping-Induced Lung Injury. *N Engl J Med*. https://www.nejm.org/doi/full/10.1056/NEJMc1911995?query=recirc_curatedRelated_article#article_citing_articles. (Accessed September 14, 2019).
6. Edwards, E. NBC News. Kansas Resident Dies from Vaping-related Illness, as Cases Continue to Rise. https://www.nbcnews.com/health/vaping/kansas-resident-dies-vaping-related-illness-6th-death-nationwide-n1051866. September 10, 2019, (Accessed September 14, 2019).
7. Gore L. Alabama Media Group. Vaping Illness Blamed for 5 Deaths; CDC Recommends Against E-cigarettes: What Parents Should Know. https://www.al.com/news/2019/09/vaping-illness-blamed-for-5-deaths-cdc-recommends-against-e-cigarettes-what-parents-should-know.html. September 10, 2019. (Accessed September 14, 2019).
8. Knowles, H. and Sun, L. The Washington Post. https://www.washingtonpost.com/health/2019/09/07/what-we-know-about-mysterious-vaping-linked-illnesses-deaths/?arc404=true. September 27, 2019. (Accessed September 27, 2019).
9. Edwards, L. Alabama Media Group. 3 People Hospitalized with Vaping-related Illnesses in Mobile County. https://www.al.com/news/2019/09/3-people-hospitalized-with-vaping-related-illnesses-in-mobile-county.html. September 17, 2019. (Accessed September 17, 2019).
10. Centers for Disease Control and Prevention. CDC, States Update on Number of Cases of Lung Injury Associated with E-cigarette Use, or Vaping. https://www.cdc.gov/media/releases/2019/s0926-cdc-number-lung-injury-vaping.html. September 26, 2019. (Accessed October 1, 2019).