THE OREGON STATE DRUG REVIEW©

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

February 2016 Volume 6, Issue 1

2015 in Review: Relevant Safety Updates and Ongoing Safety Concerns

By Megan Herink, Pharm.D, BCPS, Oregon State University College of Pharmacy, Drug Use Research and Management

The U.S. Food and Drug Administration (FDA) issues drug alerts and drug safety communications to help patients and practitioners stay abreast of rapidly changing medical knowledge. These communications may or may not have serious consequences as to how patients, caretakers, and prescribers respond. However, these alerts are important to increase safety awareness and initiate a dialogue between patients and providers.

Typically, drugs are FDA approved based on relatively short-term trials that are not designed to evaluate safety end points. Furthermore, for some drugs, assessing a postmarketing safety signal can be challenging due to lack of robust evidence, leaving a potentially harmful drug on the market. Over the past 9 years, the FDA has taken a more proactive approach to the reporting of potential adverse effects, readily disseminating preliminary information regarding drug safety issues as the information becomes available. With this increased transparency, however, it is important to place these safety alerts in context and to consider them not as conclusive mandates. This article will review some of the more relevant FDA drug safety alerts and ongoing safety concerns of 2015.

2015 New Drug Safety Alerts Resulting In Drug Labeling Changes

In May 2015, the FDA warned that the sodium-glucose cotransporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin and empagliflozin) used in the treatment of type 2 diabetes (T2D), may cause ketoacidosis requiring hospitalization.[1] The concern originated from 20 reported cases of reported diabetic ketoacidosis (DKA), ketoacidosis, or ketosis that resulted in emergency room or hospital visits. SGLT2 inhibition causes a rapid increase in urinary glucose excretion including losses from daily carbohydrate availability.[5] This results in an increased use of fat oxidation for energy production and eventually ketosis. Unlike the more typical presentation of DKA, many of these were accompanied by only mild to moderately elevated blood sugar levels (euglycemic DKA). The European Medicines Agency (EMA) further corroborated this risk.[2]

After a further safety review, the FDA added a warning to the label about the risks of ketoacidosis and of serious urinary tract infections.[3] From March 2013 to May 2015, 73 cases of ketoacidosis were reported in the FDA Adverse Event Reporting System (FAERS) database with the use of the SGLT2 inhibitors. In all of these cases, patients were hospitalized or treated in the emergency room. The median time from drug initiation or dose change to symptoms was 43 days. Although these agents are currently only approved for T2D, fifteen cases were reported in patients with type 1 diabetes (T1D). The FDA also warned about serious urinary tract infections or urosepsis resulting in hospitalization that was reported in 19 cases from March 2013 through October 2014. [3]

Overall, the absolute risk of DKA in T2D associated with the use of SGLT2 inhibitors is relatively low.[4] However, patients and practitioners should be aware of the risk as well as patient specific risk factors. The cause of ketoacidosis is usually multifactorial and potential contributing factors are concurrent illness, reduced food and fluid intake, reduced insulin doses, discontinuation of an oral insulin secretagogue, T1D or patients with long-standing T2D with marked B-cell insufficiency, and history of alcohol intake.[5] In addition, because of the lack of accompanying severe hyperglycemia, euglycemic DKA can easily go unrecognizable by patients and providers.[6] Any patients with diabetes who experiences nausea, vomiting, shortness of breath or malaise on a SGLT2 inhibitor should be evaluated for ketosis, despite a normal glucose level. All patients taking SGLT2 inhibitors should be advised to check their ketone levels whenever they feel unwell, regardless of their glucose level. If ketones are detected, patients should be directed to seek immediate medical care, as it can be difficult to reverse at home. There are currently ongoing, long-term randomized controlled trials evaluating the use of SGLT2 inhibitors in T1D and insulin-treated T2D to help quantify the risk in these populations. Furthermore, in September 2015, the FDA also released a safety communication strengthening the warning for the SGLT2 inhibitor canagliflozin and the increased risk of bone fractures and decreased bone mineral density.[7] SGLT2 inhibitors increase concentrations of phosphate through increased tubular reabsorption, which can adversely affect the bone.[8] Confirmatory data from nine pooled clinical trials resulted in incidence rates of bone fractures of 1.4 and 1.5 per 100 patient-years of exposure for canagliflozin 100 mg and 300 mg, respectively. This is compared to a rate of 1.1 per 100 patient-years seen in the comparator group including placebo and active comparators. Fractures occurred as early as 12 weeks after initiation of therapy and were more likely to be from low trauma and affect the upper extremities. The FDA is continuing to assess the risk of fractures with the other SGLT2 inhibitors, including dapagliflozin and empagliflozin to determine if this is a class effect. The FDA also added new information about decreased bone mineral density at the hip and lower spine based on data from a postmarketing double blind placebo controlled trial in elderly patients with T2D (n=714). [7]

The FDA added a new Warning and Precaution that the dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, linagliptin and alogliptin) may cause joint pain that can be severe and disabling.[9] Cases have been reported in the literature as well as the FAERS database that have started anywhere from 1 day to years after starting a DPP-4 inhibitor.[9,10,11] Symptoms resolve after discontinuation of the medication.

NSAIDs have been pivotal drugs for the treatment of pain management and are available by prescription and over the counter. However, ever since refocoxib was withdrawn from the market in 2004, the cardiovascular (CV) safety of the class has been uncertain.[12] After a recent review of the current safety data, the FDA opted to strengthen the label warning that non-aspirin NSAIDs do in fact increase the chance of a heart attack and stroke.[13] A review of a meta-analysis of RCTs[14] and observational trials were reviewed by the FDA Advisory Committee in 2014.[15] Based on this review, the following conclusions were made: 1) A multitude of studies support the finding that NSAIDs can cause serious CV thrombotic events (relative risk [RR] 10% - 50%) and this risk is also evident in healthy individuals; 2) It appears there could be a significant risk within days to weeks of initiation and there may be a higher risk with longer NSAID use; 3) Some observational data suggests that naproxen may have a lower CV risk compared to other NSAIDs. However, this is based on limited data from studies not designed to compare the safety of one NSAID to another. The ongoing randomized safety trial comparing CV events with celecoxib, naproxen and ibuprofen among high CV risk patients[16] will help determine if there are differences between individual agents; and 4) There is an approximately two-fold increase in hospitalizations due to heart failure with use of both COX-2 selective and nonselective NSAIDs.

Other notable FDA warnings that resulted in label changes include the safety caution of possible increased risk of heart attack and stroke with use of testosterone products.[17] Further definitive high quality studies are needed to confirm this risk as the current data is conflicting and has many limitations.[18]
There were also two new concerns regarding treatments for hepatitis C. In March, the FDA warned of an increased risk of symptomatic bradycardia when sofosbuvir, with or without another direct acting antiviral, is used in combination with amiodarone.[19] In October 2015, the FDA released a drug safety communication warning that hepatitis C treatments ombitasvir, paritaprevir and ritonavir +/- dasabuvir (Viekira Pak® and Technivie®) can cause serious liver injury, mostly in patients with underlying advanced liver disease.[20] As a result, drug labeling was updated to include this risk.
Lastly, the FDA made changes to the varenicline drug label warning that the prescription smoking cessation medication may react with alcohol, resulting in decreased tolerance or aggressive behavior. Rate reports of seizures were also reported.[21] None of the cases involved excessive amounts of alcohol.

2015 Ongoing Safety Investigations

Tramadol and codeine in children

The FDA is investigating the use of tramadol and codeine cough and cold medicines in children <18 y/o because of the risk of respiratory depression in children.[22,23] Although tramadol is not FDA-approved for use in children, it can be used off-label in this population. The FDA warns of a concern with both agents post-operatively after tonsillectomy and/or adenoidectomy. The risk with is thought to be increased as a result of some children being ultra-rapid metabolizers and subsequently having higher levels of the active form of the opioid than usual. Codeine is converted to morphine and tramadol to its active form (O-desmethyltramadol) in the liver by the cytochrome P450 CYP2D6 enzyme. Higher levels of the active opioid can lead to respiratory depression and possibly death. Fifteen deaths or overdoses of children who received standard doses of codeine have been reported in the U.S; all of which were found to have very elevated levels of morphine in their blood.[23,24] Since routine genotype testing is not recommended to assess for ultra-rapid metabolizers, tramadol and codeine should be avoided in children (particularly those under 12 years of age) and only used if the benefits clearly outweigh the risks.

Rosiglitazone

After continued monitoring of rosiglitazone for the treatment of T2D, the FDA has eliminated the Risk Evaluation and Mitigation Strategy (REMS) which put prescribing restrictions in place due to the suggested increased risk of myocardial infarction (MI) with rosiglitazone.[25] In 2013, the FDA determined that the readjudicated results from the RECORD trial did not show an increased risk of MI with rosiglitazone compared to metformin and sulfonylureas.[26] Since 2013, no new pertinent safety information was identified and as a result, the FDA has deemed the REMS is no longer necessary.

Risk of cancer or death from cancer with clopidogrel

In 2014, results from the Dual Antiplatelet (DAPT) trial suggested a reduction in cardiovascular and cerebrovascular events, but also a possible increased risk of cancer or death from cancer from the long-term use (30 months) of clopidogrel following placement of a drug-eluting stent compared to 12 months.[27] The increased risk of death was seen in patients given clopidogrel, but not those given prasugrel. However, in November 2015, the FDA determined that the long-term use of clopidogrel does not increase the overall risk of death in patients with high CV risk.[28] A meta-analysis of other long term clinical trials did not result in a change in the overall risk of death with long-term DAPT (12 months or longer) with clopidogrel and aspirin compared to short-term (6 months or less) or aspirin alone (6.7% vs. 6.6%; respectively). There was also no apparent increase in the risk of cancer-related adverse events (4.2% vs. 4.0%) or cancer-related deaths (0.9% vs. 1.1%) with long term DAPT compared to short term DAPT, respectively. The American College of Cardiology/American Heart Association currently recommends DAPT for at least 12 months after drug eluting stent implantation.

Peer Reviewed By: Jonathan White, Pharm D, BCPS, Clinical Pharmacy Specialist, Primary Care, Providence Medical Group and Andrew Gibler, Pharm.D., Oregon State University College of Pharmacy Drug Use Research and Management

References

1. US Food and Drug Administration: Drug Safety and Availability - FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm.
2. European Medicines Agency. Review of diabetes medicines called SGLT2 inhibitors started: risk of diabetic ketoacidosis to be examined [Internet],12 June 2015.
3. US Food and Drug Administration: Drug Safety and Availability: FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm.
4. Erondu N, Desai M, Ways K, et al. Diabetic Ketoacidosis and Related Events in the Canagliflozin Type 2 Diabetes Clinical Program. Dia Care. July 2015:dc151251.
5. Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. Diabetes Care. 2015;38(9):1638-1642.
6. Peters AL, Buschur EO, Buse JB, et al. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015;38(9):1687-1693.
7. US Food and Drug Administration. Invokana and Invokamet (canagliflozin): Drug Safety Communication - New Information on Bone Fracture Risk and Decreased Bone Mineral Density. September 2015. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm461876.htm.
8. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. Lancet Diabetes Endocrinol. 2015;3(1):8-10.
9. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain. August 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm459579.htm.
10. Sasaki T, Hiki Y, Nagumo S, et al. Acute onset of rheumatoid arthritis associated with administration of a dipeptidyl peptidase-4 (DPP-4) inhibitor to patients with diabetes mellitus. Diabetol Int. 2010;1(2):90-92.
11. Crickx E, Marroun I, Veyrie C, et al. DPP4 inhibitor-induced polyarthritis: a report of three cases. Rheumatol Int. 2014;34(2):291-292.
12. Trelle S, Reichenbach S, Wandel S, Hildebrand P. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011;342(7789), p. 154
13. US Food and Drug Administration. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. July 2015. Available at http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm.
14. Bhala N, Emberson J, et al Coxib and traditional NSAID Trialists' (CNT) Collaboration, Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013;382(9894):769-779.
15. Food and Drug Administration [Internet]. Silver Spring, MD. FDA Briefing Information for the February 10-11, 2014 Joint Meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM383180.pdf.
16. Becker MC, Wang TH, Wisniewski L, et al. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. Am Heart J. 2009;157(4):606-612.
17. US Food and Drug Administration: FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. March 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm.
18. Goodman N, Guay A, Dandona P, et al. American Association Of Clinical Endocrinologists And American College Of Endocrinology Position Statement On The Association Of Testosterone And Cardiovascular Risk. Endocr Pract. 2015;21(9):1066-1073.
19. US Food and Drug Administration: FDA Drug Safety Communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another Direct Acting Antiviral drug. March 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm439484.htm.
20. FDA Drug Safety Communication. FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. 10/22/15. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm468634.htm.
21. US Food and Drug Administration: FDA Drug Safety Communication: FDA updates label for stop smoking drug Chantix (varenicline) to include potential alcohol interaction, rare risk of seizures, and studies of side effects on mood, behavior, or thinking. March 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm436494.htm.
22. US Food and Drug Administration: FDA Drug Safety Communication: FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger. September 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm462991.htm.
23. US Food and Drug Administration: FDA Drug Safety Communication: FDA evaluating the potential risks of using codeine cough-and-cold medicines in children. July 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm453125.htm.
24. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med. 2009;361(8):827-828..
25. US Food and Drug Administration: Rosiglitazone-containing Diabetes Medicines: Drug Safety Communication - FDA Eliminates the Risk Evaluation and Mitigation Strategy (REMS). December 2015. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm477601.htm. 26. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373(9681):2125-2135.
27. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. New England Journal of Medicine. 2014;371(23):2155-2166.
28. US Food and Drug Administration: FDA Drug Safety Communication: FDA review finds long-term treatment with blood-thinning medicine Plavix (clopidogrel) does not change risk of death. November 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm471286.htm.