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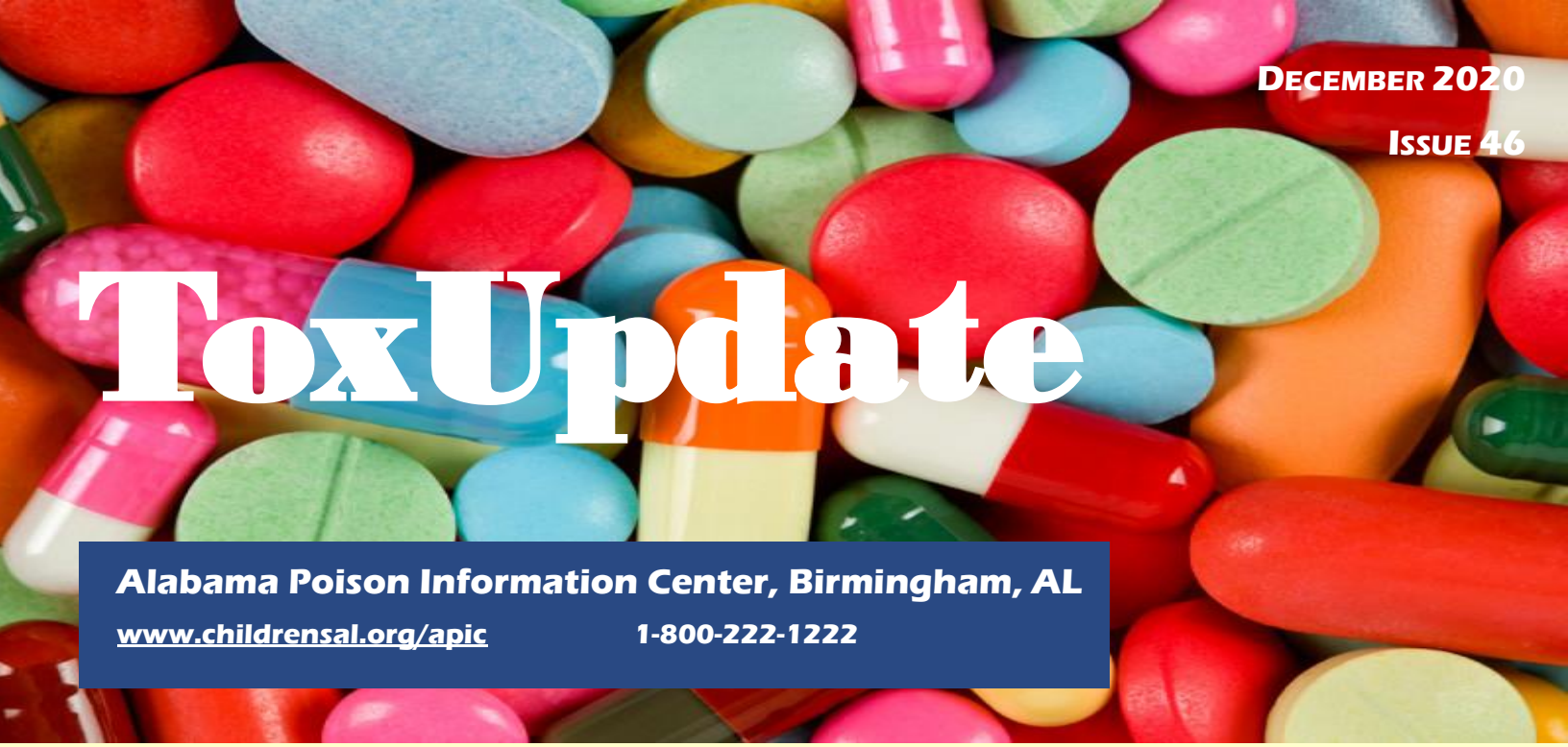

ToxUpdate

Alabama Poison Information Center, Birmingham, AL
www.childrensal.org/apic 1-800-222-1222

A Closer Look at Remdesivir's Adverse Effects and Toxicity

By Mayank Modi, Samford University PharmD Candidate

Background

In late 2019, a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) caused a global health threat and an ongoing pandemic all over the world. The virus possesses an unsegmented, single-stranded, positive sense RNA genome enclosed by 5'-cap and 3'-poly(A) tail. Coronaviruses are encircled with an envelope containing viral nucleocapsid. The nucleocapsid is arranged in a helical symmetry that reflects an atypical attribute in positive sense RNA. The virus spreads rapidly and those who are infected by the virus typically have flu-like symptoms, fever or chills, body ache, cough, nausea, vomiting, loss of taste or smell, fatigue, or sore throat. Covid-19 infection is also associated with pneumonia and acute respiratory distress syndrome (ARDS). Some people infected with the virus have had no symptoms while some have experienced neurological symptoms with or without signs of respiratory symptoms.

Veklury (Remdesivir) is an IV nucleotide prodrug of an adenosine analog. Its major role is to bind to the viral RNA-dependent RNA polymerase and inhibit the viral replications through premature termination of RNA transcriptions. In vitro studies conducted by drug company Gilead, showed activity against SARS-COV-2. Remdesivir is approved by the U. S. Food and Drug Administration (FDA) for the treatment of adults and pediatric patient age 12 and above and weighing 40 kg or more that require hospitalization for COVID-19. The FDA has also issued an Emergency Use Authorization for treatment in hospitalized patients weighing 3.5 kg to less than 40 kg or patients less than 12 years of age weighing at least 3.5 kg. The recommended dose for adults, children, and adolescents 12 years of age and above who also weigh 40 kg or more is 200 mg on day 1 followed by 100 mg once daily for four days or until discharged from the hospital, whichever is

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Special Interest Articles

- Remdesivir
- Lyumjev™

Did you know?

According to a report by the Surgeon General, cigarette smoking is at it's lowest point since 1965, 13.7%. However, smoking still remains the United State's leading preventable cause of death and disease. Smoking costs the United States more than $300 billion annually. Smoking kills nearly half a million Americans each year, accounting for nearly one in five deaths in the United States.

Lyumjev™ - Ultra-Rapid Lispro Insulin

By Rodney Nguyen, Samford University PharmD Candidate

"Lyumjev is an ultra-rapid lispro (URLi) formulation that uses two inactive ingredients to improve absorption at the site of injection."

Elevated postprandial plasma glucose (PPG) is a persistent challenge for both type 1 and type 2 diabetic patients. The current rapid-acting insulins were developed to combat these PPG excursions, but it is unable to fully control the excursions due to its inability to match the physiological insulin secretion. Therefore, Lyumjev was developed to better control the excursions. Lyumjev is an ultra-rapid lispro (URLi) formulation that uses two inactive ingredients to improve absorption at the site of injection. Treprosinil is used in Lyumjev to induce vasodilation. The other ingredient, citrate, increases vascular permeability. These two ingredients allow lispro to be absorbed faster which leads to a faster onset and a shorter duration of action. In relative terms, URLi is capable of a six to sevenfold insulin exposure in the first 15 minutes compared to lispro.

URLi has a similar safety profile to lispro. Mild to moderate lispro overdose leads to hypoglycemia. Some signs of hypoglycemia are hunger, anxiety, diaphoresis, palpitation, tachycardia, inability to concentrate, headaches, and tremors. Lispro overdose could also lead to electrolytes abnormalities such as hypokalemia, hypomagnesemia, and hypophosphatemia. In a severe case of lispro overdose, patients could have confusion, seizure, and coma. If hypoglycemia is left untreated, permanent brain damage could occur or even death.

URLi is an insulin, therefore, the treatment for URLi is the same as any other insulin overdoses. In severe cases of insulin overdose, the patient should undergo supportive care with intravenous dextrose. Dextrose is the mainstay of therapy in insulin overdose. Another option is glucagon, which is considered to be the antidote for insulin. Glucagon is ideal in patients whose IV access cannot be established because it is given SubQ or IM. In some cases, the patient could be seizing while in a hypoglycemic state and this warrant intravenous benzodiazepines, but if the patient is still seizing after correction of hypoglycemia, barbiturates should be used. Patients could be discharged after hypoglycemia is corrected and a few hours of observation in the emergency department.

. *References*

1. Miura J, Imori M, Nishiyama H, Imaoka T. Ultra-Rapid Lispro Efficacy and Safety Compared to Humalog® in Japanese Patients with Type 1 Diabetes: PRONTO-T1D Subpopulation Analysis. Diabetes Ther. 2020;11(9):2089-2104. doi:10.1007/s13300-020-00892-0.
2. Malecki MT, Cao D, Liu R, et al. Ultra-Rapid Lispro Improves Postprandial Glucose Control and Time in Range in Type 1 Diabetes Compared to Lispro: PRONTO-T1D Continuous Glucose Monitoring Substudy. Diabetes Technol Ther. 2020;22(11):853-860. doi:10.1089/dia.2020.0129.
3. Insulin Lispro, Recombinant. Micromedex® 2.0, (electronic version). Truven Health analytics, Greenwood Village, Colorado, USA. [Accessed 11/13/2020]

Remdesivir (Continued from page 1)

first; may extend duration up to 10 days in patients without significant clinical improvement at day 5. Remdesivir is not recommended for patients who do not require supplemental oxygen.

Adverse Effects

Remdesivir has many side effects, the most common are nausea and vomiting. The drug can also cause lab abnormalities such as increasing alanine transaminase (ALT) and aspartate transaminase (AST), increased prothrombin time and also hypersensitivity reactions. Signs and symptoms of hypersensitivity reactions include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Administration site reactions were also commonly seen in patients with cases of anaphylaxis reaction. Generalized seizure were seen in less than 2% of adult subjects in clinical trials.

Monitoring Parameters

Baseline liver function test and prothrombin time should be obtained prior and during the course of treatment. Consider discontinuing remdesivir if ALT levels increase to greater than 10 times the upper limit of normal. Monitor fluids and electrolytes in patients with significant vomiting.

Special population

Studies that were done excluded pregnant women therefore there is no clinical evidence for the safety and efficacy of remdesivir for pregnancy or lactation. Remdesivir is not recommended for patients with an eGFR <30 mL/min.

Toxicity/Overdose

For remdesivir, it is anticipated that potential toxicity may be an extension of adverse effects reported at therapeutic dose.

References

1. Dhama K, Khan S, Tiwari R, et al. Coronavirus Disease 2019-COVID-19. *Clin Microbiol Rev*. 2020;33(4):e00028-20. Published 2020 Jun 24. doi:10.1128/CMR.00028-20 (Accessed November 24, 2020)
2. CDC. Symptoms of Coronavirus. Cdc.gov. Published November 10, 2020.. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.(Accessed November 24, 2020)
3. Remdesivir. POISINDEX® System (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (Accessed November 24, 2020).
4. Remdesivir (VEKLURY) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf. (Accessed: November 23, 2020).
5. Remdesivir. Nih.gov. https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir, (Accessed November 24, 2020).
6. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32020029. (Accessed November 24, 2020)
7. KinkD. New study finds the Coronavirus outbreak boosts dating app usage. PR Newswire. Published February 28, 2020.. https://www.prnewswire.com/news-releases/new-study-finds-the-coronavirus-outbreak-boosts-dating-app-usage-301013337.html, (Accessed November 25, 2020.)
8. EMA recommends authorization for remdesivir to combat COVID-19; Europeanpharmaceuticalreview.com. https://www.europeanpharmaceuticalreview.com/news/122139/ema-recommends-authorisation-for-remdesivir-to-combat-covid-19/; (Accessed November 25, 2020)
9. COVID-19: When the body overreacts. Sharp.com. Published April 21, 2020. https://www.sharp.com/health-news/covid-19-when-the-body-overreacts.cfm; . (Accessed November 25, 2020)
10. First case of vertical transmission of COVID-19 reported in India. Myupchar.com. https://www.myupchar.com/en/disease/covid-19/covid-19-pregnancy-advice/first-case-of-vertical-transmission-of-covid-19-reported-in-india; (Accessed November 25. 2020).