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Andexxa®: First FDA Approved Factor Xa Inhibitor Reversal Agent

By Ryan Taylor, Samford University PharmD Candidate

Direct factor Xa inhibitors such as apixaban (Eliquis®), edoxaban (Savaysa®), and rivaroxaban (Xarelto®) have been shown in randomized clinical trials to be safe and effective for the treatment and prevention of thromboembolism and stroke prevention in atrial fibrillation. Betrixaban (Bevyxxa™), is another direct factor Xa inhibitor that is approved for prevention of venous thromboembolism only. Factor Xa inhibitors have demonstrated a more favorable adverse effect profile and require less laboratory monitoring compared to the vitamin k antagonist, warfarin. However, these agents are still associated with an increased risk of death and complications due to major bleeding. Patients undergoing urgent surgery or experiencing major bleeding require rapid reversal of the anticoagulant effects of these agents.

Andexxa (andexanet alfa) is a first-in-class specific antidote developed by Portola Pharmaceuticals and approved under the FDA's accelerated approval pathway. While proposed as an universal antidote for all indirect or direct Xa inhibitors, Andexxa is currently only approved for reversal of rivaroxaban or apixaban in cases of life-threatening or uncontrolled bleeding. Andexanet alfa is a recombinant modified human factor Xa protein analog designed to be void of catalytic activity. The mechanism of action is achieved through sequestration of factor Xa inhibitors and restoration of endogenous factor Xa function.

Andexxa was evaluated in two randomized, placebo-controlled phase III trials in healthy older volunteers to reverse the effects of rivaroxaban (trial-arm ANNEXA-R) or apixaban (trial-arm ANNEXA-A). In ANNEXA-A, anti-factor Xa activity was reduced by 94% with andexanet bolus compared to 21% in placebo within 2-5 minutes. In ANNEXA-R, 92% of anti-factor Xa activity was reduced in 2-5 minutes compared to 18% with placebo. The primary endpoint of percent change from baseline in anti-FXa activity was statistically significant in both andexanet groups vs. placebo ($p<0.001$). More data is needed to support the use of Andexxa for the reversal of other direct or indirect factor Xa inhibitors. As a condition of the FDA's accelerated approval, additional prospective trials are ongoing to assess the safety and efficacy of Andexxa for this indication.

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Special Interest Articles

- Andexxa
- Xyrem
- SGLT2 Inhibitors

Did you know?

According to JAMA Network Open, benzodiazepine prescribing patterns have increased substantially in a cross-sectional study of ambulatory care visits. From 2003 - 2015, benzodiazepine prescribing, including co-prescribing with other sedating medications, went from 3.8% to 7.4% of visits.

Xyrem®: Treatment for Cataplexy and Excessive Daytime Sleepiness in Narcolepsy

By John Michael Herndon, Auburn University PharmD Candidate

"The effects of Xyrem are thought to be mediated through GHB and GABA- B receptors, which ultimately induces REM sleep and decreases delta sleep."

Sodium oxybate (Xyrem®) is an agent used to reduce cataplexy and daytime sleepiness in patients with narcolepsy. It is the sodium salt of gamma-hydroxybutyrate (GHB), which is a naturally occurring neurotransmitter with sedative and anesthetic properties. GHB has primarily been used as a substance of abuse and is commonly referred to as the date-rape drug. In 2000, the DEA classified GHB and its analogs as Schedule I substances. Sodium oxybate was initially approved in 2002 for the reduction of cataplexy in adults with narcolepsy. In 2018, it was approved for the treatment of catplexy and excessive daytime sleepiness in pediatric patients aged 7 - 17 with narcolepsy. Xyrem is designated as a Schedule III drug.

The effects of Xyrem are thought to be mediated through GHB and GABA-B receptors, which ultimately induces REM sleep and decreases delta sleep. The usual adult dosage range is 4.5 to 9 grams/night (see package insert for pediatric dosing) and is given as 2 doses- the first given at bed time and the second given 2.5 - 4 hours later. The drug is rapidly absorbed, and sedation occurs within 15-45 minutes. The maximal effect occurs within 45-90 minutes; and, the total duration of action is 2-3 hours.

Common adverse drug reactions include weight loss, CNS effects, and urinary incontinence. Sodium oxybate readily crosses the blood-brain barrier and toxicities result in general anesthesia and respiratory depression. Doses of 10 mg/kg may result in mild toxicities such as amnesia and hypotonia; 20 mg/kg could result in moderate toxicity. These effects usually occur within 15 minutes of ingestion. There is no antidote for Xyrem overdose and neither flumazenil nor naloxone have shown clinical efficacy. In the setting of an overdose, treatment consists of supportive care, including airway protection and ventilation if needed. Due to the short duration of action, patients with severe toxicities that require ventilation are often extubated within a few hours. Xyrem is contraindicated with concurrent use of alcohol or other sedative agents, and in patients with succinic semialdehyde dehydrogenase deficiency. Caution should be taken in patients who use other CNS depressants.

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Sodium- Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes

By Drew Hoagland, Samford University PharmD Candidate

Sodium-glucose cotransporter 2 (SGLT2) inhibitors (Invokana® (canagliflozin), Farxiga® (dapagliflozin), Jardiance® (empagliflozin)) are a newer class of medication used in the treatment of Type 2 diabetes mellitus (T2DM). SGLT2 inhibitors work by lowering the renal threshold for glucose and increase urinary glucose excretion by interfering with the reabsorption of renally filtered glucose across the tubular lumen of the proximal renal tubules. The most common adverse effects observed with SGLT2 therapy include urinary tract infections, polyuria, and female genital mycotic infections.

In the most recent update of American Diabetes Association Standards of Care 2019, SGLT2 inhibitors were considered first line agents in the treatment of T2DM after metformin in patients with a previous cardiovascular event or those considered high risk for a cardiovascular event. This update may lead to increased use of these medications which could potentially lead to more toxic exposures.

In the event of a toxic exposure there are several monitoring parameters that can be used to assess the patient. Ingestion of SGLT2 inhibitors alone is not expected to cause severe hypoglycemia, but when combined with insulin or insulin secretagogues, severe hypoglycemia can develop. In patients with SGLT2 overdose who are also on insulin or insulin secretagogues, blood glucose and clinical evidence of hypoglycemia should be monitored hourly for 8- 12 hours. Patients should also have their vital signs monitored. If a patient is symptomatic, fluid and electrolyte balance need to be monitored as well as arterial blood gases and urinalysis if clinically indicated. High anion gap metabolic acidosis accompanied by presence of ketones in urine and/or blood has been associated with the development of diabetic ketoacidosis (DKA) in patients taking SGLT2 inhibitors.

In a retrospective cohort study of toxic exposures calls to 13 poison control centers around the US from 2013 – 2016, there were 88 calls received for toxic exposures due to to SGLT2 inhibitors in patients ranging from 1 - 75 years old. Eighty patients were asymptomatic and the remaining developed only mild-moderate symptoms. While the sample size is small, this evidence suggests SGLT2 inhibitors may be preferred not only for their clinical effects, but also for their relatively mild toxicity and safety in overdose compared to sulfonylureas.

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John Michael Herndon, Auburn University pharmacy student, and Drew Hoagland and Ryan Taylor, Samford University pharmacy students, visited Edgewater Senior Citizen Center on March 5, 2019 to talk about Medication Safety.