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NEW DRUGS FOR TREATMENT OF DIABETES

Photo Credit: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

by Megan Dryer, PharmD

Introduction

Several new diabetic agents have been approved in the past few years with the ability to manage hyperglycemia and avoid the metabolic adverse effects of weight gain, hypoglycemia and fluid retention. Recently approved agents are exenatide, (Byetta®), sitagliptin, (Januvia®), and saxagliptin (Onglyza™). These compounds have pharmacological effects that are glucose-dependent and therefore result in a low incidence of hypoglycemia.

This paper aims to review the pharmacokinetic and adverse effect profiles of these agents and extrapolate possible overdose effects based on these profiles and data available in the current literature.

Pharmacology

Exenatide is the synthetic form of the amino acid peptide exendin-4, which was originally found in Gila monster saliva.[1] This synthetic peptide has many similarities to glucagon-like peptide-1 (GLP-1), an incretin hormone found in humans. GLP-1 has important antihyperglycemic functions, and exenatide, as an incretin mimetic or GLP-1 agonist mimics these antihyperglycemic functions.

The specific mechanism of action of exenatide includes glucose-dependent increases in the secretion of insulin from pancreatic beta cells. Exenatide also lowers glucagon secretion when glucose concentrations are high and slows gastric emptying to reduce the amount of glucose entering the blood at one time.

Gila Monster *Photo Credit: Hogle Zoo*

Sitagliptin and saxagliptin are dipeptidyl peptidase (DPP)-IV inhibitors. DPP-IV is a peptidase responsible for the degradation of GLP-1, the incretin hormone that exenatide mimics. Through the inhibition of DPP-IV, the inactivation of the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) is slowed, which results in increased glucose-dependent insulin secretion and decreased glucagon secretion.

Pharmacokinetics

Peak plasma concentrations of exenatide occur in about 2 hours and the elimination half-life is 2.5 hours. Elimination occurs predominantly through glomerular filtration.

Sitagliptin peak plasma concentrations are reached within 1-4 hours. The elimination half-life is about 12.4 hours and 87% of sitagliptin is excreted in the urine. Sitagliptin has been shown to be modestly removed by hemodialysis in patients with end stage renal disease. Saxagliptin peak plasma concentrations are reached within 2 hours and its active metabolite's (5-hydroxy saxagliptin) peak plasma concentrations are reached in 4 hours. Saxagliptin is metabolized by CYP 3A4/5. The elimination half-life of saxagliptin and its metabolite are 2.5 and 3.1 hours respectively. Dosing adjustments are recommended for patients with moderate to severe renal impairment and saxagliptin and its active metabolite are removed by hemodialysis.

Adverse Effects

Adverse effects reported in the package insert are collected from three 30 week clinical trials of exenatide as add on therapy to metformin or a sulfonylurea.[2] The adverse effects occurring in greater than 5% of patients and reported more frequently than placebo included nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, and dyspepsia. Adverse effects that were less common included weakness, decreased appetite, GERD, and excessive sweating. Patients receiving treatment with exenatide in combination with metformin did not experience hypoglycemia more than placebo; however, patients receiving combination exenatide and sulfonylurea therapy experienced hypoglycemia more frequently than patients in the placebo group (35.7% vs. 3.3%). One study reported a case of mild hypoglycemia in a patient receiving 0.1 mcg/kg of exenatide with neither metformin nor a sulfonylurea.[1] Post-marketing cases of acute pancreatitis have *(cont. on pg. 2)*

IN THIS ISSUE

TIME TO FOCUS ON MEDICATION DISPOSAL

Many people keep prescription medications they no longer need. This increases the risk for unintentional poisoning, misuse and abuse as well as poses environmental concerns.

Environmental Concerns

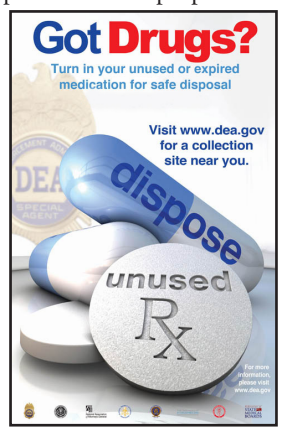
- Medications have made their way into water sources through normal urinary excretion of the drugs and metabolites as well as flushing medications down the toilet.
- Sewage treatment plants were not designed to remove these chemicals.
- Long-term effects of medications in the water on humans are unknown, but some drugs have been shown to affect aquatic life.

Unintentional poisoning, misuse and abuse

- The risk of unintentional poisoning increases when unused medications remain in the home.
- The National Survey on Drug Use and Health (NSDUH) has shown that Utah has one of the highest rates of nonmedical use of pain relievers in ages 12 and older, including 16,000 adolescents.
- The 2009 Partnership Attitude Tracking Survey (PATS) Survey showed that 63% of teens believe prescription drugs are easy to get from their parent's medicine cabinet.

There is no national policy regarding a safe and environmentally responsible method of drug disposal. Flushing many types of drugs can have detrimental effects on the environment, but disposing of certain drugs in the trash exposes the potential for retrieval by children, pets, or drug seekers. Incineration is the best option, but not readily available to the public. Medication take-back events are growing in popularity but require law enforcement on site. A new federal law allows the attorneys general to develop policy to include alternatives to law enforcement presence.

Until such time that a national policy is formulated, community sponsored drug take-back events are a safe and secure strategy for reducing drug abuse, accidental poisoning, and negative effects on the environment. Utah has been proactive in providing options for residents to dispose of medications. Several law enforcement agencies have installed permanent disposal bins. A variety of community agencies have organized take-back events. Through collaborative efforts of partner organizations, medication take-back events have demonstrated excellent results and wide acceptance by the public to practice safe and secure disposal. In Utah in 2009, 5,918 lbs. of medication were collected and so far in 2010, over 5,000 lbs. have been collected. The UPCC encourages health care providers to educate patients about proper disposal options. The following link has information about community take-back events and permanent disposal locations throughout the state: http://www.medicationdisposal.utah.gov/disposal_locations_events.htm .



(cont. from pg. 1)

been reported in patients using exenatide. One such case report describes symptoms occurring within 24 hours of exenatide initiation in a 69 year old man.[3] Overall, the adverse effects and hypoglycemia experienced by patients were similar to placebo when treated with sitagliptin in combination with metformin or pioglitazone.[3] When sitagliptin was used in combination with a sulfonylurea, the overall incidence of adverse effects, especially hypoglycemia, was greater than placebo. The adverse effects experienced in this group included hypoglycemia (12.2% vs. 1.8%), nasopharyngitis and headache. Post-marketing hypersensitivity reactions have been reported, including Stevens – Johnson Syndrome, up to 3 months following sitagliptin initiation. Similar to sitagliptin, saxagliptin was well tolerated alone and in combination with metformin and a thiazolidinedione. The incidence of hypoglycemic reactions with saxagliptin alone was similar to placebo but was higher than placebo in combination with an oral hypoglycemic agent.

Clinical Toxicology

The recommended starting dose of exenatide is 5 mcg injected subcutaneously twice daily. The dose can be increased to 10 mcg twice daily after one month of treatment if necessary. Exenatide is formulated as a 250 mcg/mL subcutaneous injection and is available as a prefilled pen. Each pen is filled with a volume of exenatide to dispense 60 doses of either 5 mcg or 10 mcg doses. From January 2008 through September 2010, nine exenatide exposures were reported to the Utah Poison Control Center; seven cases were therapeutic errors. The patients experienced primarily nausea and dizziness. One caller with a 40 mcg exenatide unintentional exposure was also on glipizide and reported the inability to get her blood glucose above 80 mg/dL and was seeing "white spots". She managed her hypoglycemia with a snack and her symptoms resolved within six hours.

There is limited published data regarding exenatide in an overdose situation. During a bioavailability study conducted by Calara and colleagues, three patients were inadvertently administered a 100 mcg dose rather than a 10 mcg dose.[4] All three patients suffered severe nausea and vomiting and rapidly declining glucose concentrations. One patient developed severe hypoglycemia requiring parenteral glucose administration. All patients recovered without complications. Concomitant use of a sulfonylurea and exenatide put a patient at increased risk of hypoglycemia. Overdose situations in which a sulfonylurea is also ingested may result in more severe hypoglycemia. Finally, if co-ingestants are suspected in an exenatide overdose, a possible delay in the clinical effects of co-ingestants may occur due to the slowed gastric emptying induced by exenatide.

The recommended dose of sitagliptin is 100 mg orally once daily. If sitagliptin or exenatide are used in combination with a sulfonylurea, the dose of the sulfonylurea may need to be decreased to avoid hypoglycemia.

Limited data also exists regarding sitagliptin and saxagliptin overdosage. Single doses of up to 800 mg of sitagliptin and 400 mg of saxagliptin were given to healthy patients in clinical trials.[5] Mean increases of 8.0 msec in QTc were seen in one trial *(cont. on pg. 3)*

(cont. from pg. 2)
with sitigliptin. While this increase may not be clinically significant, in an overdose situation with exposures greater than 800 mg, QTc increase may become more significant. No dose-related clinical adverse effects or hypoglycemia were reported in patients who received a single dose of 800 mg sitigliptin or 400 mg saxagliptin. In addition no hypoglycemic events were noted in patients receiving doses up to 600 mg sitigliptin over 10 days.[6] Hypoglycemia in a sitagliptin or saxagliptin overdose is more likely to occur if the patient also took a sulfonylurea., From 2008 through September 2010, the UPCC received 17 reports of sitagliptin exposure. Two patients experienced hypoglycemia. The UPCC has only received one report of a saxagliptin exposure. A patient who inadvertently took a double dose complained of diaphoresis and dizziness without hypoglycemia.

Another potential concern arises with regard to the selectivity of sitagliptin. Other selective agents have been shown to lose their selectivity at high doses. Sitagliptin's selectivity has been shown in vitro at concentrations similar to those achieved with therapeutic doses.[5] If selectivity is compromised in an overdose situation, severe adverse effects related to the inhibition of DPP-8 and DPP-9 could potentially occur. Some effects that have been noted in rats and dogs include anemia, thrombocytopenia, splenomegaly and multiple organ pathology.[7]

Pregnancy and Lactation

Pregnancy and lactation information is very limited for both exenatide and DDP-IV inhibitors. Very little exenatide transfers across the placenta and is not expected to increase the risk of adverse pregnancy outcomes based on animal studies.[8] It remains unknown if exenatide is excreted in human breast milk. Sitagliptin and saxagliptin have been shown to cross the placenta in animals; however, these studies have not shown an increased risk of congenital anomalies.[9] Six pregnancies exposed to sitagliptin have been reported to the manufacturer which included four spontaneous abortions and two normal babies born at term. It is not known if sitagliptin is excreted in human breast milk. No human studies have been conducted on either of these agents. At this point, the risk of increased birth defects with these agents is largely unknown and any potential risk to the fetus should be weighed against the potential benefit of the medication, keeping in mind that uncontrolled diabetes is a risk to the fetus in itself.

Treatment

Monitoring of patients suspected of an exenatide or DPP-IV inhibitor overdose should include regular blood glucose concentrations as well as electrolytes. Hydration status should be monitored in an exenatide overdose if significant gastrointestinal symptoms have been experienced. Additionally, QTc should be monitored in patients with a possible sitagliptin overdose. Asymptomatic exposures should be observed for 4-6 hours unless co-ingestants requiring longer observation are suspected.

Treatment with IV dextrose may be necessary in patients who develop severe hypoglycemia. For hypoglycemia that is refractory to IV dextrose, octreotide may be considered; however, evidence of its efficacy in this setting has not been established. Electrolyte abnormalities should be corrected and patients should be observed until euglycemic and other clinical effects have resolved.

Conclusion

Exenatide and the DPP-IV inhibitors sitagliptin and saxagliptin are new glucose-dependent, hypoglycemic agents indicated for patients with type 2 diabetes. Limited information regarding effects in an overdose is available due to the short time on the market. However, because these drugs exert their mechanism of action only during periods when there is an increase in plasma glucose concentrations, severe hypoglycemia is not expected. However, hypoglycemia is possible and these agents may enhance the hypoglycemic effects of insulin or a sulfonylurea if taken in combination.

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POISON PEARLS

METHEMOGLOBIN & METHYLENE BLUE

Nate Friedline, MD
Emergency Medicine Resident

Photo Credit: Jeannett E. Madsen, RN

Methemoglobinemia (MetHb) is induced when hemoglobin is oxidized from its normal oxygen carrying state (Fe2+ to Fe3+). RBCs are oxidized with normal cellular stress and a Methb concentration of 0.5-1% is normal. Elevated Methb is pathologic and may result from an acquired or congenital mechanism. Patients usually develop cyanosis with MetHb ≥10% and become symptomatic at ≥20%. Symptoms are related to a "functional anemia" due to the inability of MetHb to transport oxygen. Patients present with manifestations of hypoxia, such as confusion, HA, dizziness, dyspnea, chest pain, or dysrhythmias. Pulse oximetry is not an accurate measurement of oxygen saturation with very high MetHb levels. Methylene blue (1-2 mg/kg IV over 5 min) is an effective treatment for symptomatic patients with methemoglobinemia. Repeat dosing may be necessary, but if no response, consider G6PD deficiency or on-going MetHb production. The onset of effect is typically within 20-30 minutes, at which time the patient's symptoms should dramatically improve.

TOXINS IN THE NEWS

- **Ipecac syrup** is no longer being manufactured, although some product may still be available in the home and pharmacy. It is not recommended for routine management of overdose.
- The FDA has notified healthcare professionals and patients that **lamotrigine (Lamictal)**, a medication commonly used for seizures in children two years and older, and bipolar disorder in adults, can cause **aseptic meningitis**.
- **Hyland's Teething Tablets** is being voluntarily recalled due to inconsistent amounts of **belladonna** found through FDA laboratory analysis. The FDA has received reports of serious adverse events consistent with belladonna toxicity in children taking Hyland's Teething Tablets.

DID YOU KNOW?

When asked how prescription narcotics were obtained for nonmedical use, 52% of 12th graders said they were given the drugs or bought them from a friend or relative.

60% of teens who have abused prescription painkillers did so before age 15.

—Partnership for a Drug-Free America

MEET THE UPCC STAFF

ANN LYSTRUP, RN, BSN attended college at BYU then Idaho State University where she graduated in 1979. She immediately began working in the Emergency Dept. at Bannock Memorial Hospital in Pocatello, ID. A short time later, she climbed aboard a helicopter to assist in transporting a critically-ill patient, and immediately knew she wanted to be a flight nurse. Ann flew with teams in Idaho, Montana, Missouri, and Colorado before moving to Utah, where she first joined the Life Flight team in southern Utah, and then University of Utah's AirMed when her family settled in Salt Lake City. Ann holds specialty certifications as a Certified Emergency Nurse, a Certified Flight Nurse, and a Certified Critical-Care Registered Nurse. At the urging of a respected colleague, she shed her wings and accepted the position of Nurse Manager of Trauma and Orthopedic Surgery Services at the University of Utah Hospital. She later served as the Director of Cardiac and Critical-Care Services at Davis Hospital, and most recently opened the new Park City Medical Center as the Director of Inpatient Services. Her desire to join the team at the Utah Poison Control Center stemmed from a lecture given by Dr. Caravati, UPCC's Medical Director, to the AirMed flight team several years ago. The opportunity to combine principles of physiology, pharmacology, and toxicology, and relate them to individual patients and patient care situations, sounded both challenging and exciting, and has proven to be exactly that! In her spare time, Ann spends time with her six children and seven grandchildren, and enjoys music, crafts, and baking.

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*CSPI denotes Certified Specialist in Poison Information.

THANK YOU

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials and toxicology colleagues that work together to treat and prevent poisonings.

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POISON HELP 1-800-222-1222