Gastroparesis, a delay in the emptying of the stomach contents, is a type of autonomic neuropathy. Approximately 20-40% of patients with a long-standing history of diabetes develop gastroparesis. The diagnosis of gastroparesis is based upon clinical symptoms, delayed gastric emptying, and absence of an obstructing structural lesion in the stomach or small intestine. Symptoms that suggest gastroparesis include nausea, early satiation, postprandial fullness, vomiting, and bloating. Postprandial fullness is the only symptom proven to be a good indicator of delayed gastric emptying.

Complications such as poor glycemic control, malnutrition, and bothersome symptoms happen in some patients with gastroparesis. Delayed gastric emptying increases the time to peak blood sugar. Patients taking insulin may find that their insulin does not properly decrease their blood sugar due to this delayed peak. Other causes of poor glycemic control may be due to decreased absorption of diabetes medication. Malnutrition is also a problem for these patients. Postprandial fullness and nausea can result in patients eating less food or less often.

Goals of treatment of gastroparesis include relieving symptoms, improving glycemic control, and improving nutritional status. Symptomatic patients may benefit from pharmacological therapy.

Primary treatment of gastroparesis includes dietary changes and administration of antiemetic and prokinetic agents. Dietary recommendations for patients with gastroparesis include visiting a registered dietitian who may recommend eating smaller more frequent meals and changing the types of carbohydrates eaten. Pharmacological therapy options include prokinetic and antiemetic medications. Prokinetic drugs increase gastric motility. Examples include erythromycin, metoclopramide, domperidone, and cisapride. Prokinetic drugs are the most common therapy used for symptomatic gastroparesis and work in a dose dependent fashion. Erythromycin and domperidone are the best at relieving symptoms. Antiemetic medications such as ondansetron, prochlorperazine, and meclizine are good for relieving nausea and vomiting. However, they may actually result in even slower gastric emptying and should be used with caution.

Though gastroparesis can significantly affect control of blood sugar, it is important to consider other possible causes of gastric symptoms. If a patient is experiencing problems controlling their blood sugar and there are few other explanations, gastroparesis should be considered a possibility.

### Medications That Can Make Gastroparesis Worse

- Anticholinergic medications (antihistamines, TCA’s)
- Calcium channel blockers
- Opiates
- Levodopa
- Octreotide

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**Objectives:**

- Review pathophysiology, complications and treatment of gastroparesis.
- Review causes, prevention, and treatment of hypoglycemia.
- Discuss the future of GLP-1 mimetics: once weekly exenatide.

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Hypoglycemia occurs when a patient’s blood sugar drops below normal levels (<80 mg/dL). For most people, symptoms occur when levels fall below 60 mg/dL. These symptoms include cold sweats, tiredness, hunger, nausea, irritability, nervousness, fast heart rate, shakiness, headaches, confusion, dizziness, or blurred vision. Seizures can occur if the levels drop below 40 mg/dL, coma can occur if the levels drop below 10 mg/dL. Understanding what puts patients at risk of hypoglycemia and preventing its occurrence is an important component of diabetes management.

**Common Causes**

**Diabetes medications**

Diabetes medications most likely to cause hypoglycemia include insulin, sulfonylureas (glyburide, glipizide, gliniperide), and the glinides (nateglinide, repaglinide). Hypoglycemia due to injected insulin can occur when patients do not eat with their fast acting injections or inject more insulin than their body needs. Patients should be instructed on the importance of injecting fast acting insulin only when they eat a meal and should always follow proper injection technique.

Sulfonylureas also pose a risk of hypoglycemia because they increase the amount of insulin the pancreas secretes. They should be avoided in the elderly or in patients known to be at risk of hypoglycemia. When a sulfonylurea must be used, gliniperide or glipizide are preferred. Glyburide should be avoided due to an increased risk of hypoglycemia. Data suggests the risk of hypoglycemia with glyburide is about 40% higher than with glipizide. Skipping meals increases the risk of hypoglycemia in patients taking sulfonylureas. The importance of regular meals and occasional snacks should be stressed to patients. The glinides work similarly to sulfonylureas and therefore also pose a similar, yet lower risk of hypoglycemia.

**Antibiotics:**

Fluroquinolones have been shown to both increase and decrease blood sugar levels. Of the fluroquinolones studied in patients with diabetes, levofloxacin has been shown to cause the most hypoglycemia. Cases have been reported of severe hypoglycemia in patients taking ciprofloxacin also. Patients receiving ciprofloxacin, and especially levofloxacin, should be counseled to closely monitor their blood sugars while taking the antibiotics.

Other anti-infective agents have been shown to cause hypoglycemia in patients taking glipizide or glyburide. These include co-trimoxazole, fluconazole, and clarithromycin. If possible, these medications should be avoided in patients taking sulfonylureas. Azithromycin and cephalaxin have been proven safe when used with glyburide and glipizide and should be recommended when possible.

**Other Medications**

Some other unexpected medications known to cause hypoglycemia include warfarin, probenecid, aspirin, allopurinol, and fluoxetine. Hypoglycemia results from differing mechanisms of action with each medication; however, the risk of hypoglycemia is increased in patients concurrently taking these medications with diabetes medications.

Beta-blockers, though not directly responsible for causing hypoglycemia, are also a medication of concern in patients with diabetes. Due to their mechanism of action, beta-blockers may mask the shakiness and fast heartbeat associated with hypoglycemia. Care should be taken to warn these patients about the symptoms of hypoglycemia. Patients are most likely to experience irritability, blurred vision, and hunger.

**Physical Activity**

Physical activity is an important part of managing diabetes; however, increased physical activity can cause a drop in blood sugar that may last up to 24 hours. Patients undertaking a new exercise regimen or sport should closely monitor their blood sugar before engaging in the activity. A good practice is having the patient check their blood sugar before or during physical activity. If the blood sugar is ≤ 100 mg/dL, it may be prudent for the patient to have a small snack. Patients should also keep glucose tablets or another source of glucose close at hand should hypoglycemia occur.
Alcohol:

Excess consumption of alcohol has been shown to cause hypoglycemia and/or inhibit a patient’s ability to recognize a hypoglycemic attack. Patients should be counseled to avoid excessive amounts of alcohol and eat a snack rich in carbohydrates when consuming alcohol.

Prevention:

When creating a treatment plan, the desired reduction in A1C and the patient’s health status and medical history should guide medication selection. Medications known to have a high risk of hypoglycemia, such as the sulfonylureas, may not be a first choice in the elderly or patients who are at higher risk of complications. Also, the patient’s daily schedule should be taken into account. Patients who commonly skip meals are at an increased risk of hypoglycemia, and should be taught the safest way to use medication with a high risk of hypoglycemia. Self-monitoring of blood glucose is a key in preventing hypoglycemia. Patients should monitor their blood sugar levels anytime they feel sick or “funny”, are stressed, increasing their physical activity, or changing medication therapy and make changes in diabetes treatment accordingly. In addition, patients who have had at least one episode of severe hypoglycemia or have hypoglycemia unawareness may benefit from higher glycemic targets. These targets should be kept for several weeks or until reversal of hypoglycemic unawareness and reduced risk of future episodes occur.

 treatment

Every patient taking medications for the treatment of diabetes should learn how to treat hypoglycemia. Level of consciousness determines the treatment of hypoglycemia. If a patient is conscious, the preferred treatment is 15-20 grams of glucose. The patient should consume 15 grams of glucose, rest 15 minutes, and then re-check their blood sugar. If it is still below 80 mg/dL, they should repeat the process up to two more times. If blood sugar levels fail to rise to an acceptable value, the patient should contact a health care provider. Once the blood sugar level is stabilized, the patient should consume a meal or snack to prevent another hypoglycemic episode. Snack examples include a cup of milk, a small piece of fruit and 1 oz. low fat cheese, half a sandwich, 3 small cheese or 3 small peanut butter sandwich crackers. The patient should make note of their episode and speak with their health care provider about causes and prevention at their next visit.

If a patient is unconsciousness a caregiver should administer glucagon. All patients with type 1 or type 2 diabetes on multiple daily insulin injections should be prescribed a glucagon kit. The patient’s caregiver or family member should be instructed on its use (see stepwise instructions below). The adult dose of glucagon is 1 mg while children <20 kg should receive 0.5 mg or 20-30 mcg/kg/dose. The dose may be repeated in 20 minutes if necessary. A small meal or snack should be given to the patient when desired glucose levels are achieved and the patient regains consciousness. The patient should inform their health care provider about the episode.

Treatment Options

- 3-4 glucose tablets
- 2-3 tsp. honey
- 3-4 tsp. white sugar
- 8-10 lifesavers OR other small hard candies
- 5-6 large jelly beans
- 4-5 small gum drops
- 1-2 bite-sized candy bars
- 4-6 oz. regular soda pop
- 4 oz. fruit juice

How to Administer a Glucagon Injection

1. Remove the flip-off seal on the glucagon bottle.
2. Remove needle protector from the syringe. Inject entire contents of syringe into the bottle of glucagon powder. Remove syringe from bottle.
3. Swirl the bottle gently until glucagon dissolves completely.
4. Using the same syringe, hold the bottle upside down and, making sure the needle tip remains in solution, gently withdraw all of the solution from the bottle.
5. Cleanse injection site on buttock, arm or thigh with alcohol swab.
6. Insert the needle into the loose tissue under the cleansed injection site. Inject all (or 1/2 for children weighing less than 44 lbs) of the glucagon solution. Apply light pressure at the injection site, and withdraw the needle.
7. Turn the patient on side to prevent choking.

References:
On the Horizon: A Once Weekly Therapy for the Treatment of Type 2 Diabetes

Written by: Tammy L. Buntjer, RPh, PharmD Candidate 2010

While the increasing prevalence of diabetes mellitus is a known world health crisis, the complex pathophysiology of type 2 diabetes make effective treatment problematic. Insulin resistance and impaired glucose secretion each play a role in the development of type 2 diabetes. It is also known that improved glycemic control and management of additional risk factors lead to an improved cardiovascular prognosis. Despite treatment guidelines that recommend early, aggressive intervention, approximately 43% of patients in the United States have hemoglobin A1c (A1C) levels ≥7%. Many factors play a role in the failure of successful treatment, including psychosocial and economic influences, efficacy and tolerability of available treatments, noncompliance, weight gain, and more.

The glucagon-like peptide-1 (GLP-1) receptor agonists are a newer class of anti-diabetic agents known as incretin mimetics that leverage the glucose dependent stimulation of insulin secretion and concomitant glucagon suppression by GLP-1. Unfortunately, native GLP-1 is rapidly degraded in vivo, and thus is not practical for therapeutic use. The GLP-1 receptor agonists fulfill the role of native GLP-1 but are resistant to rapid degradation. There are currently two drugs available in this class, exenatide (Byetta®) and liraglutide (Victoza®). These drugs lower A1C primarily by lowering post-prandial blood glucose levels. This is achieved by augmentation of glucose mediated insulin secretion through binding to the GLP-1 receptor on the pancreatic β-cells, suppression of glucagon secretion, and slowing of gastric motility. Exenatide is currently available as a twice daily subcutaneous injection given 30 to 60 minutes prior to breakfast and dinner. Liraglutide is available as a once daily injection. Both medications are available as pre-filled pen injectors.

A once weekly investigational formulation of exenatide has been developed utilizing delivery technology that uses biodegradable polymeric microspheres to entrap exenatide, allowing extended release of exenatide. Following subcutaneous injection, the microspheres degrade over time, releasing exenatide in a controlled manner. In clinical trials, patients receiving 2mg of extended release exenatide once weekly had improved fasting plasma glucose, improved postprandial glycemic control and a significant reduction in A1C. They also showed positive changes in cardiovascular risk factors. Additionally, the once weekly formulation appears to have a lower incidence of side effects, including nausea, vomiting, and diarrhea. Because of the once weekly formulation, it is anticipated that once weekly exenatide (Bydureon®) would result in improved patient compliance.

Unfortunately, this once weekly formulation is not yet available for patient use. It was recently announced that the FDA issued a complete response letter to Amylin Pharmaceuticals, Eli Lilly, and Alkermes, Inc. requesting further study before the drug will be approved. The FDA is specifically requesting a thorough QT study as well as results from the DURATION-5 study to evaluate efficacy and labeling of safety and efficacy. The companies indicate plans to work closely with the FDA to resolve the issues raised with a goal to submit a reply to the FDA by the end of 2011, with the possibility of approval in 2012.

References:

Goal: The goal of the Diabetes Dispatch is to increase the reader’s knowledge of diabetes treatments and technologies and to provide the most current information on new drugs, therapies, and devices.
- ACPE # 01399-9999-11-014-H01-P/T
- Expiration Date 3/1/2014
- ANMC HED Activity # 11-30010

The speakers/authors disclose that they do not have significant financial interests in any product or class of products discussed directly or indirectly in this activity, including research support.

Proceed to Quiz