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Spring 2010

ALASKA NATIVE DIABETES PROGRAM

Diabetes Dispatch

A New Way to Diagnose Diabetes

Standards of Medical Care in Diabetes, *Diabetes Care January 2010*

Each January the American Diabetes Association publishes the Standards of Medical Care in Diabetes in its journal *Diabetes Care.* This year the much anticipated recommendation of using A1C to diagnose diabetes was included, with a cut point of ≥ 6.5%. The table below includes the four diagnostic criteria for diabetes. Remember in the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing. The recommendation includes confirmation by the same test that was initially suspect.

Table 1: Diagnosis of Diabetes

1. A1C 6.5%. The test should be performed in a laboratory using a method that is NGSP* certified and standardized to the DCCT assay.

OR

2. FPG 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

OR

3. Two-hour plasma glucose 200 mg/dl (11.1 mmol/l) during an Oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose 200 mg/dl (11.1 mmol/l).

*National Glycohemoglobin Standardization Program.

The Standards of Medical Care previously used the language of pre-diabetes, which has been replaced with "categories of increased risk for diabetes." In addition to impaired glucose tolerance and impaired fasting glucose, an A1C in the range of 5.7-6.4% has been included as a category of increased risk for future diabetes.

Table 2: Diagnosis criteria for categories of increased risk for diabetes

1. Impaired glucose tolerance. OGTT between 140-199 mg/dl

OR

2. Impaired fasting glucose. Fasting glucose between 100-125 mg/dl

OR

3. A1C between 5.7-6.4%

Objectives:

- *Review diagnostic criteria for type 2 diabetes*
- *Become familiar with the mechanism of action of liraglutide*
- *Recognize ways to prevent the progression of diabetic retinopathy*

Inside this issue:

A new GLP-1 choice: Victoza® (liraglutide)

Written by: Kathleen Buechter, Pharm.D. Candidate 2010

Novo Nordisk has developed a new GLP-1 analogue Victoza® (liraglutide), that only requires once daily dosing. It was approved for use in the United States by the FDA on January 26, 2010. Novo Nordisk expects to introduce Victoza® in the United States market in the coming weeks. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Mechanism of Action

Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1. GLP-1 is a hormone secreted from the small intestine in response to food ingestion. It acts via the GLP-1 receptor and results in stimulation of glucose-dependent insulin release and suppresses glucagon secretion from the pancreas. It also slows gastric emptying which helps a patient feel "full" more quickly; therefore, possibly decreasing food intake. However, it has a short half-life (less than 2 minutes) because it is quickly degraded by the proteolytic enzyme dipeptidyl peptidase IV (DPP-IV).

Like endogenous GLP-1, liraglutide activates the GLP-1 receptor, but unlike native GLP-1, liraglutide is stable against metabolic degradation by DPP-IV and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and increased stability against metabolic degradation by DPP-IV.

Dosing

Liraglutide is dosed as 0.6mg, 1.2mg, or 1.8mg injected subcutaneously at any time during the day. The medication is able to be administered once daily due to its longer half-life and 12 hour duration of action. A dose titration is necessary to prevent gastrointestinal side effects. An example dose titration could be: 0.6 mg injected subcutaneously once daily for 1 week, then increased to 1.2 mg once daily. The dose may be further increased to 1.8 mg once daily if optimal glycemic response is not achieved with the 1.2 mg daily dose. When initiating liraglutide, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycemia.

Efficacy

Liraglutide decreases A1C by about 1.1% when added to metformin and/or a sulfonylurea.

In the LEAD-6 trial, liraglutide was compared to exenatide in a head to head 26-week randomized, parallel-group, multinational, open label study. The highlights of the study are listed in the table below.

	Liraglutide 1.8mg once a day (n=233)	Exenatide 10 ug twice a day (n=231)	Statistical significance
Mean A1C reduction	-1.1%	-0.8%	p<0.0001
Mean fasting plasma glucose reduction	-29 mg/dl	-11 mg/dl	p<0.0001
Mean weight loss	-3.24 kg	-2.87 kg	not statistically significant

Safety and Adverse Events

Liraglutide's most common adverse events are nausea, vomiting, and diarrhea. These side effects occur in 28%, 11%, and 17% of patients respectively. With continued use of the medication, these effects tend to subside. Liraglutide administration, like other GLP-1 agonists, can potentially result in weight loss. Liraglutide was noted to cause dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of **rats and mice**. It is unknown whether it causes thyroid C-cell tumors in humans. Because risk could not be ruled out, liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Storage

<table>
<tr><th>Prior to first use</th><th>After first use</th></tr>
<tr><td>Refrigerated
36°F to 46°F
(2°C to 8°C)</td><td>Room Temperature
59°F to 86°F
(15°C to 30°C)
Refrigerated
36°F to 46°F
(2°C to 8°C)</td></tr>
<tr><td>Until expiration date</td><td>Expires in 30 days</td></tr>
</table>

Important Limitations of Use

Liraglutide is not recommended as first-line therapy for patients inadequately controlled on diet and exercise. It has **not** been studied sufficiently in patients with a history of pancreatitis, so caution must be used. It is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Liraglutide has been studied in combination with metformin, sulfonylureas, and thiazolidinediones, but has yet to be studied in combination with insulin.

Noteworthy

Until recently, only one GLP-1 analogue was available in the United States, Byetta® (exenatide). This medication is given subcutaneously 30 minutes before breakfast and 30 minutes before dinner. The doses must be separated by at least 6 hours. If taken after food ingestion, the positive effects of the medication are muted. One concern with exenatide is that the timing of therapy could potentially lead to incorrect usage by the patient. Therefore, the patient would lose the benefits of the medication. The biggest advantage of Victoza® (liraglutide) is the convenience of once daily dosing that is independent of meal timing. However, even with the convenient dosing of liraglutide the cost may limit its use. It is about 50% more expensive than exenatide. It could be a recommendation for patients who can afford it and want to minimize the number of injections. Keep in mind that later this year a once weekly exenatide may be available.

References:

1. Liraglutide a once-daily human GLP-1 analogue - Novo Nordisk A/S." *A healthcare company and a world leader in diabetes care. - Novo Nordisk A/S*. Novo Nordisk A/S. Web. 12 Nov. 2009. <http://www.novonordisk.com/science/pipeline/liraglutide.asp>.

2. Liraglutide – Package insert.

3. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009 Jul 4;374(9683):39-47

Keys to the Prevention of Diabetic Retinopathy

Regular eye exams are a key step to the prevention of diabetic retinopathy, but other steps are important as well. The table below reviews the recommendation for eye exams for patients with diabetes. The exam should be a dilated exam. Other important steps include tight glycemic control, which has been shown to decrease the risk of the development of retinopathy. The Diabetes Control and Compliance Trial (DCCT) showed that patients with a standard anti-diabetic regimen were four times more likely to develop eye issues versus those with tighter glycemic goals. It was also found that patients who have already developed diabetic retinopathy, progression occurred half as often in patients who maintained stricter glycemic goals. Second, blood pressure control is essential for prevention of retinal damage. The elevated blood pressure damages the blood vessels feeding the eyes causing retinopathy. Finally, smoking cessation cuts the risk of retinopathy at least in half.

Patient Age Group	First Examination	Minimum routine follow-up
< 10 years	Only if symptoms	None
10-29 years of age	3-5 years after diagnosis	Annually
≥ 30 years of age	At time of diagnosis	Annually

Diabetes Fast Facts

- About 75% of women who develop gestational diabetes will progress to develop type 2 diabetes
- Diabetes causes more deaths a year than breast cancer and AIDS combined. Two out of three people with diabetes die from heart disease or stroke
- Diabetes is on the rise in the United States. 11.3% of US adults (22 million people) were living with diabetes in 2009
- Diabetes deaths are likely to increase by more than 50% in the next 10 years if drastic treatment and prevention efforts are not made
- Among adults with diagnosed diabetes, 12% take both insulin and oral medications, 19% take insulin only, 53% take oral medications only, and 15% do not take either insulin or oral medications
- In general, for every 1% reduction in results of A1C blood tests (e.g., from 8.0% to 7.0%), the risk of developing microvascular diabetic complications (eye, kidney, and nerve disease) is reduced by 40%

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ALASKA NATIVE DIABETES PROGRAM

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# 0139-9999-10-016-H01-P
- AkPhA# 0139-9999-10-016-H01-T
- Expiration Date 3/16/2013

Continuing Education Quiz

Diabetes Dispatch: Spring 2010

1) Which of the following is one of the four diagnostic criteria set forth by the ADA for diagnosing diabetes?
a. A1C >6.5%
b. fasting plasma glucose above 126 mg/dl
c. Oral glucose tolerance test (OGTT) above 200 mg/dl
d. Symptoms of hyperglycemia and a random blood glucose > 200 mg/dl
e. all of the above

2) True or False – In the absence of unequivocal hyperglycemia, A1C, fasting plasma glucose or the OGTT, should be confirmed on another day before diagnosing diabetes.

3) If a patient has an A1C of 6.0% the most appropriate diagnosis according to the ADA would be
a. type 2 diabetes
b. impaired glucose tolerance
c. impaired fasting glucose
d. Increased risk for diabetes

4) Liraglutide lowers blood sugars through the following actions EXCEPT:
a. glucose-dependent insulin release
b. appetite control
c. glucagon suppression
d. increased hepatic glucose output

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Circle one: Pharmacist Technician

5) Which of the following is true regarding liraglutide dosing?
a. Injected SQ once daily
b. Given 30 minutes before breakfast and dinner
c. Initiated at 5 mcg BID, then increased to 10 mcg BID
d. None of the above

6) Liraglutide belongs to which drug class?
a. exenatide
b. Gliptin
c. DPP-4 inhibitor
d. GLP-1 analogue

7) Which of the following is the most common side effect with liraglutide?
a. headache
b. increased appetite
c. nausea
d. constipation

8) True or False – When compared to exenatide, liraglutide is more efficacious at A1C reduction.

9) What is the ADA recommendation to prevent progression of diabetic retinopathy?
a. cholesterol control
b. glycemic control
c. smoking cessation
d. b + c
e. all of the above

LESSON EVALUATIONS

To obtain CPE credit for this lesson you must answer the questions on the quiz (70% correct required) and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. In May and November of each year we will mail a statement of credit, unless otherwise arranged with the AkPhA office.

This program furnishes 1.0 hour CPE (0.1 CEU) credit per lesson. EXPIRATION FOR CREDIT: Pharmacist and technicians may receive credit for completing this course if returned by March 16, 2013. The ALASKA PHARMACISTS ASSOCIATION is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

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AkPhA# 0139-9999-10-016-H01-T

LESSON EVALUATION

	Disagree				Agree		Disagree				Agree
1) Activity met learning objectives	1	2	3	4	5	4) Activity learning assessment appropriate	1	2	3	4	5
2) Amount of time was appropriate	1	2	3	4	5	5) Author was knowledgeable in topic	1	2	3	4	5
3) Increased my knowledge of topic	1	2	3	4	5	6) Overall, I was satisfied with the activity	1	2	3	4	5

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I am a current member of AkPhA _____. I am not a member of AkPhA; enclosed is a check to AkPhA for $12.00