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ALASKA NATIVE DIABETES TEAM

Diabetes Dispatch

Saxagliptin (Onglyza®)

The latest addition to the antidiabetic medication aresenal

Issue Compiled by Julie Hull, PharmD Candidate

Saxagliptin was approved on 7/31/09 as the second agent in the class of dipeptidyl peptidase IV (DPP-4) inhibitors. It is the first anti-diabetic agent to be approved since the FDA unveiled new requirements for manufacturers to prove cardiovascular safety of anti-diabetes medications in 2008.

Mechanism of Action:

Saxagliptin is a competitive DPP-4 inhibitor. DPP-4 is an enzyme responsible for inactivation of incretin hormones which cause insulin release from pancreatic beta cells in a glucose-dependent manner. DPP-4 inhibitors slow the inactivation of incretin hormones, allowing a greater release of insulin and therefore reduced blood glucose concentrations.

Indications:

For monotherapy or add-on therapy to thiazolidinediones, metformin, or sulfonylureas for the treatment of type 2 diabetes.

Dosing:

- 2.5mg or 5mg orally once daily without regard to meals.

CrCl (mL/min)	Dose
> 50	2.5 mg or 5 mg
≤ 50	2.5 mg
Hemodialysis	2.5 mg given after hemodialysis

Efficacy:

- Decreases A1c by 0.3-0.9%
- Lowers FPG by 4-31 mg/dL
- Lowers 2-hour postprandial glucose by 15-61 mg/dL

Adverse Effects:

Common adverse effects include headache, respiratory tract infection, and urinary tract infection. May also increase the risk of peripheral edema and hypoglycemia when used as add-on therapy.

Severe adverse effects may include bone fractures (1 per 100 patient years)

Noteworthy:

A dose of 2.5mg should be used when coadministered with strong inhibitors of cytochrome P450 3A4/5 (azole antifungals, clarithromycin, protease inhibitors, nefazodone).

References:

"Onglyza" Thomson Micromedex. 2009

Onglyza [package insert] Bristol-Myers Squibb. 2009

Wolf R, et al "Evaluation of CV risk in the saxagliptin clinical trials" ADA 2009; Abstract LB-8

Objectives:

- Describe saxagliptin indications, dosing, and efficacy
- Discuss benefits, costs, and considerations of using insulin pens
- Review calculations for estimated average glucose

Inside this issue:

An Introduction to Insulin Pens

By Christopher Lamer, Terry Raymer, Charles E. Rhodes, Stephen Rith-Najarian, Ryan Schupbach, and Judy B. Thompson

Introduction

There have been significant improvements in the technology of insulin development and insulin delivery since it was first administered on January 23, 1922 using a needle and glass syringe at Toronto General Hospital. Today, it is estimated that approximately five million Americans use insulin in the management of diabetes, and based on data from the Indian Health Service (IHS) Diabetes Audit, insulin is used by approximately 25% of American Indians and Alaska Natives.

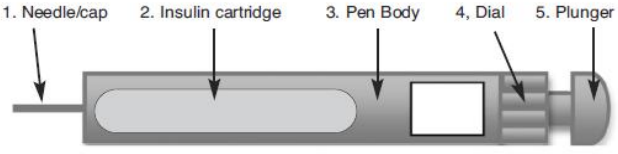
Insulin is a protein that cannot be administered orally as a tablet or liquid, because it will be digested in the gastrointestinal tract before reaching the blood stream. Currently, insulin is administered using either a vial and syringe, insulin pen, jet injector, or insulin pump. Inhaled insulin was recently released as a product called Exubera®, but was removed from the market in October 2007 due to poor sales. Additional studies on inhaled insulin as a dry powder and aerosol are being conducted, as well as investigations into the development of an insulin patch and an ultrasound delivery device.

The vial and syringe is the most common delivery method of insulin in the United States, while insulin pens have become the primary delivery method in Europe and Japan.[1] Insulin pen use in the United States has increased from 7% in 1999 to 14% in 2001, compared with greater increases in Europe (157%) and in Japan (456%).[2] Low usage rates of insulin pens in the US may be related to unfamiliarity of the benefits associated with insulin pens or a perception of increased costs associate with insulin pen use. The goal of this article is to discuss these issues and to provide a brief overview of the insulin pen.

Overview of Insulin Pens

Insulin pen devices fall into two primary categories: disposable and reusable. To use most insulin pens, patients will rotate the dial to select the number of units of insulin that are to be administered. The amount of insulin is displayed just below the dial. The cap is removed from the needle and the needle is inserted into the skin. Insulin is administered by pushing the plunger. The needle should be left in for about 5-6 seconds after injecting the insulin to ensure administration of a complete dose.

Figure 1. Insulin pens are composed of five main parts



Novolog® Flexpen® prefilled syringe

Benefits of Insulin Pens

1. ***Accuracy*:** Insulin pens have many features that facilitate accurate dosing, including audible clicks when the dose is dialed, single- or half-unit dosing increments, clear dials showing the selected dose, and automatic zeroing after administration. Many studies have concluded that insulin pens provide more accurate dosing than conventional vial and syringe delivery.[3,4]
2. ***Convenience and Confidence***: Since they are discreet and portable, and have extremely short needles, pens increase the social acceptability of insulin use and are usually preferred to vial and syringe delivery.[4] Patients using a pen have expressed greater confidence in their ability to achieve glycemic control.[5]
3. ***Improved Quality of Life and Acceptance***: Use of insulin pens has demonstrated increased patient acceptance and participation in the treatment plan.[6] A questionnaire-based study showed that patients preferred an insulin pen device for convenience, flexibility, and quality of life; insulin-naive patients reported the greatest preference for pens.[7]

Insulin Pen Cost Considerations

1. ***Acquisition cost***: The cost is the most commonly stated barrier to the procurement of insulin pens. Examining only the acquisition cost per unit of insulin, based on IHS pricing in 2009, insulin pen cost is greater than the cost of vial insulin (see Table 1). However, this misrepresents the cost implications to IHS of a decision to use vial or pen insulin.

2. ***Wastage***: For most insulin preparations, any remainder must be discarded 28 days after the stopper is first punctured (exceptions to the 28 day in-use shelf life rule are Detemir (Levemir®): 42 days; Humalog® premix pens: 10 days; and Novolog® premix pens: 14 days) . Thus, low daily doses can result in considerable wastage. For example, glargine has the greatest extra cost for using pens. A patient using 10 units of glargine daily will use 280 units per 28 days. Using vials, 720 units will be discarded, and cost is $46.61 per 28 days. Using pens, 20 units will be discarded and 28-day cost is $20.90; this affords a saving of $25.10 (54%) for the insulin pen. The actual cost difference depends on the pricing and the doses used.

3. ***Needles*****:** A basal-bolus regimen commonly uses four injections daily, or 120 needles per 30 days. In 2009, 1 box of 100 insulin syringe-needle units cost the IHS $4.14, while 100 pen needles cost $7.50.

4. ***Special cost issues in institutional settings*****:**
   a. Using pens will generally reduce nursing time for preparation of the injection.[8,9]
   b. Frequent changes of regimen and short inpatient stays may exaggerate the wastage, increasing the cost savings of using pens.
   c. Pen needles represent less hazardous medical waste for disposal, compared to syringes.

5. ***Changes in resource utilization*****:** Patients tend to have greater confidence when using pens and take a more active role in their care. This can reduce both hyperglycemia and hypoglycemia, resulting in fewer visits to clinic and emergency departments.

Cost analyses considering all effects on the health care system, including secondary effects, have generally shown a net cost savings from a switch to insulin delivery via pens.

Other Issues to Consider when Using Insulin Pens

1. ***Acceptance***: Although insulin pen devices represent a potentially easier approach to insulin delivery, not all patients will openly accept pen devices. Some patients using insulin vials will prefer to maintain their current method of insulin delivery due to their historical level of comfort. As with any device, non-familiarity with insulin pens coupled with the patient's anxiety and "learning curve" during the syringe-to-pen transition will require an additional time commitment from the diabetes care team. However, the majority of the literature documenting patient preference following transition clearly favors pen device utilization.[4,5,6]

2. ***Multiple injections for large doses*****:** Pen device design presents a limiting factor for patients requiring large individual doses of insulin. Most insulin pens sold in the US have a maximum capacity for insulin delivery of 60-80 units per injection, compared to 100 units for syringes.[10] Patients with insulin requirements exceeding the pen device threshold may require an increased number of daily injections; however, this inconvenience would only pertain to those patients using more than 80 units, but less than 100 units, per injection.

3. ***Appropriate administration technique*****:** Users must be aware of appropriate insulin pen administration techniques[9]:
   a. The insulin pen must be primed.
   b. Injection time - the mechanism of forcing insulin through small gauge syringe tips creates a pressure gradient which requires prolonged subcutaneous insertion to ensure complete delivery of the desired insulin. Patients will need to be informed that it generally takes 5 seconds after pressing the plunger to make sure the complete insulin dose is injected.
   c. Remove the needle from the cartridge after the injection to prevent passage of undesired air into the insulin reservoir. Unwanted air backfilling the insulin container (by failure to remove the needle between injections) could result in a dosing error.[4,11,12]

Continued on page 4...

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Estimated Average Glucose (eAG) - A Teaching Tool

The A1C-Derived Average Glucose study (ADAG) supported there is a linear relationship between A1c and average glucose values for patients with type 1 and type 2 diabetes. ADAG found that A1c can be converted to estimated average glucose by the following formula:

eAG = 28.7 x A1c - 46.7

A1c can be a difficult concept for patients to grasp since it is reported as a % unlike the mg/dL value they are used to seeing from self-monitoring. eAG allows patients to focus on a single concept and set of values rather than learning new confusing concepts. Patients should understand that their eAG may look different than their self-monitoring values which tend to fluctuate during the day. An eAG calculator is available on the American Diabetes Association Website at www.diabetes.org/professional/eAG.

eAG may not be right for all patients. ADAG only included patients with stable glucose control and without erythrocyte disorders (anemia, etc.). It also did not include children and pregnant women. eAG may overestimate mean glucose levels in African American patients.

A1c	eAG	
%	mg/dL	mmol/l
6	126	7.0
6.5	140	7.8
7	154	8.6
7.5	168	9.4
8	183	10.2
8.5	197	10.9
9	212	11.8
9.5	226	10.9
10	240	13.4
11	269	14.9
12	298	16.5

References:
1. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine R. Translating the A1C Assay Into Estimated Average Glucose Values. Diabetes Care. August 2008; 31(8):1473-8.
2. www.diabetes.org

An Introduction to Insulin Pens, continued:

Conclusions

Insulin pens provide patients with a number of advantages over a vial and syringe. Some of these advantages can help overcome the major barriers to initiating insulin therapy. Insulin pens are accurate, convenient, and discreet. Insulin pens improve patient satisfaction, fostering increased patient participation in the treatment plan. The increased pharmacy acquisition cost per unit is offset to a variable degree by reduced wastage. Examined from a systems perspective, decreases in overall resource utilization (fewer visits to physician offices, clinics, and emergency departments; fewer hospitalizations; reduced staff time; reduced hazardous waste; and others) with pen utilization have been found to result in a net savings.

Table 1. Cost comparison of insulin pens and vials, based on 1,000 units of insulin

Costs and differences per milliliter (100 units per 1 ml)				In-use storage
Insulin Product	**15 ml Pen**	**10 ml Vial**	**Cost per ml Difference**	**(days)**
Glulisine (Apidra®)	$87.60	$44.96	$1.34	28
Lispro (Humalog®)	$75.64	$44.35	$0.61	28
Aspart (Novlog®)	$42.43	$24.48	$0.40	28
Glargine (Lantus®)	$104.51	$46.61	$2.30	28
Detemir (Levemir®)	$41.82	$16.29	$1.16	42

Judy B. Thompson, PharmD, BCPS, CDE
4315 Diplomacy Drive
Anchorage, AK 99508

ALASKA NATIVE DIABETES TEAM
Phone: 907-729-2164
Fax: 907-729-2119
Email: jbthompson@anthc.org
Diabetes Office phone: 907-729-1125
Diabetes Clinic Appointments: 907-729-1500

Check out our website:
www.anmc.org/services/diabetes/

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Continuing Education Quiz

Diabetes Dispatch: Fall 2009

1) What class of medication is saxagliptan (Orlynza®)?
   a. Glucagon-like peptide-1 agonist
   b. Dipeptidyl peptidase IV inhibitor
   c. Sulfonylurea
   d. Thiazolidinedione

2) JM has type 2 diabetes and presents to the pharmacy with a prescription for saxagliptin. His creatinine clearance is 38 mL/min. What dose of saxagliptin should he be given?
   a. 2.5 mg daily
   b. 5mg daily
   c. 10mg daily

3) True or False – Insulin pens typically improve patients' confidence and participation in their own care.

4) Insulin glargine (Lantus®) can be stored at room temperature for _____ days.
   a. 14
   b. 28
   c. 42
   d. 90

5) Benefits of using insulin pens include:
   a. Pen needles are more hazardous medical waste to dispose of than syringes.
   b. Insulin pens increase social acceptability of insulin.
   c. Pens provide more accurate dosing.
   d. b and c

6) Drawbacks of using insulin pens include:
   a. Doses are less accurate
   b. Patients with insulin doses > 60-80 units may require multiple injections.
   c. Pens may increase nursing time for preparation of injections.
   d. b and c

7) Special administration techniques required for use with pens include:
   a. Pens must be primed before use.
   b. Patients should hold the plunger in for 5 seconds following each injection.
   c. Needles should be removed from cartridges after each injection to prevent air getting into the reservoir.
   d. All of the above.

8) RJ, a 49yo Caucasian male tells you that his A1c is 10%. He is very confused and does not understand what this value means. You tell him that it means his glucose is running about _____ on average.
   a. 212 mg/dL
   b. 240 mg/dL
   c. 280 mg/dL
   d. eAG is probably not accurate for this patient.

9) KL, a 85yo African American female tells you that her A1c is 8%. She is very confused and dose not understand what this means. You tell her that it means her glucose is running _____ on average.
   a. 169 mg/dL
   b. 183 mg/dL
   c. 197 mg/dL
   d. eAG may overestimate mean glucose levels in African American patients.

Mail to: AkPhA
203 W. 15th Ave. # 100
Anchorage, AK 99501

Fax to: (907) 563-7880

Circle one: Pharmacist Technician

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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.
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