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Diabetes in Focus

UGA College of Pharmacy Student Diabetes Club

Keeping pharmacy students informed on current and pertinent diabetes information!

Inside this issue:

Afrezza® Inhaled Insulin: A Breath of Relief for Diabetics?

Written by: Camille Haile-Selassie, 2nd Year Pharm.D. Candidate

Insulin therapy is a significant concern for many patients with diabetes. Whether it is a fear of needles, hypoglycemia, or worsening of their condition, traditional insulin is marked with stigma. Although most of these misconceptions can be clarified through patient counseling, a new option, Afrezza®, may be a medication of interest for many diabetics.

SDC would like to thank Johnny Chung, Mannkind Corp, for donating Afrezza® demo kits for use in upcoming diabetes health fairs.

Afrezza® is a man made, rapid acting, inhaled insulin approved for use in adults with type 1 or type 2 diabetes. It is used similarly to a diskus inhaler with disposable cartridges. Afrezza® is administered before mealtimes and begins working within 12 to 15 minutes of inhalation. Maximum effect occurs in approximately 53 minutes and activity can continue for up to 3 hours. Currently, the rapid acting subcutaneous forms of insulin include insulin glulisine (Apidra®), insulin lispro (Humalog®), and insulin aspart (NovoLog®).[1] Afrezza® has the most similar onset of action to Humalog® despite being the fastest absorbed insulin available.[3]

Clinical trials have been conducted comparing Afrezza® with various insulins and oral diabetic medications. In many of the trials, an A1C reduction of less than 7%, a standard goal recommended by the American Diabetes Association, was the primary endpoint. When tested against NovoLog® and Novolin® 70/30, more patients achieved an A1C below 7% on traditional agents compared to Afrezza®, but these findings were not statistically significant. When compared with oral glucose lowering agents, more patients on Afrezza® achieved a reduction in A1C below 7% after 24 weeks, enough to be statistically significant.[2]

Another major concern with insulin is the side effect profile. The main difference with Afrezza® is associated with lung function. A spirometry test is conducted to ensure a patient's lung function is adequate for inhaled insulin.[1] Data illustrated that differences in forced vital capacity between treatment groups diminished after 1 month of discontinuing inhaled insulin, revealing that effects on the lungs can be eversible if Afrezza® is used for shorter durations.[2] Other respiratory side effects include cough (2.8%) and dyspnea (0.5%). Therefore, patients who smoke or have asthma or COPD are not candidates for Afrezza®. In terms of hypoglycemia risk, Afrezza® is more favorable: it demonstrated less hypoglycemia of any severity in trials versus NovoLog.[2]

Pharmacists should be prepared to explain the concept of inhaled insulin to diabetic patients, along with the pros and cons. Data doesn't strongly suggest that Afrezza® is preferable over other rapid acting insulin

Afrezza® Inhaled Insulin Cont.

products in terms of achieving blood sugar reduction long term. It also requires unique monitoring. For patients prone to hypoglycemia, Afrezza® has been shown to lessen episodes of low blood sugar. Another practical factor to consider is price. Some insurance companies may not have Afrezza® on the formulary or require that a patient try another insulin product before covering it. Savings cards are available through the manufacturer's website to assist with the cost. Overall, Afrezza® is an innovative, appealing option for certain diabetic patients, and consideration of all aspects of a patient's condition is key when selecting this medication.

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Gimoti® for Diabetic Gastroparesis

Written by: Ebonne Ugbo, 4th Year Pharm.D. Candidate

Diabetic gastroparesis is a microvascular complication of diabetes that is characterized by delayed gastric emptying and subsequently nausea, vomiting, and early satiety. Metoclopramide, available both orally and intravenously, has been approved by the United States Food and Drug Administration (FDA) since 1980 for the relief of symptoms associated with acute and recurrent diabetic gastroparesis. Metoclopramide is a dopamine receptor antagonist in the chemoreceptor trigger zone, resulting in antiemetic properties. It also works to increase lower esophageal pressure, small bowel transit time, and gastric emptying rate.[1]

Gimoti® is a novel formulation of metoclopramide that delivers the medication systemically via intranasal administration. The mucosa layer of the nasal cavity consists of a single epithelial cell layer with significant vascularity, which allows metoclopramide molecules to enter the systemic circulation directly. This formulation was developed with the intention of providing a systemically-available outpatient treatment for acute symptoms or disease flares of diabetic gastroparesis. Also, this formulation is thought to be better tolerated for patients experiencing nausea and vomiting, unlike the oral formulation of metoclopramide.

There is one phase 3 clinical trial of intranasal metoclopramide that had results announced in June of 2016. This was a multicenter, randomized, double-blind, placebo-controlled trial that assessed efficacy and safety in adult female patients with diabetic gastroparesis. When compared to placebo, intranasal metoclopramide was not statistically significant in reducing symptoms of diabetic gastroparesis. However, a clinically meaningful benefit in patients with moderate to severe symptoms at baseline may have been demonstrated. Treatment-related adverse events were similar between both groups, and most were determined by the investigators to be mostly mild to moderate in severity.[2] One smaller study exists that demonstrated statistically significant benefit in symptom control of intranasal metoclopramide over the oral tablet. However, this trial was small in scale and was of an open-label design.[3]

Metoclopramide has been the only medication approved for symptom control of diabetic gastroparesis. There have been few other drugs in clinical development over the years before the emergence of intranasal metoclopramide.[4] There does appear to be an unmet need for rapidly effective outpatient therapy for disease flares, and this new nasal spray formulation appears promising. However, more investigation and clinical evaluation is necessary to determine efficacy of this new formulation over conventional delivery methods.

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Fiasp®: A new fast-acting mealtime insulin

Written by: Sonam Patel, 2nd Year Pharm.D. Candidate

As an essential component of drug therapy in type 1 and advanced type 2 diabetes mellitus, insulin serves as a key mediator of glycemic control. In recent years, focus has shifted towards fast-acting formulations of insulin, which simulate physiologic insulin release when administered before meals by counteracting the rapid rise in blood glucose seen after meals[2]. Fiasp®, one such rapid-acting insulin, is a new faster-acting formulation of insulin aspart (NovoLog® or NovoRapid®) manufactured by Novo Nordisk[2]. This formulation has been approved for the treatment of type 1 and type 2 diabetes mellitus in adults, and it is currently available for use in Europe and Canada[2].

Fiasp® elicits its blood glucose lowering effect by binding to insulin receptors in the body, which stimulates the uptake of glucose into muscle and adipose tissue and inhibits the breakdown of glycogen in the liver[3]. It is a clear, colorless solution that is available in three preparations: 100 units/mL injection, 10 mL multiple dose vials, and 3 mL FlexTouch pens[3]. The appropriate dose may be given subcutaneously by injection into the thigh, upper arm, or abdomen, or through continuous infusion via a pump[3]. It is typically given in combination with an intermediate or long-acting insulin regimen[3]. Fiasp® can be administered up to two minutes prior to the start of a meal or up to 20 minutes after starting a meal[3]. The possibility of postmeal administration, which is not seen with the conventional insulin aspart, makes this formulation a convenient option for many patients[2].

Compared with conventional insulin aspart, Fiasp® has a faster rate of action because of quicker absorption[1]. What distinguishes Fiasp® from insulin aspart is its unique formulation, which contains niacinamide (vitamin B6) and l-arginine[2]. Niacinamide causes the formation of insulin aspart monomers, allowing for the increased rate of absorption, and l-arginine contributes to the product's stability[2]. Studies show that the use of Fiasp®, compared to that of conventional insulin aspart, results in a twofold decrease in onset time and a twofold increase in insulin concentrations in the blood[1]. Fiasp® appears to have an onset time of 2.5 minutes compared with 6-12 minutes for the conventional form[2]. Although Fiasp® has a quicker rate of onset, it also has a shorter duration of action with an effect that typically lasts 12 to 14 minutes in the body[2]. A 74% increase in insulin activity in the body has also been seen within the first thirty minutes of Fiasp® administration when compared with insulin aspart[2].

Like most insulin formulations, Fiasp® can cause hypoglycemia due to its rapid action[3]. Additional adverse reactions that are common with Fiasp® include allergic reactions, injection site reactions, nasopharyngitis, upper respiratory tract infections, nausea, diarrhea, and weight gain[3]. The incidence of hypoglycemia and the overall effectiveness of Fiasp® in glycemic control, when compared with conventional insulin aspart, was studied in detail in several phase 3 clinical trials. Two of these trials, Onset 1 and Onset 2, are described here.

The Onset 1 trial was a 26 week phase 3 trial that compared the safety and efficacy of fast-acting insulin aspart (Fiasp®) with that of conventional insulin aspart in type 1 diabetes[4]. This study concluded that mealtime Fiasp® was noninferior to insulin aspart for HbA1c reduction, superior to insulin aspart for postprandial glucose (PPG) reduction, and similar to insulin aspart for measures of adverse hypoglycemic event occurrence in patients with type 1 diabetes[4]. Onset 2 was a 26 week trial that compared the safety and efficacy of Fiasp® with that of insulin aspart in type 2 diabetes[1]. From the results of the study, it was concluded that Fiasp® was noninferior to insulin aspart in HbA1c reduction, it reduced one hour PPG levels with statistical significance, and it showed no difference to insulin aspart in terms of overall rates of hypoglycemia in type 2 diabetes patients[1]. However, the results did show increased rates of hypoglycemia in the Fiasp® group within the first two hours after a meal[1]. Details of these studies can be found in Table 1 below.

Results from phase 3 clinical trials, such as those described above, have favored the efficacy of Fiasp® in glycemic control when

Table 1: Fiasp® vs. Insulin Aspart

	ONSET 1	ONSET 2
Trial Design	Double-blind, randomized, active control[4]	Double-blind, randomized, active control[1]
Method	8 week run-in on long-acting basal insulin detemir followed by randomization into treatment groups: double-blind mealtime Fiasp® (n=381), insulin aspart (n=380), and open-label postmeal Fiasp® (n=382)[4]	8 week run-in on insulin glargine U100 and maintenance on metformin followed by randomization into treatment groups: mealtime Fiasp® (n= 345) and insulin aspart (n=344)[1]
Inclusion Criteria	44-46 yrs with type 1 diabetes[4]	Mean age of 60 yrs with type 2 diabetes[2]
Primary Outcomes	HbA1c reduction[4]	HbA1c reduction[1]
Secondary Outcomes	2 hour PPG reduction and occurrence of hypoglycemia[4]	2 hour PPG reduction and occurrence of hypoglycemia[1]

Fiasp®: A new fast-acting mealtime insulin Cont.

compared with conventional insulin aspart. Hence, as of Fall 2017, Fiasp® has been approved by the U.S Food and Drug Administration for use in the United States[2]. The product will be sold for the same price as NovoLog, and it is expected to become available in the U.S. by early 2018[2]. With the arrival of Fiasp® to the market, patient's can look forward to a novel and possibly more effective treatment option for their glycemic control.

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Hyperglycemia Despite High Doses of Insulin?

Written by: Nikesh Patel, 2nd Year Pharm.D. Candidate

Believe it or not, hyperglycemia is actually a beneficial evolutionary process that increases host's survival rate during acute injury or illness. For generations, this process has benefited a myriad of species by eliciting a comparable response to fight or flight. In essence, the damaging tissue will propagate the HPA axis, sympathoadrenal system, and pro-inflammatory cytokines to amalgamate and activate a stress response, to restore homeostasis.[1] During this intense moment, important prognostic factors like insulin resistance and glucose tolerance are evident for diagnosing stress hyperglycemia. The pathology of hyperglycemia paves an important road for establishing clinical treatments. It also spotlights why the use of insulin may not be the proper therapeutic we posit. Therefore, understanding insulin use and other non-pharmacological factors are equally important for optimal patient outcomes during acute and chronic hyperglycemia.

Insulin is a natural hormone synthesized by the pancreas. Its primary action is to allow glucose, generated by the small intestines, to enter body cells and provide working energy.[2] Once insulin is administered, it travels through the bloodstream to the cells, binds to cell receptors, and signals activation of glucose transporters that pull glucose across cell walls into the cells for storage and energy utilization.[3] The total process is similar to a lock and key mechanism; if you don't have the right key (insulin), the lock (cell transporters) will not open.[1] Therefore, insulin works to unlock the cells that allow glucose entry and lower blood sugar. Meanwhile in diabetes, insulin deficiency results in glucose build up in the blood, causing hyperglycemia. The pancreas responds to this deficiency by clearing the blood sugar with more insulin secretion. But over time, the continuous high blood sugar will cause cell receptors (locks) to wear off due to continuous insulin binding. The down regulation of insulin receptors will lead to insulin resistance and ineffectiveness to high doses of insulin therapy.[2] If hyperglycemia continues over longer a period of time, mortality and morbidity increase from complications like cell starvation.[1]

Similarly, hyperglycemia and insulin resistance is more appropriately explained in events of an acute injury or illness, such as a car accident or bacterial infection. During the initial period, the body alerts and activates homeostatic systems like the hypothalamus, sympathoadrenal gland and the immune system.[1] This triage mechanism releases stress hormones like cortisol, immune inflammatory mediators like TNF-α, IL-1 and IL-6, and adrenal hormones like epinephrine and norepinephrine to synergize and rebalance the diffusional gradient of blood glucose.[1] Glucose transport is paramount for vital organ function like the brain and immune system. In principle, the acute period will focus centralize energy towards vital necessities and cause peripheral glucagon synthase and end-organ insulin signaling to disrupt.[2] This disruption is initiated by inflammatory mediators and will essentially lead to insulin resistance if the injury or illness is chronic and will fail to rebalance despite high doses of insulin.[2]

Lastly, the process of short term hyperglycemia benefits mortality; while chronic hyperglycemia works the opposite. However both can lead to insulin resistance and complicate insulin treatments depending on injury duration. Despite these occurrences, changes in diet, exercise and health monitoring can provide a role in insulin receptor longevity and lowering hyperglycemia. In conclusion, even though short-term hyperglycemia is an evolutionary benefactor, the extent of body damage and duration of treatment are prominent determinants of insulin resistance and precautions with non pharmacological therapy are crucial factors of patient outcome. [2]

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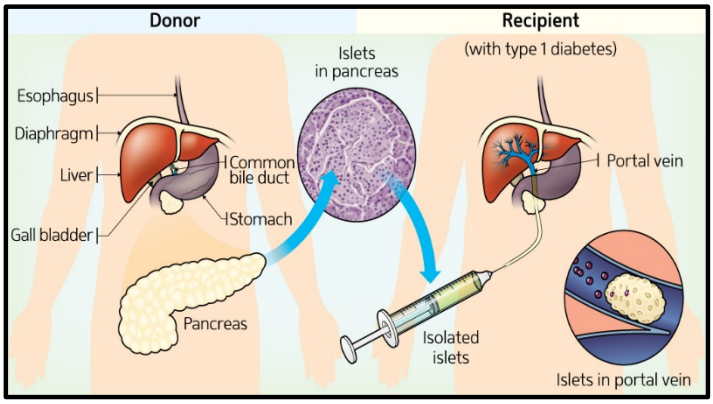
Pancreatic Islet Cell Transplant – Is Insulin Independence in the near future?

Written by: Laura Pyronneau, 2nd Year Pharm.D. Candidate

Type 1 diabetes is an autoimmune disorder where the immune system attacks the insulin-producing islet cells of the pancreas.[1] There has been a great deal of research to help type 1 diabetics live an insulin-independent life; however, the only current treatment is lifelong daily replacement of insulin to maintain glycemic control. Unfortunately, insulin cannot always prevent associated chronic complications, such as kidney damage, blindness, heart disease and amputations. [1] The only widely accepted alternative procedure for patients with severe type 1 diabetes is a pancreas transplant. [2] Current research is developing new, safer ways to improve the quality of life of patients with type 1 diabetes. Now, the most promising and ideal treatment in clinical trials is a pancreatic islet cell transplant.[2]

For those who have had serious complications and have been exhausted all other options, whole organ pancreas transplants have been found to provide a substantial benefit of glycemic control. Pancreas transplants are typically performed simultaneously with a kidney transplant.[2] A double transplant provides the tremendous benefit of both improved kidney function and increased glycemic control, with little additional risk to the patient. However, as with any transplant, pancreatic transplants come with a risk of rejection. [3] To delay or avoid rejection, immunosuppressants must become a permanent component of a patient's medication regimen. These often come with significant side effects such as increased risk of infection.[4]

Even though these transplants are usually highly successful, they are not recommended for people who have control of their diabetes or for those with only mild complications, due to the risk of surgical complications.[4] An encouraging procedure doctors have been actively researching involves transplanting insulin-producing islet cells, which account for 3% of the pancreas. In an islet cell transplant, the islet cells are taken from the donor pancreas and placed in the liver of the recipient.[3] Normally, only local anesthesia is needed, and the incision is relatively small. After the transplant, glycemic control takes time; the cells need to attach to new blood vessels to release insulin. The procedure is exciting because of the decreased risk of infection, lower incidence of serious complications, quick recovery, and the significant improvement of glycemic control.[3]



Patients tend to experience great success. Because blood glucose levels are better controlled with the islet cells, an islet cell transplant delays the progression of some of the chronic complications of diabetes; in some cases, it even reverses them. Even though the procedure does not always lead to a patient being fully insulin-independent, having these cells does provide major improvement of glycemic control, and an overall better quality of life for many years after the transplant.[3]

However, unlike with pancreatic transplants, which last 10 years, failure begins to arise around 5 years post-transplant, with the cells progressively losing their function. [2] Patients with islet cell transplants still must take immunosuppressants to avoid rejection. Because the islet cell transplant is not yet streamlined, it is still currently an investigational procedure. Due to costs and risk associated with these transplants, it is currently reserved for patients with severely uncontrolled diabetes.[3]

Despite all the problems currently associated with islet cell transplant, new research looks very promising. Future research includes techniques to protect the islet cells from the immune system rather than the whole organ. Also, animal islet cell transplants, or xerographs, may be an alternative option due to the shortage of human organs. [3] These new emerging techniques could potentially lead to insulin independence in the near future.

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SDC Highlights

- Presented on the basics of insulin and managing hypoglycemia at AU Medical Center's Diabetes Health Fair
- Fundraising opportunities this semester: cookie drive ($36), bake sale ($30), Barnes & Noble gift wrap ($182)
- Raised over $50 at cookie drive and bake sale held in Athens & Augusta
- Student members, Emma Chee-How and Taylor Clark, obtained various insulin demo kits at ASHP Midyear for future outreach opportunities.
- Participated in a diabetes education class at Barney's in Augusta

FDA Warns of Amputation Risk with Canagliflozin

Written by: Darshan Patel, 3rd Year Pharm.D. Candidate

Canagliflozin is an oral antidiabetic medication used as adjunct therapy to diet and exercise to lower blood sugar in adults with type 2 diabetes. It belongs to the sodium-glucose cotransporter-2 (SGLT2) inhibitors class, which inhibit SGLT2 in the proximal renal tubule of the kidneys. Inhibition of SGLT2 lowers blood sugar by reducing the reabsorption of glucose by the kidneys, allowing the kidneys to remove more glucose from the body in the urine. Currently, canagliflozin is available as a single ingredient product under the brand name Invokana® and also in combination with metformin under the brand names Invokamet® and Invokamet XR®.

Recent data from two large randomized, placebo controlled clinical trials, CANVAS and CANVAS-R, show an approximately twofold increased risk of lower limb amputation associated with Canagliflozin.[1] In CANVAS (Canagliflozin Cardiovascular Assessment Study), the risk of lower limb amputation was 5.9 amputations per 1,000 patients per year for canagliflozin compared to 2.8 amputations per 1,000 patients per year for placebo.[2] In the other study, CANVAS-R, the risk of lower limb amputations was 7.5 amputations per 1,000 patients per year for canagliflozin compared to 4.2 amputations per 1,000 patients per year for placebo.[1] This risk was observed at both the 100 and 300 mg doses. Overall, amputations of the toe and midfoot were the most frequent. The results of these studies have prompted the Food and Drug Administration (FDA) to place a boxed warning for lower limb amputation for this drug. For healthcare professionals, consideration of factors that may predispose patients to the need of amputations should be evaluated before a patient starts canagliflozin. Factors include history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Patients should also contact a healthcare professional immediately if they develop new pain or tenderness, sores or ulcers, or infections in their legs or feet. Other side effects of canagliflozin include low blood pressure, serious urinary tract infections, low blood sugar when combined with other prescription diabetes medications, and yeast infections.

Table 1. CANVAS Amputations

	Placebo N=1,1441	Canagliflozin 100 mg N=1,445	Canagliflozin 300 mg N=1,441	Canagliflozin (pooled) N=2,886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations*	33	83	79	162
Amputation incidence rate (per 1,000 patient-years)	2.8	6.2	5.5	5.9
Hazard ratio (95% CI)	-----	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

*Some patients had more than one amputation.

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University of Georgia, College of Pharmacy

Editors:
Emma Chee-How, 4th year Pharm.D. Candidate
Taylor Clark, 4th year Pharm.D. Candidate

Faculty Advisor:
J. Russell May, Pharm.D., FASHP