Could New Options for Insulin Delivery Soon be Available?

If you use insulin to treat your diabetes, chances are you keep up with the latest news and reports about alternative forms of insulin delivery that are pain-free and more convenient to use than insulin injections.

Currently, there are a few different ways for someone with diabetes to get much needed insulin into their body. Syringes can be used to inject insulin into the fatty tissue just beneath the skin. Insulin pens operate similar to syringes in that the insulin is injected via a needle inserted just beneath the skin. However, some people find insulin pens to be more convenient and easier to use than a syringe if they have impaired coordination or vision. An insulin infuser works by inserting a catheter beneath the skin and injecting insulin into the catheter rather than into the skin, but infusers usually only remain in place for 48 to 72 hours. Insulin pumps are a very popular method of insulin delivery because they allow people more freedom and flexibility in their lifestyle. By inserting a catheter into the abdomen, insulin can be continuously delivered into the body without the need for additional injections. Finally, jet injectors are currently the only needle-less alternative and work by using pressure to force a narrow stream of insulin into the skin. To read more about the currently available methods of insulin delivery, see the American Diabetes Association's annual Resource Guide printed in *Diabetes Forecast* every January. The Resource Guide can also be found on the Association's Web site, http://www.diabetes.org/diabetes-forecast/resource-guide.jsp.

Researchers are working hard to develop alternative forms of insulin delivery that do not involve needles or catheters; however, they have come across a few roadblocks. When insulin is not being directly delivered to the cells by injection or a catheter, much of it can be lost en route. For example, if insulin is inhaled, absorbed through the skin or taken orally, it has to travel a longer distance to get to where it needs to go and research into these methods has shown that higher insulin doses are often required with these methods of delivery compared to subcutaneous delivery. This can make these methods of delivery more expensive and dosing less accurate. Nevertheless, alternatives to insulin injection may soon become available.

Buccal Insulin (oral spray)

One form of insulin delivery that is currently being researched is buccal or oral delivery. With this method, insulin is sprayed into the mouth and absorbed by the tissue at the back of the mouth and throat. The challenges with this method of delivery include determining the amount of insulin required to achieve optimal dosing. One company, Generex Biotechnology, recently announced results of a small clinical trial using an oral insulin spray at the September 2005 annual meeting of the European Association for the Study of Diabetes. The study of 10 patients found that injected insulin (Humulin) and the oral spray showed similar glucose control during a 12-day observation period in patients with type 1 diabetes. The purpose of this trial, according to the company, was to determine

Artist rendering of Generex RapidMist Oral Insulin Delivery System.

the dosage and formulation of the oral spray for use in a larger, multi-center trial. The company recently announced that their oral spray known as Oral-lyn™ has been approved for commercial sale by the Ecuadorian Ministry of Public Health for the treatment of both type 1 and type 2 diabetes.

Insulin Pill

One of the challenges of developing an effective insulin pill is that the insulin gets broken down during the digestion process and never makes it into the bloodstream. Researchers working to develop an oral insulin pill have explored different ways of encapsulating the insulin so that it survives the digestive tract as well as changing the structure of the insulin by combining it with other chemicals and particles in order to effectively deliver it to the cells of the body.

Insulin Patch

The insulin patch seems like an easy idea. After all, there are nicotine patches to help people quit smoking so why not an insulin patch? While a nicotine molecule is small enough to be absorbed easily into the skin, the insulin molecule is much larger and is not easily absorbed. However, this is not stopping researchers from exploring ways to get insulin to penetrate the skin. One way they are doing this is through ultrasound or electrical currents. Another way is by using chemicals to help move the insulin through the skin.

Samir Mitragotri, PhD

ADA-funded scientist, Samir Mitragotri, PhD of the University of California, Santa Barbara, is investigating a novel way of administering insulin by combining the convenience of an oral medication with the technology of a patch. According to Dr. Mitragotri, his research project, *Oral insulin delivery by intestinal patches,* "utilizes novel multi-component patches that are placed in an ingestible capsule. The capsule is covered by a polymer that protects it from dissolution in the stomach. The capsule dissolves in the intestine and releases the patches. These patches adhere to the intestine due to the mucoadhesive characteristics of the patches. The patches then slowly release insulin into the intestinal membrane." Dr. Mitragotri explained recently to an audience of ADA volunteers and staff that the oral patches can potentially be made in different insulin doses to help people with diabetes better control their glucose levels.

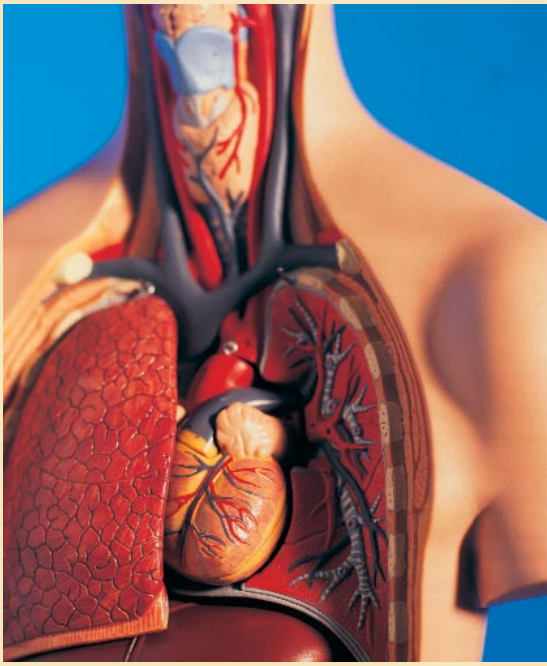
Dr. Mitragotri has made significant progress in this study. In the second year of his project, he was able to confirm adhesion of the patches to the mucosal layer and found that insulin was able to penetrate and move through the surface of the intestine. Dr. Mitragotri and his team have also discovered new adhesive agents and developed methods to screen new chemicals that can enhance the permeability of

the intestine. Dr. Mitragotri states, "With these methods, we plan to discover new materials that will lead to better mucoadhesive agents and permeation enhancers which will collectively improve the performance of intestinal patches."

Inhaled insulin device for Exubera®

Inhaled Insulin

Inhaled insulin is the one alternative method of insulin delivery that is closest to becoming a reality. A recently published Phase III clinical trial has shown that inhaled insulin taken before meals can be as effective as injecting fast-acting insulin. (A Phase III trial is the final phase of drug testing before a manufacturer can ask the Food and Drug Administration [FDA] for approval.) A study led by Jay Skyler, MD of the University of Miami and published in the July 2005 issue of the American Diabetes Association journal, *Diabetes Care*, is the largest study to show that inhaled insulin can safely and effectively replace a pre-meal insulin shot in people with type 1 diabetes. The study took place over six months and included 328 people, ages 12 to 65. Study participants were randomized to receive two daily injections of long-acting insulin and either pre-meal injected insulin or pre-meal inhaled insulin. At the beginning of the study, the average A1c for both groups was 8.1 percent. At the end of the study, the average A1c for the inhaled-insulin group was 7.9 percent, and the average A1c for the injected-insulin group was 7.7 percent. A similar number of patients in each group achieved A1c levels of less than seven percent.



Study participants who received inhaled insulin experienced mild to moderate coughing which decreased in severity as the study continued. Lung function was similar in both groups. Other side effects in both study groups included hypoglycemia and weight gain; however, while patients in the inhaled-insulin group had fewer episodes of hypoglycemia than patients in the injected-insulin group, the inhaled-insulin group experienced more episodes of severe hypoglycemia characterized by dangerously low blood glucose levels. Despite these side effects, the patients on inhaled insulin reported a higher quality of life and greater satisfaction with their treatment. Researchers and patients are buoyed by the success of this study although additional, more long-term studies must be performed to assess safety and long-term effects on the lungs.

The insulin used in this study was Exubera®, a dry powder formulation developed by Pfizer, sanofi-aventis and Nektar Therapeutics. The insulin was administered through a device similar to an asthma inhaler and most patients needed one to three inhalations for any given dose.

Another study published in the August 2005 issue of *Diabetes Care* detailed the results of an inhaled-insulin study in people with type 2 diabetes.

Ralph DeFronzo, MD from the University of Texas Health Science Center, San Antonio, studied 143 patients with type 2 diabetes who were not able to adequately control their blood glucose levels with diet and exercise. He compared pre-meal doses of inhaled insulin with rosiglitazone (Avandia), an oral medication used to treat insulin resistance by making muscle and fat tissue more sensitive to insulin. Dr. DeFronzo found that more patients (44 percent) who took inhaled insulin achieved an A1c below the ADA goal of seven percent than those who took rosiglitazone (17.9 percent).

Inhaled-insulin use in the type 2 diabetes study did result in more episodes of low blood glucose; however, there were no episodes of severe hypoglycemia. Mild coughing was also reported among a few patients (six of 75 using inhaled insulin).

Dr. DeFronzo and his study team write that, “this represents the only demonstration that ADA goals for glycemic control can be achieved in many type 2 diabetic patients using only a rapid-acting insulin.” The authors go on to state that if additional studies confirm these findings, inhaled insulin could become an effective means of controlling blood glucose in patients with type 2 diabetes who cannot achieve adequate blood glucose control with diet and exercise alone.

On September 9, 2005 a U.S. FDA panel voted to advise the FDA to approve Exubera® for use in patients with diabetes. The FDA usually follows the advice of these advisory panels and it is possible that the FDA will approve Exubera® by early 2006.

Artificial Pancreas

Many people with diabetes are eager for researchers to develop a single system of insulin delivery and glucose sensing that can replace the need for continuous needle sticks and insulin injections. Researchers call this an "artificial pancreas" or a “closed-loop system.” The theory behind this type of system is that treatment is controlled in a feedback manner with insulin being released in response to changes in glucose levels to mimic the body’s natural regulation of glucose. Most, if not all, efforts to date have combined an insulin pump with a device that continuously monitors glucose and regulates the pump based on current glucose levels. One of the main roadblocks in developing an effective artificial pancreas involves calculating an algorithm or equation that will allow the glucose monitor to successfully calculate the necessary dosage of insulin that should be delivered by the insulin pump or other implantable insulin delivery system. Some research groups are using algorithms which utilize a mathematical look into the future that helps them predict the best insulin delivery rate. Researchers have also had difficulties in developing glucose monitors with an ability to make accurate, real-time glucose readings. Fibrous tissue can also develop around the implanted sensor which can keep the glucose molecules from reaching the device and giving accurate readings.

W. Kenneth Ward, MD at Legacy Health System in Portland, Oregon is an ADA-funded investigator who is working to develop a closed-loop insulin delivery system. With funding from his ADA grant, *Interface of a telemetric subcutaneous glucose sensor with an external insulin pump*, his team has developed an algorithm that is based on the degree of error (how far the current glucose level is from the goal glucose level) and the rate of change of the glucose signal. He and his research group in Portland have developed this algorithm in collaboration with Dr. Bala Gopakumaran, a bioengineer based in Cleveland. The team has tested this system in animals with success and will begin testing in humans with type 1 diabetes in several months as soon as they achieve research protocol approval from the FDA.

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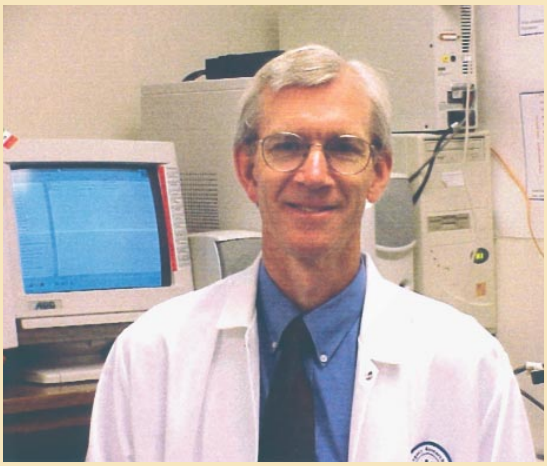
These individuals will have a minor surgical procedure to implant a glucose sensor the size of a paper match book under the skin. The sensor will remain in place for six to 12 months where it will give a continuous readout of the sensed glucose values every five minutes. Every several weeks the study participant will come in to the research clinic where Dr. Ward and his team will attach the sensor to a computer which will in turn be attached to an insulin pump. The participant will then undergo a totally closed-loop study for a seven to eight hour period with close observation by research staff. Dr. Ward is also collaborating with other scientists to find ways of preventing fibrous tissue from encapsulating the implanted glucose sensor.



W. Kenneth Ward, MD

Jeffrey Zahn, PhD from Penn State University College of Medicine, is also working on a closed-loop insulin delivery system through his ADA study, *Microneedle insertion actuators for minimally invasive insulin delivery to diabetic patients.* This study focuses on developing a tool that will enable very small microneedles to penetrate the skin and effectively deliver insulin on a continuous basis. Dr. Zahn feels that microneedles are well-suited to provide a continuous infusion of insulin as part of a miniaturized artificial pancreas; however, one problem in developing an effective microneedle is making a needle small enough that is also durable and able to withstand insertion and removal as well as the everyday movements of the patient without breaking. Dr. Zahn intends to use ultrasound waves to decrease the amount of force required for insertion and maintain optimal performance. He will also work on developing a miniaturized microdialysis probe to monitor interstitial glucose as part of the closed-loop system.

Jeffrey Zahn, PhD

Researchers are exploring every avenue possible to develop more convenient, pain-free methods of insulin delivery. While there are challenges ahead, progress is being made on all fronts and, with the continued perseverance of the scientific community, one or more of these alternative forms of insulin delivery may be commercially available in the near future. ■