Recent Advances in Insulin Delivery Systems: An Update

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Abstract: Insulin remains indispensable in the management of diabetes mellitus since its discovery in 1921. Relatively, a large percentage of world population is affected by diabetes mellitus, out of which approximately 5-10% with type 1 diabetes while the remaining 90% with type 2. It has been now well proven that adequate control of blood sugar delays or prevents the complications associated with diabetes. Transdermal Injections are available as current insulin delivery systems as which may be considered as invasive. The non-invasive delivery of insulin has been a major goal for the treatment of diabetes mellitus (DM). Needle phobia and stress of multiple daily injections led researcher to investigate and explicit of all promising technologies and discoveries for advances in insulin delivery. Needle-free insulin delivery appeared to be astonishing approach and its allure rested in being comfortable and safe. The document present here encompass, in brief, the emerging technologies and discoveries that are in pipeline, including insulin inhalers, implantable insulin pumps, insulin spray, smart cells, insulin pill, insulin complement, islet cell transplant, insulin nanopump and the other promising advances in safe and comfortable insulin delivery. Therefore it will be a tripartite task for the researcher, health authorities and community pharmacist to foster the long term safety profile and to provide comfortable insulin delivery.

Key words: Insulin • Diabetes • Novel Drug Delivery System

INTRODUCTION

Insulin is a hormone with intensive effects on both metabolism and several other body systems (eg; vascular compliance). Insulin causes most of the body's cells to take up glucose from the blood (including liver, muscle and fat tissue cells), storing it as glycogen in the liver and muscle and stops use of fat as an energy source. When insulin is absent (or low), glucose is not taken up by most body cells and the body begins to use fat as an energy source (i.e. transfer of lipids from adipose tissue to the liver for mobilization as an energy source). As its level is a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells). It has several other anabolic effects throughout the body. When control of insulin levels fails, diabetes mellitus results. [1,2]

Insulin is used medically to treat some forms of diabetes mellitus. Patients with Type 1 diabetes mellitus depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with Type 2 diabetes mellitus are insulin resistant, have relatively low insulin production, or both; some patients with Type 2 diabetes may eventually require insulin when other medications fail to control blood glucose levels adequately.

Diabetes develops due to a diminished production of insulin (in type 1) or resistance to its effects (in type 2 and gestational). Both lead to hyperglycemia, which largely causes the acute signs of diabetes: excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy and changes in energy metabolism. Monogenic forms, e.g. MODY, constitute 1-5% of all cases.

Diabetes affects a large percentage of population around the world and has assumed epidemic dimensions. The current estimate of the number of diabetic patients in the world is 171.2 million (2.8%) in the year 2000 and predicted to be 366.2 million (4.4%) by the year 2030. Type 2 diabetes is the main type of diabetes mellitus rather type 1 diabetic occurs 5-10% only.
The patients requiring insulin may have to take more than 60,000 injections throughout their life. Compliance is currently a major drawback in current diabetes delivery devices, with several patients suffering from Type 2 diabetes irregularly following or, in some cases, even discontinuing their insulin therapy due to pain or fear of injections.

Through more convenient drug delivery methods, pharmaceutical companies, regulatory bodies and other government institutions can introduce better diabetes care and reduce costs related to diabetic complications caused by poor compliance."

At present, several methods of non-invasive insulin delivery, including oral, transdermal, nanotechnology-based and gene therapy-based ones, are under research. Efforts are also on to develop a diabetes vaccine. One of the most promising modes of delivery under investigation is that of inhaled insulin.

Global Market on Insulin Delivery: The Global Diabetes Market will exceed $21 Billion by 2011. The research report “Insulin Delivery Systems Market Analysis (2007-2010)” by RNCOS gives an exhaustive analysis on the global insulin market and various Insulin delivery methods. The report investigates the market for various devices used for delivering insulin, including syringes, pens, pumps, needle-free injectors and inhalers. It also takes into account pros and cons of each device and gives a detailed analysis on their future prospects. [3]

The insulin market, driven by the increasing prevalence of diabetes, is presently witnessing robust double-digit growth, thus pushing strong demand for insulin delivery devices. Most of the insulin today is available in injectable form through syringes, pens, pumps and needle-free devices, however, the pain and inconvenience of most of these devices are driving pharmaceutical companies to discover other ‘painless’ modes of insulin delivery, particularly oral methods.

Advances in Insulin Delivery

Needle and Syringe: A common way of administering insulin is with a needle and syringe. Syringes come in a range of capacities (1 mL, 0.5 mL or 0.3 mL) and with a range of needle types (different gauges - that is thicknesses - and lengths) attached. The needles have very fine points and special coatings to make injections relatively pain-free. Select a syringe that suits the size of the insulin dose you take and that has your preferred needle type and needle size attached. One of the main advantages of the syringe system is the variety of products available. Needles and syringes also make it easy to use a mixture of different types of insulin ('mixed insulin') and to draw up a week's supply in advance, to be stored in the refrigerator. However, some people find syringes daunting and not very convenient. For this reason a number of other delivery devices have been developed, including insulin pens, jet injectors and pumps.

Patient preferences in insulin delivery options. [4]

Insulin Pens: Insulin pen injectors are a convenient and discreet way of administering insulin. They have a built-in dial that allows you to determine the amount of insulin to be injected, a short needle at one end and a plunger at the other. Some are disposable and don't need to be assembled before use, while others have a replaceable insulin cartridge that needs to be inserted (much like a fountain pen cartridge).

Insulin pens are particularly useful if you need to take premixed insulin. They have become popular for use by people with both type 1 and type 2 diabetes.

Insulin Jet Injectors: Jet injectors offer an alternative to needles and work by sending a fine spray of insulin into the skin using a pressurized jet of air instead of a needle. However, jet injection isn’t any less painful than administering insulin with a needle and may cause bruising or altered absorption levels. Jet injectors also require frequent cleaning and maintenance.

External Insulin Pumps: External insulin pumps are small devices the size of a pager that can be attached to your belt or placed in your pocket. They run off batteries. They are made up of an insulin reservoir connected to a tube, ending in a cannula or catheter, which is inserted under the skin of your abdomen. They can be set to deliver insulin at a slow, continuous rate throughout the day, or to release larger quantities at meal times or when blood sugar levels are high.
The main advantage of a pump is that it closely mimics the slow but continual release of insulin by the pancreas. However, you will still need to monitor your blood glucose levels regularly. Pumps have been useful in helping people with diabetes achieve tighter blood glucose control, but the risk of episodes of low blood sugar (hypoglycaemia) is higher. Another drawback of pumps is the risk of ketoacidosis if the catheter becomes blocked. Expense may also be an issue.

**Implantable Pumps:** Implantable pumps which deliver insulin either intravenously or directly to the liver are currently being tested in people with diabetes (they are not yet available in Australia). They are usually implanted into the left side of the abdomen and are designed to work in a similar way to external insulin pumps, that is, by giving a continuous ‘basal’ dose of insulin with the ability to deliver additional ‘bolus’ doses at meal times. Also under investigation is a version of the pump that measures blood glucose as well and so delivers the correct insulin dose automatically. However, these devices are complicated and expensive and can become blocked. If there are complications or infection at the implantation site the pump may have to be removed.

**Insulin Patches:** Insulin patches are also currently under development, but it is difficult for insulin to be absorbed through the skin. The patch is designed to release insulin slowly and continuously. Additional doses can be administered by pulling off a tab on the patch.

**Insulin Inhalers:** Insulin inhalers are a new way of delivering pre-mealtime insulin. Insulin inhalers work like an asthma inhaler, but deliver dry powdered insulin into the bloodstream via the lungs. However, because the system can only be used to deliver fast-acting insulin, long-acting insulin must still be injected. Large doses are needed because only around 10 per cent of the dose actually reaches the bloodstream and that amount may vary, for instance, if you have a cold or asthma.

The inhalers are not yet commercially available in Australia, but have been approved for use in the USA.

**Future Trends for Insulin Delivery Systems:** Insulin sprays, either for the nose or mouth and oral insulin (insulin pills) are methods of insulin delivery that continue to be investigated. These options represent long-term possibilities for insulin delivery, as difficulties in obtaining adequate amounts of insulin in the bloodstream are yet to be overcome.

**Islet Cell Transplantation:** This is a recently developed surgical procedure - called the Edmonton protocol - whereby islet cells from a donated human pancreas are injected into the liver of a recipient with type 1 diabetes. The transplanted cells begin to secrete insulin, while the recipient needs to take immunosuppressive medications for life to prevent rejection of the transplanted tissue. Clinical trials continue to establish the safety and long-term effectiveness of this procedure as a means of supplying insulin.
Insulin Nanopump: The nanopump is a powerful device and has many possible applications in the medical field. The first application of the pump, introduced by Debiotech, is insulin delivery. The pump injects insulin to the patient's body in a constant rate, balancing the amount of sugars in his or her blood. The pump can also administer small drug doses over a long period of time. [5]

Gene Therapy: Two recent reports describe research into gene therapy for different aspects of diabetes. These reports are in the forefront of what will no doubt be ongoing and exciting research arising from the decoding of the human genome.

- Scientists have identified a gene called SHIP2 that appears to regulate insulin. Such findings make SHIP2 a potential gene therapy target for the treatment of type 2 diabetes aimed at improving the individual insulin regulation.
- A protein that blocks the overgrowth of blood vessels in the eye is being studied as possible gene therapy for diabetic retinopathy. A recent study showed that treatment with the protein, called pigment epithelium-derived factor, or PEDF, prevented excessive new blood vessel formation in an animal model of retinopathy. It may also be used to treat macular degeneration. [6]

As scientists identify specific genes whose absence or improper functioning are associated with specific conditions, more possibilities for gene therapy are offered for diabetes as well as all disease.

Types of Other Insulin

New Insulins: In the past year, three new formulations of insulin have become available which have been designed to offer the advantages of simpler regimens and better glucose control for people whose diabetes must be treated with insulin. All are human insulin analogs derived from recombinant DNA technology. [6] They are:

- Glargine (from Aventis Co.) is a basal insulin, offering a more continuous activity with much less of a peak than NPH insulin. It can be used with a very-rapid-acting insulin such as lispro or aspart and should provide a flatter basal amount of insulin. Until now this has only been possible with twice daily injections of ultralente or by the basal rate of an insulin pump. This approach tries to permit more normal mealtimes patterns individualized to a person's own habits.
- Aspart (from Novo Nordisk) is a very-rapid-acting insulin that can be injected 15 minutes prior to eating. Its fast action also allows more freedom in the timing of meals and the amount of food eaten.
- A 75/25 lispro mixture is the first of the analog mixtures available (from Eli Lilly); it contains Lilly's very-rapid-acting lispro and a novel human insulin analog called NPL. It is designed for those who need better control after meals and want to use an insulin pen.

Closed-loop' Insulin Delivery: A fully functional external "closed-loop" insulin delivery system for patients with diabetes is still down the road, but the availability of continuous glucose monitoring has brought that long-held goal within sight. [7]

Iontophoresis/Reverse Iontophoresis: Iontophoresis refers to transdermal delivery of insulin or other peptides by a direct electric current. A weak current carries the drug ions through the skin to cause vasodilation and increased blood perfusion. In diabetic patients, drug permeation of the endothelial cells forming the walls of the micro vessels are altered which results in significant reduction in blood flow. [8]

Rectal Delivery: The major advantage of insulin delivery via the rectal route is the bypass of the hepatic first pass metabolism. The delivery is safe from intestinal motility, gastric emptying time and the presence of diet and encounters less degrading enzymes.

CONCLUSION

As it is portrayed by the global market of insulin that there is a high demand of insulin consumption, so it becomes a vital role of researcher to develop more convenient, compliance and a safe delivery of insulin to target the more population all around the globe.
The advances made in insulin delivery could surely provide intensive insulin therapy regimens that can reduce the multiple daily subcutaneous injections and heavy burden of compliance on patients. Therefore research and investigation must go on the development of more safe and effective delivery of insulin.

REFERENCES