Insulin administration Devices–an update

B H N Yasmeen¹

Insulin is a peptide hormone used to treat all patient with Type 1 diabetes (T1DM) and many patients with advanced Type 2 diabetes (T2DM). The main milestone in the history of Insulin was that on 30 July 1921, when Frederick Banting and Charles H Best successfully isolated an extract (isletin) from the pancreas of a dog and injected it into a diabetic dog, found that the extract reduced its blood sugar by 40% in 1 hour.¹ Then in 1922 for the first time they successfully used it to a diabetic patient, Leonard Thompson. Leonard was a type 1 diabetic patient and bounced back to life with that insulin otherwise he was close to death that time.²

In 1923 the Company Lilly began marketing animal insulin. Purified animal-sourced insulin was initially the only type of insulin available. Then in the early 1960s the first synthetic insulin was produced simultaneously in the labs of University of Pittsburgh and RWTH Aachen University.³

In 1978 the first genetically engineered, synthetic "human" insulin was produced using E. coli.⁴ The first commercially available biosynthetic human insulin under the brand name Humulin introduced in 1982.⁵ The vast majority of insulin currently used worldwide is now biosynthetic recombinant "human" insulin or its analogues.⁶

For administration of insulin many devices have been developed since its discovery. Now a day the most common route of insulin administration is subcutaneous route and to deliver the insulin subcutaneously the devices are **vials and syringes, insulin pens and insulin pumps**. In our country insulin vials and syringes, insulin pens are widely used. Therefore, most of the physicians and patients are accustomed with these devices but Insulin pump is not so much familiar to them.

The commonest Subcutaneous insulin delivery route is associated with injection pain, needle phobia, lipodystrophy, noncompliance and peripheral hyperinsulinemia. Therefore, for the last few decades extensive researches is going on to administration of insulin through a minimally invasive or noninvasive oral, buccal, nasal, peritoneal and transdermal route. Side by sidemany insulin devices have become available and many more are coming.

This editorial tries to focuses on the various insulin delivery techniques and devices with its advantages and limitations.

**Inhalation insulin**

It was the first reported alternate to subcutaneous injection. Advantages of the pulmonary route include a vast and well perfused absorptive surface, absence of certain

¹ Prof. Dr. B H Nazma Yasmeen
MBBS, MCPS, MD (Paed)
Editor
Northern International Medical College Journal

Professor and Head
Dept. of Paediatrics
Northern International Medical College, Dhaka
e-mail: prof.nazma.yasmeen@gmail.com

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peptidases that are present in the gastrointestinal (GI) tract that breaks down insulin and the ability to bypass the "first pass metabolism." 

Some studies showed that bovine or porcine insulin delivering through a nebulizer produced a rapid hypoglycemia in both diabetic and non-diabetic subjects. 

In 2006 the first inhaled insulin, Exubera® was approved by the US Food and Drug Administration (FDA). But this product was withdrawn from the market in 2007. 

In June 2014, Sanofi has launched Afrezza (dry powdered formulation) in the United States market for the patients with T1DM. It’s an inhaler with pre-measured, rapid-acting insulin should use before meals. The onset of action is 15 min and duration is 2-3 h, which is ideal for postprandial blood glucose control.

Oral insulin
The oral route of insulin administration may be the most patient-friendly way of taking insulin because patient simply take a pill. However, the challenges in making oral insulin include: Inactivation by proteolytic enzymes in the GI tract and low permeability through the intestinal membrane due to larger size and hydrophobicity of insulin resulting in poor bioavailability.

Several pharmaceutical companies are engaged in developing oral insulin in a way to overcome these challenges.

Oramed Pharmaceuticals Inc. a clinical-stage pharmaceutical company focused on the development of oral drug delivery systems, is working to bring the first oral insulin capsule (ORMD-0801) to market. The company has launched its largest and most advanced clinical trial under direction of the US FDA. An earlier trial for Oramed’s oral insulin – involving 180 patients across the U.S. over 28 days – demonstrated strong promise for the technology, showing it to be a safe oral insulin delivery method with no serious adverse events related to the treatment.

Currently its oral insulin is in a pivotal clinical study going through FDA regulatory channels and is considered a game-changer for more than 100 million diabetic or prediabetic American adults.

Oral insulin spray
A new formulation and delivery system that allows a liquid oral insulin spray to be delivered into the mouth via an aerosolized spray. It is a tasteless liquid aerosol mist formulation (recombinant human insulin) that is administered to the buccal mucosa. When oral insulin sprayed into the mouth, it gets into the bloodstream very quickly.

In all of the studies conducted with the oral insulin spray showed that it was generally well tolerated. Some healthy individuals and subjects with T1DM experienced transient (1–2 min) mild dizziness during dosing; these symptoms were mild and self-limited.

The ease of use of the insulin spray formulation may increase patient acceptance and treatment compliance, improving quality of life for patients with insulin-dependent diabetes.

Nasal insulin
In theory, intranasal delivery has several advantages over oral (bypass GI peptidases), subcutaneous (noninvasive and painless) and inhalation route (no issue with lung function) which makes this route attractive for the delivery of insulin. 

However, intranasal delivery has shortcomings such as limited permeability of a large molecule through the nasal mucosa and rapid mucociliary clearance resulting in variable absorption.

Currently, two technologies are under investigation: Nasulin™ (CPEX pharmaceuticals) and nasal insulin by Nastech Pharmaceutical Company Inc. Both insulin preparations have bioavailability of about 15-25% with the onset of action ~10-20 min. Results from the phase 2 and 3 clinical trials are awaited.

Treatment with intranasal insulin improved memory, preserved caregiver-rated functional ability and preserved general cognition without any significant hypoglycemic event. Based on this, large randomized controlled trials (NCT01595646, NCT01767909) are ongoing to evaluate the usefulness of this agent for the treatment of Alzheimer’s disease.
Several researchers developed a skin patch (a thin square not bigger than a penny) covered in painless microneedles (more than one hundred tiny needles, each about the size of an eyelash) that are loaded with tiny insulin-carrying pouches. The pouches are engineered to break apart rapidly and release the insulin in response to rising glucose levels. Diabetic mice wearing the patch maintained consistent concentrations of insulin in their blood. When these mice received a shot of glucose, their blood sugar levels spiked initially, but then fell to normal levels within two hours.

On further development recently a newer device the Smart insulin patch developed and introduced in mice combines the nanotechnology of tiny pyramid-shaped microneedles with pancreatic cells that detect glucose levels. The needles in the patch—each 800 micrometers long and thinner than a human hair—penetrate only the top layer of skin, making it painless. The mouse patch is about the size of a fingernail, with an array of needles, in rows 11x11.

Hopefully the Smart insulin patch, once translated for humans, could eliminate the need for constant blood testing and help diabetics maintain a more consistent level of blood glucose. Though the project is still in animal trials, human trials are still years away.

Other nonconventional routes

Intra-peritoneal (intra-portal)24 The limitations of this route of insulin administration include it is invasive, may be associated with subcutaneous infections, cannula blockage, higher cost, portal-vein thrombosis and peritoneal infection.25

Rectal route showed fair results. However, this route is not commercially viable.26

Researchers, doctors, and people with diabetes agree that injected insulin works well to manage the disease. But everyone also agree that getting insulin into our body through something other than a needle would be even better. That is why since the discovery of insulin till now research is going on, focusing on identifying a route of administration for insulin which is minimally or noninvasive, effective, safe, convenient and cost-effective for the patient. Researchers are still looking for the best option.

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