REVIEW ON NOVEL ROUTES OF INSULIN FOR DIABETES TREATMENT

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ABSTRACT

Diabetes mellitus is the chronic pathogenic condition which is primarily due to inadequate insulin secretion and is responsible for major healthcare problems worldwide cost billions of dollars annually. Diabetes complications include both microvascular and macrovascular disease, both of which are affected by optimal diabetes control Novel routes of insulin administration are an area of interest in the diabetes field, given that insulin injection therapy is burdensome for many patients. This review will discuss pulmonary delivery of insulin via inhalation. Subcutaneous insulin has been used to treat diabetes since the 1920 however, despite a number of different formulations, intensive insulin therapy with multiple daily injections has not gained widespread clinical acceptance. However, a growing body of evidence suggests that inhaled insulin is an effective, well-tolerated, noninvasive alternative to subcutaneous regular insulin. Critically, inhaled insulin shows a more physiological insulin profile than that seen with conventional insulin. Further studies are needed to confirm long-term efficacy and pulmonary safety, to compare the different approaches, and to characterize better their relative places in practice. As a result of the recognition of the importance of tighter control of glycaemia and the growing number of patients with type 2 diabetes who receive insulin, inhaled insulin could become an increasingly integral part of managing diabetes.

KEYWORDS: Type 1 and Type2 diabetes mellitus, drug formulations, drug administration routes, insulin, Glycemic control, Insulin Treatment.

INTRODUCTION

Insulin is a hormone with intensive effects on metabolism and several other body systems (e.g.; 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 Risk factors associated with diabetes are lifestyle change, insulin resistance, generalized obesity etc. which may be responsible for multiple damages like neuropathy, vasculopathy etc.3 Subcutaneous routes of insulin delivery having number of disadvantages like itching, allergic reactions, local pain etc. and in order to overcome the scenario, insulin delivery routes has been extended to oral, trans-dermal, nasal, rectal, pulmonary,and implants as well.

Type1 diabetes: Type 1 diabetes develops when the cells of the pancreas stop producing insulin. Without insulin, glucose cannot enter the cells of the muscles for energy. Instead the glucose rises in the blood causing a person to become extremely unwell. Type 1 diabetes is life threatening if insulin is not replaced. People with type 1 diabetes need to inject insulin for the rest of their lives. Type 1 diabetes often occurs in children and people under 30 years of age, but it can occur at any age. This condition is not caused by lifestyle factors. Its exact cause is not known but research shows that something in the environment can trigger it in a person that has a genetic risk.

Type 2 diabetes: Type 2 diabetes develops when the pancreas does not make enough insulin and the insulin that is made does not work as well as it should (also known as insulin resistance). As a result, the glucose begins to rise above normal levels in the blood. Half the people with type 2 diabetes do not know they have the condition because they have no symptoms. People from certain ethnic backgrounds, such as Aboriginal or Torres Strait Islander, Polynesian, Asian or Indian are more likely to develop type 2 diabetes. When first diagnosed, many people with type 2 diabetes can manage their condition with healthy diet and increased physical activity.

DISCOVERY OF INSULIN AND DEVELPOMENT

Insulin was discovered in year 1921 by Banting and Best after a lot of controversy over it, for patients suffering from diabetes mellitus (DM) Islets were described by Paul Langerhans, a german medical scientist but couldn't correlate any function for them.20 Later in 1950, Frederick Sanger determined the molecular structure of insulin for which he was awarded with a nobel prize.21 Isletin (a crude form of pancreatic extract) was recognized by Banting. James Collip, a chemist from university of Toronto helped him to remove impurities from pancreatic extract and to change name of purified pancreatic extract to Insulin. Eli Lilly made potent Insulin preparations from pork pancreas. First, insulin was administered to a 14-year-old boy called Leonard Thompson suffering from type-

1 DM on January 11, 1922 which played crucial role in transforming his life.1,2 Earlier insulin preparations produced a quick action and peak effect but lacked efficacy to provide low basal level of insulin as pancreatic beta cells. As source of insulin was non-human, many recipients suffered from allergic reactions. This increased focus of researchers to create better insulin preparations.

PHARMACOLOGICAL ACTIONS OF INSULIN

Insulin is a two-chain polypeptide having 51 amino acids and molecular weight 6000. Major role of insulin is in management of patients suffering from type 1 DM having advanced beta cell deficiency. Insulin directly acts on tissues to regulate glucose homeostasis, unlike other oral hypoglycemic agents requiring presence of sufficient endogenous insulin to act as insulin sensitizers, insulin secretagogues, incretin mimetic, amylin analogs and other factors. Insulin has anabolic action and insulin signaling is critical for promoting uptake, use and storage of major nutrient like glucose, lipids and amino acids. Insulin stimulates glycogenesis, lipogenesis, and protein synthesis. Some effects of insulin (e.g., activation of glucose and ion transport systems, phosphorylation or dephosphorylation of specific enzymes) occur within seconds or minutes; other effects (e.g., to promote protein synthesis and regulate cell proliferation and gene transcription) manifest over minutes to hours to days.

Insulin initiates its action by binding to a glycoprotein receptor on the surface of the cell. This receptor consists of an alpha-subunit, which binds the hormone, and a betasubunit, which is an insulin-stimulated.

Types Of Insulin:

Insulin is according to how long it works in the body. Rapid- or short-acting insulin helps reduce blood glucose levels at mealtimes and intermediate or long-acting insulin helps with managing the body's general needs. Both help manage blood glucose levels.

The 5 different types of insulin range from rapid- to long-acting. Some types of insulin look clear, while others are cloudy. Check with your pharmacist whether the insulin you are taking should be clear or cloudy.

Before injecting a cloudy insulin, the pen or vial needs to be gently rolled between your hands to make sure the insulin is evenly mixed (until it looks milky). If your insulin is meant to be clear, don't use if cloudy.

Often, people need both rapid- and longer-acting insulin. Everyone is different and needs different combinations.

There are 5 types of lnsulin as follows:

1. Rapid Acting Insulin
2. Short Acting Insulin
3. Intermediate Acting Insulin
4. Intermediate Acting Insulin
5. Long Acting Insulin

1. Rapid-acting insulin: Rapid-acting insulin starts working somewhere between 2.5 to 20 minutes after injection. Its action is at its greatest between one and three hours after injection and can last up to five hours. This type of insulin acts more quickly after a meal, similar to the body's natural insulin, reducing the risk of a low blood glucose (blood glucose below 4 mmol/L). When you use this type of insulin, you must eat immediately after you inject.

2. Short acting insulin: Regular insulin (Novolin R) is also known as short-acting insulin. It is also used to cover your insulin needs at mealtime, but it can be injected a little bit longer before the meal than rapid-acting insulin.

3. Intermediate acting: Insulin NPH (Humulin N, Novolin N) is an intermediate-acting insulin that is a suspension of crystalline zinc insulin combined with the positively charged polypeptide protamine. Unlike the shorter-acting insulins, NPH has a longer duration of action, yet not as long as the newer longacting insulin

4. Mixed Insulin: Mixed insulin contains a pre-mixed combination of either very rapid-acting or short-acting insulin, together with intermediate-acting insulin.

5. Long acting insulin: Tresiba (insulin degludec) is the longest acting insulin available, and there don't appear to be any coming down the pipeline that give this duration of effect. What makes Tresiba a hero is its long duration of action (more than 40 hours) with minimal fluctuations in blood levels of the drug.

Table No. 1.1: Pharmacokinetic Profile Of Various Insulin Analogue

Insulin Type	Onset	Peak Time	Duration	Method
Rapid Acting	15 minutes	1 hour	2 to 4 hours	Usually taken right before a meal. Often used with longer-acting insulin.
Short Acting	30 minutes	2 to 3 hour	3 to 6 hours	Usually taken 30 to 60 minutes before a meal.
Intermediate Acting	2 to 4 hours	4 to 12 hours	12 to 18 hours	Covers insulin needs for half a day or overnight. Often used with rapid- or short-acting insulin
Long Acting	2 hours	Does not peak	Up to 24 hours	Covers insulin needs for about a full day. Often used, when needed, with rapid- or short-acting insulin
Mixed Acting	5 to 60 minutes	Peak vary	10 to 16	Combines intermediate- and shortacting insulin. Usually taken 10 to 30 minutes before breakfast and dinner

- **Onset**: How quickly insulin lowers your blood sugar.
- **Peak Time**: When insulin is at maximum strength.
- **Duration:** How long insulin works to lower your blood sugar

INSULIN DELIVERY METHOD – FROM PAST TO PRESENT

1.Syringe or Pen:

Syringes and insulin pens deliver insulin through a needle. Pens may be more convenient, and children may find them more comfortable than syringes.

Syringe

- Doctor will tell us how much insulin you need per dose. Smaller-capacity syringes are easier to use and more accurate.
- If your largest dose is close to the syringe's maximum capacity, buy the next size up in case your dosage changes.
- If you need doses in half units, choose a syringe with half-unit markings.

2.Insulin pen

Some pens use cartridges that are inserted into the pen. Others are pre-filled and discarded after all the insulin is used. The insulin dose is dialed on the pen, and the insulin is injected through a needle.

Advantages of syringes and pens

- Injections require less training than a pump.
- Injections may cost less than a pump.
- Pens are more portable and easier to use than syringes.
- Needles in pens are small, thin, and more comfortable.

Disadvantages of syringes and pens

- Syringes are less discreet than pens.
- Not all types of insulin can be used with a pen.
- Pens are more expensive than syringes and may not be covered by insurance

3.Insulin Pump

An insulin pump is about the size of a small cell phone. It gives you a basal dose of short- or rapid-acting insulin per hour. When you eat or when blood sugar is high, you calculate the dose, and the insulin in the pump delivers the bolus.

The pump delivers insulin through a thin plastic tube placed semi-permanently into the fatty layer under your skin, usually in the stomach area or back of the upper arm. Your doctor or health education specialist will show you how and where to place the tube.

Advantages of insulin pumps

- Have been shown to improve A1C.
- Deliver insulin more accurately.
- Deliver bolus insulin easier.
- Eliminate unpredictable effects of intermediate- or long-acting insulin.
- Provide greater flexibility with meals, exercise, and daily schedule.
- Can improve physical and psychological well-being.

Disadvantages of insulin pumps

- May cause weight gain.
- Can be expensive.
- May cause infection.
- Can be a constant reminder of having diabetes.
- Training is necessary.

4.Insulin Inhaler

Inhaled insulin is taken using an oral inhaler to deliver ultra-rapid-acting insulin at the beginning of meals. Inhaled insulin is used with an injectable long-acting insulin.

Advantages of insulin inhalers

- Is not an injection.
- Acts very fast and is as effective as injectable rapid-acting insulins.
- Can be taken at the beginning of meals.
- Could lower risk of low blood sugar.
- Could cause less weight gain.

- Inhaler device is small.

Disadvantages of insulin inhalers

- Might cause mild or severe coughing.
- May be more expensive.
- Still requires injections or a pump for basal insulin.
- Dosing isn’t as precise.

INSULIN DELIVERY: GENERAL TO NOVEL APPROACHES

Subcutaneous routes of insulin delivery was established in the early 19th which was the first device to combine an injection port and an inserter in one complete set that eliminates the need for multiple injections without having to puncture the skin for each dose and the device was helpful for the insulin requiring patients having needle phobia and helps them to achieve glycemic control Novel approaches in comparison to the common approaches of insulin delivery includes: Inhaled insulin delivery, Oral, colonic, Nasal, Buccal, Transdermal, Intra-peritoneal, ocular, rectal, Vaginal delivery etc.

1. Oral Delivery

- Joslin tried for first oral insulin in 1922-1923.
- The oral route of insulin administration may be the most patient-friendly way og taking insulin and it could more closely mimic physiological insulin delivery (more portal insulin concentration than peripheral).
- Challenges to development of oral insulin are Proteolytic enzymes in the GI. • When it is given orally, insulin is directly channeled from the intestine to the liver and a high level of insulin is reached in the portal blood.

Advantages of oral delivery

- Easy to administer.
- Compliance or adherence from the patient.
- Better glycemic control.
- Prevention of complications of diabetes.
- Improve b-cell function by providing beta cell rest.
- Reduces systemic insulin exposure and avoid the excessive weight gain sometimes seenwith subcutaneous insulin.

Disadvantages of oral delivery

- Resistance to injectable insulin.
- Lack of achievement of target glycemic goals.
- Fear to complexity of insulin regimens.
- Risk of hypoglycemia.
- Chances of weight gain.
- Chances of weight gain.
- Needle prick.

2. Inhaled Delivery

Insulin delivery to the lungs was the first reported alternate to subcutaneous injection. It has long been appreciated that insulin delivery by aerosol reduces blood glucose. Early studies showed that delivering bovine or porcine insulin using a nebulizer produced a prompt hypoglycemia in subjects with and without diabetes.

- Inhaled drugs are absorbed into the alveolar capillary network, which has the advantage of having a large surface area and thin diffusion barrier.
- Provide larger surface area (100 square metres).
- **Advantages**: Faster onset of action & Longer glucose lowering activity.
- Addition of zinc caused an enhancement of the hypo glycemic effect a dry powder form of insulin having higher bioavailability than a ph 7.4 insulin solution.
- Citric acid added to insulin dry powder increased the hypoglycemic effect with bioavailability of 42 and 53 for dry powder containing 0.025 and 0.036mg/dose citric acid respectively.

3. Buccal Delivery

- The drug is delivered through an aerosol spray into the oral cavity.
- The molecules absorbed via the buccal route enter the internal jugular vein and reaches the systemic.
- Circulation bypassing hepatic first metabolism and improving bioavailability.
- In the buccal mucosa the blood supply in reticulated veins is very high, so absorption will be also high.
- Factors influencing: molecular weight, hydrophilicity, solubility, and partition coefficient of proteins & peptides.

4.Transdermal Delivery

Trans-dermal insulin delivery eliminates the problems associated with needles and injections and large surface area of the skin makes it a convenient route for insulin delivery. However, the penetration of insulin is halted by the stratum corneum, the outer most layer of the skin. Numerous methods have been explored to overcome the barrier of stratum corneum.

There are several ways insulin can be delivered transdermally such as:

a) Iontophoresis, the technique that uses small electric currents
b) Sonophereis or phonopheresis uses ultrasound waves
c) Microdermal ablation by removing the stratum corneum
d) Electroporation utilizes high voltage pulses that are applied for a very short time
e) Transfersulin is the insulin encapsulated in transferosome, an elastic, flexible vesicle which squeeze by itself to deliver drugs through skin pores
f) Insupatch, a device developed as an add-on to an insulin pump that applies local heat to the skin in order to increase the absorption of insulin
g) Recombinant human hyaluronidase (rHuPH20) to increase insulin absorption fromsubcutaneous tissue.

Advantages of transdermal delivery

- Good patient compliance.
- Prolonged therapy

Disadvantages of transdermal delivery

- Requires the usage of Microneedles.
- Insulin molecules are large enough to penetrate the skin at therapeutically useful rates.

5.Nasal Delivery

Nasal insulin crosses the blood brain barrier hence it has a hypothesized effect on memory function. In a randomized placebo controlled trial with 104 adults with amnestic mild cognitive impairment or mild to moderate Alzheimer's disease were randomized to receive either placebo or 20 IU or 40 of intranasal insulin.

- Nasal cavity has large surface area (150 Sq. cm.)
- Epithelial surface is covered with numerous microvilli,hence absorption is greater and also avoiding loss of insulin from first pass hepatic metabolism.

6. Rectal Delivery

• There are Porto-systemic anatomoses in rectal vessels. These vessels connect the portal system to systemic system, hence allowing absorbed drugs to directly enter the systemic circulation.
• The technique to improve rectal absorption is by creating an adhesive interaction b/w. the delivery system & rectal mucosa, increasing drug residence time at the absorption sites.
• Suppositories containing 100 U insulin & 200 mg Sodium Salicylate as an absorption enhancer were tested in humans. Hypoglycemic effects were achieved in 15 mins. & lasted upto 90 mins. Post administration.

7.Ocular Delivery

• The rate of absorption was seen fast in the ocular route than the injection.
• Delivered by use of nanoparticles, liposomes, ocular inserts and gels.
• **Advantages**: Less development of immunological reactions in eye tissues, less side effects, no tolerance and avoidance of hepatic first pass metabolism.
• **Limitations**: low bioavailability and irritation & loss of drug molecules via blinking, tearing, and drainage.
• Until date no human trial has been reported with this route and an animal study failed to achieve significant plasma insulin concentration

DISCUSSION

In above review article we study about insulin type, mechanism of action and structure of insulin. For insulin delivery different delivery system are used such as insulin syringe and pen, insulin pump, insulin inhaler. The main point of this project is to study novel routes of insulin for diabetes treatment. The conventional form of insulin delivery is through subcutaneous injection. But the diabetic

patients goes through trauma and pain associated with this technique. Therefore, we study some other routes for insulin delivery such as oral delivery, buccal delivery, transdermal delivery, nasal delivery, rectal delivery, ocular delivery. I observed that oral route of insulin administration may be the most patient-friendly way of talking insulin and it could more closely mimic the physiological insulin delivery.

There should be a new millennium with full of promises of revolutionary changes in the delivery of insulin, which can't come too soon for the billions of sufferers who are reliant on subcutaneous administration.

CONCLUSION

There is a long history of research focusing on identifying a route of administration for insulin that is minimally or noninvasive, effective, safe, convenient and cost-effective for patients. Each route and delivery method has its own potential advantages and disadvantages. However, if successful, alternative routes of administration could revolutionize the treatment of diabetes mellitusand help improve patients' quality of life.

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