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Review article ***Insulin***

Review on oral insulin

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ABSTRACT

Oral insulin delivery which is more advanced and superior version of the insulin delivery. Diabetes mellitus is a chronic metabolic disease characterized by lack of insulin in body leading to failure of blood glucose regulation. Diabetic patients often require insulin injections which is a very painful administration method. If insulin administered orally, it cause enzymatic degradation in stomach, inactivation and digestion by proteolytic enzyme in intestinal lumen, poor permeability across intestinal epithelium and poor stability. This review article summarizes the problems associated with present route of insulin delivery, advantages of oral insulin delivery, existing barriers and encounter methods of oral insulin delivery.

Keywords: Oral insulin, diabetes, insulin delivery, Blood glucose.

INTRODUCTION

DIABETES MELLITUS

Globally about 537 million adults are suffering with diabetes mellitus .The total number of people living with diabetes is projected to rise to 643 million by 2030 and 783 million by 2045. For every 5 sec 1% peoples in the world are died due to acute or chronic complications of diabetes mellitus. Diabetes was mentioned as early as 1500 BC in Egyptian, Indian and Chinese literature, including description of sweet or honey like urine. Diabetes is a Greek word means “pass through” and Mellitus means “sweet”. Diabetes mellitus is a term refers not only a single disease. A group of metabolic abnormalities with common thread such as chronic hyperglycaemia. Diabetes mellitus occurs due to

- Decreased secretion of insulin
- Increased insulin resistance

Based on that diabetes mellitus was classified into following types:

1) ***BASED ON DECREASED INSULIN PRODUCTION***

A) **Type I diabetes mellitus:** it occurs at young age due to destruction of β cells of pancreas by auto immune disease.

B) **LADA (**Latent Autoimmune Diabetes of Adults): The conditions similar to type I but occurs at later age.

2) ***BASED ON INCREASED INSULIN RESISTANCE***

A) **Type II diabetes mellitus:** it occurs at older age in which cell become deaf to insulin.

B) **MODY (**Maturity Onset Diabetes of young): The condition similar to type II diabetes but it occurs in young age.

3) ***BASED ON BOTH CONDITIONS***
(Problem in insulin production + peripheral insulin resistance)

A) **Gestational Diabetes:** During pregnancy the pregnant women developed a tendency for hyperglycaemia.

Overtime, people who have diabetes can develop serious life threatening complications including, heart attack, stroke, kidney failure, nerve damage (numb, cold legs or feet, decreased sexual ability in men and women), eye problems including changes or loss of vision, or gum disease[1].

HISTORY OF INSULIN

Insulin is a hormone that is made by islet of langerhans of pancreas. Insulin tells other organs to take in glucose from blood stream. Insulin was discovered 100years ago. Before 1920 children and young people diagnosed with type I diabetes mellitus only fewdays, weeks, months to live. In 1921, researchers from University of Toranto discovered insulin, the world's first life saving treatment for diabetes mellitus.

1. **Frederick Banting (**orthopedic surgeon from war).
2. **Charles Best**

They both together extract insulin form pancreas of dog and that pancreatictomised dog kept alive but that insulin extract is impure. Dr. James Collip developed a method to make pure extract of insulin but this time not from dogs, from cow under the supervision of MacLeod. 10.jan.1922 Leonard Thompson (14yrs old boy) diagnosed with type I diabetes mellitus treated with insulin for 1st time in Toronto hospital. These human insulin only controls high blood sugar level but does not cure diabetes. Oral insulin may improve b-cell function by providing b-cell rest.[2]

INSULIN FROM CATTLE

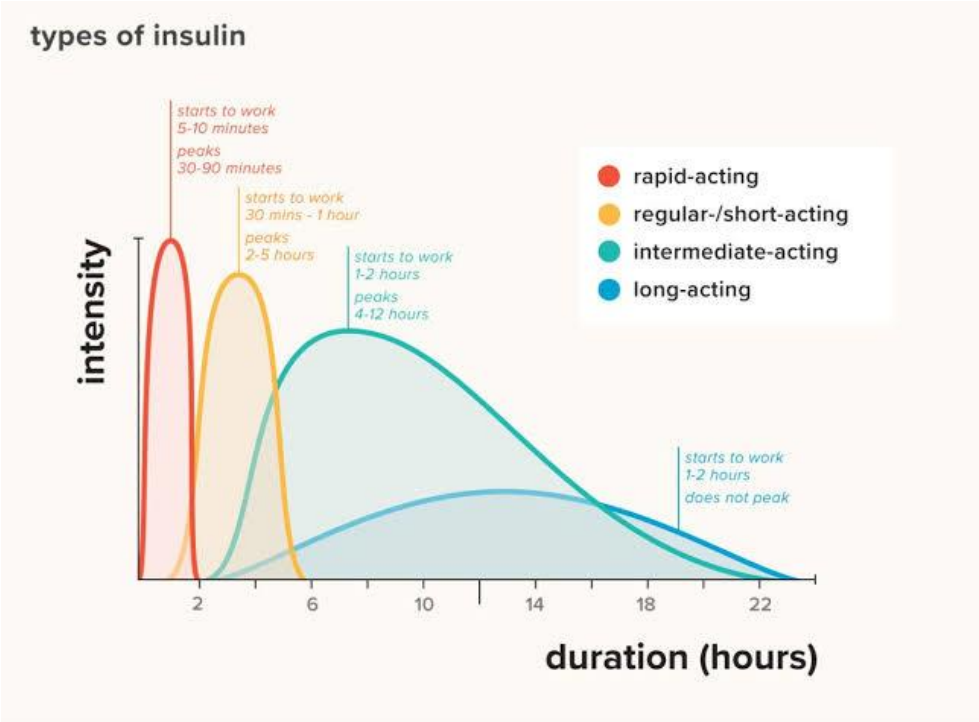
At first insulin was isolated from cattle such as cow but purification process was complex and crude. George walden discovered isoelectric precipitation method (process of extracting, purifying and stabilizing insulin) paved way for mass production of insulin , an epoch making achievement, which has ultimately provided a life giving treatment for millions of people world wide .In 1923 ,first commercial insulin discovered by researchers of university of Toronto [3].

INSULIN FROM RECOMBINANT DNA TECHNOLOGY

The earliest animal derived insulin were short acting and contained many impurities that cause adverse reactions, thereby limiting their therapeutic potential. In 1970, to reduce difficulties of using animal insulin, insulin was produced by recombinant DNA technology (insert a human gene into the genetic material of common bacterium i.e. E.coli or Saccharomyces cerevisiae. This recombinant microorganism could now produce the protein encoded by the human gene). It is a highly sophisticated process of creating synthetic insulin. In 1982 first human insulin produced by recombinant technology was made available.

Although insulin discovery is an epoch achievement much improvement was needed, such as further purification, increased yield and production capacity, improved time action profiles, reducing risk of hypoglycaemia and simplifying modes of delivery, efficacy and ease of glucose monitoring.

TYPE OF INSULIN



PRESENT ROUTE OF INSULIN DELIVERY AND PROBLEMS ASSOCIATED WITH IT.

Currently the most common methods for administering insulin remains via subcutaneous tissue, either using syringes, insulin pens, implantable devices or insulin infusion pump(IIP) and recent advancement such as oral spray or pulmonary inhaled insulin. These more automated systems can further reduced burden of diabetes.

INJECTABLE TYPE INSULIN

In 1923 first insulin commercially available was in concentrations of 3-5 units/ml .But now 100 units/ml insulin became standard concentration. The original glass vials and

reusable syringes with large bore needles have since been replaced by disposable syringes with smaller, finer gauge needles, which improved convenience, safety and reduced injection pain [4].

EVOLUTIONS OF INSULIN INJECTIONS

i. ***Insulin pen:*** people with diabetes use insulin pens it inject insulin which contain a catridge, a dial to measure dosage, and a disposable needle. It allows greater dose accuracy and easier administration of doses. They are more convenient, less painful, and easily stoable and transportable.

ii. ***Insulin infusion pump(IIP):*** It is an external battery powered device that delivers insulin at regularly scheduled intervals day and night (through a short, flexible plastic tube inserted just under the skin), into the body at programmed rate to control blood sugars.

PROBLEMS IN SUBCUTANEOUS ROUTE OF INSULIN DELIVERY

- It causes **local pain and inconvenience** due to repetitive injection.
- Due to overdosing leads to hypoglycaemia(decreased blood sugar level)
- It causes itching and allergy at the site of injection.
- It may result in hyper insulanemia.
- It leads to insulin lipodistrophy benign tumor like swelling of fatty tissue around injection site.
- This route of insulin administration as the result of systemic hyperinsulinemia leading to a disproportional anabolic effect on muscle and adipose tissue leads to weight gain.

INHALED TYPE INSULIN

i. ***Oral spray (Oralin):*** These are liquid formulations of insulin that are sprayed into mouth using proprietary rapid mist device. They are absorbed by mucus membrane in cheeks, tongue, throat which are rich in vasculature.

ii. ***Pulmonary or inhaled insulin (Exubera*)**: In this type insulin are in the form of liquid or powder that is delivered through mouth directly into lungs which is high permeable alveolar epithelium and has large surface area provide efficient and effective portal for insulin absorption[5].

PROBLEMS IN INHALED INSULIN DELIVERY

- Due to overdosing leads to **hypoglycaemia**(decreased blood sugar level)
- It causes allergic reaction such as cough, scratchy or sore throat.
- Smokers and asthma patients not able to use.
- It may cause lung cancer.

ORAL INSULIN DELIVERY

Oral insulin would closely mimics the physiology of endogeneous insulin secreted by pancreas in our body than injectable insulin does. Moving insulin more quickly into liver could help our body absorb and use glucose better. This could mean the insulin works faster.[6]

ADVANTAGES OF ORAL DELIVERY OF INSULIN

- To eliminate pain caused by injection.
- To eliminate physiological barriers associated with multiple daily injection such as needle anxiety &possible infection.
- It delivered directly on liver (primary site of action) via portal circulation.
- Oral insulin has potential to protect pancreatic β cell from auto immune destruction.

APPROACHES TO ORAL INSULIN DELIVERY

i. ***TABLET:*** chitosan-6-mercaptonicotinic acid or chitosan-4-thiobutylamidine (2 imino thiolane+chitosan) is thiolated chitosan with strong mucoadhesive properties and pH independent reactivity. These thiolated chitosan insulin tablets are 80 folds mucoadhesive to protect the insulin degradation by gastric acid. It serves as a most promising excipient for oral delivery of insulin.

ii. ***MICROEMULSION*:** In this Insulin serves as a aqueous phase and triacetin or lecithin, nonesterifies, fatty acids, cholesterol in critical proportion serves as a oily phase forms microemulsion which causes substantial reduction in blood glucose level. In this preparation Didoceyldimethyl ammonium bromide (DMAB) act as a surfactant and propylene glycol act as a cosurfactant. These insulin microemulsions are 10 fold enhancement in availability than plain insulin. To enhance the potential of emulsion eccentric coated dry emulsion formulation prepared from solid in oil in water emulsion. Its stability is confirmed by spectroscopy, fluorescence etc[7].

Existing barriers and Encounter methods

ENZYMATIC BARRIERS IN GI TRACT

Insulin degraded by pepsin & pancreatic proteolytic enzyme (trypsin&α-chymotrypsin),cytostolic enzyme (insulin degrading enzyme)and also subjected to acid catalysed degradation in stomach. But Brush border enzyme doesnot cause proteolytic breakdown of insulin.

ENCOUNTER METHODS

a. Encapsulation of insulin by gelled submicron particles (sodium alginate+$CaCO_3$) as immobilizing agent, pH sensitive copolymer (methacrylic acid-co-N-vinyl caprolactam), enzyme inhibitor (serpins) and variant-specific surfaceproteins (VSPs) obtained from *Giardia* spp. as carriers for the delivery of insulin causes resistant to acidic pH and to proteolytic degradation.

b. Use of buffer (phosphate buffer)

c. Dosage form modification: single-chain insulin precursors that are more stable against proteolytic degradation than their double-chain mature analog. This single-chain insulin precursor has a general structure of D–B–C–A–E.

A is the human insulin A chain,

B is the human insulin B chain,

C is a peptide chain of 0–15 amino acid residues connecting the C-terminal amino acid residue in the B chain with the N-terminal amino acid residue in the A chain,

D is a N-terminal extension peptide onthe B chain of 0–15 amino acid residues and

E is a C-terminal extension peptide on the A chain of 0–15 aminoacid residues[8].

INSULIN LOW PERMEABILITY TO INTESTINAL MUCOSA

Insulin is a hydrophilic macromolecule so it can't diffuse into epithelial cells through lipid-bilayer cell membranes of intestinal mucosa to the blood stream. In this case active transport of insulin is not possible. It is found to be insulin delivery to the mid-jejunum protects insulin from gastric and pancreatic enzymes and release from the dosage form is enhanced by intestinal micro flora[9].

ENCOUNTER METHODS

a. ***Encapsulation of insulin by nanoparticles*:** encapsulating insulin into polymeric nanoparticles. These nanoparticles can be easily absorbed through Peyer's patches or M cells of GIT, which have good drug particle absorption.
b. ***Use of permeation enhancers*:** uses a peptide (with 6–15 amino acid residues) as a zonula occludens toxin (ZOT) receptor agonist. ZOT is capable of reversibly opening the tight junctions between cells and increasing the paracellular transport of insulin. And also use fatty acid acylated amino acid (sodium lauroyl alaninate) .they are mild biodegradable surfactant with low toxicity and are soluble at intestinal pH which increases the insulin permeability.
c. ***Vitamin B_{12} as carrier:*** Insulin covalently linked to vitamin B_{12} at 5'hydroxyl group of ribosome moiety of α-ligand. The conjugation of insulin with vitamin B12 facilitates insulin's absorption in the GIT via the vitamin B12-intrinsic factor uptake mechanism.

RECEPTOR MEDIATED DEGRADATION

Insulin binds to receptor of cells and it was taken inside the cells by endocytosis. The bio efficacy and bioavailability of insulin can be increased by minimizing its receptor-mediated degradation.

ENCOUNTER METHODS

Betaines are *N*-trimethylated amino acids with a positive charge. The negatively charged insulin becomes covalently bonded with the positively charged betaine (insulin-betaine complex), thereby decreasing the receptor binding capacity and lowering receptor-mediated degradation[10]. The physiological barriers to absorption of oral insulin, its low bioavailability and low biopotency, and the high inter-patient variability, are challenges that researchers need to overcome before oral insulin can be considered as suitable candidate for treatment of diabetes mellitus.

CONCLUSION

Oral insulin delivery is the most reliable and promising way to improve the quality of life of diabetes patients who routinely receive insulin injection if all it's existing barriers are encountered. But since 1980s, this way of insulin delivery has not worked because it have not shown a clear clinical advantage over the subcutaneous route of insulin. Early-stage development programs of oral insulin are under way and appear promising –challenges remain but seem surmountable. With these points in mind, it is clear that a lot of works are needed to bring the first oral insulin delivery system to the market. If this can be fixed, it will be a cornerstone of diabetes history.

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