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Review Article

Overview of novel routes of insulin: current status

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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. For more than 84 years of time, Insulin replacement therapy had been used to manage to overcome the complications and this present review is based on the various routes of insulin delivery based on its safety and efficacy. Depending upon the effective duration of action, insulin activity varies from 1.5 to 27 hours and to reduce insulin burden, now a days it can be delivered in sensor-augmented pump therapy, various types of insulin Pen as well as routes like inhalation, colonic insulin, buccal, intra- peritonea and ocular, rectal, vaginal delivery of insulin etc. had been added to it. This review examines some of the recent proposals for various routes of application of Insulin delivery system along with the particular attention to its latest intervention of novel drug delivery system.

Keywords: Glycemic control, Mellitus, Drug administration routes, Inhalation insulin

INTRODUCTION

Insulin is the hormone responsible for serious pathogenic issues like diabetes mellitus-which have turned out to be a global issue worldwide in developed as well as developing country.[1] Absence or low level of insulin causes less reuptake of glucose in most of the body cells as well as responsible for signal controlling to other body systems.[2] 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.[4-7]

HISTORICAL BACKGROUND, STRUCTURE AND ANALOGUES OF INSULIN

Diabetes word was derived from the Greek word 'Siphon' and in early nineteenth century, it was to be believed that diabetes mellitus is the malfunction of digestive system associated with pancreas as well as according to the hypothesis, it is also associated with controlled carbohydrate metabolism.[8,9] Life expectancy of children with diabetes mellitus was short and the prognosis for the adult onset diabetes was very poor, but the above diet allowed them to live for some years.[10] Initially insulin was prepared from extracts of Islet cells and was not successful due to the purity issue, but later it was proved to be a successful research and Banting was awarded Nobel prize in physiology of medicine in 1923.[11]

INSULIN ANALOGUES AND USES

Insulin is the protein formed of with chains of amino acids known as A Chain (21 amino acid residues), B Chain (30 amino acid residues) and C chain connects A and B is liberated along with insulin after the break down of Pro-insulin. Monomers of insulin have the tendency to form dimmers and hexamers.[12,13] Insulin is basically synthesized from β-cell of pancreas-in the form of pre-courser named Pre-pro-insulin and genes responsible for the same is found at chromosome 11-which is close to the factor IGF2.[14] Pro-insulin with a C chain is transported into Golgi apparatus by micro-vesicles and is released by the action of pro-hormone convertase 2 and 3 and carboxy peptidase, the conversion of pro-insulin to insulin continues in maturing granules.[13]

The most recent rapid-acting insulin analogue was insulin glulisine-which was launched on 2004 and here asparagine was replaced by lysine at position 3 and lysine was replaced by glutamic acid at position 29. Its action was found to be same as that of the insulin lispro.[15-17] Insulin glargine was found to be the first long-acting man-made version of human insulin analogue. Here chain-A the asparagine is replaced by glycine at 21 position and chain-B is elongated by addition of 2 arginine residues at the carboxy terminus. It basically works by replacing the insulin produced normally in body and helps to move sugar from the blood into other tissues as well as its action stops the liver from producing excess amount of sugar.[18,19] Insulin aspart is the rapid acting insulin where proline amino acid had been replaced with the charged Aspartic acid amino acid at the position of 28. These changes can reduce the self-aggregation tendency and action time of the product and can be used as the treatment of hyperglycaemia type 1 and type 2.[20,21] Insulin detemir showed prolonged pharmacodynamics action due to binding of the reversible albumin at the injection site and it can be distinguished easily by the process of acylation from myristic acid to lysine residue at position 29 and lastly by deletion of threonine at position 30 of the β-chain.[22,23] Short acting insulin / regular having the onset of action 30-60 minutes after subcutaneous injections and effective duration is approximately 6-8 hours whereas onset of action for intermediate acting insulin (Isophane) are 2-4 hours and its effective duration is 10-16 hours and duration for long acting insulin like ultralente is around 24-28 hours.[24]

Insulin and its analogues are used for the purpose of maintaining of blood glucose, wound healing, common parenteral nutrition solution, as an anti-ageing agent, in some cases for cell culture and organ preservation, prevention of septic shock etc.[25-34]

INSULIN DELIVERY: GENERAL TO NOVEL APPROACHES

Subcutaneous routes of insulin delivery was established in the early 19th century (design was known as 'I-Port') 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 effectively.[35] After that insulin pen was discovered which was less painful, convenient delivery and a reusable device and can be combined with vials and syringes easily.[36] Insulin pump therapy was discovered in 1976 and it was used as a substitute of long acting insulin; the device can be used to deliver variable amount of insulin to the patient even just after consumption of meals.[37,38] Threshold suspend pump added another wing to the conventional insulin delivery system, here a glucose sensor was introduced with the insulin pump therapy and automatic suspension of insulin delivery occurs when a present sensor glucose threshold is reached to mitigate hypoglycaemia. Threshold suspend (TS) system can reduce severity of nocturnal hypoglycaemia by 30-40% and it has the ability to reduce hypoglycaemia duration; the system suspends the delivery of insulin for up to 2hours, if patient does not take action with a low glucose alarm.[39,40]

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.

Inhaled insulin

Inhaled or pulmonary routes of insulin are basically recombinant insulin in the powdered form: delivered directly to the lungs with the help of an inhaler which may be used as a substitute to the subcutaneous insulin delivery and appears to be effective, well tolerated and well accepted in patients.[41] Inhaled insulin (i.e. Exubera: launched in 2006, Afrezza: launched in 2014) was advantageous due to its immense capacity for solute exchange, thin diffusion barrier and absence of some peptides of GIT which are responsible for the destruction of oral insulin. On the other hand, inhaled insulin has the tendency to increase risk of Respiratory infections, pharyngitis etc.[42,43]

Oral insulin

In comparison to other routes, oral routes are the most preferred, suitable and patient friendly and having some advantages like as higher compliance, greater convenience, and reduced risk of cross infection and needle stick injuries.[44] There are three possible approaches in order to overcome the problems regarding the oral insulin delivery: physico-chemical properties of the insulin, for example, lipophilicity; cross-linking with macromolecules; use of carrier systems. Novel methods of Oral insulin delivery include liposome, microsphere, nanoparticle, mouth dissolving strips, sprays exploiting oral and pulmonary route.[45] These next generation efficient therapies may help to improve the quality of life

of diabetic patients especially in insulin dependent diabetes Mellitus.[46]

Colonic insulin delivery

The major obstacles for colonic insulin delivery are the absorption and degradation pathways in the upper gastrointestinal tract. However, a successfully designed colon-targeted system can overcome these obstacles and has proven quite valuable in a variety of disorders and the significance of this site-specific drug delivery system can be measured by its usefulness for delivering a variety of therapeutic agents, both for the treatment of local diseases or for systemic therapies. Oral delivery systems intended for colonic release of insulin were devised according to microflora-dependent, pH-dependent and time-dependent strategies.[47,48]

Nasal delivery

Theoretically, intranasal delivery has several advantages over oral (bypass GI peptidases), subcutaneous (non-invasive and painless) and inhalation route (no issue with lung function) which makes this route attractive for the delivery of insulin which can lead to a better patient compliance.[49] Some limitations of this route includes rapid mucociliary clearance of the drug from the site of deposition resulting in short time span available for absorption and low permeability of the nasal membrane for peptides.[50]

Ocular delivery

Insulin can also be instilled into eyes as eye drops which are non-invasive and relatively convenient which allows rapid systemic absorption because of bypassing the GIT and liver. Nasal meatus is the site where the systemic absorption of instilled drug majorly takes place, although some absorption takes place from the conjunctival sac and further research is going on regarding ocular delivery of insulin.[51,52]

Rectal delivery

In absence of absorption enhancers, bioavailability of therapeutic peptides and proteins through rectal administration is less than that achieved by intramuscular, intravenous or subcutaneous administration.[53] Thus absorption enhancers are used and sodium salicylate is proved effective in enhancing the rectal absorption of insulin in humans. Insulin suppositories could control the postprandial glycaemia in a more physiological manner than conventional insulin therapy because substantial amounts of insulin absorbed from the rectum enter directly into the portal vein.[54]

Buccal insulin

Buccal delivery of insulin involves aerosol delivery of the drug into the oral cavity, after which absorption occurs through the inner surfaces and reaches to the systemic circulation by placing the buccal formulation inside the mouth. Buccal and sublingual insulin administration provide better results due to the low levels of proteolytic enzyme activity, high vascularization of the tissue, large surface area for absorption and ease of administration.[48,50] Drug delivery via the Buccal mucosa has a number of advantages, such as Pre-systemic metabolism in the GI and liver can be avoided; relatively large surface for absorption (100-200 cm^2); level of vascularization is very high in some areas; weak variations of pH etc.[55] But also, a number of drawbacks are promoting absorption from the Buccal mucosa is a challenge, great variations of permeability among the different areas of the oral mucosa exists, sublingual area is thin and non-keratinized (highly permeable), cheek mucosa is thicker and non-keratinized (fairly permeable) and palate is thin epithelium but highly keratinized, negligible permeability.[56]

Transdermal insulin delivery

Passive transdermal delivery systems are incapable of delivering large molecule formulations (insulin) whereas active transdermal delivery systems are capable of delivering proteins and other large molecule formulations through the skin and into the bloodstream. Skin's primary role is to provide protection against infection and physical damage due to which it also prevents many pharmaceutical compounds from crossing into the bloodstream as well as absorption of useful amounts of insulin. To overcome this defence, both passive and active drug transport across the skin (transdermal) barrier are being developed. Characteristics of transdermal insulin drug delivery system are: It gives passive delivery of insulin; patch, cream, and spray forms can be used; and it requires a day to diffuse through skin and to have systemic effect.[56,57] Various approaches have been studied to increase transdermal delivery of insulin, including the use of chemical enhancers and iontophoresis, liposomes, ultrasound, thermal ablation and micro-needles. Transdermal systems designed to prevent insulin degradation and offer controlled sustained release of insulin. A challenge for transdermal insulin delivery is the inefficient passive insulin absorption through the skin due to the large molecular weight of the protein drug.[58,59]

Vaginal route

According to the literature review, attempts were made with lyso-phosphatidylcholine-containing insulin as an aqueous solution and as lyophilized powder with bio-adhesive starch microspheres administered intra-vaginally to sheep.[52] According to Golomb et al insulin has been administered through intrauterine delivery in rats and found to be absorbed in a biologically active form in the uteruses of rats. He described the absorption and the systemic biological effect of peptide drugs after instillation into the uterus of the rat. The purpose of this

investigation was to first screen for potential effectiveness several gels as insulin delivery systems and to select one promising dosage form as candidate for further evaluation in rabbits and man.[53,54] Further research is going on regarding the vaginal route of insulin delivery in future.

Intra-peritoneal insulin delivery

Intraperitoneal (IP) insulin delivery is a promising alternative to the conventional subcutaneous route and delivering insulin to the Intra-peritoneal space results in faster pharmacokinetics or pharmacodynamics, hence it could be easier for an artificial pancreas controller to quickly respond to glycaemic disturbances. The advantages of Intra-peritoneal insulin administration include a more physiologic effect of insulin in patients with diabetic nephropathy during CAPD or IPD treatment and disadvantages include a high insulin requirement in intra-peritoneal insulin administration which depends on dilution effect and in particular on insulin binding to the surface of the dialysis fluid reservoir.

DISCUSSION

The ultimate of for the treatment of DM should either be transplantation of some kind of β cells of pancreas or by correction of some genetic sequences.[62,63] Emphasis must be given to prevent or delay the disease which may be somehow related to lifestyle modifications.[64] The current insulin therapy involves multiple daily subcutaneous injections which is really a heavy burden on patients and has prompted interest in developing alternative. It has been found that, despite of theoretical superiority, insulin analogues are having more efficacies as well as cost effective in comparison to normal insulin.[65] Modern science and technology have made high-quality insulin products and designed delivery systems that have benefitted more than 15 million diabetics; researchers are also investigating several non-invasive routes for insulin delivery and the most promising approaches must be consolidated and converted to a working protocol.

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.

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