

Insulin therapies: Current and future trends at dawn

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INTRODUCTION

Insulin therapy is effective at lowering blood glucose in patients with diabetes [diabetes mellitus (DM)]. Insulin is a key player in the control of hyperglycemia for type 1 diabetes patients while it is required at later stage or in selective individuals in patients of type 2 diabetes. The discovery of insulin was considered as one of the most dramatic events in the history of the treatment of diabetes. It was isolated in 1921 with its first clinical use in 1922^[1]. The major advances achieved in this area include the synthesis of human insulin analogues by recombinant technology. Insulin delivery systems that are currently available for the administration of insulin include insulin syringes, insulin infusion pumps, jet injectors and pens. The traditional and most predictable method for the administration of insulin is by subcutaneous injections. The ultimate goal would be to eliminate the need to deliver insulin exogenously and regain the ability of patients to produce and use their own insulin.

The major drawback of current forms of insulin therapy is their invasive nature. In type 1 diabetes, good glycemic control usually requires at least three or more daily insulin injections. To decrease the suffering and improve the adherence in insulin regimens, the use of supersonic injectors, infusion pumps, sharp needles and pens has been adopted. The search for more acceptable methods for administering insulin continues. Several non-invasive approaches for insulin delivery are being pursued. The success of the route of administration is measured by its ability to elicit effective and predictable lowering of blood glucose level and minimizing the risk of diabetic complications. The newer methods explored include the artificial pancreas with closed-loop system, transdermal insulin, and buccal, oral, pulmonary, nasal, ocular and rectal routes. This review focuses on the new concepts that are being explored for use in future.

Abstract

Insulin is a key player in the control of hyperglycemia for type 1 diabetes patients and selective individuals in patients of type 2 diabetes. Insulin delivery systems that are currently available for the administration of insulin include insulin syringes, insulin infusion pumps, jet injectors and pens. The traditional and most predictable method for the administration of insulin is by subcutaneous injections. The major drawback of current forms of insulin therapy is their invasive nature. To decrease the suffering, the use of supersonic injectors, infusion pumps, sharp needles and pens has been adopted. Such invasive and intensive techniques have spurred the search for alternative, more acceptable methods for administering insulin. Several non-invasive approaches for insulin delivery are being pursued. The newer methods explored include the artificial pancreas with closed-loop system, transdermal insulin, and buccal, oral and pulmonary routes. This review focuses on the new concepts that are being explored for use in future.

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Key words: Diabetes; Insulin therapy; Insulin delivery systems; Oral insulin; Transdermal insulin; Inhaled insulin

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CURRENT METHODS IN INSULIN THERAPY

Use of syringes for insulin delivery is the most common method in use and it offers a wide choice of products that are easy to read and operate. Intravenous infusion of insulin was initially introduced in 1974^[2,3] and low dose continuous subcutaneous infusion, in 1978^[4]. Continuous subcutaneous insulin infusion (CSII), also referred to as insulin pump systems, is a way to simulate the physiology of daily insulin secretion except bypassing the liver. CSII provides a continuous supply of insulin infusion around the clock and can be individualized and can be adjusted as per the specific needs of the patient. Appropriate amounts of insulin are delivered through an infusion set. Benefits of the use of the insulin pump include avoiding change of injection sites, and providing more freedom, flexibility, and spontaneity in the person's daily life. Insulin pump therapy is very expensive as compared to the use of traditional syringes and vials. Benefits outweigh the disadvantages. Meta-analysis of CSII therapy compared to multiple daily injections in adults and adolescents with type 1 diabetes mellitus noted that CSII resulted in a greater reduction of glycated haemoglobin, in adult patients without a higher rate of hypoglycemia^[5]. No beneficial effect of CSII therapy could be detected for patients with type 2 diabetes mellitus^[5].

Insulin Pens: Insulin pens more discreet compared with vials and syringes^[6]. Insulin pens combine the insulin container and the syringe into a single modular unit. Insulin pens eliminate the inconvenience of carrying insulin vials and syringes and are more accurate and less painful. Insulin pens are user-friendly, with decreased discomfort of injection, ease of cartridge replacement, insulin-dose setting dial use and prominence of audible clicks can all affect overall dose accuracy. These are the advantages over syringes and needles^[7]. Reusable insulin pens offer a wide range of advantages such as their durability, eliminating the need for cartridge refrigeration and providing flexibility in carrying a three to five day supply. Patient satisfaction and preference is higher with pen use compared to syringes and needles^[8,9].

Resistance to initiation of insulin use by many patients and some clinicians is due to concerns about its complexity or a general resistance to injections. Effective glycemic control remains an important clinical goal. Patient barriers to accepting insulin initiation with current delivery systems include fear of hypoglycemia, fear of injections, possible weight gain, and reluctance to accommodate the inflexible timing of scheduled insulin doses. Adherence issues, including dose omission, are common and are associated with some of the same factors. In addition, the invasive nature of the syringe, pump, and pen remains an obstacle for patients.

FUTURE TRENDS

Newer injectable insulins

Newer insulins that are promising include long acting basal insulin analogue called insulin degludec and ultra fast acting insulin, human insulin Linjeta™ (formally called VIAject).

Insulin degludec

Insulin degludec, a novel ultra-long acting basal insulin, is almost identical to human insulin in structure except for the last amino acid deleted from the B-chain and addition of a glutamyl link from LysB29 to a hexadecanoic fatty acid^[10]. This insulin forms soluble multihexamers after subcutaneous injection, resulting in an ultra-long action profile with half life more than 24 h.

Insulin degludec has proven to be non inferior to insulin glargine in clinical trials carried out in both type 1 and type 2 DM. Exploratory studies in type 1 diabetes have shown insulin degludec to be safe with reduced rates of hypoglycemia and comparable glycemic control to long acting insulin analogue insulin glargine^[11]. Phase 3 clinical trials in adults with type 1 DM^[12] and type 2 DM glycemic controls was comparable to insulin glargine at one year follow up with fewer hypoglycemic episodes. As insulin degludec has an ultra-long acting profile, insulin degludec was studied using injections three times a week compared with insulin glargine once a day and found to have comparable response^[13]. The advantages of insulin degludec were reviewed in several recent publications^[14-16]. Comparative studies of efficacy and safety of insulin degludec and insulin glargine, both administered once daily with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes^[12] and type 2 diabetes^[17] noted effective glycaemic control with a lower risk of nocturnal hypoglycemia than insulin glargine. Similar studies comparing insulin degludec along with aspart insulin compared to insulin detemir with aspart insulin noted improved overall glycemic control while lowering the risk of nocturnal hypoglycemia and fewer injections^[18]. Insulin degludec is not yet approved by Food and Drug Administration.

VIAject™: VIAject is a recombinant human insulin with ultra fast onset of action. Pharmacodynamic and pharmacokinetic studies have shown the onset of action of VIAject is faster than that of human soluble insulin and insulin lispro^[19]. VIAject was reported to have less within-subject variability of plasma insulin compared to human regular insulin^[20], and has a faster absorption/onset of action than insulin lispro^[21,22]. Two pivotal phase III clinical studies in both type 1 and type 2 DM are ongoing with VIAject. As the amount of insulin circulating several hours after a meal is low, a possible reduction in hypoglycemia and prevention of weight gain are predicted.

ARTIFICIAL PANCREAS

Introduction of continuous glucose sensors^[23] has led

to development of the artificial pancreas, which made improved care possible. Even with the use of continuous glucose monitors and insulin pumps, most people with type 1 DM do not achieve glycemic goals and continue to have unacceptable rates of hypoglycemia. Closed-loop insulin delivery, also referred to as the artificial pancreas, is an emerging therapeutic approach for people with type 1 DM. In this closed-loop, blood glucose control is achieved using an algorithm, wireless communication of a continuous glucose monitor linked to insulin infusion pump that facilitates automated data transfer and delivers insulin, without the need for human intervention. The goal of closed-loop therapy is to achieve good glycemic control with the use of a control algorithm that directs insulin delivery according to glucose levels while reducing the risk of hypoglycemia.

Beta cells respond to circulating glucose levels by feedback mechanism. Insulin delivery in the closed loop system is modulated at intervals of 1 to 15 min, depending on interstitial glucose levels. The novelty of this approach resides in the real-time feedback between glucose levels and insulin delivery, similar to that of the beta-cell. The algorithms that are most relevant of the available various algorithms include the proportional-integral-derivative control and the model-predictive control. True closed-loop systems, that determine minute-to minute insulin delivery based on continuous glucose sensor data in real-time, have shown promise in small inpatient feasibility studies, using a variety of algorithmic and hormonal approaches^[24]. To have a near normal closed-loop system, several areas need to be improved. First and foremost is the rapid onset of action. Lag period of current fast-acting insulin analogs is 90-120 min. The limitations of current glucose sensors include a lag period, as they measure interstitial fluid rather than blood glucose, and errors from transient loss of sensitivity^[24]. Rapid acting insulins are being developed. Addition of recombinant human hyaluronidase (rHuPH20) accelerates insulin absorption. Current trials show promise. Both lispro and recombinant human insulin with rHuPH20 in phase 2 studies noted earlier and greater peak insulin concentrations and improved postprandial glycemic control and reduced hypoglycemia^[25]. Use of monomeric insulins that cannot form hexamers are being developed^[26]. As mentioned earlier, ultrafast insulin VIAject, a formulation of human soluble insulin improves the rate of insulin absorption. Steiner and associates have reported that VIAject has higher metabolic activity in the first 2 h after injection as noted in their study to evaluate the pharmacodynamic and pharmacokinetic properties^[19].

BUCCAL DELIVERY OF INSULIN

Transmucosal delivery is a suitable route for insulin non-injection administration. Insulin delivered by buccal delivery system is through an aerosol spray into the oral cavity and hence, differs from inhalers. The insulin is absorbed through the inside of the cheeks and in the back of the

mouth instead of the lungs. Nanoparticles are pelleted to impart three-dimensional structural conformity and coherence thereby facilitating of buccal delivery of insulin. *In vivo* studies performed on diabetic rats showed promising results with stable blood glucose profile with a significant hypoglycemic response after 7 h^[27]. Similar studies in the rabbit and rat have shown that buccal spray of insulin is an effective insulin delivery system, which is promising for clinical trial and future clinical application^[28]. Though results are promising in rat models, rats are not appropriate models as rats have a keratinized buccal mucosa. The only animal models comparable to the human buccal permeability are pigs. The continuous, but variable, saliva flow and the robust multilayered structure of the oral epithelium constitute another effective barrier to penetration of drugs. Oral-Lyn, Generex Biotechnology Corporation, Toronto, Canada is developing a buccal insulin formulation, based on RapidMist, advanced buccal drug delivery technology^[29] (www.Generex.com/technology.php). Oral-lyn is a liquid formulation of human regular insulin with a spray propellant for prandial insulin therapy. The insulin formulation is said to be stable at room temperature for more than six months. The formulation results in an aerosol with relatively large micelles (85% of that having a mean size > 10 µm) and therefore cannot go into the lungs. Each puff is claimed to deliver 10 U of insulin. Absorption rate of insulin administered as a puff is 10% and that corresponds to 1 U when one puff of 10 U is delivered. That translates to use of 10 puffs to deliver 10 U insulin for a meal; this undertaking can be considered time-consuming and not user friendly. The insulin is claimed to be released from the device as a metered dose, identical from first puff to the last^[29].

Clinical studies in healthy volunteers and subjects with type 1 DM and type 2 DM have shown that the oral insulin spray was absorbed in direct relation to the amount given and had a faster onset and a shorter duration of action when compared with regular insulin given subcutaneously. In all of the studies conducted, the oral insulin spray was generally well tolerated. Only side effects noted include mild, self-limited episodes of transient (1-2 min) mild dizziness during dosing in some healthy volunteers and subjects with type 1 DM. No changes in vital signs, laboratory values or physical examination results were said to have occurred^[30]. The product is said to be on the market in a number of countries (*e.g.*, Ecuador and India)^[29]. Without appropriately designed and performed phase II and III trials at hand, it is not possible to make any clear statement about the benefits/risk ratio of the different buccal insulin^[29]. Some companies are quite active and a small Israel-based company Oramed is in phase 2b^[29].

ORAL INSULIN

Since the initial discovery of insulin by Banting and Best in 1922, an oral form of insulin was the elusive goal. Oral insulin has benefits in terms of fostering compliance and adherence among patients, as well as physiologic advan-

tages due to the fact that oral insulin can mimic the physiological fate of insulin through the portal vein and target the liver directly and inhibit the hepatic glucose production^[31]. Insulin being a protein, difficulties encountered in oral delivery include degradation by low pH of the stomach and different digestive enzymes in the stomach and small intestine; and the major barrier for absorption is the intestinal epithelium. All these lead to low bioavailability and that leads to significant inter- and intra-subject variability.

Nano technology has brought some hope. Nano particles composed of naturally occurring biodegradable polymers have emerged as potential carriers of various therapeutic agents for controlled drug delivery through the oral route. Nanotechnology application to delivery of hydrophilic drugs such as insulin is still a challenge, and includes prodrugs (insulin-polymer conjugation), micelles, liposomes, solid lipid nano particles (NPs) and NPs of biodegradable polymers. Chitosan, a cationic polysaccharide, is one of such biodegradable polymers, which has been extensively exploited for the preparation of nano particles for oral controlled delivery of several therapeutic agents^[32-36]. The area of focus has shifted from chitosan to chitosan derivatized polymers that improve drug retention capability, and provide improved permeation, enhanced mucoadhesion and sustained release of therapeutic agents^[37,38].

The newer products that are being tried include water-soluble, long-acting insulin derivative, [(2-Sulfo)-9-fluorenylmethoxycarbonyl]3-insulin^[39], vitamin B12-dextran nano particles^[40], lipid nano particles^[41] and PEGylated calcium phosphate nano particles as oral carriers for insulin^[42]. Protection of insulin from the gastric environment has been achieved by coating the nano particles with a pH sensitive polymer that will dissolve in the mildly alkaline pH environment of the intestine. A sustained release of insulin was observed at neutral (intestinal) pH for over 8 h and it was concluded that PEGylated calcium phosphate nano particles are an excellent carrier system for insulin^[42]. So far the studies are in animals, both in normal and diabetic rats, respectively^[43]. Biocon company that is manufacturing IN-105 seems to be aggressively working on development of oral insulin, IN-105 and is in late phase 3 clinical trials^[29].

IN-105

Oral insulin IN-105 is an insulin analog. It is a second-generation of oral insulin that has an attractive stability profile at ambient conditions. It is a human recombinant insulin molecule conjugated on position B29 with polyethylene glycol *via* an acetyl chain. IN-105 is said to have improved half-life in the digestive tract and improved absorption, lower immunogenicity as compared to insulin. It said to have lower mitogenic potential as compared to insulin but retains a similar pharmacological activity as insulin, and conserves the safety profile and good clearance profile as compared to insulin. Extensive preclinical studies in different species have shown no issues in acute

dose toxicity studies. Studies to address genotoxicity, mutagenicity, reproductive toxicity and teratogenicity have shown nothing. Maximal circulating insulin levels after oral administration of 5 mg IN-105 were observed after 20 min with maximum drop in glucose at 40 min. However, the rapid decline in blood glucose might have induced a counter regulatory response that induces an increase in glycemia *per se*^[29]. Phase 1 and phase 2 trials were promising. In a dose escalating study, IN-105 absorption was shown to be proportional to the dose administered. The 2-h postprandial glucose excursion was also said to have reduced in a dose proportional manner^[44].

INHALED INSULIN

The lung provides an attractive and ideal route on account of its accessibility and its large surface area and large alveolar-capillary network for drug absorption. Insulin inhalers would work much like asthma inhalers. The products fall into two main groups: the dry powder formulations and solution, which are delivered through different patented inhaler systems. Exubera[®], containing rapid-acting insulin in powder form, has been studied extensively in patients with type 1 and type 2 diabetes mellitus^[45,46]. A patient preference study, using a comparison of utility scores, showed that a majority prefers the inhaled route and the minority prefers the injectable route^[47]. However, issues like cost, bulky device, fear for lung safety, and the small number of studies in subjects with underlying respiratory disease prevented widespread use of this new mode of delivery^[48,49]. Exubera[®], was available for a short time (August 2006 to October 2007). In October 2007, Pfizer took off Exubera off the market as the drug failed to gain market acceptance.

Afrezza

Afrezza is recombinant human insulin, using the technosphere concept and administered using MannKind's next-generation inhaler called Dreamboat. Technosphere is a drug delivery system created by micro particles (2-3 μm), which form microspheres, which are then lyophilized into a dry powder for inhalation^[50]. Technosphere insulin is an inhaled form of regular human insulin with a rapid onset of action (about 15 min) that is being considered for approval for the treatment of type 1 and type 2 DM and is currently in phase 3 clinical trials.

Most of the published evidence regarding Technosphere insulin's efficacy has been in patients with type 2 DM. The observed changes in lung function with Technosphere insulin were reported to be small and said to have occurred within the first 3 mo of therapy that remained non-progressive over 2 years^[51]. In comparison with insulin aspart, in a phase 3 randomized controlled trial, meal-time Technosphere insulin plus insulin glargine was found to be noninferior^[52]. Technosphere insulin was reported to be well tolerated by the patients in clinical trials. Rates of hypoglycemia and weight gain were similar to other insulin regimens. The most commonly reported signifi-

cant side effect was an increase in the frequency of cough reported. Since Exubera, the previously marketed inhaled insulin, mentioned a potential link to lung cancer in its product labeling, even though causation had not been established, long term studies with Technosphere insulin were requested by the Food and Drug Administration to detect potential additional harms, such as lung cancer.

Transdermal insulin

Transdermal insulin delivery is an attractive needle-free alternative and avoids the disadvantages associated with the invasive parenteral route of administration and other alternative routes such as the pulmonary and nasal routes. Permeation of compounds is limited to small, lipophilic molecules, as the stratum corneum, the outermost layer of the skin constitutes the major barrier. Several chemical and physical enhancement techniques, such as iontophoresis, ultrasound/sonophoresis, microneedles, electroporation, laser ablation and chemical enhancers, have been explored to overcome the stratum corneum barrier to increase skin permeability. The advantages of transdermal drug delivery include convenience, good patient compliance, prolonged therapy, and avoidance of both the liver's first-pass metabolism and degradation in the gastrointestinal tract. To improve transdermal delivery, microneedles have been regarded as a potential technology approach to be employed alone or with other enhancing methods such as electroporation and iontophoresis, as well as with different drug carriers (*e.g.*, lipid vesicles, micro- and nanoparticles)^[53]. As microneedles inserted into the skin of human subjects are reported to be painless, microneedles are a promising technology to deliver drugs into the skin^[54].

Methods to improve transdermal delivery

Chemical enhancers alter the lipid structure of the stratum corneum thereby reducing its barrier properties and increasing its permeability for drugs which would not pass through the skin passively. Iontophoresis is a technique that enhance the transdermal delivery of compounds through the skin *via* the application of a small electric current^[55]. Microneedle technology offers a cost-effective, minimally invasive, and controllable approach to transdermal drug delivery. It involves the creation of micron-sized channels in the skin, thereby disrupting the stratum corneum barrier. Upon creation of the microchannels, interstitial fluid fills up the channels, resulting in hydrophilic pathways^[56]. Microneedles deliver the drug into the epidermis without disruption of nerve endings^[57]. Sonophoresis (phonophoresis) uses ultrasound and it has been shown to increase skin permeability to various low and high molecular weight drugs, including insulin. However, its therapeutic value is still being evaluated^[58]. Microdermabrasion is a method to increase skin permeability for transdermal drug delivery by damaging or removing skin's outer layer, stratum corneum^[59]. Microdermabrasion can increase skin permeability to deliver insulin^[60].

Patches deliver basal insulin rather than a fast-acting

bolus, hence are not useful for meal time boluses. Preliminary data on insulin-loaded micro-emulsions for transdermal delivery showed promise on goat skin^[61]. Altea Development Corporation is planning to introduce a product which will either be a one- or half-day patch, depending on the outcome of testing.

CONCLUSION

Recent developments in insulin therapy have potential for reducing some of the negative aspects of current methods. Long-acting insulin, such as insulin degludec, may require less frequent injections. Fast-acting insulin, such as Viaject, have been shown to improve postprandial glycemic control and reduce hypoglycemia. The artificial pancreas (closed-loop systems with insulin pumps that deliver insulin in response to sensors) may prove to be a valuable therapy for type 1 diabetes patients, particularly if the lag period can be shortened through improved glucose sensors and the use of ultra-fast acting insulin. Of the alternative methods of administration, the oral route is the most promising, especially with nanotechnology allowing for several types of encapsulations to bypass the gastric acidic environment. Oral delivery offers the benefits of ease of administration (leading to greater acceptance by patients), improved absorption rates, and mimicry of the normal route of insulin through the liver.

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