

30 Upcoming and New Insulin Delivery Systems

Abstract: Alternate forms of insulin delivery are being developed to overcome problems with current subcutaneous insulin injection therapy like poor compliance due to pain, variable absorption and lack of feedback control.

Nasally administered insulin is more rapidly absorbed than subcutaneous insulin. However, it has low bioavailability and causes nasal irritation.

Intrapulmonary inhaled insulin shows promise, is absorbed quickly and peaks at 30 minutes and is therefore for prandial use only. Bioavailability is 10-20%. Current inhalers are cumbersome and need repeated spirometry. The Technosphere inhaler, undergoing trials, is small and simple to operate and may be more acceptable.

Encapsulated Oral Insulin or insulin incorporated into liposomes, polymers or emulsions have been partially successful. Paracellular insulin absorption by increasing tight junction permeability is successful and is in Phase 2 trials.

Transdermal insulin, using iontophoresis and, recently, sonophoresis, with use of specialized particles shows improved absorption.

Continuous subcutaneous insulin infusion (CSII) via a portable pump has become a routine therapy for selected Type 1 diabetic patients. Frequency of hypoglycemia is much less during CSII than multiple injection therapy (MIT), though mean blood glucose and HbA1C are only slightly better with CSII.

Totally implanted pumps deliver intraperitoneal or intravenous insulin. Fluctuations in blood glucose are less. They are limited by invasiveness, delivery problems and infection.

Closed loop insulin delivery employs continuous *in vivo* glucose sensing and automatic adjustment of insulin dose delivered (feedback control). Its safety in clinical practice will depend on the development of a really accurate and reliable glucose sensor. Small sized nanopump has been developed with closed loop insulin delivery system mounted on a disposable insulin skin patch and is undergoing trials.

Gene therapy with transfected gut or liver cells are also showing some promise.

Stem cell therapy in Type 1 diabetics has shown encouraging results.

INTRODUCTION

There are more than 100 million diabetics in the world of which about 35 million are in our country. Out of this 5-8% are Type 1 diabetics. All Type 1 diabetics need to be on insulin, while all Type 2 diabetics will ultimately need insulin at some stage in their lives. The problem diabetics face is injecting insulin many times a day for the rest of their lives and carrying the drug with its needles, swabs, etc. at all times if they travel. Poor compliance due to pain and hassle of injections, variable absorption of subcutaneous insulin and lack of feedback control, hypoglycemia and hyperglycemia due to unphysiological insulin delivery, poor diabetes control and weight gain are some of the other problems with the current subcutaneous insulin therapy.

It is, therefore, an endeavour of researchers to find a painless and simple way of delivering insulin, which would control diabetes to target and also prevent the long-term morbidity and mortality. The following routes of insulin delivery have been tried:

1. Oral insulins (including buccal and enteric insulin)
2. Intranasal insulin
3. Inhaled insulin
4. Transdermal insulin
5. Insulin pens
6. Intravenous insulin
7. Rectal insulin
8. Insulin pumps
9. Implanted insulin producing cells (gene therapy)
10. Beta cell transplant/pancreatic transplant
11. Periocular insulin
12. Stem cell therapy.

ORAL INSULIN

Oral Insulin Spray

Buccal mucosa forms a good surface for rapid absorption of insulin. It is easily accessible, highly vascularized and has a large surface area 100-200 cm². The convenience being easy to spray before each meal, painless and the action lasts 2 hours, therefore no fear of hypoglycemia. Added to a basal 24 hour insulin it appears to be the ideal way to control diabetes. The disadvantage is that the patient still needs a basal insulin injection.

Cavallo, et al¹ had found the plasma insulin levels comparable between the oral aerosol spray and subcutaneously injected insulin. Oral insulin is commercially available by the name of Oralyn in Ecuador, where most of the trials, have taken place. Cernea, et al (2005)² reported a good dose response relationship in the absorption and metabolic profile of Oralyn, the oral spray had a faster and shorter duration of action than subcutaneous regular insulin. Guevara-Aguirre, et al (2007)³ presented a study comprising 25 Type 1 diabetics, comparing subcutaneous preprandial insulin with split prandial doses of oral spray over 9 days and found near normalization of DM metabolic control in all cases and better levels of HbA1C in the oral insulin group. Oralyn may soon be available in India, as the government has given it a regulatory approval.

Oral-Enteric Insulin

Advantages: Rapid absorption, direct delivery to liver, which restores glycogen status, results in lower systemic insulinemia, controls hepatic glucose output and enhances compliance.

Disadvantages: Effect of food types, gastrointestinal dysmotility, taste/smell of the preparation.

Biologically, active insulin taken directly by mouth is denatured in the intestine and degraded by proteolytic enzymes. Only 1% of insulin swallowed is absorbed. Earlier attempts were made with basic and acidic dyes to inhibit proteolysis, combined with insulin surfactants in tablet form and were partially successful in reducing blood glucose. However, they were discontinued because of skin coloring by the dye.⁴ Liposomally entrapped insulin also lowers blood glucose but the effect is not predictable or dose dependent.⁵

Insulin incorporated into biodegradable polymeric particles, which are absorbed via portal circulation and taken up by Kupffer cells in the liver, from where there is slow dissolution and release of insulin.⁶

Absorption enhancers have also been evaluated including surfactants like cetomacrogol,⁷ 5-methoxysalicylate,⁸ sodium cholate and deoxycholate bile salts⁹ and emulsions.¹⁰ A protein from the bacteria, *Vibrio cholerae* called zonula occludens toxin (ZOT), induces a reversible, dose dependent opening of the tight junction confined to the small intestine. ZOT induces a tenfold increase in insulin absorption from the rabbit jejunum and ileum, with no effect on the colon. The bioavailability of 10 U oral regular insulin with ZOT, was similar to that of about 2 U of subcutaneous insulin in diabetic BB rats.¹¹ Yu-Hsin Lin, et al (2007)¹² reported sustained effect of oral insulin in the form of novel nanoparticles coated with Chitosan, lasting up to over 10 hours in diabetic rats.

Hexyl insulin monoconjugate 2 (HIM2) an oral insulin, has been tried with some success in trial on Type 2 patients.¹³ Modified human insulin I-105 produced by Biocon India, by adding a polymer to the B chain of insulin has been shown to resist degradation in the intestine and be absorbed significantly, and was also shown to be superior in bio-effectiveness to HIM2 which was a first generation oral insulin not commercialized. A trial of I-105 on Type 2 diabetics was presented at the EASD 2007, with promising results.

Oradel™ is another insulin encapsulated in tablet form, under Phase 1 and 2 trials.¹⁴ Oral insulin is also being studied for the prevention of Type 1 diabetes.

INTRANASAL INSULIN

First investigated in the 1920s and 1930s, it has recently been shown that with absorption enhancers, intranasal insulin is more rapidly absorbed than subcutaneous insulin. Nasal mucosa provides about 150 cm² area for absorption.

However, there is low bioavailability (10-20%), nasal irritation (25% of subjects), and unpredictable responses. There is a potential to damage of nasal-ciliary function in long-term exposure. Increased absorption has been achieved by bile salts, proteolysis inhibition, increased monomer formation and Ca⁺⁺ ion binding which loosen the tight junction between the cells. Other enhancers are ethers and esters that disrupt membranes, other enhancers are phospholipids, that increase absorption. Incorporating insulin in gelling microspheres increases contact time with the nasal mucosa. Gelified preparations were found to be more effective than liquid aerosolized preparations. Repeated administration of nasal insulin is often required for bioeffectiveness.¹⁵

Nasal insulin is effective in the short-term in controlling postprandial hyperglycemia in Type 2 diabetics.¹⁶ Type 1 diabetics need an injectable basal insulin in CSII or as long acting basal insulin along with nasal administration, and clinical trials have not shown any improvement in control compared to entirely injection-based regimens.¹⁷ Nasal insulin has recently been tried with some success in patients of Alzheimer's disease in improving memory. Nasal insulin is also being tried as a vaccine for the prevention of Type 1 DM in early phase, with encouraging results.

INHALED INSULIN

Under investigation since the 1920s, inhaled insulin has recently emerged as a promising needle-less method of insulin delivery.¹⁸ The alveoli, with a huge surface area of >100 m² (70 times the surface area of the body), and a rich blood supply, form a large absorptive surface. Inhalation can

be aerosolized as dry powder^{19,20} or a solution.²¹ The peak action and plasma insulin concentration of inhaled insulin is about 30 minutes, comparable to that after injection of lispro or aspart and earlier than that after regular short-acting insulin²⁰ (Fig. 1). Therefore, it is best given at mealtimes. Long-acting inhaled insulin formulations have not yet been successful.²² Bioavailability is low at 10-20% and can be increased by adding absorptive enhancers to the insulin.²³ The inhalation flow rate, particle size (1-3 μm), and position of the insulin bolus in inhalation determine the absorption. Asthma decreases its absorption,²¹ and smoking increases the bioavailability²² of inhaled insulin, both conditions being contraindications to inhaled insulin therapy at present.

Clinical trials have been reported both on Type 1 and Type 2 diabetics. In a 12 weeks trial¹⁹ in 73 Type 1 diabetics, in which pre-prandial inhaled insulin and ultra-lente at bedtime were compared with the usual subcutaneous insulin injections given two to three times a day, glycaemic control was similar with the two regimens. Smokers and patients with respiratory diseases or impaired lung function were excluded. The inhaled insulin was well tolerated and had no effect on respiratory function.

In Type 2 diabetics who were switched from injection therapy to inhaled insulin, there was only a slight reduction in HbA1c, and moderate hypoglycemia occurred at a rate that was greater than that often seen with insulin-treated Type 2 diabetics.^{22,25} Effect on blood glucose was better in younger patients compared to that in elderly subjects.²³ In some patients, where a slight fall in FEV1 was noted, complete reversibility of the abnormalities were seen on stopping the inhaled insulin and switching back to injected insulin.²⁴ In one study a fall in diffusing capacity (Dlco) was seen in the inhaled insulin group.²⁶ Follow-up up to 2 years in both Type 1 and Type 2 patients the glycaemic control and lung function have remained stable.²⁸ Inhaled insulin regimens have demonstrated improved patient satisfaction and quality of life in trial questionnaires.²⁷

Inhaled insulin (Nektar/Exubera) (Fig. 2) was approved by the FDA and was commercially available. The device uses compressed air to disperse an insulin powder into a 'spacer' reservoir prior to inhalation. However, it has recently been withdrawn by Pfizer due to poor sales. Large size of the inhaler, cumbersome inhalation technique, and additional cost of pulmonary function tests required, as well as the high costs of the inhaled insulin therapy, have been cited as the reasons for the poor sales.

An aqueous mist inhaler in which single-use insulin strips are combined with a hand-held, breath-activated, microprocessor-controlled device (AERx Insulin Diabetes Management System, Novo Nordisk) (Fig. 3) is currently under phase 2 trials. Fifty percent of extruded dose deposits in the lungs uniformly, the absorption is rapid and maximum plasma insulin concentration is reached in 7-20 mins compared to 100-120 mins of subcutaneously administered insulin, and thereby similar to rapid acting insulin analogues. In a 3-month trial on non-smoking Type 2 diabetics, the effectiveness of AERx was similar to subcutaneous insulin, overall HbA1C was similar, though the fasting blood glucose was lower in the inhaled insulin group. Bioeffectiveness of AERx was 16% compared to subcutaneous insulin.²³ No changes in lung function were observed.

Advanced Inhalation Research (AIR), (Eli Lilly) have developed biodegradable polymer matrix containing insulin, which can be used with short as well as sustained release insulin formulations. Human trials are underway.²⁹

Technosphere™ insulin is another drug delivery system that captures insulin and self assembles it into an ordered lattice array at low pH and dissolves at neutral pH of the alveolar surface thereby rapidly releasing the insulin. It is used in capsule-based high-impedance inhalers (Fig. 4). It shows more bioavailability than subcutaneous insulin (26% vs 16%), more biopotency (19% vs 14%), peak effect was 47-56 min, and intra-subject variation was comparable to subcutaneous insulin.³⁰ This formulation appears to hold promise. Recent trials in patients with Type 1 and Type 2 diabetes,

comparing Technosphere™ inhaled insulin with subcutaneous Aspart insulin, showed similar improvement in glycemic control. The inhaled insulin group had no weight gain compared to the Aspart group who had weight gain during the study.³¹

Inhaled insulin has clear potential, but the long-term effects on lung function and the impact of intercurrent lung disease on pulmonary absorption have yet to be reported, therefore it has not been approved for pediatric use. Trials also need to be done in cities where air pollution is a major problem.

TRANSDERMAL INSULIN

The stratum corneum of the skin makes it impermeable to insulin. Acceleration of insulin transport across the skin can be done with iontophoresis with some experimental success.³¹ Low-frequency ultrasound (sonophoresis) and photomechanical waves applied to the skin are also able to promote transdermal insulin delivery.^{32,33} U-Strip™ (Fig. 5) has been patented which has a dermal patch containing up to 100 unit of insulin and can be changed once daily, with an ultrasonic device that increases pore size and delivers insulin without needles. It is still under development and not yet approved by the FDA.

Insulin Jet Injectors

Deliver insulin through the pores of the skin by high air pressure, without needles. Advantages are of being needle free and less incidence of fat atrophy at injection sites. Disadvantages are of higher cost, issues of absorption of insulin, maintenance and cleaning of the injector, bruising of the skin if the subcutaneous fat is less (as in elderly), and the jets being at times even more painful than the needle prick (Figs 6A to D).

INTRAVENOUS INSULIN

Intravenous insulin infusion into a peripheral vein with its 100% bioavailability and immediate access to the circulation is a well-established treatment for DKA, in the ICU for other conditions, in surgery in diabetics and in pregnant patients at the time of delivery. Long-term intravenous insulin infusion through an indwelling catheter has been used in the management of brittle diabetics,³⁴ but several serious complications were noted, including insertion site infection, septicemia, and catheter blockage with extensive thrombosis. Earlier, implantable insulin pumps also used the central venous delivery route, with serious complications,^{35,36} therefore, intraperitoneal route has replaced intravenous route in these pumps.³⁷

RECTAL INSULIN

This mode of insulin delivery has been tried in some experiments and found to show poor and erratic absorption, with short-lived effects. There is a potential of mucosal damage in long-term use of rectal route. Future options may be gels or emulsions.³⁸ So far it has no clinical application.

INSULIN PENS

Subcutaneous insulin injections have become much easier and simplified with the use of prefilled pen delivery system. These pens need not be refrigerated and can be easily carried by the patient. There are disposable pens made of plastic and have prefilled syringes inside. The dose required can be dialled and the pen delivers the exact amount dialled when the plunger is pressed. Human insulin (rDNA), Aspart insulin, Lispro, Glargine, Glulisine, Exanetide, Pramlintide are all given in prefilled pens (Figs 7 and 8). A new Humapen Memoir (Fig. 9) has digital memory to help keep track of doses. The disadvantage of a pen is that the short and long acting preparations cannot be mixed as in a syringe.

INSULIN PUMPS

- a. CSII
- b. Implantable insulin pumps
- c. Closed insulin delivery system with CGMS insulin delivery (artificial endocrine pancreas)
- d. Nano pump with closed insulin delivery system and continuous glucose sensing.

Continuous subcutaneous insulin infusion (CSII) was first developed in the 1970s as a research tool for investigating the long-term effect of near normoglycemia on the development of microvascular complications.³⁹ The current CSII uses a battery driven pump to infuse insulin via a fine canula terminating in a subcutaneously implanted needle or flexible catheter (Fig. 10).

The excellent control of glycemia on pump therapy has been confirmed by many studies,⁴⁰ improved lipids, ketones, amino acids and quality of life with patient satisfaction accompany this.⁴¹ Large clinical trials across the world (UK, USA, Norway, Denmark)⁴² have shown marked reduction in long-term morbidity and mortality associated with diabetes, and any new therapy is compared to glycemic control by the CSII.

The pump is programmed to deliver a basal rate and a bolus at mealtimes. Multiple programs are available which can be adjusted, pre-programmed for day, night and boluses, and the patient self monitors his/her blood glucose. Extensive education with regard to adjustments of doses, exercise, meals and self-monitoring is required. Children with adult supervision, pregnant women, brittle diabetics, selected Type 2 diabetics, have used the CSII effectively. Hypoglycemia, infusion site infections, DKA are the potential complications of CSII. The cost is much more than conventional therapy and multiple injection therapy.

Specific Indications for CSII

Type 1 diabetics, who fail to achieve good control with multiple injection therapy including reeducation, dietary advice, exercise, etc. because of frequent hypoglycemia and a marked dawn phenomenon.

Pre-requisites for CSII

Patient should be willing, motivated, able to perform the procedures involved in CSII, able to perform frequent blood glucose self-monitoring. Patient should have no significant psychological problems and should be under the supervision of a health-care team experienced in CSII. Funding should also be possible.

IMPLANTABLE INSULIN PUMPS

These insulin pumps are totally implanted in the body and infuse the insulin intraperitoneally or intravenously. An external electronic communicator controls the operation, and a side port allows direct access to the delivery cannula for clearing occlusions. The cost is much more, so is the invasiveness and the attendant complications of underdelivery, catheter blockage, skin erosion, hematoma, local infection, pump migration, electrical and mechanical pump failures.

The advantages of this pump, specially, intraperitoneal delivery being, it is more physiological and directed to the portal circulation, also the user cannot tamper it with. There is total freedom from needles or cannula and the pump is not visible. Trials in Type 1 diabetics have shown significant reduction in glycated hemoglobin as well as reduction in episodes of severe hypoglycemia in implantable pumps when compared with CSII.⁴³ There were fewer fluctuations in the glucose levels.

Closed-loop Insulin Delivery

Feedback controlled insulin delivery, in which the rate of insulin dosage is altered automatically according to the prevailing blood glucose concentration. Over the years devices have been made which use intravenous insulin as per preset algorithms and these were large bedside apparatuses like the Biostator and were used for short-term studies. Currently an implantable insulin pump with closed loop control via an indwelling glucose sensor placed in a central vein is under trial.⁴⁴

Nanopump

Recently developed by the Swiss company Debiotech has reduced the size of the pump, which has a closed loop insulin delivery. The microchip glucose sensor is of the size of a penny. The pump has an alarm system that triggers with the slightest underdelivery or overdose. There are small disposable skin patches with microneedles, which are virtually painless. The insulin is delivered by the microfluidic MEMS (micro-electro-mechanical system) technology, from a small pump about a quarter of the size of the existing pumps (Fig. 11). The pump is mounted on the skin patch and being about an inch in size, is hardly visible outside the patient's clothes.⁴⁵

PERIOULAR INSULIN

Low dose insulin-loaded hydro gel, injected subconjunctivally has been shown to ameliorate degenerative and inflammatory responses in diabetic rats and may have a future in prevention and treatment of diabetic retinopathy.⁴⁶

GENE THERAPY

Transfection of the pancreas by retrograde ductal injection of a plasmid containing the human insulin coding sequence **Gut Gene Therapy** is under investigation^{47,48} so is transfection of human fibroblasts which can then release insulin at slow or rapid rates, controlled by ligands (Fig. 14).

Gene therapy can be used to **manufacture insulin directly**: an oral medication, consisting of viral vectors containing the insulin sequence, is digested and delivers its genes to the upper intestines. Those intestinal cells will then behave like any viral infected cell, and will reproduce the insulin protein. The virus can be controlled to infect only the cells, which respond to the presence of glucose, such that insulin is produced only in the presence of high glucose levels. Due to the limited numbers of vectors delivered, very few intestinal cells would actually be impacted and would die off naturally in a few days. Therefore, by varying the amount of oral medication used, the amount of insulin created by gene therapy can be increased or decreased as needed. As the insulin producing intestinal cells die off, they are boosted by additional oral medications.

Gene therapy might eventually be used to cure the cause of beta cell destruction, thereby curing the new diabetes patient before the beta cell destruction is complete and irreversible.

Gene therapy can be used to transform duodenum cells and duodenum adult stem cells into beta cells, which produce insulin and amylin naturally. By delivering beta cell DNA to the intestine cells in the duodenum, a few intestine cells will turn into beta cells, and subsequently adult stem cells will develop into beta cells. This makes the supply of beta cells in the duodenum self-replenishing, and the beta cells will produce insulin in proportional response to carbohydrate rates consumed.

BETA-CELL TRANSPLANTATION/ PANCREATIC TRANSPLANTATION

This is the ideal method of insulin delivery where there is biofeedback, basal and prandial insulin throughout the day and life of the patients (Fig. 12). The attendant immunosuppression needed for the transplant to survive is a major problem.⁴⁹ Pancreatico-renal transplant has fewer

complications than the pure pancreatic transplant. Encapsulated beta-cells with protective nonantigenic covering are being investigated (Fig. 13).

STEM CELL THERAPY

Embryonic or bone marrow derived stem cells are a hot topic for research. Voltarelli, et al (2007), transplanted 15 Type 1 diabetics with autologous stem cells and 14 were able to stop their insulin for 7 to 35 month.⁵⁰ The stem cells from the bone marrow are more likely to differentiate into insulin producing cells and also become glucose responsive (Fig. 14). This method holds great promise for the future.

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MULTIPLE CHOICE QUESTIONS

1. Which of the following statements are correct?
 - A. Oral insulin spray has a 24 hour action similar to basal insulin
 - B. Oral insulin spray has high bioavailability
 - C. Oral insulin spray is a prandial insulin
 - D. Oral insulin spray can also be used for intrapulmonary inhalation
 2. Indicate whether the following statements are true or false
 - A. Inhaled insulin works better in asthmatics and should be used in diabetics with asthma
 - B. Inhaled insulin improves lung function due to the anabolic effect of insulin
 - C. Inhaled insulin can be in powder or in liquid form
 - D. Inhaled insulin is the drug of choice at present for type 1 diabetes
 - E. The time action profile of inhaled insulin is like that of Aspart or Lispro insulin
 - F. Technosphere™ inhaler is cumbersome and large
 3. Which of the following statements are true?
 - A. Intranasal insulin improves memory in Alzheimer's disease
 - B. Intranasal insulin may prevent progress of diabetes in early onset Type1 diabetes
 - C. Intranasal insulin is very well tolerated
 - D. Intranasal insulin has excellent bioavailability and predictable response
 - E. Intranasal insulin acts through the hypothalamopituitary pathway
 4. Indicate which of the statements are true
 - A. Regular insulin taken orally along with subcutaneous can cause hypoglycemia due to additive effect
 - B. Oral-enteric insulin is delivered to the liver and helps restore glycogen status
 - C. Oral-enteric insulin can reduce hepatic glucose output
 - D. Vibrio cholerae derived toxin helps enhance absorption of insulin from the small intestine
 5. Which of the following are true?
 - A. Transdermal insulin is another name for subcutaneous insulin injections
 - B. Ultrasonic device that increases absorption of transdermal insulin is under investigation for insulin therapy
 - C. Insulin jet injectors can be more painful than insulin needle pricks
 - D. Intravenous insulin is preferred over intraperitoneal in implantable insulin pumps
 - E. CSII is the best form of treatment for brittle Type 1 diabetes
 6. Indicate whether the following statements are true or false
 - A. Closed-loop insulin delivery is another name for totally implantable pumps
 - B. Closed loop insulin delivery has a feedback controlled insulin delivery depending on blood glucose level
 - C. Nanopump has a closed loop insulin delivery system
 - D. Pancreatic transplant is taken from a live donor
 - E. Beta cell transplant is taken from a live donor
 - F. Stem cells are taken from cadavers
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1. C 2. (A) False, (B) False, (C) True, (D) False, (E) True (F) False 3. A, B 4. B, C, D 5. B, C, CSII 6. (A) False, (B) True, (C) True, (D) False, (E) True, (F) False