Review

ALTERNATE ROUTES OF INSULIN DELIVERY

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ABSTRACT

Insulin therapy is likely to change within the next decade. Inhaled insulin is likely to be marketed within a year. Buccal insulin also shows promise. Oral insulin therapy is in a nascent phase but holds promise. Nasal and dermal insulin formulations are also being experimented with.

KEY WORDS: Aerosol/Pulmonary insulin; Oral insulin; Nasal insulin; Buccal insulin; Insulin patches.

For the past 75 years subcutaneous injections have been the only route of delivery of insulin therapy for diabetic patients. While the purity of insulin has increased and the needle size for injections has decreased, thus reducing the discomfort associated with subcutaneous (SC) insulin injections, the acceptance of insulin is still very poor, just because it has to be given by injection. Hence, there has been a search for alternate route of insulin delivery. Possible alternate routes of insulin delivery which have been explored are the pulmonary, nasal, buccal and dermal.

PULMONARY INSULIN

To date, the most promising alternative route of insulin administration, is the pulmonary delivery of insulin by inhalation, which is likely to lead to a practically usable system within the next few years. For maximal rate of absorption, insulin must be applied deep into the lung, i.e., into the alveoli. Once in the lungs, insulin is quickly and efficiently absorbed from the air sacs (alveoli) into the bloodstream. A considerable number of inhalers (in combination with appropriate insulin formulations), which generate insulin particles with an appropriate size for pulmonary delivery, are currently in the clinical phase of development [1]. The pharmaco-dynamic effects of insulin formulations administered via the lung are comparable to, or even faster than, those of subcutaneous injected regular insulin or rapid-acting insulin analogues. The relative biopotency of inhaled insulin in most cases is approximately 10%, i.e., the dose of insulin administered must be 10-fold higher than with subcutaneous injection. The published results of clinical trials thus far, indicate that metabolic control is comparable to that of conventional insulin therapy. As of date, no serious side effects have been reported from these human trials. In summary, it appears that after several decades of research, for the first time, a feasible alternative route for insulin administration is within reach. [2,3]

Inhalation of regular insulin for meal time glucose control has been found to be safe, efficacious and reliable in both type 1 and type 2 diabetics. The administration of regular insulin through the human lungs by inhalation has been conducted in at least 14 short studies in both normal and diabetic subjects beginning as early as 1925. In all studies, significant insulin absorption and lowering of blood glucose was observed in the absence of penetration enhancers. Although a concern of variable dosing was raised in early studies, the development of new reproducible delivery systems has ensured that the variability of aerosol insulin can be as good, if not better, than subcutaneous (SC) injection. In the longest controlled studies in humans to date, both type 1 and type 2 diabetics used a novel inhaled dry powder insulin delivery system for 3 months for meal time glucose control. The study results indicate that inhaled insulin provides equivalent glucose control, measured by HBA_{1C}, when directly compared to SC injection. Interim results from an additional study with type 2 diabetics who were not controlled by oral hypoglycemic agents, suggest that adjunctive therapy with inhaled insulin markedly improved glycemic control with a low risk of hypoglycemia. In all the 3 month studies, the system was efficacious, well tolerated, well liked, and resulted in reproducible results. A potential advantage of aerosol insulin is that it is more rapidly absorbed (serum peak at 5-60 min) and cleared than SC injection (peak at 60-150 min), which provides a more relevant and convenient therapy for meal time glucose control. [2]

Early clinical trials showed that taking inhaled insulin before meals was as safe and effective as injections, with greater patient satisfaction. However, inhalers are more costly than injections because only 20% to 50% of the insulin from the device is delivered to the lungs. A number of potential problems must still be assessed before inhalers can go to the market, including the risk of lung irritation and whether

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the device can be used when patients have a cold or respiratory infection. Researchers must also perfect the dose measurement techniques so that patients will get accurate and consistent doses each time. Inhalers presently use only rapid-acting insulin to be taken before meals; longer acting insulin formulations are under development.

One problem with inhaled insulin is higher frequency of development of antibodies against insulin. In a phase 3 study presented at the ADA meeting of 2001 that compared inhaled insulin with SC insulin, insulin antibodies quadrupled at 24 weeks in the inhaled-insulin group, whereas the SC insulin-treated group exhibited only a 5% increase. Another problem is that the bioavailability of inhaled insulin is low (10% to 20%), because a large portion of the insulin is taken up by the reticuloendothelial system. Further, approximately 25% to 50% of the insulin remains in the device or goes out directly or indirectly, after being brought out of the lungs by the bronchial cilia transport mechanism, into the oropharynx and is swallowed.

Inhaled insulin products currently in development include [4].

1. AERx® Insulin Diabetes Management System, an aerosol liquid human insulin being developed by Novo Nordisk and Aradigm Corporation.
2. AIR® pulmonary drug delivery technology, being developed by Eli Lilly and Alkermes.
3. Exubera® dry powder insulin, being developed by Aventis Inc and Pfizer Pharma in cooperation with Inhale Therapeutics Systems Inc.
4. Technosphere® dry powder micro-particles delivered by a cartridge system, being developed by Aerogen, Disetronic and Pharmaceutical Discovery.

All the approaches deliver insulin to the lungs, leading to rapid absorption of insulin similar to that seen with insulin lispro but with somewhat longer duration of action. The bioefficacy of inhaled insulin is approximately 10% with the Exubera and AERx systems. Technosphere insulin particles appear to be the most rapidly absorbed, with 30% to 45% bioactivity. The intra-subject coefficient of variation is approximately 15%, which is similar to that seen with SC insulin.

With all systems, cigarette smoking leads to more rapid and greater degrees of absorption. There is little change in bioavailability with respiratory infection though some patients cannot tolerate inhaled insulin during a respiratory infection. There is some decrease in absorption with asthma [1].

The most-studied inhaled insulin is Exubera®, which has been the subject of phase 3 clinical trials carried out thus far in 1256 persons with type 1 and type 2 diabetes. These studies have shown no loss of glycemic control and somewhat variable changes in hypoglycemia frequency, suggesting that insulin can be delivered through the lungs in a fashion similar to that of rapid-acting SC insulin in both type 1 and type 2 diabetes[5].

Additional devices, for delivering insulin to the lungs are being studied. Researchers at Profil Institute for Metabolic Research, Neuss, Germany, are trying to develop another inhaler device, Aerodose® (AeroGen, Inc, Sunnyvale, California), while Eli Lilly & Company are working on an inhaler device, Spiros® (Dura Pharmaceuticals, Inc. and Spiros Development Corporation II) based on dry powder technology.

Long-term safety of inhaled insulin still needs to be established. Cough has been shown in a number of studies to be a side effect of inhaled insulin treatment. There is also concern about increase in pulmonary fibrosis with pulmonary insulin[3]. The cost of inhaled insulin and the delivery device still continues to be very high. Further, as the inhaled insulin has a short duration of action, all subjects need a bed time dose of injectable long or intermediate acting insulin for proper control of diabetes.

NASAL INSULIN

Nasal insulin application was considered for a number of years as a potential method, because of the rapid absorption of insulin across nasal mucosa. However, relative bioavailability was low and required use of absorption enhancers and more importantly, the metabolic effect lasted too short to be of clinical usefulness. Use of nasally-administered insulin has been tested for up to three months, but so far results have been discouraging because only 10% to 20% of the dose is absorbed. Other probiems associated with nasal insulin include irritation of the nasal passages and upper respiratory infections. While this method may one day be possible, it is not the most promising technique under investigation.

ORAL INSULIN

Insulin is degraded very quickly by the stomach's

acidic environment and proteolytic enzymes. The dream of an "insulin tablet" has also not become a reality, the main problem being digestion and a lack of a specific peptide carrier system in the gut. Researchers are currently examining whether insulin absorbed into a microsphere can bypass these enzymes and pass through the wall of the intestine. But this research is still in its early phases. Provalis is trying to develop an insulin based oral pill (Macrulin®). The technology uses a water-in-oil microemulsion in which aqueous phase contains insulin and the oil phase contains cholesterol, lecithin and non-esterified fatty acids. Nobex oral insulin is based on a technology of covalent attachment of low molecular weight polymers to insulin creating drug polymer conjugate. This is now in phase II trial in USA. Chemical engineers at Purdue University, USA recently claimed that they have developed a polymer, to shepherd insulin past the stomach. The polymer in acid collapses into a tight ball that traps the insulin. In about 30 minutes, the pill reaches the non-acidic intestine, where the polymer expands to release the insulin. The pill has worked in rats and dogs, but so far it has been hard to predict how much insulin will be absorbed and how fast. Also, at least 85 percent gets wasted.

BUCCAL INSULIN

Several trials are testing an insulin preparation that is placed under the tongue or in between the cheek and gum, and is slowly absorbed. Generex and Eli Lilly are trying to develop an insulin spray (Oralin®) which can be delivered via the company's Rapid Mist device. The technology consists of the target molecule, excipient and non-CFC-propellant to produce a stable solution that may be rapidly absorbed from the buccal mucosa. In a single-blind, randomized, crossover study, 11 patients with type 2 diabetes received Oralin, 15 puffs from the Rapid Mist device, or subcutaneous insulin injection, 0.11 U/kg, followed in 10 minutes by a 360 calorie meal. Oralin® outperformed subcutaneous insulin in rapidity of absorption and elimination, in glucose and C-peptide lowering capacity, and rise in serum insulin levels. A second study by the same group compared the efficacy of Oralin® in combination with oral hypoglycemic agents vs. oral hypoglycemic agents alone in a single-blind, randomized, crossover design with 13 subjects. It was concluded that Oralin can be used safely in combination with oral hypoglycemic agents to control post-prandial glucose levels. Taking it a step further, they also evaluated 22 patients with type 2 diabetes and found that Oralin® spray at meals produced insulin peaks significantly greater than endogenous insulin production in patients receiving oral hypoglycemics and less post-prandial glucose elevation compared with oral agents alone (9% vs. 27%) [6].

INSULIN PATCHES

Dermal insulin application does not result in a reproducible and sufficient transfer of insulin across the highly efficient skin barrier. Attempts have been made to develop dermal patches to be placed on the skin to provide a continuous, low level of insulin, supplemented by pre-meal doses that are released by pulling a tab. However, insulin is poorly absorbed through the skin, and to date, this method has proved inefficient. [7]

REFERENCES

1. Smaldone GC. Concepts of aerosol therapy for the modern clinician. Symposium: Alternate routes of insulin administration. 62nd Scientific Sessions, of the American Diabetes Association. September 14-18, 2002; San Francisco, California. Diabetes 2002; 51, Suppl 2.
2. Heinemann L, Prutzner A, Heise T., Curr Pharm Des. 2001, 7, 1327-51.
3. Skyler J. Pulmonary inhaled insulin: an overview and prediction for the future. Symposium: Alternate routes of insulin administration. 62nd Scientific Sessions of the American Diabetes Association. September 14-18, 2002; San Francisco, California. Diabetes 2002; 51, Suppl 2.
4. Patton JS, Bukar J Nagaragan S. Adv Drug Deliv Rev. 1999, 32, 235-47.
5. Poster 535-P. Annual Meeting of ADA, June 2002, San Fransico. Diabetes 2002 51, Suppl 2.
6. Modi P, Yutzy P, Klein K, Levin P. Oral insulin increases post-prandial insulin peaks and improves glucose control in type 2 diabetic patients. 62nd Scientific Sessions of the Ameriean Diabetes Association. September 14-18, 2002; San Francisco, California. Poster 440-P. Diabetes, 2002; 51, Suppl 2.
7. Smith AM, Woods TJ, Williams DJ, et al. Transdermal basal insulin delivery through microspheres. 62nd Scientific Sessions of the American Diabetes Association. September 14-18, 2002; San Francisco, California. Abstract 191-OR. Diabetes, 2002; 51, Suppl 2.