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Practitioners section

Newer insulin analogues and inhaled insulin

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Abstract

Diabetes is a metabolic disease with high prevalence worldwide. Exogenous insulin is used in the management of this condition. The development of human insulin has provided tighter control of glycaemia in diabetic patients. Insulin analogues like insulin lispro and aspart were developed to closely match its profile with physiological secretion. The newer additions to this armamentarium are insulin glulisine, insulin detemir and albulin. Insulin glulisine is a short acting analogue with a rapid onset of action. The antiapoptotic property, mediated through insulin substrate receptor-2 has a favourable protective action on beta cells. Insulin detemir is a long acting analogue, soluble at neutral pH, which reversibly binds to albumin in plasma, prolonging its action. Its lower affinity for insulin receptors necessitates higher doses compared to human insulin. The reduction in body weight is an additional advantage of detemir. A major concern about all newer insulin analogues is their altered mitogenic properties and resultant risk of carcinogenicity on long term use. Albulin is a latest addition of insulin analogue which is under various in vitro and in vivo studies. Inhaled insulin in powder form (Exubera) is recently approved by FDA and appears promising.

Keywords: Diabetes, Insulin glulisine, insulin detemir, albulin, inhaled insulin

Introduction

Diabetes is a metabolic disease, affecting 171 million people around the globe and will be expected to rise to 366 million by the year 2030.[1] Human insulin is the main stay of treatment in type 1 diabetes and also in the later stages of type 2 diabetes. In normal individuals, insulin concentration peaks at 30-45 minutes after a meal and returns to basal levels after 2-3 hrs where as regular human insulin peaks at 1-2 hrs after an injection. This dissimilarity from physiological secretion of insulin may lead to early postprandial hyperglycemia. Also, its action may last for about 6 hrs with a resultant risk of hypoglycemia. So it is recommended to administer regular human insulin (RHI) 30-45 min before meals, which restricted patients' lifestyles and compliance. These limitations prompted the development of insulin analogues, by modifying human insulin chains by recombinant technology.

Structural-function studies indicated that amino acids essential for binding the insulin receptors include A1Gly, A2Ile, A3Val, A19Tyr, B6Leu, B12Val, B23Gly, B24Phe and B25Phe. The B26-B30 region is particularly critical for insulin receptor recognition and has been a preferred site for structural alterations aimed at modifying the pharmacokinetic profile of insulin molecule.[2] This resulted in the development of insulin lispro and insulin aspart which are short acting and insulin glargine, which is a long acting analogue. Newer insulin analogues - insulin glulisine and insulin detemir are developed for their unique characteristics and approved by US FDA and European Union respectively.

Insulin glulisine

Insulin glulisine is a short acting and subcutaneously administered analogue, created by substitution of asparagine at position B3 by lysine and lysine at position B29 by glutamine in the human insulin [Figure - 1]. Insulin glulisine has more rapid onset of action and shorter duration of action compared to RHI. This time action profile provides better treatment convenience and patient compliance. The pharmacokinetic data of subcutaneous insulin glulisine is comparable with insulin lispro, with duration of action of 5-6 hours.[3]

Mechanism of action

Apoptosis of the pancreatic beta cells, mainly due to autoimmune reaction or oxidative stress plays an important role in the pathogenesis of type 1 and type 2 diabetes. In obese patients, fatty acid induced apoptosis of the beta cells is a major factor to the progression to type 2 diabetes. Insulin receptor substrate- 2 (IRS-2) has been implicated in the growth and survival of beta cells. Insulin glulisine, by its unique property of preferential IRS-2 phosphorylation, exerts an antiapoptotic activity against cytokine and fatty acid induced beta cell destruction. This is even seen at therapeutic dose.[4] This may provide an additional therapeutic benefit in the management of diabetes.

Advantages

Insulin glulisin, like other short acting analogues, mimics endogenous insulin secretion more closely than recombinant human insulin. Due to its rapid action, insulin glulisine can be administered just before meals, which avoids risk of hypoglycemia. The novel antiapoptotic property of glulisine may serve to counteract autoimmune and lipotoxicity induced beta cell destruction.

Disadvantages

The COOH- terminal part of the insulin beta chain appears to be implicated in insulin binding to the insulin like growth factor-1 (IGF-1) receptor. Studies have shown that IGF-1 receptor affinity of insulin was also altered by amino acid substitution at position B28-B30. So insulin glulisine has a more affinity to IGF-1 receptor leading to an increased mitogenic effect which may have more importance in long term use.[5] As adverse effect data from clinical trials are sparse, the potential tumorigenic potency of this insulin analogue needs to be studied.

Insulin detemir

Insulin detemir is a soluble (at neutral pH) long-acting insulin analogue, in which the amino acid threonine at B30 is removed and a 14-carbon, myristoyl fatty acid is acetylated to the epsilon- amino group of LysB29. After subcutaneous injection, detemir dissociates, thereby exposing the free fatty acid which enables reversible binding to albumin molecules.[3] So at steady state, the concentration of free unbound insulin is greatly reduced resulting in stable plasma glucose. Unlike NPH and glargine, insulin detemir remains as a liquid depot after sc injection, providing a larger surface area for absorption with less within subject variability.[3], [6]

Detemir was studied in comparison with other long acting analogues for its kinetic profiles. A study which compared glucose lowering effect of insulin detemir with NPH suggested that detemir was as effective as NPH in maintaining glycaemic control when administered at a higher molar dose. Also detemir provided more predictable blood glucose levels with lower intrasubject variation and fewer hypoglycemic incidents than NPH. [7]The peak effect of detemir appears at 6-7 hrs compared with 4-6 hrs for NPH insulin.[3] Isoglycemic clamp studies has shown that the action of detemir lasts for about 20 hours, with a waning effect seen after 10-12 hours.[8] So detemir is administered twice daily in most patients. Detemir, when used in patients with type 1 diabetes on a basal-bolus regimen with insulin aspart (a rapid-acting insulin analogue), showed better glycaemic control compared with NPH.[9] Insulin detemir is suitable for use in diabetic patients with different age groups as basal insulin. Insulin detemir showed a consistent pharmacokinetic profile when used in children and adolescents with type 1 diabetes compared with an adult reference group. The doses of detemir can be titrated using similar guidelines to adults, offering a more predictability than NPH insulin.[10]

Insulin detemir has a relatively low insulin receptor binding affinity and metabolic potency than human insulin at equimolar doses. Also it is less potent in binding to IGF-1 receptor and stimulating mitogenesis, with reduced tumorigenic risk. [2]Albumin is a binding site for many other drugs, which might result in clinically significant drug interactions with detemir. But the binding of detemir is shown to be independent of binding of drugs in the two major binding

pockets that are located in domains IIA and IIIA of the albumin molecule excluding such possibilities.[11]

Advantages

Insulin detemir may provide more predictable fasting blood glucose with lower intrasubject variation and reduced risk of hypoglycemia compared with NPH. The reduction in body weight with insulin detemir is a potential additional advantage. Possible mechanisms may be an indirect or direct effect on the hypothalamus and less chance of hypoglycemia. This is of benefit in long-term use.[12]

Disadvantages

The dose requirement of detemir is nearly double than NPH insulin to achieve comparable 24 hr glucose profiles.[7] This may be due to lower potency of detemir and the delay in dissociation from albumin before it can exert its cellular effects.[3] The long term safety profiles also should be studied.

Albulin

The search for more stable and long-acting insulin analogues resulted in the introduction of the latest insulin analogue, 'albulin' developed and reported by Duttaroy *et al*, in 2005. Albulin is a single chain insulin analogue that can be produced in yeast or in mammalian cells. It consists of the B and A chain of human insulin linked together by a dodecapeptide linker and fused to the NH[2] terminals of the native human serum albumin. The initial receptor binding studies in various cell lines has shown that Albulin has a lower affinity than insulin for binding to insulin receptors.[13] A competition binding assay using 125 I labeled IGF-1 in L-6 cells revealed that the binding affinity of albulin is slightly less than insulin. Further experimental and clinical studies are in progress.

Inhaled insulins

The attempts to deliver insulin by noninvasive techniques resulted in exploration of many alternate modes of administration including oral and nasal routes. But the limited success with these routes changed the focus to lungs, which is naturally permeable for some proteins and identified as optimal for insulin delivery. Some attractive features about pulmonary route are the faster onset of action comparable to i.v. administration and its large surface area of about 70 m² for systemic absorption of drugs.[14]

The rate of drug absorption is expected to vary at different sites within the lungs due to the variable thickness of mucosal surface. [15] From upper airways, there is a steep increase in surface area towards the lower airways with the alveolar region having the maximum surface area which is the target site for drug deposition where systemic drug absorption is desired. [14] The alveolar regions of the lungs are highly perfused by a dense network of blood capillaries that allow the passage of 5L blood per minute. The alveolar membranes are thin enough and sufficiently permeable to allow the crossing of proteins like insulin with lesser

degradation by proteolytic enzymes.[16]

The inhaled insulin delivery systems

Pulmonary inhaled insulin delivery systems deliver insulin in to the lungs, which can be a powder formulation or a solution.[17] Each of these formulations is based on regular human insulin.[14]

Exubera is an insulin product for pulmonary delivery in powder form. This rapid acting product contains insulin (approximately 60%) combined with excipients, principally mannitol as a stabilizer. The insulin powder is packed in to single-dose blisters containing 1 or 3 mg (about 28 and 84 units) of insulin. For delivery, an individual blister is placed in to a slot on the inhaler and is dispersed by the inhaler in to an aerosol cloud which is captured in a holding chamber, which is to be inhaled. The standing cloud of aerosol eliminates high velocity impact of insulin on the throat and upper airway. The device encourages a slow, deep inspiration for maximum deep-lung delivery.[18] The bioavailability of this product is about 10% compared to regular human insulin given by subcutaneous route with a duration of action between 5 to 10 hrs.[14]

The AERx Insulin Diabetes Management System (AERx iDMS) delivers a liquid form of human insulin. In this, single use insulin stripes are combined with a hand-held, breath-activated, microprocessor-controlled device. The device delivers a low velocity; fine particle aerosol spray early during inhalation. [18]The drug is delivered to the lungs only when the breathing is correct, which is its unique feature.[14] This helps to minimize patient related variations in inhaled lung dose. The need for holding breath for better drug delivery is also not necessary with this system. The bioavailability is shown to be about 13-17%.[14],[18]

Some of the other pulmonary insulin delivery systems are ProMaxx, AIR, Spiros and Technosphere. Aerodose insulin, which is designed to deliver the proprietary liquid formulation with dose adjustment facilities according to dose requirements. [14]A study in type 2 diabetes mellitus patients showed relative bioavailability of about 21% with this device and appears promising. [19]

Pharmacokinetics

In comparison with subcutaneous route, inhaled regular insulin is more rapidly absorbed with peak concentrations achieving within 49-65 min. The time required to reach maximum insulin concentration in blood after inhalation route is comparable to subcutaneous injection with lispro and aspart.[14] The duration of action is slightly shorter than the subcutaneously administered regular insulin.[14] so patient may be able to inhale a dose 5-10 min before a meal to achieve adequate glycemic control, but should be used in combination with a once daily injection of long acting insulin.

The major problems with the inhaled insulin are the loss of drug within the inhaler and mouth during inhalation, variations in absorption due to age related differences, respiratory tract infections and smoking. The long term effects of the inhaled insulin deposited in the lungs are

not known as it is known for its growth-promoting properties. There is also the risk of production of anti-insulin antibodies against inhaled insulin. [14] Since the bioavailability of inhaled insulin is relatively low, very high doses of insulin (about 8 times that of s.c. dose) may need to achieve the same glycemic control, can increase the financial burden on patients.

Adverse effects

Some of the reported side effects with inhaled insulin (Exubera) are mild to moderate cough which disappeared with increased exposure. Since there is a danger of low blood sugar, patients should carefully monitor their blood sugars regularly. Other side effects associated with Exubera therapy seen in clinical trials included cough, shortness of breath, sore throat and dry mouth.[20]

Summary

Human insulin is used in the treatment of type 1 and type 2 diabetes. Insulin analogues are developed for better glycaemic control and have lesser chance of hypoglycaemia. Newer insulin analogues-insulin glulisine and detemir have antiapoptotic property and propensity for weight reduction respectively. The imbalance between metabolic and mitogenic potential may give them a tumorigenic property on long term use. Inhaled insulin in powder form (Exubera) is recently approved by US FDA for the treatment of adult patients with type 1 and type 2 diabetes.[20]

The perceptions by many patients are strongly positive, in particular, regarding the overall quality of life, but in objective efficacy, the potential to improve the degree of metabolic control appears to be only minor. That would place in perspective the role of newer insulin analogues.

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