SUMMARY

In the last few years, huge progress has been witnessed in the development of new drugs. In insulin therapy, there have also been novelties with the advent of new insulins (insulin analogs) specially designed to elicit better pharmacokinetic and pharmacodynamic properties. New possibilities for insulin delivery are in development, which could spare patients from painful injections. These novelties are reviewed in the article.

INSULIN ANALOGS

Insulin is an essential component of the treatment of type I diabetes, and is indispensable to achieve good glycemic control in many of the patients with type II diabetes. Our effort to achieve near-normal glycemia in diabetic patients is directed towards prevention or delay in the development of chronic complications (1,2). In insulin treated patients hypoglycemic episodes are often the limiting factor in the achievement of good glycemic control (3).

In order to achieve near-normal glycemia, exogenous insulin administered subcutaneously should have similar pharmacokinetic properties as the insulin secreted from the pancreas in healthy individuals. This means a rapid rise in insulin concentration upon administration, short duration of peak insulinemic concentrations, and rapid decline in insulinenia upon administration for short-acting insulins and steady insulinenia without peaks for long-acting insulins. Purified porcine or human insulin preparations do not meet these requirements (4,5). Therefore attempts have been made to remodel insulin molecule to change its pharmacokinetic properties and render them more favorable. By changing the primary amino acid sequence, changes in the tertiary structure can be achieved that could influence the association of molecules as well as duration of insulin receptor binding or IGF-1 receptor affinity. Prolonged binding to insulin receptor or stronger IGF-1 receptor binding can also lead to increased mitogenic action of insulin analog (6). Such an unwanted carcinogenic potential was demonstrated in rats treated with insulin analog Asp B10 (7,8).

More than a thousand analogs of human insulin have been developed, and twenty of them were tested in humans (9). Today, four insulin analogs are in clinical use.

RAPID ACTING INSULIN ANALOGS

Regular human insulin comes as a hexamer in solution. Upon subcutaneous application there is a delay in action due to dissociation and resorption (10,11). Peak plasma concentrations are reached 45-
120 minutes after the application. Such insulinemic profile does not reproduce the dynamics of endogenous insulin secretion in healthy individuals after beta cell stimulation. Therefore an interval of at least 15 minutes between the application and meal is mandatory, and snacks between the meals are needed to avoid postprandial hypoglycemia due to prolonged insulin action.

Ideal rapid acting insulin would have the peak action after 30-60 minutes and rapid return to basal levels after 180 minutes.

Two preparations with similar features are today in clinical use: insulin lispro and insulin aspart.

In the insulin lispro molecule, the sequence of 28th and 29th molecule is inversed (proline-lysine into lysine-proline). This results in the modification of the conformation of the insulin molecule, which becomes more similar to IGF-1 molecule and the affinity to form dimers and hexamers decreases (9). The pharmacokinetics of insulin lispro is more similar to the insulin response in healthy individuals (12). The rise in insulin concentration is faster and peak concentrations are higher than with regular insulin (13,14). Insulin lispro can better manage postprandial hyperglycemia than regular human insulin without increasing the risk of hypoglycemia (15-23). This difference remains significant also when comparing insulin lispro immediately before the meal with regular insulin administered 30-45 minutes prior to the meal (16). Postprandial hyperglycemia is not only contributing to the metabolic regulation in general but is also an independent risk factor for cardiovascular morbidity and mortality (23-27).

In several multicenter studies in patients with type I diabetes there was no improvement in metabolic regulation as assessed by HbA1c (17,18). Patients were switched from regular insulin to the analog without modification in the dosage of basal insulin, and glucose escape before the next meal (glucose increase due to the short action of the analog) probably caused the lack of regulation improvement (28). Adding a small amount of NPH to the analog (30%) helps avoid this phenomenon (28).

Some smaller studies comparing insulin lispro immediately before the meal and regular human insulin 30 minutes prior to the meal showed a decrease in HbA1c by 0.3% - 0.8% without increasing the number of hypoglycemic episodes (21,29,30).

With insulin lispro there were less hypoglycemic episodes, especially nocturnal hypoglycemias were less frequent than with regular insulin. The decrease in the frequency of hypoglycemia has not been related to changes in HbA1c or number of basal insulin doses (19). With insulin lispro hypoglycemia most frequently occurs about 90 minutes upon application, whereas regular insulin usually causes late hypoglycemias (21). From the patient’s point of view, the principal advantages of insulin lispro are application immediately before the meal (31) and less hypoglycemias (21,29).

The IGF-1 receptor affinity of insulin lispro is increased as compared with regular insulin (6). Clinical significance of this fact is not known, although a more rapid progression of diabetic retinopathy was observed in few pregnant diabetic patients using insulin lispro (32).

In the insulin aspart molecule, the 28th aminoacid of B-chain proline is substituted for aspartate. The charge of the molecule is changed and the affinity for self-association decreased.

The pharmacokinetic and pharmacodynamic profile of insulin aspart is similar to insulin lispro, although minor differences exist. Apparently insulin aspart has a slightly longer duration of action than insulin lispro (33). Glucose escape is therefore less pronounced (22,34). IGF-1 receptor affinity and mitogenic potential are similar to those of human insulin (6).

In clinical studies, insulin aspart given immediately before the meal was more successful than regular insulin 30 minutes prior to the meal in reducing postprandial hyperglycemia (35-38), and the number of nocturnal hypoglycemic episodes decreased as well (37,38).

LONG-ACTING INSULIN ANALOGS

Human insulin preparations with prolonged action are aimed to cover the basal insulin requirements (fasting and between the meals). There are two basic types of these preparations: NPH (neutral protamine Hagedorn) and zinc-insulin, both of them associated with two
major problems. Both preparations are suspensions, and thorough mixing prior to use is critical, which bears the possibility of mistake (39). Also, there are significant inter- and intraindividual differences in the absorption rates and bioavailability (40-43). Neither of the preparations can cover the basal insulin needs for entire 24 hours (44,45). In the multiple injection therapy regimen with regular insulin, the prolonged action of regular insulin also covers the basal insulin needs between the meals during the day. With the advent of new and shorter-acting insulin analogs the necessity for more than one dose of basal insulin has emerged (30).

A special problem is unfavorable pharmacokinetic profile of NPH insulin. The peak action of NPH insulin is 5-7 hours after the application (46). If the evening dose is given at bedtime (around 10.00 p.m.), the peak action will be between 3.00 and 5.00 a.m. when the need for insulin is lowest, bearing a high risk of hypoglycemia. In patients with type I diabetes treated with multiple injection therapy, about 50% of all hypoglycemic episodes occur during the night (47,48). Between 5.00 and 8.00 a.m. insulin sensitivity decreases, and so does insulin concentration, which leads to the dawn phenomenon.

To avoid these disadvantages of human long-acting insulin preparations, efforts have been made to produce an analog of human insulin with prolonged and even action without noticeable plasma peaks.

The only insulin analog with such properties, which is in routine clinical use, is glargine. The molecule of glargine has isoelectric point of pH 6.7 in contrast to pH 5.4 of human insulin (49,50). Modification has been made on the C-terminal end of B-chain, where two arginine molecules are added, and glycine on A-21 position is substituted by arginine. The pH of the preparation is 4.0, at which glargine is completely soluble. At a more neutral pH of the tissue, microprecipitation takes place, which delays resorption. Resorption is also additionally delayed with a small amount of zinc added.

Glargine has the same affinity for insulin receptor as human insulin, but the affinity for IGF-1 receptor is 3-14 times greater, however, without known clinical significance (6). After subcutaneous application glargine reaches its maximum activity after 4-5 hours, which then remains even without pronounced peaks (51).

In a study in 534 patients with type I diabetes, one or two doses of NPH insulin were substituted for one evening dose of glargine. Patients receiving glargine had significantly less nocturnal hypoglycemias, less symptomatic hypoglycemia and less severe hypoglycemia (with blood glucose less than 2 mmol/l). Patients treated with glargine had better perception of hypo- and hyperglycemias as well as better satisfaction with treatment. The mean dose of glargine was 23.8 units, while the mean dose of NPH insulin was 31.3 units (52).

In several other studies with patients with types I and II diabetes, a decreased frequency of hypoglycemia and a significant decrease of fasting glycemia were observed, however, without a significant decrease in HbA1c (31,53-55).

In type II diabetes glargine has been studied as monotherapy or in combination with metformin, sulphonylurica, metformin and sulphonylurica, or acarbose.

Another long-acting insulin analog is detemir, which is currently in phase III clinical trials. In the detemir molecule, the threonine on B30 position is removed, and myristoyl fatty acid is acylated to lysine at B29. Prolonged action is believed to be due to a combination of hexamer formation and reversible albumin binding (56). About 98% of detemir in plasma are bound to albumin, and only the free fraction can activate insulin receptor. Detemir is soluble at neutral pH and subcutaneous depot remains in soluble state, which makes the resorption surface larger and diminishes resorption variability. Detemir has a lower receptor affinity than human insulin, and even lower IGF-1 affinity and mitogenic potential (6). It has been demonstrated that detemir needs to be given in four times equimolar doses to NPH insulin to achieve the same hypoglycemic potential (57). No interactions with other albumin-bound drugs were observed (58). Detemir has a lower intraindividual pharmacokinetic variability than NPH insulin (59). Detemir also has a relatively stronger effect on the liver than on peripheral tissues (60,61).

PREMIXED INSULIN ANALOGS

After rapid-acting analogs, biphasic premixed formulations have also appeared. The NPH component also contains an analog, otherwise the exchange
between protamine-bound and soluble phase would cause change in the pharmacokinetics over time. Low-mixture preparations contain 25-50% of rapid-acting component, and high-mixtures contain 75% of rapid-acting component.

Using premixed analog preparations it is not possible to achieve as good regulation as with intensified multiple injection therapy. However, a better management of postprandial hyperglycemia than with premixed human biphasic insulin can be achieved, and target population are patients who fail to achieve satisfactory control on human premixed insulin but are not able to deal with multiple injection therapy (62-65). The use of premixed analogs resulted in better postprandial plasma glucose control without an increase in hypoglycemia in general or exercise-induced (66,67).

NEW METHODS OF INSULIN DELIVERY

One of the principal disadvantages with insulin therapy, from the patients' point of view is the need of painful injections. Patients have to learn to manage the injection technique themselves, and also to overcome reluctance to such therapy. Alternative methods of insulin delivery would represent a big advantage in therapy and quality of life in diabetic patients.

Enteral insulin

There are two technologies used to obtain enteral insulin. One technology uses carriers to enable insulin resorption through membranes. After resorption the carriers separate from insulin. It has been developed by Emisheer technologies.

At the 63rd Annual Scientific Sessions of the American Diabetes Association (ADA) in June 2003, two clinical studies were presented. In the first study 11 mg of oral insulin preparation (about 300 units) were compared to 0.6 mg of regular insulin (15 units) using glucose clamp technique. The results showed an appropriate reduction in blood sugar following oral insulin administration as well as a tight range of time to maximum insulin concentrations (27.0 ± 9 minutes for 11 mg oral insulin compared to 160.5 ± 82.78 minutes for 0.6 mg by injection) (68).

The other study suggests that a single dose of oral insulin given to patients with type II diabetes at bedtime suppresses the overnight endogenous insulin secretion, thus reducing the demand on the islet cells (69).

Nobex has developed technology based on attachment of amphophilic oligomers to insulin resulting in stability to enzymatic degradation. Insulin is absorbed into portal circulation, reaching high concentrations in the liver, which better mimics physiological secretion. The frequency of hypoglycemic events is expected to be lower. This preparation is in phase II clinical trials and showed fast dose-dependent absorption and reduction of fasting and postprandial hyperglycemia (70).

Orally absorbed insulin (Oralin)

Generex has been developing an aerosol containing insulin for buccal absorption, using an applicator similar to those used for asthma medications. Studies have shown benefit from Oralin comparable to insulin injections in reducing blood sugar levels, alone or in combination with oral hypoglycemic agents (71).

Inhaled insulins

Pfizer and Aventis together with Inhale Therapeutic Systems have developed insulin in the form of powder for inhalation. It can be used as a short-acting insulin and was successful for prandial blood sugar control in type I and type II diabetes (72,73). The inhalator consists of a plastic cylinder and air compression system. Insulin containing blisters are punctured with a needle, and insulin is aerosolized into particles of less than 5 microns.

Novo Nordisk and Aradigm have developed inhalatory insulin for use with the Airx device. Insulin solution is nebulized into droplets of 2-3 microns. The device signalizes to the patient the rhythm of inhalation, and when the correct rhythm is achieved the aerosol begins to form. It demonstrated similar pharmacokinetic and pharmacodynamic properties as human soluble insulin (74), and was as successful in terms of glycemic control as human soluble insulin in intensified therapy in patients with type II diabetes (75).
Other insulin inhalation systems in the development are AIR system (Elly Lilly and Alkermes), Aerodose (Aerogen and Disetronic) and Insulin Technospheres (Mannkind/PDC).

The advantages of alveolar resorption over oral (buccal) resorption are greater surface and thinner membrane, and the difficulty is producing particles small enough to reach the alveoli.

The main disadvantage is the high cost of treatment because only about 30% of insulin are absorbed.

Transdermal insulins

Alteca has developed transdermal patches for insulin delivery. The electronic adhesive patch is first applied to the skin, vaporizing superficial dermal cells and forming micropores for insulin to pass through, and then the insulin patch is applied. It provides basal insulin delivery over 12 hours (76).

Transferosulin has been developed by Idea, using particles called transformers. Transformers are similar to lyposomes but more deformable and can easier pass through the skin. Their membrane contains phospholipids and has hydrophilic inside where insulin is carried. Studies in type I diabetes patients showed similar pharmacokinetic profile to long-acting human insulin (Ultratard) with less intraindividual variability in insulin absorption (77).

Artificial beta cell prototype

Medtronic Minimed (part of Medtronic Inc.) presented initial results of artificial beta cell prototype studies at the 62nd Scientific Sessions of ADA. It is a closed loop device consisting of implantable peritoneal insulin pump and glucose sensor implanted in the vena cava superior. The sensor part was tested for six months and showed good correlation with capillary blood glucose (cumulative r-value 0.83-0.93). The complete system was tested for a shorter period (2 days). Results showed better glycemic control (50% more ideal glycemic values in the range of 3.9-6.8 mmol/l than with intensified therapy) and frequency of hypoglycemia reduced by more than 50% (78).

CONCLUSION

The progress in pharmacology has resulted in the development of new insulins with different pharmacokinetic and pharmacodynamic properties. Today every patient with diabetes treated with insulin can be offered individualized therapy matching his needs, enabling him to achieve and maintain good glycemic control and decrease the risk of both chronic complications and hypoglycemias.

New technologies in drug delivery systems appear promising in that the current unpleasant method of insulin applications may soon become history, and better patient compliance with insulin therapy will be possible to achieve.

REFERENCES


