Review

INSULIN ANALOGS AND INTENSIVE INSULIN THERAPY IN TYPE 1 DIABETES

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ABSTRACT

Unless contraindicated, intensive insulin therapy should be the treatment of choice for patients with type 1 diabetes. The principle of intensive insulin therapy is to provide an adequate amount of basal insulin and also provide insulin to prevent the anticipated hyperglycemia following meals; thus mimicking the "physiologic" insulin profile. In the past, basal insulin has been provided as NPH, Lente or Ultralente insulin, but is better provided by the newly developed insulin analog, insulin glargine, because the latter has no peak effect. The insulin analogs (insulin lispro and insulin aspart) may be better suited as the "insulin for meals" compared to regular insulin because of their quicker onset and shorter duration of action. Alternatively, continuous subcutaneous insulin infusion may be used to provide basal, as well as insulin for meals; but it is much more expensive than multiple injections of insulin. Home glucose monitoring is an essential component of intensive insulin therapy; and it is now possible to monitor glucose continuously. With continuous glucose monitoring and appropriate insulin delivery, it should be possible to "close the loop" of glucose and insulin. Although this goal has not been realized for practice so far, it should be possible to achieve this in the not too distant future. Such closed loop systems will allow patients to keep their blood glucose in the desired range with minimal (or no) risk of hypoglycemia.

KEY WORDS: Intensive insulin therapy; Insulin analogs; Insulin lispro; Insulin aspart; Insulin glargine; Continuous subcutaneous insulin infusion (CSII).

INTRODUCTION

The worldwide prevalence of diabetes has continued to increase. In the year 2000, there were 151 million people with diabetes. This number is expected to reach 300 million in the year 2025 (1). Presently, India leads the world with the largest number of adults with diabetes (2).

Type 2 diabetes is the most prevalent type of diabetes. More than 90% of people have type 2 diabetes, and the remainder have type 1 diabetes (3).

Type 1 diabetes results from insulin deficiency due to destruction of ß cell of pancreas by an autoimmune process. This group of patients requires administration of exogenous insulin for survival and was previously called insulin dependent diabetes mellitus.

The microvascular and macrovascular complications of diabetes are the major cause of morbidity and mortality associated with diabetes (4). Until the publication of the Diabetes Control and Complications Trial (DCCT) in 1993, there was a great deal of controversy regarding the relationship of diabetes control and vascular complications of diabetes. DCCT in type 1 diabetes (5) and subsequently United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes (6) clearly demonstrated that strict control of hyperglycemia delays the onset and slows the progression of microvascular complications. Since then, the American Diabetes Association (ADA) has recommended that unless contraindicated, all patients with type 1 diabetes should be treated to achieve the level of hyperglycemia, which was obtained in the intensively treated group of patients in DCCT (7). This can only be achieved by intensive insulin therapy. In this article, I have described various insulin regimens available to achieve these goals and provided evidence for the preferred insulin regimens.

HISTORY OF DEVELOPMENT OF INSULINS

A brief review of the history of the development of insulin is of interest and has been summarized by Rosenzweig (8). Insulin was first isolated by Banting and Best in 1921 (9), and the first injection of insulin was administered in 1922 (9). In 1936, Hagedorn discovered that addition of basic proteins such as fish (Protamine) lead to slower absorption of insulin, and therefore, prolonged its action. In the same year, it was discovered that addition of zinc prolonged the action of insulin further, leading to the development of Protamine Zinc insulin (PZI). PZI had duration of action up to 72 hours and could be given once a day. NPH insulin was introduced in 1946 and has been the most commonly used insulin in the USA. Lente insulin series, suspensions of insulin with zinc but containing

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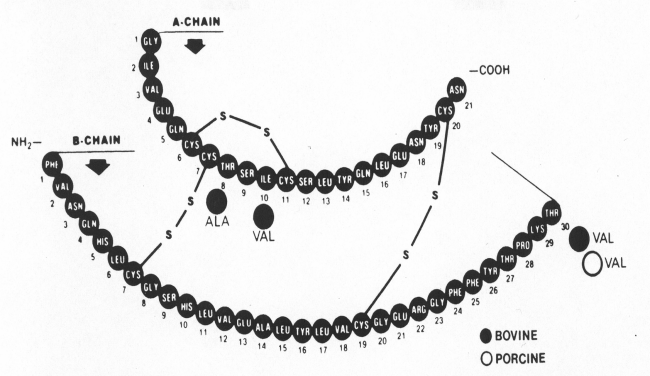

Fig 1: Structure of Human Insulin. Differences from Insulin of Bovine and Porcine Origin are also Shown.

no proteins, were developed in the early 1950's. Over the next 20 to 30 years, there has been a progressive improvement in the purity of available insulins, but all insulins were derived from animal sources (8). Human insulin produced biosynthetically was first introduced commercially in 1982 (10). Almost all the insulins currently in use in the USA are 'human insulins" biosynthetically produced (11). Human insulin is a 51 amino acid peptide arranged in two chains connected by a disulfide bridge with a third disulfide bridge within the A chain. It differs from pork insulin by one amino acid and from beef insulin by three amino acids (12) (Fig 1). Human insulin molecules have a natural tendency to self associate (13, 14). Reversible bonds form insulin dimers and in the presence of zinc (used in commercially available formulations) three dimers join to form a hexamer. However, insulin hexamers must dissociate to monomeric form before insulin can be absorbed in to systemic circulation.

INSULIN ANALOGS

In order to achieve better control of diabetes, efforts have been made to modify the insulin molecule leading to the development of insulin analogs. The pharmacologic characteristics of the insulin analogs allow clinicians to use them in specific situations to achieve better control of diabetes. Currently available insulin analogs can be divided into two categories based on their duration of action. The chemical structure of the currently available insulin analogs is shown below (Fig 2).

SHORT ACTING INSULIN ANALOGS

Insulin Lispro (Lys (B_{28}), Pro (B_{29}) human insulin.

Insulin lispro was the first insulin analog introduced in 1994 (15). In lispro insulin, amino acids, Lysine and Proline, are reversed in their position in the B chain of insulin molecule. Insulin lispro also forms hexamers but dissociates more rapidly, as a result of which, it is more rapidly absorbed when administered subcutaneously. In addition, higher peak insulin levels are achieved, and the duration of action is shorter compared to human insulin (16). The action begins in 5 to 15 minutes, reaches its peak in 1 to 1 ½ hours, and its effects last for 3 to 5 hours (15). When the dose of human regular insulin is increased, the duration of action is also prolonged, but not so with human lispro. When the pre-meal dose of insulin lispro is increased, the peak action of insulin is increased, but the duration of action remains practically unchanged (16). The absorption of regular insulin also varies depending on the site of injection. The absorption of human insulin is slower from the deltoid and femoral regions compared to the abdominal area, whereas the absorption rate of lispro is greater and similar from all three sites (17).

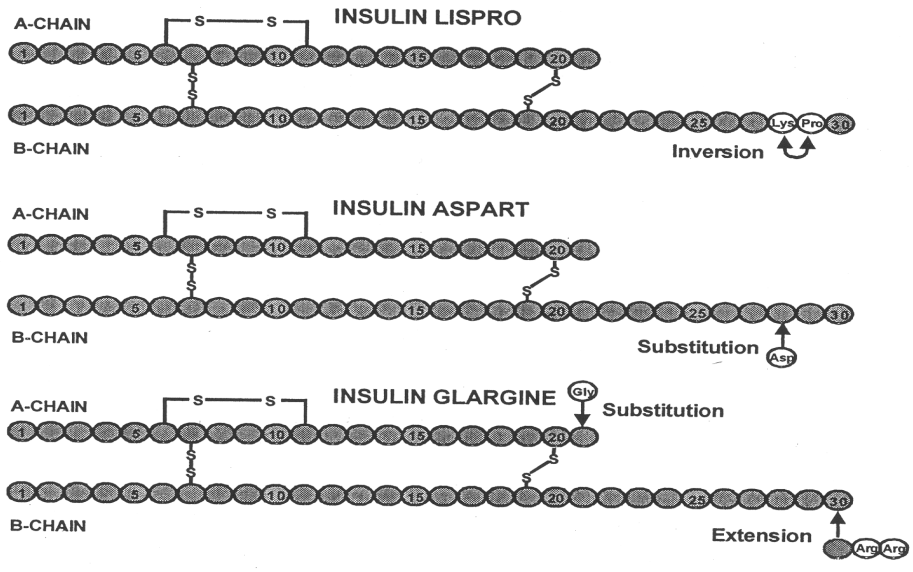

Fig 2 : Primary Molecular Structures of the Synthetic Insulin analogs Lispro, Aspart, and Glargine

The consistency of response and less intra-individual variation with subcutaneous injection of lispro allows patients to have more sites for subcutaneous injections with an assured rapid metabolic response (17). Although insulin is rarely given intramuscularly in clinical practice, it is of interest to note that the metabolic response to injection of lispro is similar whether given subcutaneously or intramuscularly (18). On the other hand, regular insulin effect peaked earlier when given intramuscularly compared to when given subcutaneously (18).

Pampanelli et al (19) compared post meal metabolic control using lispro insulin given 5 minutes before a meal, with regular insulin given 30 minutes before a meal, or 5 minutes before meal in a dose of 0.1 u/kg and a standard lunch. Regular insulin given 30 minutes before meals caused the blood glucose levels to drop initially but following meals resulted in much higher postprandial blood glucose level. Regular insulin given 5 minutes before a meal resulted in much higher postprandial blood glucose levels and hypoglycemic levels at 5 hours. The post meal glucose concentration at 2 hours and also the 0-420 minute, mean value was lower with lispro insulin compared to regular insulin, whether given at 5 minutes or 30 minutes before meals (Fig 3A). Plasma insulin levels with lispro insulin were higher at 30 minutes and lower at 180 minutes compared to regular insulin (Fig 3B). Compared to regular insulin; therefore, lispro offers the advantage that it can be given within 15 minutes before the meal, rather than 30 to 40 minutes before meals. Similarly a rapid peak action should prevent postprandial hyperglycemia, and the short duration of action should reduce postprandial hypoglycemia.

Insulin Aspart (B Aspart) Human Insulin

In this analog, amino acid, Proline, at position B-28 has been replaced by aspartic acid. Because of this change, the onset of action occurs at 10-20 minutes with maximal serum concentrations reaching at 45 minutes, and the duration of action is 3 to 5 hours (20, 21). In a prospective, multicenter trial, use of insulin aspart was compared with human (regular) insulin as the before meals insulin with NPH as basal insulin in patients with type 1 diabetes. It was determined that there is a small but useful advantage for rapid acting insulin aspart as a tool to improve long-term blood glucose control, hypoglycemia and quality of life (22).

Hedman et al (23) compared directly the plasma insulin profiles of insulin aspart and insulin lispro. They observed that free insulin profiles of both these analogs resemble each other, but insulin lispro showed a more rapid uptake, reached the maximum peak concentration earlier (50% max peak in 20 minutes with insulin lispro versus 30 minutes for insulin aspart) and a more rapid decline (the decrease to 50% peak occurred in 113 minutes with lispro, compared to 154 minutes in insulin aspart). The course of blood glucose fall, however, was similar. Although the authors suggest that these findings may be of clinical significance, the differences are minor and not likely to be clinically important (Fig 4).

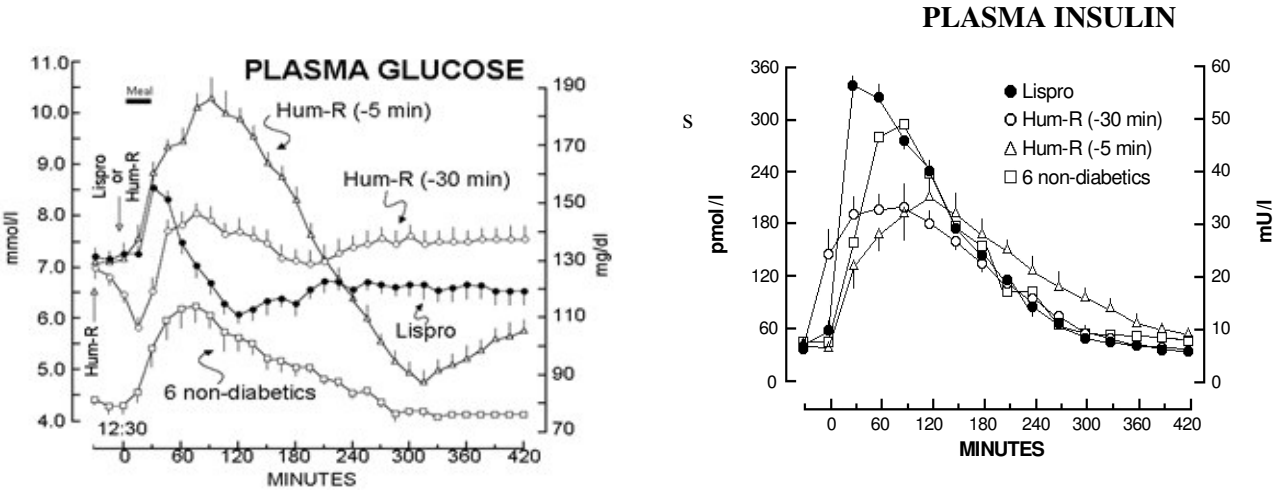

Fig 3A & 3B: Plasma glucose concentration (3A) and plasma insulin concentration (3B) after subcutaneous injection of 0.1 U/kg human regular insulin 30 min before a meal [Hum-R (-30 min)] or 5 min before a meal [Hum-R (-5 min)] or lispro 5 min before a meal (1230, time 0 min) in six patients with a short duration of IDDM and residual pancreatic β cell function. Six nondiabetic subjects given the same meals as IDDM patients are shown for comparison. Two IDDM patients in the lispro study and four patients in the Hum-R (-5 min) study required glucose to prevent hypoglycemia. Data are means ± SE. Diabetes Care 1995; 18: 1452-9

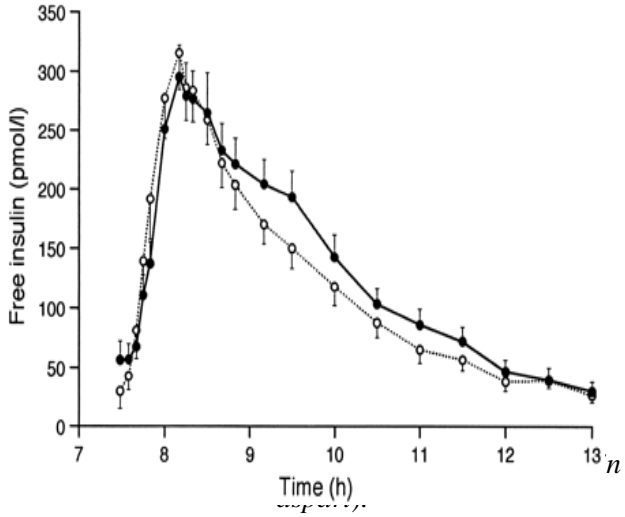

Fig 4: Plasma concentrations of free insulin in 13 patients with type 1 diabetes after a 10 U single subcutaneous injection insulin lispro (o) and insulin aspart (•) at 7:30 A.M. immediately before breakfast. The values are means ± SEM.

LONG ACTING INSULIN ANALOGS

Insulin Glargine

In this analog, asparagine in A chain at position 21 is replaced by glycine, and two arginines are added to the of ß chain at position 31 and 32 of the insulin molecule. This change results in a shift of isoelectric point, making it a soluble insulin preparation at an acidic pH. At pH 4.0, it is completely soluble, as it is in the injection vial. After subcutaneous injection, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine is released and absorbed slowly, resulting in a relatively constant concentration over a 24 hour period with no pronounced peak (24, 25).

Raskin et al compared the use of insulin glargine with NPH insulin as the basal insulin in 619 patients and determined that insulin glargine once a day appears to be as safe and at least as effective as using NPH insulin once or twice a day in maintaining glycemic control in patients with type 1 diabetes (26). There were no significant differences in the occurrence of hypoglycemia in this study. However, in another study in which bedtime insulin glargine was compared with NPH insulin taken once or twice a day, there was a significant reduction in the occurrence of severe and nocturnal hypoglycemia with insulin glargine (27).

INTENSIVE DIABETES THERAPY

deteriorates, and insulin deficiency develops. Patients with type 1 diabetes are insulin deficient, their β cells

As previously mentioned (7) and recently reaffirmed by ADA, a primary treatment goal in type 1 diabetes should be glucose control at least equal to that achieved in the intensively treated cohort of DCCT (28). The treatment must be individualized, and patients should aim for the best level of glucose control they can achieve without placing themselves at undue risk of hypoglycemia. The intensified insulin therapy therefore is only a part of a total care of diabetes. Other components of this therapeutic plan should also include the following (29):

1. Individually prescribed meal plan with carbohydrate counting
2. Daily self monitoring of blood glucose at home
3. Individualized target for blood glucose level
4. Patient education and motivation
5. Psychological support
6. Intensified insulin treatment program (may be a program of multiple injections of insulin or administration of continuous subcutaneous insulin infusion using an insulin pump)
7. An objective assessment of the effectiveness of the program (glycosylated hemoglobin)

PHYSIOLOGY OF INSULIN SECRETION

Before we discuss intensive insulin therapy, it is helpful to review the physiology of normal insulin secretion. β cell studies have demonstrated that insulin is released in an oscillating fashion. These oscillations occur every 8 to 15 minutes. These oscillations are highest after meals and revert to fasting levels after up to 340 minutes (30, 31). It has been estimated that approximately 50% of total amount of insulin secreted by pancreas represents basal secretion and remainder is secreted in response to meals (30). Normally, insulin is secreted into the portal system in the basal state at a rate of approximately 1 unit/hour. The intake of food results in a prompt 5 to 10 fold increase in the rate of insulin secretion. The total daily secretion of insulin is approximately 40 units/day (32). With each meal ingestion, there is a prompt short burst of insulin release, which minimizes the postprandial increase in glucose (33) (Fig 5). The burst of insulin release is short lived so that there is minimal (or no) risk of hypoglycemia. In response to stimulation by glucose, there is an initial transient rapid rise in the release of insulin (first phase). This is followed by a progressively increasing second phase of insulin secretion (34). A progressive diminution of phase 1 insulin response to glucose can be demonstrated a number of years before the development of type 1 diabetes (35). The β cell function progressively do not respond to glucose or non glucose stimuli, and

they require exogenous administration of insulin for survival.

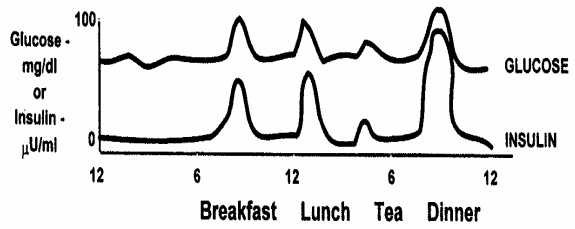

Fig 5: Twenty-Four-Hour Plasma Glucose and Insulin Profiles in Hypothetical Nondiabetic Individual.

INSULIN PREPARATIONS

When regular insulin is injected subcutaneously, there is an initial delay in the onset of insulin action, with peak insulin concentration occurring 45-120 minutes later, unlike the much earlier postprandial insulin peak in non-diabetic individuals. (36) Therefore, it is expected that with use of regular insulin only, there will be early hyperglycemia after a meal, but due to its prolonged action of 6 to 8 hours, there is the possibility of delayed postprandial hypoglycemia. For these reasons, patients are advised to take regular insulin about 30 minutes before meals, but many patients either ignore this advice or choose not to follow it. With the addition of protein and zinc, different insulin preparations have been developed with differing onset of actions, time to peak action, and the duration of action, as shown in Table 1:

Table 1: Pharmacokinetic Properties of Various Insulin Preparations

Insulin Type	Onset of Action (hr)	Peak Effect (hr) (hr)	Duration of Action
Rapid-acting			
Regular	0.5-1.0	2-4	6-8
Lispro	0.25-0.5	0.5-1.0	3-5
Insulin Aspart	0.3-0.6	0.5-1.0	3-5
Intermediate-acting			
NPH	1-2	6-12	18-24
Lente	1-3	6-12	18-26
Long-acting			
Ultralente	4-6	10-16	24-28
PZI	3-8	14-24	24-40
Glargine	4-6	No peak	>24

Several factors, such as site of insulin injection, depth of injection, dose of insulin, type of insulin (such as regular insulin mixed with NPH, lente or ultralente insulin), exercise, local heat or massage of the injection site can affect the bioavailability and absorption rate of subcutaneously injected insulin. also produced less hypoglycemia compared to when NPH insulin was used as the basal insulin. (27) (37) Intra-individual variation in time required to absorb 50% of injected dose of insulin is approximately 25%, and between patients is up to 50%. (38) This variation of insulin absorption between patients, and also in same individuals, accounts for much of the difficulty in achieving consistent levels of glycemia. As mentioned above, the intra-individual variation of absorption of lispro insulin is much less compared to human regular insulin. (17)

INTENSIVE INSULIN THERAPY

The principle of intensive insulin therapy is to provide an adequate amount of basal insulin and also to provide short-acting insulin to prevent post meal hyperglycemia, thus mimicking the "physiologic" profile. Basal insulin can be provided by using intermediate acting (NPH or lente insulin) given at least twice daily. A single injection of intermediate acting insulin is almost always inadequate to provide basal insulin over a 24-hour period. When NPH insulin is given at suppertime, in combination with either regular or lispro insulin, there is an increased risk of nocturnal hypoglycemia and fasting hyperglycemia. (39) Fasting hyperglycemia can be improved by administering NPH injection at bedtime, instead of suppertime. (40) Clinically, lente insulin appears to have an effect similar to that of the NPH insulin. However, both lente and ultralente insulin contain excess zinc. Therefore, when regular insulin is mixed with either of these two insulins, regular insulin gets precipitated out of solution due to binding with excess zinc. This complex results in blunting of the action of regular insulin if the mixture remains in the syringe for more than a few minutes (41).

Basal insulin may also be provided as ultralente insulin. Although ultralente insulin is frequently thought to have no peak, it actually has a very broad peak ranging from 8 to 16 hours with duration of action ranging from 20 to 24 hours. (42, 43) The onset of action is more rapid and the duration of action of human ultralente insulin is somewhat shorter compared to ultralente insulin of animal origin. Therefore, ultralente insulin is also best used as a twice-daily preparation. (44) The recently introduced insulin glargine appears to be the ideal insulin preparation to provide basal insulin, since it has essentially no peak and has a duration of action of 24 hours. (25, 26, 27) As previously mentioned, insulin glargine was as effective as NPH insulin, (26) but

Lepore et. al. directly compared the pharmacodynamics of subcutaneously administered

glargine, NPH insulin, ultralente insulin and continuous subcutaneous insulin infusion (CSII) as basal insulins. (25) **See Figure 6 A&B.** They confirmed that both ultralente and NPH insulins had a peak. Duration of action of ultralente insulin was greater than NPH, and so was the intersubject variability. Glargine was peakless, lasted for 24 hours and had lower intersubject variability than NPH and ultralente.

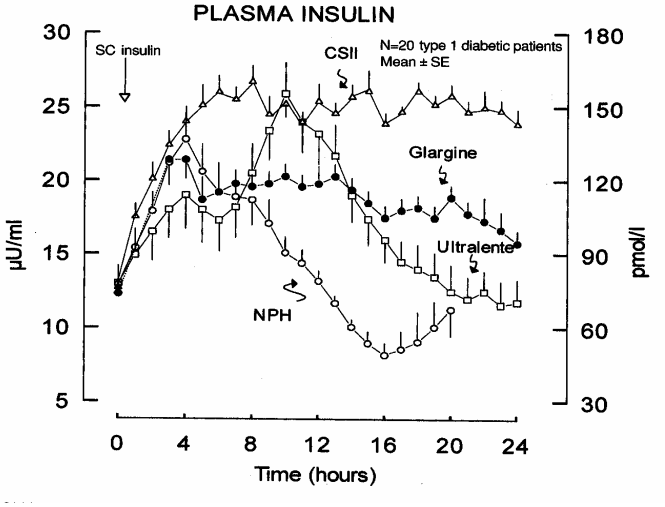

Fig 6A : Plasma (free) Insulin Concentrations after SC Injection of Glargine, NPH and Ultralente and after CSII of Lispro

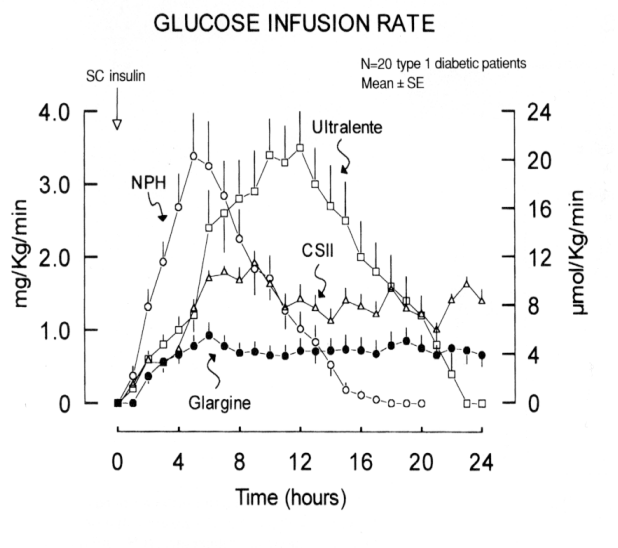

Fig 6B: Rates of Glucose Infusion Needed to Maintain Plasma Glucose at the Target Value of 130 mg/dl after SC Injection of Glargine, NPH, and Ultralente and after CSII of Lispro.

Basal insulin can also be provided by CSII. Use of CSII using insulin pumps is a popular mode to mimic "physiologic" insulin profile. (45, 46, 47) The principle of the CSII is to establish a basal rate and at meal times, the pump is programmed to deliver a mealtime "bolus" to prevent post prandial hyperglycemia. It is, therefore, possible to delay or omit a meal without fear of hypoglycemia if the basal insulin dose is correct. The anticipated increase in plasma glucose following meals can be estimated by counting carbohydrates in the meals. Most patients require 1 unit for 10 to 15 grams of carbohydrates ingested. (48) Some patients may experience a significant elevation of blood glucose in the early hours of the morning due to the "dawn phenomenon". The pump can be programmed to increase the basal rate 2 to 3 hours before arising, thus preventing morning hyperglycemia. (49) Several studies have suggested that CSII could provide better glycemic control (50, 51, 52) with a reduction in the risk of hypoglycemia, (53, 54) compared to conventional insulin treatment. The question, however, still remains whether CSII offers a clear advantage over multiple daily insulin injections (MDI) in achieving better control of hypoglycemia. Several earlier studies when comparing CSII and MDI concluded that both regimens provided similar degrees of improved glycemic control and similar degrees of hypoglycemia. (55, 56) Many of the earlier studies reporting beneficial effects of CSII were not randomized, (50, 51) and all of them used regular insulin. More recent studies have demonstrated that when used in external pumps, the short acting insulin analog lispro provided better glycemic control than regular insulin without increasing the frequency of hypoglycemia. (57, 58, 59) It has also been demonstrated that another short acting insulin analog, insulin aspart, can also be used in the CSII as effectively as buffered regular insulin. (60)

Helve et. al. (61) compared the effectiveness, safety and compliance of CSII and conventional insulin treatment under ordinary outpatient conditions in 170 patients. They concluded that the glucose control was slightly but significantly better in the CSII group than in the conventional insulin treatment group. There was no difference in the frequency of hypoglycemic episodes between the two groups. However, two recent studies using a crossover design have produced conflicting results. Hanaire-Broutin et. al. (62) observed that when used with external pumps, lispro provided better glycemic control compared to multiple daily injections, where as Tsui et. al. (63) failed to demonstrate any difference between the two regimens. Another study in which insulin aspart was used in CSII and in multiple insulin injections also showed that similar degree of glycemic control was

achieved in both regimens. (64) Safety assessment (hypoglycemia and adverse events) were also comparable for both groups but this study was carried out in patients with type 2 diabetes. (64) Therefore, for intensive insulin therapy, the use of insulin pump or multiple daily injections of insulin remains a matter of personal preference of patients and their physicians at this time.

Short-acting insulins can be used to provide coverage for anticipated increase in blood glucose with meals. Regular insulin has been used for this purpose. It should be taken about 30 minutes before meals to provide "adequate" control. However, most patients take it immediately before meals; and consequently, it may result in postprandial hyperglycemia and delayed hypoglycemia. Short acting insulin lispro has been shown to be more effective in controlling postprandial hyperglycemia without causing delayed hypoglycemia. (65, 66) In a meta-analysis of the studies comparing regular versus lispro insulin, Brunelle, et. al. also confirmed the advantage of lispro. (67)

Similarly, insulin aspart has been shown to provide adequate coverage for meals, resulting in better control of diabetes without increased risk of hypoglycemia. (68, 69, 70)

Therefore, it appears that for patients with type 1 diabetes, either a long-acting insulin such as insulin glargine in combination with a short-acting insulin, such as insulin lispro or insulin aspart would provide the most suitable regimen for multiple daily injections of insulin. Alternatively, use of a short-acting insulin analog (insulin lispro or insulin aspart) in CSII will provide an equally effective regimen although the latter is much more expensive. CSII is considered by some to be the best therapeutic option to achieve near normal blood glucose control for patients with type 1 diabetes. (71) Although the combination of glargine and a short acting insulin such as insulin lispro or insulin aspart has the potential of being as effective as CSII, the two regimens have not been directly compared. We believe that this combination will be equally effective but much less expensive. However, this remains to be established by definitive studies. A diagramatic representation of insulin profiles achieved with various insulin regimens is summarized in the figures below. **See Figure 7 A to E.**

Figure 7: Diagramatic Representation of Insulin Profiles Obtained with Various Insulin Preparations. B=breakfast, L=Lunch, S=supper, HS=bedtime.

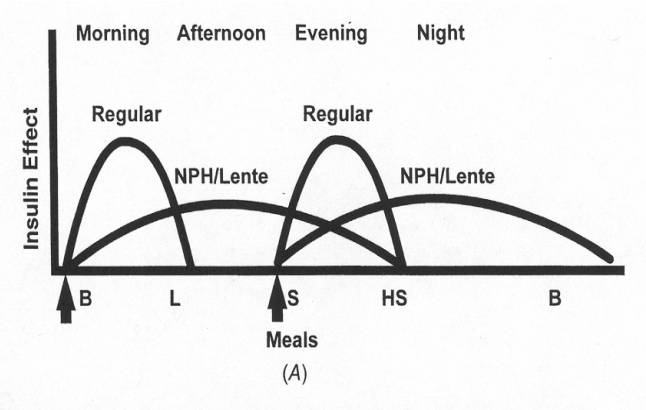

Fig 7A: Insulin Profiles Obtained with Twice Daily Regular Insulin and Twice Daily Intermediate Acting Insulin.

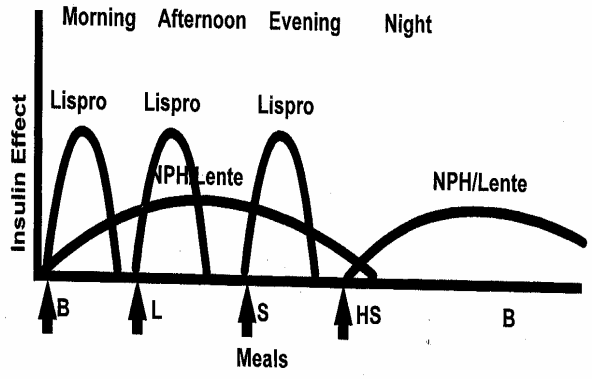

Fig 7B: Multiple Injections of Lispro and Twice Daily Intermediate Acting Insulin

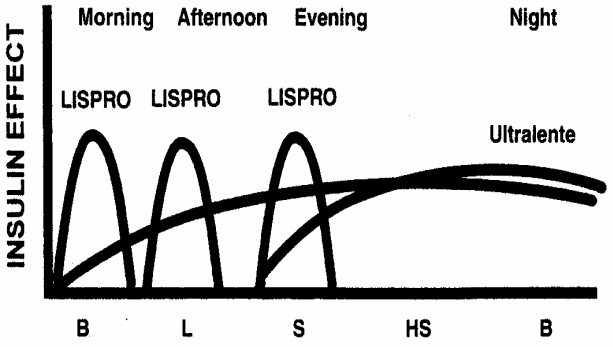

Fig 7C : Multiple Injections of Lispro and Twice Daily Injection

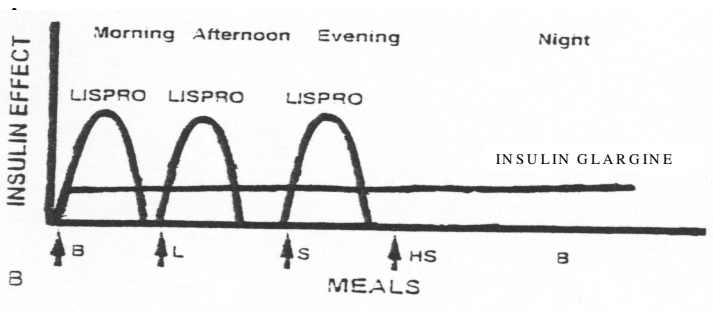

Fig 7D: Multiple Injections of Lispro (or Aspart) and Insulin Glargine.

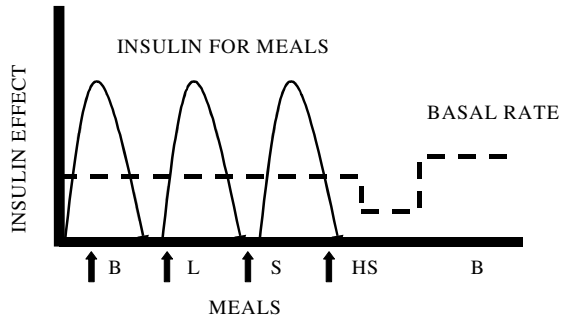

Fig 7E: Insulin Profile Achieved with Continuous Subcutaneous Insulin Infusion. *The basal rate can be decreased during the day if needed and may also be increased during the night to compensate for "dawn phenomenon". Insulin for meals may be given as a "bolus" or may be prolonged over several minutes.*

Blood Glucose Monitoring

Self-monitoring of blood glucose is essential for patients who are being treated with intensive insulin therapy for adjustment of their insulin dosage. (72, 73) Although the ideal number of blood glucose determinations to achieve a satisfactory control of diabetes has not been determined, most clinicians recommend at least 4 times/daily. In a crossover clinical trial conducted by Schiffrin, et. al., 4 blood glucose determinations/day resulted in better control of diabetes compared to two blood glucose determinations. (74) An inverse correlation between HbA_{1c} and the frequency of daily blood glucose determinations has also been demonstrated, i.e., the more the number of blood glucose determinations, the lower the HbA_{1c} level. (75) It would, therefore, appear that continuous glucose monitoring may result in improved control of diabetes without an increased risk of hypoglycemia. Hypoglycemia has been a major impediment towards better control of diabetes. (76) In the DCCT, there was a threefold increase in hypoglycemic events in the group that was intensively treated. (5) Moreover, as many as 7 blood glucose measurements per day were not sufficient to detect a number of severe hypoglycemic and hyperglycemic events detected by continuous glucose monitoring (CGM). (77) CGM appears to be making in roads in to clinical practice. The United States Food and Drug Administration has recently approved two CGM devices for use.

(1) Gluco Watch® (Cygnus Inc., Redwood City, California)

DCCT study, the risk of hypoglycemia was nearly threefold in patients treated with intensive insulin

Gluco Watch provides a means to obtain painless automatic glucose measurements noninvasively. Glucose is extracted through the skin using a process called reverse iontophoresis. Iontophoresis is a process in which a low level current is passed through intact skin, and glucose molecules, which are neutral, are extracted by the electro-osmotic flow of charged ions. Extraction and detection are achieved by means of 2 hydrogel pads containing glucose oxidase. Each glucose reading is a result of 'time averaged" measurements over a 20 minute period. It also stores up to 4000 data points, which can be used for retrospective trend analysis. Clinical efficacy and accuracy of Gluco Watch has been demonstrated in both home and clinical settings. (78, 79) Use of this technology makes it possible for patients (and their physicians) to become immediately aware of hypo/hyperglycemia, to track the day-to-day glucose excursions, make adjustments in their therapeutic regimen and evaluate the effectiveness of the changes made.

(2) Minimed Continuous Glucose Monitoring System (CGMS)

CGMS uses a subcutaneously inserted sensor to monitor interstitial glucose. The assay method is based on electrochemical detection of glucose through its reaction with glucose oxidase. Data is collected once every 5 minutes and can be downloaded into a computer for analysis and interpretation. (80) The sensor is inserted subcutaneously and is capable of reliable operation for up to 3 days in the glucose range of 40-400 mg/dl. In it's present design, the monitor does not display real time tissue glucose while the unit is in operation. After the patient has worn the device for up to 72 hours, the sensor is removed, and the data is downloaded to a computer. The comprehensive data analysis along with other clinical information allows the health care professional to design an individualized optimal therapeutic plan for the patient. (81) This device has been found to be reliable, stable over time, not clinically different across demographic subgroups and is clinically useful. (81, 82)

RISKS OF INTENSIVE INSULIN THERAPY

The most common side effect of intensive insulin therapy is the development of 'hypoglycemia". In the therapy. (5) However, the risks of hypoglycemia can be minimized by careful attention to detail; such as

meal planning, exercise regimen and use of appropriate combination of insulins. Some patients with strict glycemic control may develop hypoglycemia associated autonomic failure and hypoglycemia unawareness". (83) This is the result of low glucose levels in the setting of absent glucagon response and reduced autonomic and neurogenic responses, and thus a vicious cycle of recurrent hypoglycemia. (83, 84) However, as little as two to three weeks of avoidance of hypoglycemia reverses hypoglycemia unawareness. Therefore, setting individual goals for hypoglycemia becomes extremely important. The goal should be to obtain the best glycemic control with the lowest risk of hypoglycemia.

CONCLUSION

With further improvement in the continuous glucose monitoring technology and insulin administration, it should be possible to develop computer algorithms to deliver appropriate amounts of insulin, so as to keep the plasma glucose levels in a relatively narrow range. Such a "closed loop" system will allow for maximum lifestyle flexibility for patients with diabetes while keeping their blood glucose and HbA_{1c} at a desired level with a minimal risk of hypoglycemia. However, so far, this goal has not been realized in practice.

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