INSULIN TREATMENT

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The aim of treatment of type 1 (insulin dependent) diabetes is to achieve the best possible blood glucose control without excessive swing to high or low extremes, particularly avoiding problems from hypoglycemia. An optimal level of glycemia may be 4-7 mmol/1 fasting and preprandial, values below 10 mmol/1 postprandial, and a H_{BAIC} level below 7.5%, which corresponds to a mean blood glucose level of 8-8.5 mmol/1. Some preliminary data indicates that this therapeutic goals may delay the development of nephropathy (Microalbuminuria)[1-3]. Whether strict metabolic control may influence the development of retinopathy is at present unknown[1-3]. Once significant diabetic complication occur, even normoglycemia seems to cause a reversal but some slowing of the progression may be possible[3-5]. However, intensive treatment can not be recommended to all patients. The treatment is very expensive both to the patient and to the health-care system. The ever-present danger of insulin-induced hypoglycemia also exists[2-5]. Until the results from large-scale clinical trials is presented careful decisions about which patient to enroll in intensive treatment programs are necessary[1]. Candidates are patients with newly diagnosed Type 1 diabetes and without or only with minimal occurrence of late diabetic complications[1-3]

To obtain near-normalization of glycemic control it is necessary to balance food intake with daily activity and insulin requirements. Furthermore, an education and motivation of of the patient are fundamental[4-6].

During the past years, there has been marked improvement in our ability to control hyperglycemia effectively in patients[1-3]. Perhaps the most important of these advances is the development of patient self-monitoring of blood glucose together with renewed interest in insulin availability and insulin regimens[4-6]. The following report will outline the clinical use of insulin.

Insulin Preparation and Insulin Absorption

Insulin preparations are classified as short, intermediate and long-acting. Table 1 shows the duration and time of peak action of the various insulin. These are useful as a rough guide, but may be misleading as a wide within and between patient variation in insulin absorption has been demonstrated[7-8].

The onset of action of short-acting insulin is some minutes after injection and maximum activity is seen one to two hours after injection. After about eight hours no short-acting insulin is remaining in the injection site.

On the average about 80 per cent of an injected intermediate-acting insulin is absorbed after 24 hours (8), which is important to notice. If, for example, 20 units of intermediate-acting insulin are given, approximately 16 units are absorbed during the first 24 hours and about 4 units remain at the injection site. In the subsequent 24 hours, following the

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next injection, the patient will absorb about 19 units (80 per cent of 20+4 units) and have 5 units remaining in the subcutis. Not until the third day will the absorption be about 20 units and a steady state have been reached. Consequently, if the dose of intermediate-acting insulin is changed every day, steady state will not be reached and lability in day-to-day glycemic control will be the result. The interval between adjustments of long-acting insulin should be even longer. If supplementary insulin is needed during this period short-acting insulin should be used.

The factors responsible for the inter-(50%) and intrasubject (25%) variations in insulin absorption (the coefficient of variations may be as high as 60 per cent) are only partly understood, but anatomical site, depth of injection, exercise, smoking, mixing of short-and intermiaiate-acting insulin and local insulin degradation may all be of importance[7-9].

Insulin absorption is fastest from the subcutaneous tissue in the abdominal area, intermediate from the arm and slowest from injection sites in the leg. The absorption rate is approximately twice as fast in the abdomen as in the leg. Unsystematic rotation of injection sites to different anatomical regions might thus, contribute to lability of metabolic control In contrast, the deliberate use of abdominal injections can be useful in situations where rapid action of insulin is desirable, i.e. during treatment with multiple injections. It is very difficult to inject to the same depth with every injection and this may, therefore, be a factor contributing to different day-to-day insulin availability. Especially, patients using perpendicular injection technic have the risk of accidentally i.m. injections. On the average the rate of insulin absorption after i.m. injection is 2-4 times faster compared with the absorption after s.c. injection. Therefore, especially lean patient has to use 45° angle injection after pinching up the skin at the injection site to reduce the possibility of injecting intramuscularly. The rates of insulin absorption did not differ after s.c. or i.m. using the abdomen and is comparable to that observed after i.m. injection on the leg. Therefore, we usually suggest using abdomen before meals in patients treated with multiple injections.

Temperature changes have effect on insulin absorption, presumably due to a change in capillary blood flow. High temperature increases the absorption rate, whereas a low temperature will reduce insulin absorption rates and this may be a factor contributing to exercise-induced hypoglycemia. This effect of exercise is especially pronounced after i.m. injection of both fast and intermediate acting insulin. During smoking, the rate of insulin absorption is reduced to about 50 per cent and for the following 30 min after the cessation of smoking it is decreased about 30 per cent. Smoking before breakfast will delay the desirable brisk rise in plasma insulin and aggravates the post-prandial hyperglycemia.

Table 1
Timing of action

Activity after s.c injection (hrs.)			
Type	Onset	Max.	Duration
Fast	1/10-1/2	1/2-4	4-10
Intermediate	1-4	4-18	18-30
Prolonged	4-8	8-30	>36

When mixing short and intermediate-acting insulin some inter-coverstion occur. To prevent this, mixtures prepared in the syringe must be injected as soon as possible after drawing up. Variation in local degradation of subcutaneously injected insulin may also in some patients

contribute to wide dose to dose variations in insulin absorption,

Insulin Regimen

Ideally, in the treatment of diabetes, the plasma insulin profile should closely resemble that of insulin secreted by the normal pancreas with high insulin concentrations during the meals and low concentrations between the meals and during the night.

One daily injection of insulin can never mimic the plasma insulin profile of normal subjects. One daily injection with or without short-acting insulin produces a relatively constant background of insulin rather than the peaks which are necessary to overcome postprandial hyperglycemia. The insulin concentration, relative to the normal pattern, is lower after the meals and higher between the meals. This fully explains the differences in blood glucose between diabetics and normal subjects with high postprandial blood glucose level and risk of hypoglycemia preprandial or during late evening or night.

With one daily injection of insulin high fasting blood glucose values are often observed[7]. When increasing the daily dose of insulin to improve the glycemic control, hypoglycemia is a serious risk. If frequent hypoglycemic attacks are a problem—and these can not be avoided by changes in carbohydrate content in the meals or snacks— the daily dose of insulin is divided into a pre-breakfast and pre-dinner injection.

Short-acting insulin is used prior to meals to achieve a less pronounced increase in blood glucose after eating. It is important to inject the short-acting insulin half an hour before instead of just before the start of the meal. This will lead to better matching of insulin delivery to the physiological insulin need and lower postprandial glucose peaks.

Twice daily injection of a combination of short-and intermediate-acting insulin provides insulin availability with each major meal and sustained insulin availability overnight. The initial distribution is often two thirds of the total daily dose in the morning and one thirds of the daily dose in the evening. The pre-breakfast dose is divided into one third of short and two thirds of intermediate-acting insulin. The morning short-acting insulin has the major effect between breakfast and luncheon and the intermediate-acting insulin between luncheon and dinner. The evening short-acting insulin acts between dinner and bedtime and the evening intermediate-acting insulin during the night. Because of the timing of action of the evening intermediate-acting insulin, some patients will experience noctural hypoglycemia when normal fasting blood glucose values are aimed for. This is, in part, explained by the fact that the insulin requirements throughout the night are not constant. The requirements are minimal between two and four am and increases during the following hours (dawn phe-nomenon). These problems have led many to split the evening dose of insulin with the fast acting component still injected before dinner, but the intermediate acting insulin at 22.00-23.00 p.m.. The peak effect of insulin then coincides better with physiological needs and the waking period. A simple reduction in evening intermediate insulin dose may prevent nocturnal hypoglycemia, but only at the cost of increasing fasting and postbreakfast hyperglycemia.

During the last few years, treatment with three daily injections of insulin has gained popularity. Short-acting insulin is given half an hour before each meal and the intermediate-acting insulin is given either

before the evening meal or at bedtime. This “four components” insulin regimen provides a brisk rise of insulin with each meal and a basal insulin level throughout the night.

The decrease in plasma insulin concentrations after meals is still slow. Therefore to avoid hypoglycemia, snacks two to three hours after meals are of importance.

Attempts to use four injections of short acting insulin only impose the risk of nocturnal hypoglycemia (the peak effect of the bedtime insulin) and fail adequately to control pre-breakfast blood glucose values.

In the four injection regimen about a 35% of the total dose is given as intermediate insulin, and of the remainder about 25 per cent is given before breakfast, 20 per cent before luncheon and 20 per cent before dinner.

Multiple injections regimen has the potential advantage of permitting greater flexibility in meal timing and in meal size because preprandial insulin is administered at the time the meal is consumed with the possibility of changing the insulin dosage according to the size of the meal.

A meal can be omitted if the preprandial insulin injection is omitted as well. This flexibility is not possible with conventional regimens as the delay or omission of a meal will lead to hypoglycemia.

Intensified insulin regimens in combination with home blood glucose monitoring and education have made the maintenance of near normal blood glucose levels a therapeutic reality.

Adjustment in daily dose of insulin

Before the insulin dose is adjusted it should be ascertained that alterations in food intake, physical activity or rebound hyperglycemia cannot explain the blood-glucose findings. When the insulin dose is adjusted only one component of insulin is altered, starting with the component controlling pre-breakfast blood glucose, for instance, evening intermediate-acting insulin, or Ultralente in the Ultralente-regimen. After pre-breakfast hyperglycemia is correct, the component responsible for post-breakfast hyperglycemia, for instance morning short-acting insulin is adjusted, and then sequentially the other insulin components: Adjustments are made in steps of two to six units at a time, no more frequently than every three to four days.

Hypoglycemia. The recognition of over-treatment with insulin is difficult, even for physicians who are aware of the problem. Chronic overtreatment with insulin can present intermittent hypoglycemia separated by periods of hyperglycemia and, occasionally ketonuria (rebound hyperglycemia, Somogyi reactions). It is important to document hypoglycemia and not to increase the daily dose of insulin in response to rebound hyperglycemia and thereby to start a vicious circle which causes instability in blood glucose control.

Nocturnal hypoglycemia, especially, is frequently unrecognized, but morning headaches, lassitude, and night sweats are common symptoms. Often, the patient’s insulin doses have been increased during illness, but not subsequently reduced after recovery when the insulin requirements have returned to normal. The treatment is, of course, reduction of the daily dose of insulin. The diagnosis of insulin overtreatment is confirmed when the dose reduction leads to improved control,

The patients should be educated to take 10

g of rapidly absorbed carbohydrate during hypoglycemic attacks, and during unusual physical activity to take extra food (about 10 g of carbohydrate/30 min activity) to avoid hypoglycemia.

Insulin Antigenicity. The impurities in insulin preparations provoke the formation of antibodies in the patients (10, 11). These antibodies bind insulin and thus, change the activity of the injected insulin. They delay the onset and duration of action and thereby increase the risk of severe hypoglycemia[12],

When changing to highly purified insulin preparations the amounts of antibodies decline, and a reduction in daily dose of insulin is necessary during the following months (up to 20-30 per cent).

Insulin antigenicity has through the years complicated therapy for many patients with regard to allergy, lipoatrophy, lipohypertrophy, and insulin resistance. These complications to insulin treatment improve during treatment with highly purified insulin and are very rarely seen in patients who have been treated with highly purified insulin from the time of diagnosis[10,11].

Human Insulin. Human insulin has now been available for clinical use for a few years, produced either by semisynthesis (enzyme modified porcine, emp), or genetic engineering (cloned recombinant DNA bacteria, crb).

As expected, it appears that human insulin is less immunogenic when compared with highly purified porcine insulin and evokes no or minimal antibody response. The amounts of immune complexes and insulin specific IgE have also been less in patients treated with human insulin [10,11,13].

The pharmacokinetics of human insulin differ little from porcine insulin. The former is absorbed slightly faster from the subcutaneous tissues, giving a more rapid onset of action and a shorter half-life[14].

Human insulin is the treatment of choice in the rare patients with generalised or local allergy to procine or bovine insulin, with anti-body-mediated insulin resistance and those with lipoatrophy. Furthermore, it may be useful in diabetics requiring insulin therapy inter-mittently (for example gestational diabetes, emergencies in non-insulin dependent diabetes mellitus).

Finally, it is important to point out that improvements in insulin regimens as such are not necessarily sufficient to lead to improved metabolic control. Indeed, a better dietary compliance, improved patient knowledge, and home blood glucose monitoring may be of a equal importance in attaining good metabolic control. Several studies have shown that blood glucose measurements by the patient (rather than urine glucose measurements) may result in an improvement in metabolic control, primary because of a better dietary adherence and by stimulation attention to all elements of diabetes management.

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