Insulin Therapy

Q. How does treatment of IDDM differ with the use of human insulin regarding the does, time of Action, hypoglycemic effects and hypoglycemia unawareness and stability of control. What Are the disadvantages and advantages?
A. We should first look at these facts as they relate to insulin therapy in general:

I. Dose: The normal requirement of insulin is about 0.5 – 0.7 units/kg body weight. Thus, a child of 30 kg would require 15-20 units of insulin per day, and a young adult of 70 kg about 35-50 units of insulin. It is not uncommon to find both children and adults "over-insulinized". On the other hand rarely patients require large doses of insulin for control of blood glucose. The *appropriate does of insulin* is the minimum does which is adequate to "control" blood glucose. This is itself a relative issue, because goals of control in a young IDDM are different from those in an IDDM with chronic renal failure. The appropriate does should not cause hypoglycaemia, undersirable weight loss or gain, nor excessive hunger.

The dose of insulin is based on "units". By definition unit for unit insulins of all species have the same effect.

2. Times of action: The inter-individual coefficient of variation (cv) of absorption of 50% of injected sub-cutaneous does is about 50%; I.e. the time taken for absorption of 50% of injected does in different individuals for short acting insulin ranges from 2 to 4 hours, and for intermediate acting insulin from 17 to 31 hours. Within the same individual the cv is 25% (ranges of 3-4 and 20-28 hours respectively). Thus, with the use of same species of insulin there is a large variation in the rate of absorption and duration of action.

3. Hypoglycemic effects: Sensitivity to insulin is specially high in illnesses like renal failure , adrenal and pituitary deficiency, and not ant specific reason in about a quartile of the population without any specific reason.

In addition, other factors affecting insulin absorption are :

a) Concentration : higher :slower
b) Volume: higher : faster
c) region of injection: abdomen faster compared to arms/tighs.
d) lipodystrophy: slower
e) body weight: leaner: faster
f) exercise of injection site: faster
g) temperature : cooling: slow
h) local message: faster
i) neuropathy : faster.

Against this backdrop let us now look at only one variable factor viz. species of insulin.

The discrepancy between does/duration of action/hypoglycemic effects etc. of unmodified of NPH insulin in various reports is so much that the British Medical Bulletin, 1989, comments that "there remains no consensus on the possible subcutaneous pharmacokinetic difference between unmodified or NPH human versus porcine insulin".

Dose: The determination of a "unit" of insulin is by bioassay. For a pure compound, this should be fixed amount, i.e. unit to unit each insulin should have same bio-potency. Thus, only those patients requiring more than physiological doses of insulin (> 0.5-0.7 unit/kg in an otherwise healthy individual) may need does changes when switching from highly purified animal to human insulin. When switching from less purified insulins, it is recommended that the dose of insulin be reduced by about 20%.

Times of action: Insulin zinc suspension with human insulin dissolves much more rapidly, and so may not be able to control overnight blood glucose. This has been shown to be significant enough to result in increased glycosylated hemoglobin. The opinion regarding absorption rates of other formulations is still divided. As regards plain insulin, the issue may remain unresolved with availability of monomeric insulin whose kinetics is very different (almost immediate absorption, and rapid peakin) from :regular" insulin, because of (a) convenience : there is no need for the usual 20-40 min gap between injection and food, and, (b) the absence of continuing action of insulin after the absorption of is over.

Hypoglycemic effects and hypoglycemia unawareness: Controversy had arisen whether routine shift of insulin from porcine to human would cause hypoglycemia-unawareness. This was because it was demonstrated that adrenalin and noradrenalin response and the symptoms of hypoglycemia were less with human insulin than

why should the species of insulin affect the adrenergic response to lowering of blood glucose , rather than the level of the blood glucose per se? The controversies seem to be clearing now with a landmark study which demonstrated in a double blind control, cross over trial that there was no difference in hypoglycemia-unawareness produced by human and porcine insulin, and that the subjects under study could not predict correctly as to which insulin they were taking.

On the other hand it has become amply clear that the awareness of diabetes, presence of autonomic neuropathy, and overall control. The last point needs a little elaboration. The lower the glycosylated hemoglobin levels, the lower is the threshold for recognition of hypoglycemia. However , the threshold for neuroglucopenia remains unchanged, resulting in a direct passage to more severe forms of hypoglycemia. "hypoglycemia, without awareness to hypoglycemia: hypoglycemia unawareness" Since the targets for control are being revised and lowered over the last decades, the occurrence of hypoglycemia unawareness should not surprise us. An increase in hypoglycemic unawareness produced by human insulin has not been substantiated as earlier reported by some investigators. [P.S.]

In the use of human insulin, a few practical guidelines are as follows:-

Dose: A modest reduction in dosage of biosynthetic human insulin may be necessary in patients currently stabilized on high doses of mixed species of less purified animal insulin. For patients receiving > 40 units daily, a 20% reduction is recommended.

Time of Action: Because of its greater hydrophilic nature, following subcutaneous injection, human insulin is absorbed slightly faster and thus interval between injection and meal should be reduced.

Bio –effectiveness: Though hypoglycaemic effect is equivalent, human insulin lowers betahydroxy-butyrate to a greater extent.

Stability: Human insulin is less stable and more likely to clump with heat or agitation, reducing its biopotency. We understand the newer formulations contain some stabilizing agents.

Advantages of human insulin are:

1) less allergenic.
2) useful as treatment for lipodystrophies.
3) produces less antibodies and thus probably its kinetics are more consistent.

Disadvantages are:

1) price
2) stability

Postscript: The golden rule of J. Pirart is , "Becautious in taking any decision to change something that is running well, however odd the treatment seems to be."

Q. What is the algorithm in insulin dosage in relation to blood glucose value? Can a child take Decision by himself on this issue?

A. Currently available insulins includes short-acting , intermediate-acting and long-acting types. They are available in concentrations of 40 U/ml or 100 U/ml. Appropriate dilutions have to be made for younger children requiring low doses. These insulins are extracted from beef or pork pancreases and marketed separately or as a insulin synthesized by recombinant DNA technology or by semisynthetic methods is also available for therapy.

Exogenous insulins are injected subcutaneously. Their rate of absorption is variable. Thus, They lack precision of endogenous insulins secreted directly into the portal system. Single dose of intermediate insulin cannot duplicate the pattern of normal insulin secretion. Injections of regular fast-acting insulins prior to each meal also do not achieve normalization of blood glucose value even though the degree of control is definitely better. Thus, the regimen of insulin selected represents a compromise. It tries to achieve a near-normal intermediary metabolism and normal growth and development. It should avoid frequently hypoglycemic reactions and prevent consequences of unrestrained hyperglycemia.

The dose generally required at the onset or after recovery from DKA is about 0.7-1.5 U/kg. The actual requirement can however be judged by the 24 hours period where only regular insulin alone was given before each meal during the transition period following DKA. Insulin with duration of action of more than 24 hours are not preferred in children. In most instances one intermediate-acting insulin is combined with a short acting (regular) insulin. In this format approximately 2/3 of the dose is an intermediate-acting insulin and 1/3 regular insulin. Injection is given 30 minutes

before breakfast. The regular insulin should be drawn into syringe first and the same sequence should always be followed. Disposable syringes with fine needles, minimal dead space and easy-to-read calibration should be used.

To avoid hypoglycemia, single mixed-dose regimens are initially calculated on the basis of 2/3 of initial daily dose. Gradual increases or decreases of 10-15% can than be made daily during initial phase until the desired degree of control is achieved. The insulin requirements for first few days may be more than 1 U/kg/24 hr.

Although many children can be managed with single daily injection of insulin, two-daily-injections are now routinely recommended. When there is nocturia with fasting hyuperglycemia and morning glucosuria in response to singly daily dose of insulin , dividing the total daily doses into 2 injections should be considered. In this schedule, 2/3 of the daily requirements is given before breakfast and 1/3 before evening meal. Each injection consists of intermediate-acting and short acting insulins in proportions of 2-3:1. For example; assuming a total daily dose of 0.9 units/kg for a 30 kg child; 12 units of lente/NPH combined with 6 units of regular insulin will be given before breakfast and 6 units of lente/NPH combined with 3 units of regular insulin will be given before the evening meal. As with single-daily-dose regimen stepwise increases or decreases each consisting of 10-15% should be made to minimize hypoglycemic reaction and undue hyperglycemia.

Twice-daily injections are suitable to infants and children below 5 years (in whom intake of food and activity are not predictable) and adolescents especially during pubertal growth spurt. It results in smoother metabolic control with fewer hypoglycemic attacks and less uncontrolled hyperglycemia. In many centers including the one at AIIMS, twice daily regimen is the standard therapy followed. When complicance is poor (especially in adolescents) one injection is preferred to none.

Two daily injections may not always result in better metabolic control than one daily injections. Thus, the treating physician should in all instances attempt to decide the best regimen suitable for the metabolic control in every child.

Management on a day to day basis is a complex task. To achieve this a strong component of patient education is essential. In our experience older children can safely follow these guidelines and administer insulin and monitor blood glucose level themselves. However, a close contact with a healthcare team is essential. Success in management of a diabetic child can be measured to a considerable extent by the competence of the child to assume responsibility for daily care. [P.S.N.M.]

Q. For adjustment of commonly used insulin dosage (regular & intermediate) do you depend more often on fasting/pre-prandial blood glucose values or the post-prandial values?

A. In the outpatient clinic and during the self home blood glucose monitoring, we generally rely on fasting or preprandial blood glucose values rather than postprandial blood glucose values. We usually recommend testing and recording blood sugar levels by strips 4 times a day (before breakfast, lunch, dinner and sleeping) at least twice a week. Frequency of testing is stepped up during the periods of illness or poor control or during an adjustment of the dose.

Ideally the blood glucose concentration should range approximately 80 mg/dl in the fasting state and 140 mg/dl after meals. In practice, however, a range of 60-180 me/dl is acceptable. Blood sugar levels outside these limits are indications for a change in dose of insulin. If fasting blood glucose is high, the evening dose of intermediate-acting insulin is increased by 10-15%. If the pre-lunch levels are high, the morning regular insulin is increased. Reduction in doses of insulin is also made in a similar pattern.

Post prandial blood sugar levels, even though not routinely used by us for monitoring, can give an estimate of the effect of prescribed insulin after each meal. /they are mostly used during intensive monitoring in a hospital. [PSNM].

Q. Under what conditions, intensive insulin therapy should be instituted?

A. The limitations of "conventional regimen" of insulin [one or two doses of intermediate acting insulin or a mix of intermediate and short acting insulins (IMA+SAI) before each meal] in a subject with IDDM are :

1) It is not possible to mimic the normal complex physiological pattern of secretion of insulin.

2) It is not possible to achieve satisfactory blood glucose control in most subjects.

3) It does not provide a flexibility in the life of a diabetic as the meal pattern and timings are decided by the amount and time of the peaking insulin does already taken (eg. Lunch in relation to the morning dose containing IMAI).

4) There are often "inexplicable" wide and erratic excursions in blood glucose levels.

5) The patient can not exercise a meaningful control over the management of his life/diabetes.

6) The patients often have night time excess insulin and inadequate insulin at dawn. The evening IMAI can be shifted to bed-time covering the dawn phenomenon and decreasing the risk of nocturnal hyposlycemia.

With an aim to overcome these hurdles the concept of multiple daily insulin injections (MDI) regimen came up.

MDI regimens usually include:

1. (a) SAI before each major meals as a bolus dose (to cover the meal related excursion of blood glucose), with (b) IMAI or long acting insulin (LAI) late in the evening (basal insulin requirement for the post-absorptive state). In addition several other regimens can be worked out to meet a patient's specific needs. [1]

2. IMAI and SAI before breakfast, SAI before lunch and dinner and IMAI at bedtime can be tried for patients who are not consistent with meal timings and insulin injections.

3. Long acting insulin (LAI) eg. Protamine zinc and ultralente insulin) can be utilized to meet the basal insulin requirement especially for patients in whom the fasting glucose levels are erratic despite taking IMAI (this is especially true for those on human lente insulin because its onset and duration of action is shorter compared to bovine/procine insulin). Ultralente insulin can be given as one injection in the morning or can be divided so that half the dose is taken before breakfast and the other half before dinner.

4. MDI regimens including combinations of all three insulin (LAI, IMAI and SAI) have also been suggested. But with more varieties of insulins it would be more difficult to predict the durations and peaking of insulins, thus this regimen is usually not recommended.

The absolute indications of using intensive regimen are :

1. pregnancy
2. renal transplant

Other indications include

3. brittle diabetes
4. inconsistent life-style and
5. insulin requiring patients who are motivated and "diabetes educated" enough for frequent shots and self blood glucose monitoring.

The few prerequisites for use of MDI in practice include:

1. educated and motivated patients, and a 24-hours accessible treating team with contact facility on telephone.
2. regular insulin should be given within 4-6 hours of one another. Only occasionally the time gap between two shots can be extended to 7-8 hours.
3. if patient has to miss the lunch due to unusual circumstances, half of the prescribed regular insulin should be injected at the time of lunch. In case, patient takes half of the lunch, pertinent insulin dose can be reduced to ¾ of usual dose. In a study conducted by Trunbridge FK, the effects of half-sized lunch with reduced insulin dose and a evening meal delayed by 2 hrs were assessed. The results of glycemic control and hypoglycemias were same as in the control group.
4. frequent self blood glucose monitoring (almost four times a day; before each injection, and at night) is essential to adjust the dose of insulin.

Advantages of MDI use:

1. more flexibility in life style. In a retrospective survey of the attitudes of 137 patients, 90% appreciated better flexibility in the meals. Two further long term studies, one in a group of 15 children and the other in 169 adults have reported an improvement in patient's life style in 77% and 90% subjects respectively.
2. better self insulin dose adjustments.
3. improvement in glycemic status, decrease in wide fluctuations of blood glucose. In studies referred to above a reduced rate of hypoglycemia and ketoacidosis on MDI (compared with conventional regime)are reported.
4. overall feeling of well being.

5. a reduced daily dose of insulin (reducing hyperinsulinemia).
6. a reduced rate of development of chronic microvascular diabetic complications.

The disadvantages of MDI include:

1. increased requirement of syringes/needles/monitoring devices and the "sticks, ultimately mounting cost of managing diabetes. Moreover, the insulin pen injectors which make injection procedure convenient and are available in India and the insulin (human) used with them turn out to be almost four times costlier than conventional animal insulin.
2. some restrictions in life-routine (especially in summer in India) because of concern of safety of carrying the insulin/pen in heat.
3. more frequent significant hyupoglycemias, and hypoglycemia unawareness (with a better glycemic control this is a necessary price the diabetic pays). Several studies have reported that use of intensive insulin regimen (MDI and/or continuous subcutaneous insulin injection therapy) results in unacceptable rates of severe hypoglycemias. A study conducted by P. Scanlan et al for a period of five years demonstrated that with a better HbA_1C, severe hypoglycemias occurred 1.1 times per patient per year (compared to 0.4 in the control conventionally treated group). In DCCT study also HbA_1C levels are lower and severe hypoglycemia is more frequent (26% vs.9.8% in control) in the MDI group.
4. the repeated testing and fear of nocturnal and "unaware-hypoglycemias" can be associated with almost obsessive-compulsive behaviour regarding diabetes and glycemic control.

If we compare the advantages & disadvantages of MDI regimens, advantages certainly outweigh disadvantages.

Q. Is there any indication to use insulin in :
(a) sibling of a child with IDDM with normoglycemia but islet cell antibody positive.
(b) during ‘honeymoon phase’ of IDDM
(c) in a patient with IGT
(d) early NIDDM

A. (a) sibling of a child with IDDM has a 5-10% chance of developing diabetes; HLA identity and islet cell antibody positivity increase the risk several fold. However, this risk remains much less than that of identical twins (30-40%). On development of insulin antibody positivity the risks increase manifold and certain mathematical models can predict the time lag for development of clinical diabetes mellitus.

Several measures have been tried to prevent development of clinical disease in those at a high risk of developing IDDM. These primarily include immune modulation. Intensive insulin treatment of early IDDM has been shown to be effective in preserving better beta cell function after a period of time. However, there is no role of insulin in a non-diabetic/pre-diabetic sibling.

(b) In addition to the facts mentioned above there is no indication for use of insulin in the "honeymoon Phase", provided on frequent monitoring the blood glucose is normal. Some diabetologists however, recommend use of a very small dose of insulin (say, 0.5- I unit/day) with an aim of ensuring that the diabetic child does not forget the routine of dietary regulations, injection and monitoring.

(c) The relevance of impaired glucose tolerance is two fold. About 1-5% of subjects with IGT would develop overt diabetes every year. Moreover, they are at a higher risk of developing large vessel disease (LVD) (coronary, cerebrovascular and peripheral vascular). Hyperinsulinemia is implicated in the pathogenesis of LVD. Sulfonylureas (which increase insulin levels) have been shown to be ineffective in reducing the chances of development of diabetes in IGT. Likewise, there seems to be no indication to recommend insulin in IGT.

(d) The chief defect in NIDDM (early, or otherwise) is insulin resistance. The chief mode of therapy, thus, is reducing insulin resistance. This is best achieved by regular physical exercise, small frequent high fiber and calorie restricted meals, loss of excess weight (especially truncal), and drugs as a last resort. Most "early" NIDDM would be controlled on non-pharmacological measures if they are followed. If pharamacological agents are needed, oral hypoglycemic drugs [biguanide for the obese (>130%), sulfonylurea for the not so obese]: a combination of oral drugs; oral drugs with insulin; are then followed by insulin alone. Thus, there is no role for insulin in "early" NIDDM, except when indicated for other reasons (pregnancy, major surgery of stress). [P.S]

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