Diabetes Mellitus: Insulin Use

Part 3

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Insulin is required for normal carbohydrate, protein and fat metabolism. Patients with Type I diabetes depend on exogenous insulin for their survival while Type II diabetics may require insulin at a later stage of their disease.

A history of insulin

The discovery of insulin in 1921 by Banting, Collip, MacLeod and Best was one of the medical breakthroughs of this century. These first insulins were of animal origin, excreted from the pancreata of cows and pigs. Addition of protamine and zinc allowed the development of longer acting insulins that were developed by 1951. By 1972, insulins were purer and this made them less immunogenic with a more reliable onset and duration of action. In the early 1980s, genetic engineering allowed the production of insulin identical to human insulin by bacteria and yeast.[1,2]

Indications for insulin therapy

All patients with Type I diabetes require replacement insulin therapy upon onset of the disease.[3,4] Most patients with Type II diabetes initially secrete enough insulin to be treated with diet, exercise and oral hypoglycaemic agents. However as the disease progresses, the secretory capacity falls making insulin treatment necessary. About 50% of patients require insulin due to beta-cell exhaustion. Other indications for insulin include pregnancy, ill health precluding oral treatment, during and after major surgery, any illness that may place the body in a stress situation, fasting blood glucose of more than 17mmol/l on diagnosis and diabetic ketoacidosis or hyperosmolar coma.[3,5,6]

The aims of treatment with insulin, are whether Type I or Type II diabetes mellitus are:

a) to achieve optimum metabolic control by mimicking production of endogenous insulin as closely as possible
b) to avoid experience and risks of hypoglycaemia.[4]

Types of insulin

Since insulin is a protein that is acted upon by the gastrointestinal enzymes, it must be administered parenterally. Insulins may be classified depending on their pharmacokinetic profile into three types - short, intermediate and long acting.

Regular insulin is a soluble, short-acting insulin and since it is the only one available in solution, it is the only insulin that may be administered intravenously.[6,7] Intermediate and long acting insulins are suspensions of insulin that have been modified to prolong absorption from the site of administration. This is achieved by producing insulin-protamine or insulin-zinc mixtures. Insulin zinc mixtures may be amorphous or crystalline, with the latter having a longer duration of action.[6,7] The insulins available within the Government Health Services (GHS) together with a comparison of their pharmacokinetic characteristics are summarised in Table 1. When applying data linked to pharmacokinetics, one must keep in mind that most data were obtained through assessment in healthy volunteers or in well-controlled diabetics under specific metabolic conditions. In actual fact, there is wide inter and intra subject variation in response to insulin.[8,9] Since many patients require a combination of intermediate or long acting insulin with short acting insulin, ready mixed insulin in the form of biphasic insulins are available.[6]

Fast acting analogues (insulin lispro, insulin aspart), have been developed in an attempt to mimic physiology more closely. Conventional soluble insulin forms hexamers when in solution. These need to dissociate before absorption and this delays the onset of action. The newer analogues are monomeric insulins and do not associate. These insulins start to act within 15 minutes of injection, peak at 50 minutes and have a duration of action of 3-5 hours, which more closely resembles human insulin. They are therefore administered immediately before a carbohydrate meal and this is likely to enhance patient compliance.[2,6,16]

All insulins available within the GHS are human in origin. The two forms of biosynthetic recombinant DNA insulins using Eschericia coli (Lilly) and Saccharomyces cerevisiae (Novo-Nordisk) are therapeutically equivalent.[17] One should also keep in mind that insulins from foreign countries may be of animal origin. It is important that there is no inadvertent exchange of insulins. When in doubt, human insulin should be used.[18]

All locally available insulins are of the 100 unit strength implying that they contain 100 units of insulin per millilitre (ml). Therefore care must be taken to instruct the patient about the correct dose in units and not in millilitres (mls) of insulin. One must also exercise caution when instructing tourists since different strengths of insulin may still be available internationally - 40 units/ml or 500 units/ml.[17]

Designing insulin regimens

There is no generally accepted approach to initiating insulin therapy and much depends on the preferences of the diabetologist. An empiric way of calculating the dose may be the following:[7]

A) Type I: Initial dose: 0.5-0.8U/kg
B) Type II: With ketosis, during illness: 1-1.5U/kg
C) Type II: Adolescents in growth phase: 1-1.5I/kg
D) Type II: With insulin resistance: 0.7-2.5U/kg

Different dosing regimens may be administered and these are tailored according to the patient's motivation, the ability to monitor control and adjust doses and the level of control desired.[17] Factors

that may alter the onset and duration of insulin action need to be considered. This includes the site of injection (absorption is fastest from the abdomen and slowest from the thigh), ambient temperature (heat increases the rate of absorption) and massage of the local area (increases rate of absorption).[7] Table 2 offers a comparison of possible insulin regimens.

Administration of insulin via a continuous subcutaneous infusion offers intensive glycaemic control but requires training, motivation and compliance together with supervision from an experienced healthcare team. Such a system provides a basal amount of insulin (0.5-1 unit/hour) and patient-activated pulsatile doses of insulin to cover meals. Pump therapy may increase patient flexibility but it is coupled by numerous problems such as mechanical failure and hypoglycaemic and dermatological complications. Besides, there is no evidence that this intensive insulin therapy offers better control than multiple dosing.[7] Patient selection criteria are therefore cardinal to ensure safety and success of treatment.

The sliding-scale method of insulin dosing is sometimes used in a hospital setting where insulin requirements may vary drastically over a short period of time due to stress, variable calorie intake or inactivity. Capillary blood glucose concentrations are measured every 4-6 hours and insulin administered accordingly as prescribed. Sliding scales vary from institution to institution and according to the patient response. One needs to ensure that the personnel involved are adequately trained in bedside blood glucose monitoring and that meters are properly maintained and calibrated. Strips should be kept in tightly sealed containers to prevent deterioration.[7]

A dosage regimen may involve combination of insulin with oral agents and this may be an option in Type II diabetics where glycaemic control is not adequate. Insulin is normally administered as a dose at night to suppress the hepatic glucose output.[5] The reader is referred to part 2 of this series for a more detailed discussion.[19]

Patients may present to the pharmacy with nausea and vomiting due to conditions such as viral gastritis. It is very important to advice the patient to maintain the same dose of insulin despite minimal food intake and advise the patient to seek specialist medical advice immediately. At no point should such a patient be advised to stop insulin since this may precipitate ketoacidosis.

Adverse effects associated with insulin therapy

Particular problems that one needs to look out for include:

- Hypoglycaemia may be a particular problem in drivers and other high risk occupations. Patients usually become aware of dysfunction when glucose levels fall below 3.5mmol/l. This may be avoided by individualising the dosage regimens, educating the patient and regularly reviewing drug regimens. Patients should be educated to avoid factors that may increase the risk or degree of hypoglycaemia such as missing meals, having smaller meals than usual, increasing alcohol intake or a sudden increase in physical exercise. They should also be instructed on management including the ready availability of oral glucose if still conscious and administration of glucagons by relatives or companions if unconscious.[4,6] Hypoglycaemic unawareness may be a problem in patients who have been on insulin for a long time or are on beta-blocker treatment. Such patients should be encouraged to monitor blood glucose frequently. Despite reports that this phenomenon is increased when changing from animal to human insulin, there is no evidence to support this.[4,7]
- Dermatological complications include lipoatrophy (more common in women), lipohypertrophy (more common in men) and local skin reactions. Rotation of injection site, use of human insulin and use of a pure form of insulin reduces such complications.[7,17]

Newer therapies

Research is currently underway to exploit different delivery routes for insulin. Inhaled insulin is an option where insulin is absorbed over the lung alveolar surface. However the bioavailability is only 10% making this an expensive alternative. Absorption is also very erratic with considerable variation between individuals.[2,21] The possibility of delivering insulin transdermally is also being researched.[22]

Table 1: Characteristics of insulins currently available within the Government Health Services [6,7]

Type	Brand name	Active Ingredient	Manufacturer	Onset (hr)	Peak (hr)	Duration (hr)	Appearance
Short Acting							
	Actrapid (10)	Soluble insulin	Novo Nordisk[1]	0.5-1	2-4	5-7	Clear
	Humulin R (11)	Soluble insulin	Lilly[2]	0.5-1	2-4	5-7	
Intermediate							
	Monotard (12)	Mixture of Zinc amorphous & crystalline particles ratio 3:7	Novo Nordisk	within 0.5	7-15	24	Cloudy
	Humulin N (11)	Crystalline suspension of human insulin with protamine and zinc	Lilly	within 0.5	4-12	24	Cloudy
	Insulatard (13)	Isophane insulin	Novo Nordisk	within 0.5	4-12	24	Cloudy
Long Acting							
	Ultratard (14)	Suspension of insulin zinc crystalline particles	Novo Nordisk	4	8-24	28	Cloudy
Biphasic							
	Mixtard 70/30 (15)	70% isophane 30% soluble	Novo Nordisk	within 0.5	2-8	24	Cloudy
	Humulin 70/30 (11)	As above	Lilly	within 0.5	2-8	24	Cloudy

[1] All Novo products - biosynthetic recombinant DNA origin produced in Saccharomyces cerevisiae

[2] All Lilly products - biosynthetic recombinant DNA origin produced in Escherichia coli

Table 2: Comparison of methods of insulin dosing [2,5,6,17]

Time of insulin administration	7am: before breakfast	11am: before lunch	6pm: before dinner	Comments
Single injection - Intermediate acting	Total dose			Least efficient to control glucose. Most likely to result in hyperglycaemia before dose, and hypoglycaemia at peak insulin effect. Should be reserved only for elderly patients.
Two daily injections of intermediate acting	2/3		1/3	Better than above. Assumes that 2/3 of calorie intake at breakfast and lunch.
Two doses of fixed biphasic insulin	2/3		1/3	Provides average control. Usually 70/30 mixture of intermediate/short acting used. Allows change in units but not ratio.
Two doses of biphasic insulin where ratios may be altered	2/3		1/6 short acting 1/6 intermediate	Provides above-average control. Allows change in both units and ratio of mixture of insulins used.
Split regular with long acting	1/5 short	1/5 short	1/5 short 2/5 intermediate or long	Provides excellent glucose control but requires patient motivation. Use one or two intermediate long acting doses to provide background levels and regular insulin doses before each meal.

The role of transplantation in Type I diabetes is an interesting feature with the first pancreatic transplantation being carried out in 1996. An overall one-year patient survival rate of 90% and graft survival rate of 82% has been reported. Selective Islets of Langerhans cell transplantation is another option that appears more attractive since it involves only a minor surgical procedure. The number of cells available would be larger than a whole pancreas.[2,5,7] Problems associated with transplantation include lack of pancreatic donors, the need for lifelong immunosuppression and the use of steroids in the post-transplant period. Transplantation is therefore limited to Type I diabetics only when conventional therapy significantly fails.

Though there have been numerous developments to produce newer insulins and alternative therapies that are more convenient for the patient to use, it appears that more progress is required to make optimal use of the insulins that are currently available.

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