ABSTRACT

Insulin therapy is absolutely essential for patients with type 1 diabetes mellitus. Insulin deficiency, alone or in combination with increased levels of glucose counter-regulatory hormones in patients with type 1 diabetes, result in decreased peripheral utilization of glucose and increased lipolysis and proteolysis. Patients with type 2 diabetes may require insulin either for acute glycaemic control (e.g. during intercurrent illness or peri-operative period), or for long-term therapy due to secondary failure of oral anti-hyperglycaemic drugs. A significant advancement over the last few years is the development of human insulin analogues which exhibit unique pharmacokinetic profile to specifically cater for either meal-time insulin requirement (rapid-acting insulin analogues) or basal insulin requirement (long-acting insulin analogues). Recombinant human insulin inhalation powder administered via an inhaler device (Exubera®) is now available for clinical use; this offers an alternative to insulin injections in patients with significant needle phobia and who would otherwise experience delays in appropriate and timely initiation of insulin therapy.

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INDICATIONS FOR INSULIN THERAPY

Insulin therapy is absolutely essential for patients with type 1 diabetes mellitus. Insulin deficiency, alone or in combination with increased levels of glucose counter-regulatory hormones in patients with type 1 diabetes, result in decreased peripheral utilization of glucose and increased lipolysis and proteolysis. Lipolysis provides free fatty acids for ketone body production, which becomes an alternative but inefficient fuel for cellular metabolism. This state of metabolic decompensation eventually leads to potentially life threatening diabetic ketoacidosis.

Patients with type 2 diabetes may require insulin either for acute glycaemic control (e.g. during intercurrent illness or peri-operative period), or for long-term therapy due to secondary failure of oral anti-hyperglycaemic drugs. It is estimated that up to 40% of patients with type 2 diabetes will eventually require insulin augmentation for optimal glycaemic control. Because of limited data on the safety regarding the use of oral anti-hyperglycaemic agents in pregnancy, recombinant human insulin is recommended for patients with gestational diabetes or those with pre-existing diabetes contemplating pregnancy.
solution; hence its name soluble or regular insulin. The short-acting insulin has an onset within 15 minutes, peak activity at 2-4 hours, and duration of 6-8 hours after subcutaneous injection.

**B. Intermediate-Acting Insulins**

The action profile of short-acting insulin can be modified to obtain more prolonged action by making it less soluble with additives; they are dispersed as opaque suspensions at neutral pH with either protamine (derived from fish sperm) in phosphate buffer or varying concentrations of zinc in acetate buffer (Lente insulin). NPH (Neutral Protamine Hagedorn) insulin is an intermediate-acting insulin obtained by combining two parts of soluble crystalline zinc insulin with one part of protamine zinc insulin. Both Lente and NPH are intermediate-acting insulins with a 6- to 12-h span of peak activity.

**C. Long-Acting Insulins**

Ultralente insulin is a relatively insoluble crystal of zinc and insulin suspended in an acetate buffer. Its onset of action is quite delayed, with peak effects at 8-14 hours and a duration of action of 18-36 hours. However, as the ultralente formulation derived from human insulin is more soluble than the previously available beef ultralente insulin, its duration of action tends to be less sustained and human ultralente is best administered as two equal doses every 12 hours. Nonetheless, the onset, peak, and duration of activity of the long-acting insulin vary among patients and from day to day in the same patient.

**D. Premixed Insulins**

Premixed insulin preparations contain stable mixtures of fixed proportions of short-acting insulin and intermediate-acting insulin and these are particularly useful for patients who require the use of both bolus (prandial) and basal insulin. A commonly used preparation is Mmixard® 30, which consists of a pre-mix of 30% soluble insulin and 70% NPH insulin.

**HUMAN INSULIN ANALOGUES**

The availability of human insulin analogues over the last few years represents yet another milestone in insulin therapy. These insulin analogues are developed specifically for either prandial or basal insulin requirements and they provide a more physiological insulin action profile compared to the conventional short, intermediate, or long-acting insulin preparations.

**A. Rapid-acting Insulin Analogues**

Rapid acting insulin analogues have been developed with a reduced tendency to self-association of their molecules. Insulin lispro (Humulog® insulin) is produced by a switch in the positions of lysine at position 28 and proline at position 29 of the b-chain and it became the first rapid-acting human insulin analogue available for clinical use after FDA approval in August 1996. Insulin aspart (Novorapid® insulin) is another rapid-acting insulin analogue currently available and it is produced by substituting the proline at position 28 of the b-chain with negatively charged aspartic acid. Because these analogues rapidly dissociate into monomers and dimers on subcutaneous injection, they demonstrate faster absorption kinetics and can therefore be injected just before meals. They also attain higher concentrations after subcutaneous injection compared to conventional human insulin and they reduce post-prandial glucose to a greater extent. The shorter duration of action of the rapid-acting insulin analogues also lead to a lower incidence of hypoglycaemia. The rapid-acting insulin analogues allow greater flexibility and ease of use and obviate the need to wait 30-45 minutes after injection for meals as recommended with regular insulin use. Because of the unpredictable eating pattern in the very young children, rapid-acting insulin analogues can be given immediately after eating with the dose adjusted accordingly.

**B. Long-acting Insulin Analogues**

The long-acting insulin analogues have virtually no plasma peak and act for about 20-24 hours; their long duration of action coupled with the relatively peakless profile make them ideal as a once-daily administration for basal insulin requirement. These new long-acting insulin analogues provide more predictable fasting blood glucose with lower intra-subject variation and reduced risk of nocturnal hypoglycaemia compared with NPH insulin. Patients on intermediate-acting and long-acting insulin who experience frequent hypoglycaemic episodes related to their peak activity will probably benefit from the use of long-acting insulin analogues which have been shown to achieve better glycaemic control with lower incidence of hypoglycaemia.

The molecular structure of insulin glargine (Lantus® insulin) is modified by addition of two Arginine residues at the carboxyl terminal of the b-chain and a substitution of Glycine for Asparagine in position 21 of the a-chain. This induces a shift of the isoelectric point from pH 5.4 in native human insulin to pH 6.7 in insulin glargine. Insulin glargine becomes less soluble after subcutaneous injection because of micro-precipitation at pH 6.7. Absorption of insulin glargine does not require appropriate resuspension before injection and dissolution of crystals in the subcutaneous tissue, as is the case for NPH insulin, nor the formation and dissolution of microprecipitates, as is the case for insulin glargine. Insulin detemir has been demonstrated to have less intra-subject variability and it provides a more constant and reliable basal insulin supply than other basal insulin preparations.

As no clinical data on exposed pregnancies are available, the long-acting analogues are not advisable for use in pregnancy.
POINTERS ON MIXING OF DIFFERENT INSULINS

The compatibility of different insulin preparations must be established before one provides any advice on the mixing of different types of insulin. This is especially so for newer formulations of insulin analogues.

In general, the mixing of soluble insulin or rapid-acting insulin analogues with insulin zinc suspensions (e.g., Lente insulin or Ultralente human insulin) is not advised as the zinc component may retard the overall rate profile of the short- or rapid-acting insulins. In contrast to lente insulin which contains an excess of zinc ions, regular insulin retains its solubility and rapid action when mixed with NPH insulin.

Likewise, it should be noted that the long-acting insulin analogue, insulin glargine, should not be mixed with any other forms of insulin due to the low pH of its diluent.

INHALED INSULIN

Exubera® is the first formulation of inhaled insulin being granted US FDA approval for clinical use in January 2006. This recombinant human insulin is in the form of inhalation powder and it is administered using an inhaler device. The inhaled insulin powder has the onset of action similar to rapid-acting insulin analogues, but its duration of glucose-lowering activity is comparable to that of regular insulin. Exubera® is available in 1 mg and 3 mg blisters and it should be administered no more than 10 minutes prior to each meal. A 1 mg blister of Exubera® inhaled insulin is approximately equivalent to 3 IU of subcutaneously injected regular human insulin; whereas a 3 mg blister is equivalent to 8 IU. This is currently indicated for treatment of adult patients with type 1 diabetes or insulin-requiring type 2 diabetes.

Exubera® is contraindicated in patients who smoke or who discontinued smoking less than 6 months, and patients with unstable or poorly controlled lung disease. Because of potential decline in pulmonary function with its use, patients should have spirometry assessed prior to initiating therapy and at regular intervals during treatment. Because of concerns for long-term pulmonary toxicity; unpredictable variability in patients with acute respiratory conditions; and the availability of an effective, safe, and familiar alternative in subcutaneous insulin, inhaled insulin should be reserved for patients with significant needle phobia and who would otherwise experience delays in appropriate and timely initiation of insulin therapy.

SUGGESTED READINGS


| Table 1. Pharmacologic Profile of Insulin Preparations |
|----------------------------------------|----------|----------|
| A. Recombinant Human Insulin           | Onset    | Peak     | Duration  |
| 1) Short-acting insulin                | 30-60 min| 2-4 hr   | 6-8 hr    |
|   (e.g. Regular or soluble insulin)    |          |          |           |
| 2) Intermediate-acting insulin         | 1-4 hr   | 8-12 hr  | 12-20 hr  |
|   (e.g. NPH or Lente insulin)          |          |          |           |
| 3) Long-acting insulin                 | 3-5 hr   | 10-16 hr | 18-36 hr  |
|   (e.g. Humulin U or Ultratard)        |          |          |           |
| B. Human Insulin Analogue              | Onset    | Peak     | Duration  |
| 1) Rapid-acting insulin                | 5-20 min | 1-3 hr   | 3-5 hr    |
|   (e.g. Insulin lispro; Insulin aspart)|          |          |           |
| 2) Long-acting insulin                 | 4-8 hr*  | “peakless”| 20-24 hr  |
|   (e.g. Insulin glargine; insulin detemir)|       |          |           |
| C. Inhaled Human Insulin (Exubera®)    | 10-20 min| 1-3 hr   | 6-8 hr    |

*Onset time for initial dose; steady state reached after 2-4 days of once daily administration
LEARNING POINTS

- Insulin is essential for treatment of all patients with type 1 diabetes and in a significant proportion of patients with type 2 diabetes associated with progressive pancreatic beta-cell failure.

- Human insulin is a simple protein consisting of 51 amino acids in two peptide chains; it has a short circulating half-life (3-5 minutes) because of its rapid degradation by the liver and kidney.

- Synthetic human insulin produced by recombinant DNA technology has largely eliminated the problems of insulin allergy, immune insulin resistance, and insulin lipoatrophy previously associated with the use of animal insulins.

- Insulin predominantly exists in hexameric form containing two zinc ions at the injection site. The need to dissociate into dimers and monomers in the subcutaneous tissue accounts for the delay in the action of soluble insulin after subcutaneous injection.

- A significant advancement over the last few years is the development of human insulin analogues which exhibit unique pharmacokinetic profile to specifically cater for either meal-time insulin requirement (rapid-acting insulin analogues) or basal insulin requirement (long-acting insulin analogues).

- Recombinant human insulin inhalation powder administered via an inhaler device (Exubera®) is now available for clinical use; this offers an alternative to insulin injections in patients with significant needle phobia and who would otherwise experience delays in appropriate and timely initiation of insulin therapy.