RAPID ACTING INSULIN ANALOGUES

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ABSTRACT
Different kinds of insulin analogues, both short acting as well as long acting, are now available which offer several benefits over human insulins including improved physiologic profile, greater convenience, reduced risk of hypoglycemia and, in some instances, less weight gain. Combined, these elements may increase a patient’s adherence to treatment, potentially increasing the level of glycemic control and improving the prognosis in patients with diabetes mellitus. Rapid-acting insulin analogues, namely aspart, lispro and glulisine have very similar pharmacokinetic profiles that mirror endogenous insulin more closely than regular human insulin. These insulin analogues can also be given closer to mealtimes and are less likely to cause hypoglycemia. While insulin lispro differs from human insulin by substitution of proline with the lysine at position 28 and lysine with proline at position 29 of the insulin β-chain, insulin aspart is designed with the replacement of proline by aspartic acid at position 28. Meanwhile, insulin glulisine is a novel rapid acting insulin analogue designed with the substitution of lysine with asparagine at position 3 and by substitution of glutamine at position 29 by lysine in the insulin β-chain.

These analogues are present either in monomeric form or in very weakly bound hexameric form. They are rapidly absorbed in <30 minutes following subcutaneous injection and have a short time to peak insulin concentration of 1 hour and a shorter duration of action of 3–4 hours when compared with regular human insulin. The simplicity and efficacy of insulin analogues should help facilitate a patient’s transition to insulin therapy. Current guidelines advocate starting insulin therapy in patients who have not achieved glycemic targets or those with glycated hemoglobin greater than 8.5% and adjusting doses as necessary.

INTRODUCTION
Administration of exogenous insulin in a basal-bolus regimen attempts to mimic the natural release of insulin through multiple daily injections. Although this regimen provides acceptable plasma glucose levels, the exact duplication of normal insulin secretion patterns continues to be a challenge.1-3

Mealtime injection of regular human insulin can be problematic for 2 reasons. First, the delayed onset of absorption necessitates administration of regular human insulin 30 minutes before meals, a practice that many patients do not follow because of its inconvenience. Second, the peak effect of regular insulin may not occur until 3 hours after administration, whereas plasma glucose levels usually rise more quickly after meals. This disparity in insulin and plasma glucose levels creates a brief hyperglycemic period immediately after the meal, as well as a potential hypoglycemic period 3 to 4 hours after the meal. Genetic manipulation of insulin’s amino acid sequence has produced several analogues that have significantly reduced self-association and remain monomers in solution.4

DEVELOPMENT OF INSULIN ANALOGUES
The advent of recombinant DNA technology made it possible to overcome the limitations in the time-action profile of conventional insulins. Genetic manipulation of insulin has produced new molecules - commonly referred to as insulin analogues for clinical use.5 The newer insulin analogues have potential
pharmacokinetic advantages. Used as prandial, meal-related bolus or as basal insulin, the analogues simulate physiological insulin profiles more closely than the older conventional insulins. Over 300 insulin analogues have been studied, but only a few are currently available commercially.

These include insulin lispro and insulin aspart along with their pre-mixed preparations, insulin glargine and the newer insulin detemir (Fig. 1).

RAPID-ACTING INSULIN ANALOGUES

Insulin lispro, insulin aspart and insulin glulisine are the three rapid-acting insulin analogues with very similar pharmacokinetic profiles. These analogues are present either in monomeric form or in very weakly bound hexameric form. They are rapidly absorbed in <30 minutes following subcutaneous injection and have a short time to peak insulin concentration of 1 hour and a shorter duration of action of 3–4 hours when compared with regular human insulin.

PHARMACOLOGY OF RAPID ACTING INSULIN ANALOGUES

The rapidly acting analogues lispro and aspart have similar pharmacokinetic (Fig. 2) and pharmacodynamic properties.

In general, injection of these rapidly acting analogues results in twice the maximal concentration and takes about half the time to reach the maximal concentration as do equivalent doses of regular insulin.

Use of these rapidly acting analogues also results in less variability in absorption at the injection site and possibly in less variation between and within patients.

INSULIN LISPRO

Insulin lispro differs from human insulin by the substitution of proline with lysine at position 28 and lysine with proline at position 29 of the insulin β-chain; insulin aspart is designed with the single replacement of the amino acid proline by aspartic acid at position 28 of the human insulin β-chain; insulin glulisine is designed with the substitution of the amino acid lysine with asparagine at position 3 of the human insulin β-chain and by substitution of the amino acid lysine at position 29 with glutamine; insulin glargine differs from human insulin in that the amino acid asparaginate at position A21 is replaced by glycine and two arginines are added to the C-terminus of the β-chain; insulin detemir is designed to bind albumin in plasma after absorption, threonine is omitted from position 30 of the insulin β-chain and replaced by myristic acid, a C14 fatty acid chain.

The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons.

INSULIN LISPRO

Insulin lispro differs from human insulin by the substitution of proline with lysine at position 28 and lysine with proline at position 29 of the insulin β-chain (Fig 1). These substitutions result in a diminished tendency of the insulin molecule to self-associate. The change of the two amino acids in positions 28 and 29 was deduced from the structure of insulin-like growth factor (IGF)-1, which, unlike insulin, does not tightly aggregate as hexamers. This may explain the higher affinity of insulin lispro, relative to human insulin, for the IGF-1 receptor reported in some studies.

This ‘ultra fast-acting’ insulin is conveniently injected 5–15 minutes before a meal or immediately after a meal, resulting in better postprandial glucose control and less frequent late hypoglycaemia. This is especially important for individuals who have dinner at late hours of the evening or before bedtime, as the prolonged action of regular insulin may influence the overnight period resulting in early morning hypoglycaemia. In children or older adults with dementia who have unpredictable eating patterns, rapid-acting insulin analogues can be administered after the meal without excessive deterioration of glycaemic control.

The efficacy of insulin lispro has been compared to that of regular insulin in both type 1 and type 2 diabetes. All studies have consistently found that the meal-related rise in plasma glucose levels is lower when patients take insulin lispro vs. regular insulin. The pooled results of all phase III trials suggest that when people with type 1 diabetes use lispro, the plasma glucose excursion 2 hours after a meal will be 0.9 to 2.9 mmol/L lower than with regular insulin. However, the short duration of action of lispro may be problematic for subjects with type 1 diabetes. One study demonstrated that lispro provided good postprandial glycemic control in the initial 3-hour period after a meal, but as lispro activity waned, plasma glucose levels increased. When basal insulin was adjusted, lispro provided better postprandial plasma
glucose control compared to regular insulin. Development of hypoglycemia is a common and potentially severe adverse effect, especially for patients on an intensive insulin regimen. In a comprehensive analysis, severe hypoglycemic events were defined as coma or an episode requiring glucagon or IV glucose. Using the pooled data from all published and unpublished studies, 72 of 2327 subjects (3.1%) receiving lispro had at least 1 severe hypoglycemic episode compared to 102 of 2339 subjects (4.4%) who received regular insulin (relative risk 0.70; 95% CI 0.52 to 0.96).8

INSULIN ASPART

Insulin aspart was designed with the single replacement of the amino acid proline by aspartic acid at position 28 of the insulin β-chain (Figure 1). Recent head-to-head trials have shown that the pharmacokinetic and pharmacodynamic profiles of insulin lispro and insulin aspart were identical in adult patients with type 1 diabetes. However, other studies have found minor differences in the pharmacokinetics of these two rapid-acting insulin analogues.4,7

Insulin aspart was also shown to be as effective when administered pre-prandially and postprandially in a study in children and adolescents with type 1 diabetes. This study found that glycaemic control was not worse with postprandial insulin injection as assessed by fructosamine and glycosylated haemoglobin (HbA1c) values. This information could prove valuable in the treatment of diabetic patients with gastroparesis where insulin is often administered after meals as these patients often have difficulty in retaining the ingested food.4,7

The clinical effects of aspart have been evaluated in several studies10-13. In these studies, regular human insulin was used as the comparative agent and basal insulin was provided in adult patients with type 1 diabetes. However, other studies have found minor differences in the pharmacokinetics of these two rapid-acting insulin analogues.4,7

The rapid-acting insulin was administered just prior to meals and the doses were adjusted for a postprandial plasma glucose level of <10.0 mmol/L. NPH insulin was administered at bedtime and adjusted to maintain fasting plasma glucose (FPG) levels of 4.0 to 7.0 mmol/L. Overall plasma glucose control, measured by plasma glucose levels outside of the range of 4.0 to 7.0 mmol/L during a 24-hour inpatient assessment, was significantly better when subjects were receiving insulin aspart. However, there was no difference in plasma glucose control measured by fructosamine levels after the 4-week treatment period.13

Two other studies randomly assigned individuals with type 1 diabetes to aspart or regular insulin and followed them for 6 months. In both studies, insulin aspart was administered immediately before meals and regular insulin was administered 30 minutes prior to meals. After 6 months of therapy, subjects receiving aspart had a slightly, but significantly, lower HbA1c. In another multiple-dose study evaluating aspart in type 2 diabetes, 182 subjects were randomized to 6 months of either aspart or regular insulin. At the conclusion of the 6-month follow-up, there was no difference (p=0.368) in HbA1c between the 2 groups.

As with lispro, the most commonly reported adverse reaction with aspart is hypoglycemia. In all published studies, it appears that the overall incidence of hypoglycemic events is similar between aspart and regular insulin. However, in 1 study with 90 subjects, there were more (p<0.002) hypoglycaemic events when subjects received regular insulin rather than aspart. Furthermore, hypoglycemic events during the night appeared to be twice.13,11

INSULIN GLULISINE

Insulin glulisine is a novel rapid-acting human insulin analogue produced by recombinant DNA technology (Figure 1). It is designed with the substitution of the amino acid lysine with asparagine at position 3 of the insulin β-chain and by substitution of the amino acid glutamine at position 29 by lysine. Preliminary euglycaemic clamp studies in animals and humans demonstrated that insulin glulisine is a rapid-acting insulin analogue with comparable pharmacodynamic and pharmacokinetic properties to insulin lispro. Insulin glulisine has the unique property of predominantly activating the insulin receptor substrate-2 signalling pathway, which plays a crucial role in pancreatic β-cell growth and survival.4,7

Several well designed trials14 have investigated the efficacy of insulin glulisine (with and without basal insulin) versus comparator agents (with and without basal insulin) in patients with type 1 and type 2 diabetes. In patients with type 1 diabetes, insulin glulisine was noninferior to insulin lispro (in both adult and paediatric patients) and to RHI (in adult patients). In adult patients with type 2 diabetes, insulin glulisine was noninferior (and superior in one study) to RHI and (with basal insulin glargine) more effective than premixed insulin. The primary endpoint in most clinical trials, where stated, was the change in glycosylated haemoglobin (HbA1c) levels from baseline to the end of the study period. There were no significant differences between pre- and postprandial administration, or between pre-breakfast and pre-main meal administration, among patients with type 2 diabetes. Postprandial insulin glulisine was noninferior to preprandial in the primary endpoint in patients with type 1 diabetes; however, within this wide noninferiority margin (0.4% difference in change in HbA1c); preprandial insulin glulisine was shown to be significantly superior to postprandial administration.

When administered using continuous subcutaneous insulin infusion (CSII), insulin glulisine appeared to be as effective as insulin aspart in patients with type 1 diabetes. A basal-bolus
A sliding-scale regimen of RHI in hospitalized patients with type 2 diabetes.

**PLACE OF RAPID-ACTING INSULIN ANALOGUES IN DIABETES MANAGEMENT**

Although the overall glycaemic control may or may not differ with the use of rapid-acting insulin analogues compared with regular insulin, their convenient administration allows more flexibility to both adults and children who eat unplanned meals or snacks. The ultra fast-acting insulin analogues are especially effective in attenuating postprandial blood glucose excursions in both type 1 and type 2 diabetic patients.

Rapid-acting insulin analogues are not approved in pregnancy, although retrospective reviews of medical records of diabetic women treated with insulin lispro, before conception and throughout pregnancy, found that insulin lispro resulted in adequate glycaemic control, without adverse maternal or fetal outcomes.

A small short-term study evaluated the efficacy of insulin aspart in comparison with regular human insulin in women with gestational diabetes. Effective glycemic control in these women was brought about by insulin aspart.12

Currently, insulin aspart and insulin lispro are approved for continuous subcutaneous insulin infusion (CSII) in type 1 and type 2 diabetic patients. In addition, a recent study also found that insulin glulisine is a well tolerated and effective alternative for insulin pump therapy. Insulin aspart has been shown to be heat stable in pumps at 37°C (98.6°F) for up to 48 hours.

Rapid-acting insulin analogues are also conveniently available in a syringe alternative form, namely the ‘insulin pen’.

Although rapid-acting insulin analogues were thought to be less antigenic, cases of allergy to insulin lispro and insulin aspart have nevertheless been reported.

**REFERENCES**