Original Article

# Bolus insulin therapy with focus on faster aspart

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**Insulin therapy remains the mainstay of treatment in type 1 diabetes, gestational diabetes and advanced/complicated cases of type 2 diabetes. Bolus insulins are often used as part of bolus-basal regimen to control postprandial hyperglycemia. Current bolus insulins including short acting analogues have few limitations primarily unable to optimally control 1 hour postmeal blood glucose excursion. Faster aspart is one near ideal bolus insulin with pharmacokinetic profile almost mimicking normal insulin physiology and results in better control of postprandial hyperglycemia especially 1 hour postprandial hyperglycemia. This review summarises pharmacokinetic profile, clinical trial data and potential clinical uses of faster aspart insulin.**

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***Key words*** **: Insulin, faster aspart, regular insulin, postprandial hyperglycemia, prandial insulin, bolus insulin.**

The goal of diabetes management is prevention of long-term complications[1]. The United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes mellitus (T2DM) have demonstrated that with intensive therapy and a reduction in glycated haemoglobin (HbA1c) by 1% is associated with 37% reduction in the microvascular and 14% in the macrovascular complications[2-4]. Growing evidence suggest that insulin therapy is required in T2DM patients (Table 1)[5]. When considering the effectiveness, tolerability, and cost of the various diabetes treatments, insulin is not only the most potent, but also the most cost-effective intervention[6].

Table 1 — *Evidence for starting insulin in type 2 diabetes*[6]

| |
|---|
| **Strong observational and randomized clinical trial evidence** |
| • Insulin secretory capacity deteriorates with time |
| • Insulin improves glycemic control in trials and in routine clinical practice |
| • Improved glucose control improves HRQoL |
| • LADA phenotype is associated with early need for insulin therapy |
| **Randomized clinical trial evidence of variable quality** |
| • Outcomes of acute illness are improved if glycemic control is better |
| • Long-term medical outcomes are improved by better glycemic control |
| • Optimum Glycemic control (HbA1c<7.0%) is difficult to achieve and maintain without insulin |
| • Insulin is successful in combination with oral agents |
| **General knowledge and expert experience** |
| • Insulin treats and prevents ketoacidosis |
| • Severe hyperglycemia predisposes to infection |
| • Physician hesitancy in starting insulin therapy is a main barrier to insulin use |
| • Patient preferences and views of injected therapies vary markedly |
| • Insulin therapy can be tailored rapidly to changes in need during acute illness |
| • Insulin has potential powerful anabolic effects (wound healing, etc.) |

HRQoL-health-related quality of life; HbA1c-glycated hemoglobin

Although basal insulins are generally the convenient option for initiation of insulin therapy, it does not adequately control postprandial hyperglycemia[7]. Increased postprandial glucose levels contribute to overall hyperglycaemia in diabetes, and control of postprandial hyperglycaemia is an important factor for achieving HbA1c targets. Early administration of insulin restores first-phase insulin secretion and improves postprandial glucose tolerance[8]. Therefore the need for bolus insulins arises to take care of the postprandial hyperglycemia[9].

## Currently Available Bolus Insulins and Their Limitations :

Currently there are two types of bolus insulins available: short-acting and rapid-acting. Short-acting involves use of regular insulin. It is not absorbed as quickly. Therefore, it is usually injected 30 minutes before meals. Rapid-acting (insulin aspart [IAsp], insulin lispro, and insulin glulisine) are injected up to 5-10 minutes before meals as they are absorbed by the body almost immediately and begin working within 15 minutes (Table 2)[9].

A 1-hour postprandial plasma glucose value ≥8.6 mmol/l (≥155 mg/dl) has been associated with greater risk of cardiovascular disease and correlated better with insulin sensitivity and secretion than fasting plasma glucose or the 2-h postprandial plasma glucose level[10]. Despite improvements in pharmacokinetic and pharmacodynamic profiles as compared to regular insulin, current rapid-acting insulin analogues are still unable to replicate the physiological insulin secretion profile in healthy individuals. Consequently, an injection–meal interval may be required to achieve optimum postprandial glucose control and even then 1 hour postmeal control is not optimally achieved. Therefore, there is a need

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Table 2 — *Comparison of short-acting and rapid acting bolus insulins*

| | Short-acting bolus | Rapid-acting bolus |
|---|---|---|
| Available insulins | Regular | Aspart, lispro and glulisine |
| Injection timing | 30 minutes before meals | 5-10 minutes before meals |
| Absorption | Slow | Fast |
| Onset of action | 30 minutes after injection | Within 15 minutes |
| Duration of action | 4-6 hours | 3-5 hours |
| Adherence to schedule | Inconvenient and difficult to adhere | More convenient for patients and greater adherence |

to develop newer insulins that can mimic the physiological insulin profile more closely. Faster aspart (FiAsp) is one such modified formulation with excipients that accelerate the monomer formation and/or influence the injection site and thus alter the absorption kinetics[11].

## Faster Aspart (FiAsp) :

FiAsp is a modified formulation of insulin aspart (IAsp; NovoRapid®) by adding niacinamide and L-arginine. Niacinamide promotes faster initial absorption after subcutaneous injection and L-arginine is used as a stabilizing agent. With these two modifications FiAsp is predicted to create a more physiological insulin profile with a resultant improvement in postprandial glycaemic excursions[11].

## Pharmacokinetics and Pharmacodynamics in Adults with Type 1 Diabetes (T1DM)

A pooled analysis of six randomised, double-blind, crossover trials included 218 adult subjects with T1DM. Subjects received subcutaneous dosing (0.2 U/kg) of FiAsp and IAsp. In three trials, a 12-h euglycemic clamp was performed (target 5.5 mmol/L; 100 mg/dL) to assess pharmacodynamics. The pharmacokinetic and pharmacodynamic profiles for FiAsp shifted to the left compared to IAsp (Fig 1). Onset of action occurred 4.9 min earlier, early glucose-lowering effect was 74% greater and offset of glucose-lowering effect occurred 14.3 min earlier for FiAsp versus and IAsp. Total exposure and total glucose-lowering effect did not differ significantly between treatments[12].

The study concluded that FiAsp has an earlier onset and higher early exposure than IAsp, and a greater early glucose-lowering effect, with similar potency. It has the potential to mimic the physiologic prandial insulin secretion and thereby to improve postprandial glucose control compared with IAsp[12].

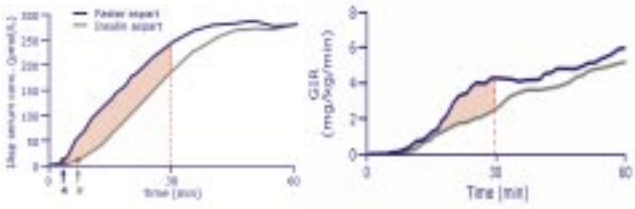


Fig 1 — Pharmacokinetic and pharmacodynamic profiles of 0.2 U/kg faster aspart and insulin aspart in subjects with type 1 diabetes (IAsp- Insulin aspart; GIR-glucose infusion rate)

## Pharmacokinetics and Pharmacodynamics in Children and Adolescent :

A randomized, double-blind, 2-period crossover trial evaluated the pharmacological properties of FiAsp *versus* IAsp in 12 children (6-11 years), 13 adolescents (12-17years), and 15 adults (18-64 years) with T1DM. Onset of appearance of FiAsp was approximately twice-as-fast (5-7 minutes earlier) and early exposure was greater than IAsp. However, there were no differences in total exposure or maximum concentration (Cmax). FiAsp reduced two-hour postmeal plasma glucose excursion more than IAsp. Differences between FiAsp and IAsp were similar across all age groups with respect to all parameters. These results suggest that FiAsp has the potential to improve postprandial glycaemia better than current rapid-acting insulins in children and adolescents[13].

## Pharmacokinetics and Pharmacodynamics in Elderly :

A randomised, double-blind, two-period crossover trial compared FiAsp and IAsp in 30 elderly (≥65 years) and 37 younger adults (18-35 years) with T1DM. The pharmacokinetic and pharmacodynamic profiles shifted to left for FiAsp compared to IAsp. In the elderly, onset of action was 10 min faster and 9 min faster in younger adults. FiAsp produced a greater early glucose-lowering effect than for IAsp in both age groups. There were no age group differences in glucose-lowering effect[14].

## Clinical Efficacy in T1DM–Onset 1 Trial:

The efficacy and safety of FiAsp was compared with IAsp in a multicentre, treat-to-target, phase 3 trial in adults with T1DM (onset 1) conducted at 165 sites across nine countries. The primary end point was change from baseline in HbA1c after 26 weeks. Both the treatments reduced HbA1c and FiAsp was noninferior to IAsp for both mealtime and postmeal glucose. With mealtime FiAsp, postprandial plasma glucose increment was statistically significantly lower at 1 h and 2 hour after the meal test. FiAsp was superior to IAsp for the 2-hour PPG increment. The overall rate of hypoglycaemic episodes and safety profiles were similar between treatments[15].

The above study was continued for additional 26 weeks (total trial duration 52 weeks). After 52 weeks, estimated mean changes from baseline in HbA1c levels were -0.08% with FiAsp and +0.01% with IAsp. There was a significant difference between the treatments favouring FiAsp. Changes from baseline in 1-hour postprandial plasma glucose increment also significantly favoured FiAsp[16].

## Clinical Efficacy in T2DM – Onset 2 and 3 Trials :

Onset 2 compared the efficacy and safety of FiAsp versus IAsp in adults with T2DM receiving basal insulin

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*(Continued from page 15)*

and oral antidiabetic agents. The primary end point was HbA1c change from baseline after 26 weeks' treatment. At the end of treatment, both treatments decreased mean HbA1c to 6.6%, suggesting non-inferiority of FiAsp versus IAsp in reducing HbA1c. Postprandial plasma glucose control after 1 hour was significantly better with FiAsp, but not after 2-4 hours. Changes in other parameters such as fasting plasma glucose level, body weight, and overall severe/blood glucose-confirmed hypoglycaemia rates were similar between treatments[17].

Onset 3 study assessed superiority of FiAsp in a basal-bolus regimen vs. basal-only insulin. Inadequately controlled T2DM patients receiving basal insulin and oral antidiabetic drugs were randomised to either a basal bolus regimen with FiAsp (n = 116) or continued on once-daily basal insulin (n = 120). Basal bolus regimen decreased HbA1c from 7.9% to 6.8% and basal regimen decreased HbA1c from 7.9% to 7.7%. There was a statistically significant reduction in mean 2-hour postprandial glucose in basal bolus regimen. However, severe/blood glucose confirmed hypoglycaemia rate (12.8 *versus* 2.0 episodes per patient-years of exposure), total daily insulin (1.2 *versus* 0.6 U/kg) and weight gain (1.8 *versus* 0.2 kg) were greater with basal bolus regimen than with basal-only treatment[18].

## Advantage of FiAsp and Clinical Implications :

Controlling postprandial glucose excursions is important for improving overall glycaemic control. Appearance of insulin in the blood is quicker with FiAsp than with IAsp after subcutaneous injection. It controls postprandial glucose better than IAsp especially the 1-hour postprandial glucose. Additionally, FiAsp could provide more flexibility in meal scheduling. This may be of particular importance for patients who have difficulties in meal planning and forget to take insulin injections before meals[13].

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