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Review

Fast-Acting Insulin Aspart and the Need for New Mealtime Insulin Analogues in Adults With Type 1 and Type 2 Diabetes: A Canadian Perspective

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Key Messages

- There is an unmet need for new mealtime insulin analogues with faster absorption that can better mimic the rapid-onset action of endogenous insulin.
- The 2018 Diabetes Canada clinical practice guidelines now include faster aspart as a mealtime insulin analogue.
- Faster aspart is a novel formulation of insulin aspart that provides effective glycemic control with a risk for hypoglycemia comparable to that of insulin aspart.

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ABSTRACT

Limiting postprandial glucose (PPG) excursions is an important aspect of overall glycemic control. Rapid-acting insulin analogues (RAIAs) aim to mimic the physiologic action of endogenous insulin observed in individuals without diabetes and prevent excessive PPG excursions. However, many people with type 1 diabetes and type 2 diabetes treated with RAIAs do not achieve glycated hemoglobin (A1C) targets, and there is an unmet need for further improvements in PPG control. Current RAIAs have a delayed onset and a longer duration of action compared with endogenous insulin secreted in response to meals. Approaches to developing new mealtime insulins with accelerated absorption kinetics include changing the route of administration (i.e. via inhalation) and changing the insulin formulation. Fast-acting insulin aspart (faster aspart) is a novel formulation of insulin aspart (IAsp) containing the excipients niacinamide and L-arginine. Faster aspart has an earlier onset of insulin exposure and a greater early glucose-lowering effect than IAsp. In large clinical trials, mealtime faster aspart demonstrated noninferiority to IAsp with respect to A1C reduction and provided superior PPG control with no increase in overall severe or blood glucose-confirmed hyperglycemia. In addition, faster aspart administered up to 20 min after the start of a meal was noninferior to mealtime IAsp in terms of A1C control, highlighting the opportunity for post-meal dosing. Faster aspart is the first of a new generation of mealtime insulins to be approved in Canada for the treatment of adults with type 1 diabetes and type 2 diabetes, and it is included in the 2018 Diabetes Canada clinical practice guidelines.

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insuline à action rapide
glycémie postprandiale
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RÉSUMÉ

La limitation des excursions glycémiques postprandiales (GPP) est un aspect important de la régulation globale de la glycémie. Les analogues de l'insuline à action rapide (AIAR) ont pour but d'imiter l'action physiologique de l'insuline endogène observée chez les individus non diabétiques et de prévenir les

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excursions GPP excessives. Comme plusieurs personnes atteintes du diabète de type 1 et de diabète de type 2 traitées par AIAR n'atteignent pas les valeurs cibles de l'hémoglobine glyquée (A1c), des améliorations sont nécessaires pour combler les lacunes de la régulation de la GPP. Les AIAR actuels présentent un début d'action retardée et une durée d'action plus longue que l'insuline endogène sécrétée après les repas. Les approches de développement de nouvelles insulines prandiales ayant une cinétique d'absorption accélérée sont les suivantes: le changement de la voie d'administration (c.-à-d. par inhalation) et le changement de formulation de l'insuline. L'insuline asparte à action rapide (asparte à action plus rapide) est une nouvelle formulation de l'insuline asparte (IAsp) qui contient des excipients de niacinamide et de L-arginine. L'asparte à action plus rapide présente un début d'exposition à l'insuline plus précoce et un effet hypoglycémiant précoce plus important que l'IAsp. Dans les grandes études cliniques, l'asparte prandiale à action plus rapide a démontré sa non-infériorité par rapport à l'IAsp en qui concerne la réduction de l'A1c et a procuré une meilleure régulation de la GPP sans augmentation du nombre global d'épisodes d'hyperglycémie sérieuse ou d'hyperglycémie confirmée par la glycémie. De plus, l'asparte à action plus rapide administrée jusqu'à 20 min après le début d'un repas n'était pas inférieure à l'IAsp prandiale quant à la régulation de l'A1c, et rend possible le dosage de la glycémie post-prandiale. L'asparte à action plus rapide est la première d'une nouvelle génération d'insulines prandiales à être approuvée au Canada pour traiter les adultes atteints du diabète de type 1 et du diabète de type 2, et fait partie des lignes directrices de pratique clinique de 2018 de Diabète Canada.

Introduction

Bolus insulin therapy aims to mimic the endogenous mealtime insulin response seen in healthy individuals to prevent excessive postprandial glucose (PPG) excursions while avoiding hypoglycemia. Individuals with type 1 diabetes have little or no endogenous insulin secretion, so rapid-acting insulins, as part of a basal-bolus regimen delivered by multiple daily injections or continuous subcutaneous insulin infusion (CSII) therapy, are the mainstay of treatment and should be initiated as early as possible after diagnosis (1,2). The progressive deterioration of beta-cell function in type 2 diabetes requires the intensification of treatment over time (3). A number of antihyperglycemic therapies are available for treating type 2 diabetes and, after lifestyle modifications, current guidelines recommend a stepwise approach to treatment (1,4). When glycated hemoglobin (A1C) targets are not met on regimens that include basal insulin with other agents, bolus insulin can be initiated, either as separate mealtime injections or as part of a premixed insulin regimen (4).

Regular human insulin (RHI), which is structurally identical to physiologically secreted insulin, was introduced as a mealtime insulin in 1982. However, compared to the endogenous insulin response to food intake seen in individuals without diabetes, the glucose-lowering profile of RHI injected subcutaneously has a delayed onset and a longer duration of action, which can lead to early postprandial hyperglycemia and late postprandial hypoglycemia (Figure 1A). After injection into the subcutaneous space, RHI molecules have a tendency to remain self-associated as hexamers, which are too large to pass easily through capillary membranes. The slow dissociation of hexamers into more easily absorbed dimers and monomers is the rate-limiting step of RHI action and necessitates that RHI be injected approximately 30 min before a meal to best limit PPG excursions (Figure 1B).

Recombinant engineering of the amino acid sequence of insulin facilitated the development of rapid-acting insulin analogues (RAIAs) with faster absorption kinetics and shorter durations of action compared to RHI (5). RAIAs were introduced into clinical practice in the 1990s and, until recently, 3 were marketed in Canada: insulin aspart (IAsp; NovoRapid), insulin glulisine (Apidra) and insulin lispro (Humalog). Preprandial injections of RAIAs result in less postprandial hyperglycemia and less late postprandial hypoglycemia compared with RHI (6).

Despite the benefits of RAIAs, there remains an unmet need for mealtime insulin analogues that better mimic the normal physiologic action of endogenous insulin secreted into the portal vein. A new generation of mealtime insulin analogues is under study; they have improved pharmacokinetic (PK) and pharmacodynamic (PD) profiles compared to standard RAIAs. In 2017, fast-acting insulin aspart (faster aspart) was the first of the new generation of mealtime insulins to be approved by Health Canada for the treatment of adults with type 1 and type 2 diabetes. This review provides an overview of the unmet need for new mealtime insulins, summarizes the clinical data concerning faster aspart and discusses this new mealtime insulin in the context of the updated 2018 Diabetes Canada clinical practice guidelines.

Unmet Clinical Needs With Mealtime Insulin Therapy

Diabetes therapy aims to optimize glycemic control, most commonly measured by glycated hemoglobin (A1C) levels, to reduce the risk of macro- and microvascular complications, the incidence and progression of which have been shown to correlate with A1C levels (7–9). Guidelines, therefore, recommend an A1C target of $\leq$7.0% for most patients with type 1 or type 2 diabetes, although targets should be individualized based on patients' ages, comorbidities and risks for hypoglycemia (10,11). However, in practice, many patients do not achieve A1C targets. A recent analysis of primary care records from ~30,000 patients with type 1 or type 2 diabetes across Canada found that 30.6% of patients had A1C levels between 7.0% and 8.5%, and 14.5% had A1C levels >8.5% (12).

Postprandial glucose and A1C levels

There are many reasons patients do not reach or maintain A1C targets, and several of these factors are related to bolus insulin therapy and PPG control. Both fasting and postprandial hyperglycemia contribute to A1C levels, and in order to achieve A1C levels $\leq$7.0%, guidelines recommend a fasting plasma glucose target of 4.0 to 7.0 mmol/L and a 2-h PPG target of 5.0 to 10.0 mmol/L (10).

Postprandial hyperglycemia has been proposed as an independent risk factor for cardiovascular disease (CVD) in individuals with type 2 diabetes (13), and elevated PPG levels have been associated with carotid intima-media thickening (14), oxidative stress and endothelial dysfunction (15), all of which are markers for CVD. Acute hyperglycemia in type 2 diabetes has also been associated with impairments in information processing and working memory and with detrimental effects on mood, including

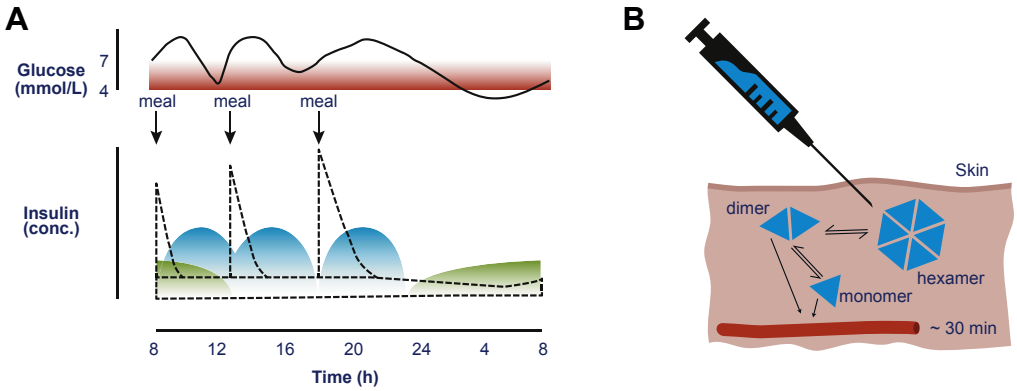

Figure 1. A, 24-h glucose and insulin profile with RHI and NPH in a basal-bolus regimen. A bolus dose of either RHI (blue) or an RAIA is injected at mealtimes, and a basal insulin dose, either NPH insulin (green) or a long-acting analogue, is injected once or twice a day. Although RHI has advantages over previously used animal insulins, its slower onset and longer duration of action do not mimic endogenous insulin secretion after a meal. The dotted line demonstrates the nondiabetic physiologic insulin profile over 24 h. With RHI, the plasma insulin concentration peaks about 2 to 4 h after injection, which can result in postprandial hyperglycemia, and the duration of action can be 6 to 8 h, increasing the risk for late postprandial hypoglycemia. B, absorption of RHI after subcutaneous injection. After injection into the subcutaneous space, RHI has a high tendency to self-associate into hexamers. The slow dissociation of hexamers into more easily absorbed dimers and monomers is the rate-limiting step of RHI action, and necessitates that RHI be injected approximately 30 min before a meal. *NPH,* neutral protamine Hagedorn; *RAIA,* rapid-acting insulin analogue; *RHI,* regular human insulin.

increased agitation and anxiety, increased fatigue and lethargy and a reduced feeling of happiness (16).

Postprandial hyperglycemic excursions also contribute to glycemic variability, which may be related to tissue damage and diabetes complications independently of A1C levels (17,18). In addition, the risk for hypoglycemia is directly related to increased glycemic variability in type 1 and type 2 diabetes (19). Hypoglycemia is the major limiting factor of optimal glycemic management with insulin therapy, especially in patients with type 1 diabetes, and hypoglycemic episodes can have significant impacts on patients' and their families' quality of life. Modern insulin therapies designed to replicate normal physiology more closely aim both to lower A1C levels and to stabilize glucose fluctuations, and the growing use of continuous glucose monitoring and flash glucose monitoring in patients with type 1 diabetes is increasing awareness of the need for faster-acting mealtime insulins as well as new algorithms for managing bolus dosing.

Treatment management and adherence

A 2016 web-based survey of individuals with type 1 and type 2 diabetes who had been prescribed bolus insulin therapy found that two-thirds of respondents had experienced postprandial hyperglycemia in the previous week for reasons that included forgetting to take their bolus insulin, calculating the dose incorrectly, eating more fat/sugar than expected and eating more than covered by their self-calculated bolus insulin dose (20).

The adjustment of mealtime insulin dose on the basis of glucose monitoring is an important aspect of diabetes management. However, many patients do not adjust their doses while their glucose levels are high, explaining, in part, the failure to achieve A1C targets. For each bolus injection, many patients with type 1 diabetes are required to estimate the carbohydrate content of their meals and determine the insulin bolus dose based on their insulin-to-carbohydrate ratios. Choosing a dose also involves including a self-monitored glucose level to calculate any correction dose. The complexity of choosing and calculating premeal doses by accounting for variations in meal sizes and composition and for physical activity is often overwhelming and can be compounded by fears of hypoglycemia (21).

Even with correct dosing, late postprandial hypoglycemia is often an issue when the duration of action of RAIAs exceeds the duration of glucose absorption. The risk for postprandial hypoglycemia is further amplified during or after physical activity. In an effort to control PPG, some patients with type 1 diabetes administer repeated "corrective" injections of bolus insulin if their postprandial blood glucose (BG) levels appear high (which may be the case if absorption of a bolus dose is delayed); if patients overcompensate, then circulating insulin levels can accumulate (known as *insulin stacking*) to the point of causing late postprandial hypoglycemia (22).

In addition, missed boluses by patients with type 1 diabetes are very common, especially for snacks, and some patients may intentionally fail to administer their required bolus injections at all times. Reasons for omission of bolus injections include avoiding hypoglycemia, injection pain, embarrassment and interference with daily activities or the intention to lose weight (23).

The timing of bolus injections is also a key factor in PPG control in both type 1 and type 2 diabetes. Education of patients often focuses on postmeal glucose levels and assumes that high postprandial glucose levels occur because the insulin dose was too low, but they may also reflect that insulin action is too late (Figure 2). The delayed onset of action of RAIAs compared with endogenously secreted insulin necessitates an injection-to-meal interval to control early postprandial hyperglycemia. IAsp, insulin glulisine and insulin lispro need to be administered approximately 15 to 20 min before the start of a meal to best meet postprandial insulin needs. However, in daily life, patients struggle to adhere to recommended injection-to-meal intervals and many use only very short premeal intervals or none at all or inject bolus insulin postmeal. A recent survey of patients with type 2 diabetes receiving bolus insulin across North America, South America and Europe highlighted that 24% never comply with guidelines for the timing of insulin dosing (24). In a second survey of patients with type 1 or type 2 diabetes, 18.9% reported bolus dosing postmeal in the previous week, while 12.7% reported dosing with meals, and 11.5% reported dosing at varying times (25). In the large type 1 diabetes Exchange Registry in the United States, 32% of patients reported dosing insulin postmeal, which was associated with elevated A1C levels and higher insulin doses (26). It should also be highlighted that results from retrospective surveys such as these are likely to underestimate the percentage of patients injecting after meals.

Clinical inertia in type 2 diabetes

For individuals with type 2 diabetes, a major limitation in achieving A1C and PPG targets is the failure to intensify treatment when clinically indicated. It has been well documented that the

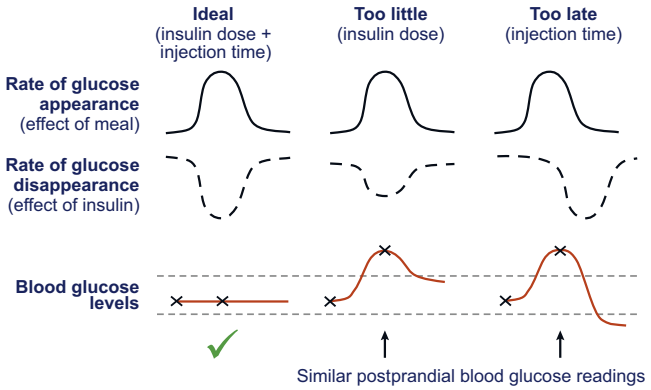

Figure 2. Ideal postprandial blood glucose levels = right insulin dose + right injection time. Ideal postprandial BG control requires an appropriate dose of insulin given at the right time so that the rate of BG appearance after a meal is matched by the rate of BG disappearance. If the insulin dose is too low, the rate of glucose disappearance will not match the rate of glucose appearance, resulting in postprandial hyperglycemia. If the insulin dose is administered too late, the rate of BG disappearance will also not match the rate of BG appearance, resulting in postprandial hyperglycemia and late postprandial hypoglycemia. Patient education often focuses on postprandial BG levels and assumes that high BG levels are due to the insulin doses being too low, but they may also reflect that insulin action is too late. Horizontal dashed lines represent the glycemic target range. *BG*, blood glucose.

addition of bolus insulin for patients with type 2 diabetes who are inadequately controlled on basal insulin and oral antidiabetes drugs improves glycemic control; however, many do not have their treatment intensified, or intensification is significantly delayed (27). Barriers to intensification include clinical inertia, fear of hypoglycemia and weight gain, the complexity of the regimen and patients' adherence and acceptance (28,29).

Bolus insulin and CSII therapy

Meta-analyses of randomized controlled trials comparing CSII therapy with multiple daily injections have shown that CSII can achieve improvements in glycemic control, hypoglycemia risk and quality of life in patients with type 1 diabetes and better glycemic control in poorly controlled patients with type 2 diabetes (30,31). CSII aims to deliver insulin in a dynamic pattern that closely mimics the physiologic insulin profile, with a low basal rate and patient-activated boluses administered at mealtimes. In addition to the need for better delivery and glucose-monitoring technologies, CSII is limited by the absorption rate of current RAIAs because there remains a lag time following the adjustment of infusion and glucose-lowering action.

The absorption kinetics of RAIAs are also a key limitation in the development of closed-loop automated insulin delivery systems, i.e. the so-called artificial pancreas (AP). Many AP glucose control algorithms have been limited by how aggressively current RAIAs can be used to control PPG due to the risk for late hypoglycemia. The use of glucagon in a dual hormone (glucagon and insulin) AP has been developed to mitigate the risk for hypoglycemic events and further improve overall glycemic control (32). A new mealtime insulin with a faster onset of action (and a faster offset) might attenuate the need for an AP with a dual hormone infusion pump, which is more complex and expensive.

Improving the Action Profile of Mealtime Insulin Analogues

In people without diabetes, insulin is rapidly released from the pancreas into the portal vein in response to food intake. Insulin acts to lower BG concentrations by directly suppressing hepatic glucose production (HGP) in the liver (in anticipation of glucose absorption from the gut) and increasing glucose uptake by peripheral tissues (Figure 3) (33). In contrast, when insulin is administered via subcutaneous injection, there is a delay in its glucose-lowering actions as it is absorbed from the injection depot. Furthermore, in normal physiology, the liver is rapidly exposed to an approximately 4-fold increase in insulin concentration compared with the periphery. Subcutaneously administered insulin, however, is absorbed directly into the systemic circulation and, thus, is unable to restore the liver:-periphery ratio and has a limited impact on glucagon suppression from the pancreas. These limitations lessen the ability of bolus insulin to suppress HGP and contribute to postprandial hyperglycemia.

Current developmental approaches to the problem of achieving faster onset of absorption and earlier glucose-lowering action include alterations to the route of administration, such as via inhalation (34) or oral delivery (35,36); modifications to blood flow at the administration site, such as with local heating devices (37); and changes in formulation to accelerate absorption (38,39). Developing hepatoselective insulin analogues that mimic the relative gradient in exposure of the liver vs. the periphery is also a promising strategy. New mealtime insulins that have reported clinical data include Afrezza; Technosphere insulin powder in an inhaler; and the subcutaneous formulations, BioChaperone Lispro, LY900014 (treprostinil lispro), insulin hyaluronidase and faster aspart.

- Afrezza uses a dry powder formulation of RHI adsorbed onto microparticles of the excipient fumaryl diketopiperazine (40). When inhaled into the deep lung, fumaryl diketopiperazine dissolves rapidly, allowing absorption of insulin into the circulation. Afrezza was approved by the US Food and Drug Administration in 2014 for use in improving glycemic control in adults with type 1 and type 2 diabetes; a label change in 2017 highlighted its rapid onset (~12 min) and offset (90 to 180 min) of action (41). Although inhaled insulin is available in the US, it has not yet been approved in Canada.
- BioChaperone Lispro is a formulation of insulin lispro with a biochaperone molecule that, together, form a reversible complex with enhanced diffusion characteristics (42). A number of phase 1 studies with BioChaperone Lispro have been completed, demonstrating more rapid absorption and improved PPG control compared with insulin lispro (43–45); however, in 2017, the research agreement for BioChaperone Lispro was cancelled, and currently, no active or recruiting trials are listed at clinicaltrials.gov.
- LY900014 is a formulation of insulin lispro with treprostinil and citrate. Treprostinil accelerates insulin lispro absorption by local vasodilation, and citrate increases vascular permeability at the injection site (46). Results of several recently completed phase 1 trials with LY900014 were presented in 2017, and they show accelerated early absorption and onset of action compared with insulin lispro (47–49). The first phase 3 trials are due to be completed in 2019.
- Recombinant human hyaluronidase (rHuPH20) is a genetically engineered hyaluronidase that rapidly depolymerizes hyaluronan, a large polysaccharide abundant in the extracellular subcutaneous space, to accelerate the flow and dispersion of insulin (50). In combination with recombinant human hyaluronidase, RHI and RAIAs achieved faster absorption and onset of action and improved PPG control compared with either insulin formulation alone in a number of clinical trials.
- Faster aspart is a formulation of IAsp containing niacinamide and L-arginine. Niacinamide is thought to accelerate monomer formation, leading to a greater permeation rate of IAsp across capillary endothelial cells (51). Faster aspart exerts a greater early glucose-lowering effect than IAsp, and this has been associated with increased early suppression of HGP and early glucose disappearance (52). Faster aspart is the first new mealtime insulin approved for use in Canada. The relevant pharmacologic and clinical data are reviewed in detail in the remainder of this article.

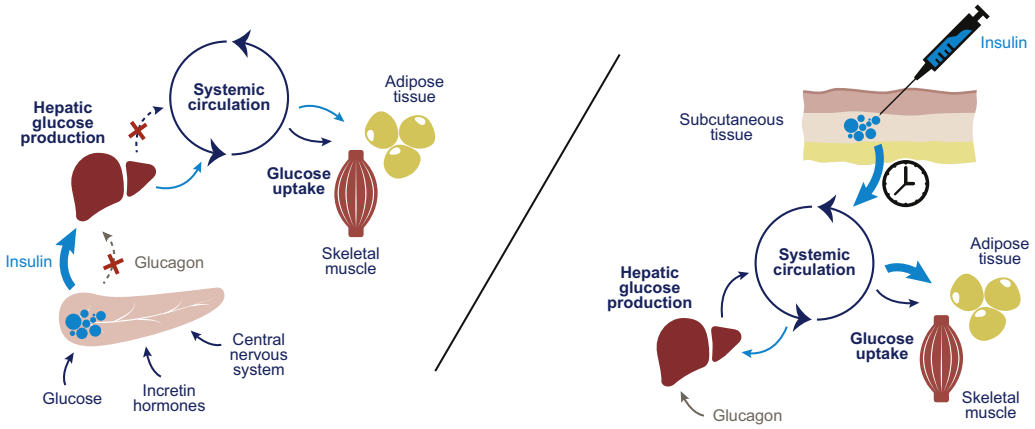

Figure 3. The glucose-lowering actions of endogenous insulin and subcutaneous insulin after a meal. As soon as food is ingested, insulin is rapidly released from the pancreas directly into the portal vein. Insulin lowers blood glucose concentrations by directly suppressing HGP in the liver and increasing glucose uptake by peripheral tissues. Insulin also suppresses glucagon secretion from the pancreas, further lowering HGP. Glucose is a potent stimulus of insulin secretion, but other factors, including amino acids, incretin hormones and neural signals, also stimulate secretion. In contrast, when insulin is administered via subcutaneous injection in individuals with diabetes, there is a delay in the glucose-lowering action as insulin is absorbed from the injection depot. Furthermore, in normal physiology, the liver is exposed to a 2- to 4-fold increase in insulin concentration compared with the periphery. Subcutaneously administered insulin absorbs into the systemic circulation and is unable to restore the liver:periphery ratio, and glucagon suppression from the pancreas is also limited, both favouring HGP and contributing to postprandial hyperglycemia (33). *HGP,* hepatic glucose production.

PK/PD Properties of Faster Aspart

The pharmacologic properties of a particular insulin formulation are assessed by using a euglycemic glucose clamp or during a standardized meal test. The euglycemic glucose clamp is a validated method and is considered the gold standard for evaluating the glucose-lowering effect of exogenous insulins. In a clamp, the glucose infusion rate needed to ensure constant BG levels at a predetermined level is used as a surrogate marker for the PD profile of exogenous insulin.

Faster aspart has demonstrated accelerated PK/PD characteristics compared with IAsp in clinical pharmacology trials (53–55). In a pooled analysis of 6 phase 1 trials employing the euglycemic glucose clamp method in adults with type 1 diabetes, faster aspart showed an approximate 5-min earlier onset of appearance, a 2 times higher early insulin exposure and a 74% greater early glucose-lowering effect vs IAsp (53). Offset of exposure and glucose-lowering effects also occurred 12 to 14 min earlier with faster aspart than with IAsp. Similar pharmacologic properties were also observed in a Japanese population and in a cohort of elderly adults as well as in meal test studies with children and adolescents (56–58). In elderly adults, total insulin exposure and maximum concentrations of faster aspart were approximately 30% greater than in younger adults; however, there were no age-group differences in the total or maximum glucose-lowering effect of faster aspart (57).

Efficacy and Safety of Faster Aspart

The phase 3a trials of the faster aspart onset clinical trial programme have been completed along with a number of phase 3b trials. Table 1 summarizes the efficacy and safety results of the onset clinical trials of faster aspart administered by multiple daily injections in adults with type 1 and type 2 diabetes (59–61).

Clinical trials in type 1 diabetes

In the onset 1 trial, the efficacy and safety of faster aspart were evaluated as part of a basal-bolus regimen with insulin detemir in adults with type 1 diabetes (60). Despite a treat-to-target design intended to achieve equivalent A1C levels, improved A1C levels were observed with mealtime faster aspart (dosed 0 to 2 min before a meal) compared with IAsp after 26 weeks of treatment; estimated treatment difference [ETD]: −0.15% (95% CI −0.23, −0.07), with significant reductions in 1-h and 2-h PPG increments measured during a standardized meal test: 1-h ETD, −1.18 mmol/L (95% CI −1.65, −0.71; p<0.0001); 2-h ETD, −0.67 mmol/L (95% CI −1.29, −0.04; p=0.0375). The improvement in glycemic control was maintained after 52 weeks of treatment (62). Faster aspart dosed 20 min after the start of a meal (postmeal) was noninferior to mealtime IAsp in terms of A1C reduction after 26 weeks of treatment (60). These results were supported by the 26-week onset 8 trial, which evaluated faster aspart as part of a basal-bolus regimen with insulin degludec (61). In onset 8, both mealtime and postmeal faster aspart were noninferior to mealtime IAsp in terms of A1C control, although there was no significant improvement with faster aspart over IAsp. There was, however, a significant reduction in the early PPG increments during a standardized meal test with faster aspart vs. IAsp: 30-min ETD, −0.52; 95% CI −0.83, −0.20; p=0.001; 1-h ETD, −0.90 mmol/L; 95% CI −1.36, −0.45; p<0.001. Significantly more participants achieved a 1-h PPG target of <7.8 mmol/L based on self-measured blood glucose with faster aspart: 27.8% vs. 21.6%; estimated treatment ratio (ETR) 1.54; 95% CI 1.05, 2.26; p=0.028).

There was no increase in the overall rate of severe or BG-confirmed (<3.1 mmol/L [56 mg/dL]) hypoglycemia with faster aspart vs. IAsp in either onset 1 (26 or 52 weeks) or onset 8 (60–62), and a pooled post hoc analysis across both trials suggested a lower rate of nocturnal hypoglycemia with faster aspart: ETR 0.84; 95% CI 0.72, 0.98 (63). Although the rates of severe or BG-confirmed hypoglycemia reported during the first hour after a meal were very low compared with the overall rate, there was an increase with mealtime faster aspart vs. IAsp in onset 1 after 26 weeks: 1.5 vs. 1.0 episodes per patient-year of exposure (PYE); ETR 1.48; 95% CI 1.11, 1.96; p=0.0073 (60), and this was maintained after 52 weeks (62). Conversely, there was a reduction in hypoglycemia in favour of mealtime faster aspart compared with IAsp 3- to 4-h after a main meal in onset 8: 2.9 vs. 4.0 episodes per PYE; ETR 0.72; 95% CI 0.54, 0.96; p=0.024 (61).

Mean body weight increase in all 3 treatment groups was <1 kg in the onset 1 trial and <2 kg in the onset 8 trial, and there was no statistically significant difference between faster aspart (mealtime or postmeal) and IAsp (60,61).

The recently completed onset 7 trial investigated the efficacy and safety of faster aspart in a pediatric population with type 1 diabetes, and the results are awaited (64).

Table 1
Summary of the onset clinical trial programme with mealtime faster aspart vs. insulin aspart administered by multiple daily injections in adults with type 1 diabetes and type 2 diabetes

Trial	Trial population	Trial duration	Basal insulin	A1C, % ETD (95% CI)	1-h PPG increment, mmol/L ETD (95% CI)	Severe or BG-confirmed hypoglycemia (episodes/PYE) ETR (95% CI)
onset 1	Adults with type 1 diabetes; A1C ≥7.0%–9.5%; n=1143	26 weeks	Insulin detemir	−0.15 (−0.23; −0.07); p=0.0003	−1.18 (−1.65; −0.71); p<0.0001	1.01 (0.88; 1.15)
onset 8	Adults with type 1 diabetes; A1C ≥7.0%–9.5%; n=1025	26 weeks	Insulin degludec	−0.02 (−0.11; 0.07)	−0.90 (−1.36; −0.45); p<0.001	0.84 (0.70; 1.01)
onset 2	Adults with type 2 diabetes; A1C ≥7.0%–9.5%; n=689	26 weeks	Insulin glargine 100 units/mL	−0.02 (−0.15; 0.10)	−0.59 (−1.09; −0.09); p=0.0198	1.09 (0.88; 1.36)

A1C, glycated hemoglobin; *BG,* blood glucose; *CI,* confidence interval; *ETD,* estimated treatment difference; *ETR,* estimated treatment ratio; *MDI,* multiple daily injections; *n,* number of randomized participants; *PPG,* postprandial glucose; *PYE,* patient-year of exposure.
Notes: In the 3 trials, after a run-in period to optimize basal insulin, participants were randomized to double-blind mealtime faster aspart or insulin aspart arms. onset 1 and onset 8 included an additional open-label postmeal faster aspart dosing arm. The primary endpoint was change from baseline of A1C, and noninferiority of faster aspart to insulin aspart was confirmed. 1-h PPG increments were obtained from standardized liquid meal tests. Severe or BG-confirmed hypoglycemia was defined as an episode requiring the assistance of another person and/or an episode confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycemia.

Clinical trials in type 2 diabetes

The efficacy and safety of faster aspart in adults with type 2 diabetes was evaluated in 2 treat-to-target, active-controlled randomized controlled trials (onset 2 and onset 3) (59,65). In the 18-week onset 3 trial, the addition of faster aspart using a simple patient-driven titration algorithm demonstrated superior A1C reduction: ETD −0.94%; 95% CI −1.17, −0.72; p<0.0001; and PPG control: 2-h PPG (self-measured blood glucose for all meals; ETD −2.48 mmol/L, 95% CI −2.92, −2.03; p<0.0001) compared with basal insulin and metformin alone (65). As expected with intensified treatment, hypoglycemia rates were higher with basal-bolus compared with basal insulin only (12.8 vs. 2.0 episodes/PYE). Nevertheless, 43% of participants taking basal-bolus achieved A1C targets of ≤6.5% without experiencing severe hypoglycemia, compared with 6.5% with basal insulin only. The onset 2 trial compared faster aspart with IAsp in participants inadequately controlled on basal insulin and oral antidiabetes drugs over 26 weeks (59). Overall glycemic control improved following intensification with either faster aspart or IAsp (A1C change from baseline, −1.38% and −1.36%, respectively), with significantly greater improvements in the 1-h PPG increment during a meal test with faster aspart (ETD −0.59 mmol/L; 95% CI −1.09, −0.09; p=0.0198). Overall hypoglycemia rates were similar in both treatments (17.9 vs. 16.6 episodes/PYE for faster aspart and IAsp, respectively), although there was an increase in hypoglycemia rates during the 0- to 2-h postmeal interval with faster aspart (2.3 vs. 1.5 episodes/PYE; ETR 1.60; 95% CI 1.13, 2.27).

Clinical trials in CSII systems

Faster aspart is also safe and effective in CSII systems (66). Pharmacologic studies demonstrated an approximately 3-fold greater insulin exposure and an approximately 100% greater glucose-lowering effect in the first 30 min with faster aspart compared to IAsp (67). An exploratory crossover trial in adults with type 1 diabetes showed that, compared with IAsp, faster aspart delivery via CSII provided a greater glucose-lowering effect during the 2 h after a liquid meal test (ETD −0.99 mmol/L; 95% CI −1.95, −0.03); p=0.044) (68). Faster aspart also significantly improved early PPG control in participants with type 1 diabetes in the large onset 5 clinical trial (1-h PPG increment, ETD −0.91 mmol/L; 95% CI −1.43, −0.39); p=0.001), with no increase in overall rates of severe or BG-confirmed hypoglycemia compared with IAsp (45.1 vs. 45.3 episodes/PYE) (69). Consistent with previous onset trials, the rate of severe or BG-confirmed hypoglycemia in the small proportion of episodes reported 1 h after a meal was significantly higher with faster aspart compared with IAsp (1.3 vs. 0.7 episodes/PYE; ETR 1.78; 95% CI 1.15, 2.75).

Diabetes Canada Clinical Practice Guidelines

The updated Diabetes Canada clinical practice guidelines were published in April 2018. The guidelines recommend that RAIAs should be used in place of RHI for greater improvements in A1C levels, reducing the risk for hypoglycemia and achieving PPG targets, and they now include faster aspart in the list of RAIAs available for use in adults.

In type 1 diabetes, faster aspart demonstrates noninferiority to IAsp with respect to A1C reduction, with superior PPG control and no overall increased risk for hypoglycemia. The 0.15% A1C difference favouring faster aspart compared with IAsp reported in the onset 1 study is similar to the average A1C improvement with RAIAs over RHI reported in a Cochrane meta-analysis (70). An improvement in PPG control has been consistently demonstrated in the clinical trial data with faster aspart vs. IAsp. Of note, all studies use a liquid meal in their meal tests, which standardizes the nutrient composition among participants but will exaggerate PPG excursions compared with a solid meal in a real-life setting. When selecting an RAIA, clinicians should keep in mind that the clinical utility of faster aspart may actually be underestimated in blinded treat-to-target trials.

The guidelines highlight that all people with diabetes on insulin therapy should be counselled about the risk, prevention, recognition and treatment of hypoglycemia (71). The overall risk for severe or BG-confirmed hypoglycemia is similar for faster aspart and IAsp, although the clinical data suggest a slight increase in risk in the first hour after the start of a meal with faster aspart. This may reflect the left-shifted time-action profile of faster aspart vs. IAsp (i.e. the increased early absorption, faster onset of action and greater early glucose-lowering effect that can lead to earlier onset of hypoglycemia following a meal) and is acknowledged in the faster aspart label, which states, “If hypoglycemia occurs, it may occur earlier after an injection when compared to other mealtime insulins” (72). The first hour after a meal is not a common time for hypoglycemic events to occur except in patients with gastroparesis or those who exercise immediately after injection. Even so, for some patients, an adjustment of dose might be necessary to mitigate the risk of early hypoglycemia seen in the clinical trials, and individual titration is important for achieving optimal glycemic control.

The clinical data highlight that faster aspart provides the opportunity for postmeal dosing. Insulin formulations with effective postprandial dosing options may help to overcome the limitations of real-world insulin dosing and are likely to be very popular with patients. The guidelines recommend that IAsp,

glulisine and lispro be administered 0 to 15 min before the start of a meal, whereas RHI should be administered 30 to 45 min beforehand (2). When required, IAsp, glulisine and lispro can be administered from 0 to 15 min after the start of a meal, although better control of postprandial hyperglycemia is seen with injections before a meal. The updated guidelines state that faster aspart may be administered up to 2 min before the start of the meal or, when necessary, up to 20 min after a meal without compromising A1C control and hypoglycemia risk compared with mealtime IAsp. Postmeal dosing is more convenient in daily life, allows for more precise calculation of carbohydrates actually consumed and reduces the risk for hypoglycemia should a meal be delayed. Postmeal dosing could be particularly useful for elderly patients with cognitive impairment and/or irregular eating patterns and also for younger age groups, in whom eating behaviour is known to vary considerably. However, as noted on the label, the safety and efficacy results in children and adolescents are not yet available, and limited evidence is available for elderly patients with type 1 diabetes (72).

The recommended injection-meal intervals are based on the concept that PPG control is dependent on insulin delivery matching the rate of glucose absorption, which is dependent primarily on gastric emptying. There may be a need for caution with new mealtime insulins in patients with gastroparesis, in which delayed gastric emptying and rapid onset of insulin action may increase the risk for hypoglycemia. However, in practice, faster acting insulins may be useful to correct postprandial hyperglycemia because many patients with known gastroparesis are directed to delay bolus administration. The nutritional content of meals also impacts PPG excursions and insulin dose/injection meal-interval requirements. However, currently, no clinical data exist concerning the use of faster aspart with differing meal types. In clinical practice, some individuals have reported that although they no longer predose with faster aspart, they may take additional doses (or use an extended bolus) when eating meals high in fat and carbohydrate.

The guidelines recommend that, in adults with type 1 diabetes on basal-bolus injection therapy who are not achieving glycemic targets, CSII with RAIAs may be used to improve glycemic control. Faster aspart in CSII is currently being evaluated in clinical trials, but has not yet been approved in Canada. When new fast-acting mealtime insulins are available for use in CSII, clinicians should note that there may be less need for bolus administration prior to a meal and, potentially, greater need for the use of different bolus types, such as a square wave bolus or an extended bolus with larger, richer meals.

For individuals with type 2 diabetes, the guidelines recommend the use of RAIAs, including faster aspart, over RHI in adults inadequately controlled by basal insulin and other agents (4). Bolus insulin should be initiated using a stepwise approach, starting with 1 injection at the largest meal and additional mealtime injections at 3-month intervals if needed. Unless contraindicated, metformin remains the first-line treatment. Of particular note in the updated guidelines is the use of second-line agents with demonstrated cardiovascular benefits (empagliflozin, liraglutide and canagliflozin) for patients with CVD. In patients without CVD, the guidelines recommend the addition of incretin therapies (dipeptidyl peptidase 4 inhibitors or glucagon-like peptide-1 receptor agonists) and/or sodium-glucose cotransporter-2 inhibitors over insulin (and insulin secretagogues) if lower risks for hypoglycemia and/or weight gain are priorities. For patients for whom bolus insulin is indicated, the onset trial data indicate that faster aspart can be added to a basal regimen using a simple patient-driven titration algorithm to improve early PPG control compared with IAsp.

Conclusions

The development of new mealtime insulins is helping to address the unmet need for improved PPG control in diabetes therapy, as demonstrated by the available clinical data for faster aspart. Faster aspart is the first in the new generation of mealtime insulins to be marketed in Canada and has been included in the 2018 update of the Diabetes Canada clinical practice guidelines. Faster aspart demonstrates noninferiority to IAsp with respect to A1C reduction, with superior PPG control and no increased risk for hypoglycemia in those with type 1 or type 2 diabetes. Importantly, the accelerated absorption of faster aspart compared with IAsp provides the option of postmeal dosing with no compromise of glycemic control and hyperglycemia risk.

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