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New faster-acting insulin Fiasp® — do we need a new meal-time insulin?

ABSTRACT

Studies aiming at improving the treatment of patients on insulin therapy are conducted bidirectionally. On the one hand, there are attempts to find modified insulin that acts even faster and has shorter effect than currently used short-acting insulin analogs, and on the other hand researchers work to develop more stable basal insulins.

Fiasp® is one of the new developments in this field. Addition of two excipients — niacinamide and L-arginine — resulted in faster hypoglycemic effect of insulin aspart while maintaining the stability of drug formulation.

Clinical trials assessing pharmacokinetic parameters of Fiasp® showed a 2 times faster onset of action (4 *vs.* 9 min), 2 times higher exposure to insulin 30 minutes after its administration and 74% more hypoglycemic activity during the first 30 minutes following subcutaneous injection.

Clinical trials of Fiasp® were conducted under the acronym Onset. Overall, these studies included over 3,000 patients with diabetes, both type 1 and type 2. In patients with type 1 diabetes (DM1) comparable or better diabetes control was observed in the Fiasp® groups compared with groups treated with Novorapid, with significantly lower blood glucose levels in the early postprandial period. It has also been demonstrated that administration of insulin Fiasp® within 20 min of the beginning of the meal was associated with comparable results to Novorapid administered before the meal.

Fiasp® is commercially available in Poland, but it is not yet widely used due to the high price and no reimbursement from NFZ. (Clin Diabetol 2018; 7, 6: 282–286)

Key words: Fiasp®, type 1 and 2 diabetes, niacinamide, basal insulin, short-acting insulin

Introduction

Insulin was discovered in 1922 by Banting and Best. Commercially available insulin was obtained from pancreases of slaughter animals (cows and pigs) and first used in 1923. It had different amino acid composition than human insulin and contained many xenogeneic-protein contaminants. Improvement of therapeutic insulin consisted in purification of the insulin solution, changes in the amino acid sequence, attachment of various molecules, and finally modification of the primary structure itself, i.e. the change of individual amino acids in the native insulin chain. Thanks to the use of biotechnology for the production of insulin it became possible to obtain preparations practically free from other proteins.

Nowadays, patients with diabetes can use many insulin preparations that are either human insulin equivalents (short-acting human insulin, NPH insulin) or its modified forms (insulin analogs). The group of currently manufactured insulin analog includes 3 rapid-acting analogs, aspart, lispro and glulisine, and 3 analogs providing a sustained, stable release of insulin — glargine, detemir and degludec. There are also so-called biosimilar insulins. Thus, there are dozens of commercially available insulin preparations that can be used in diabetic patients.

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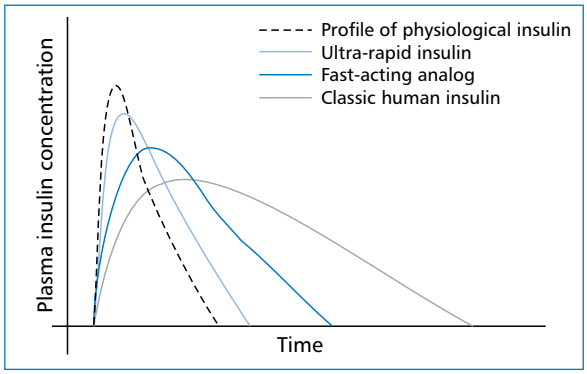

Figure 1. Profiles of action of different insulins

Do we need new insulin preparations, considering such a wide range of available therapeutic products? What are the expectations of doctors and, above all, the needs of patients?

The aim of the currently conducted research is to create such insulin preparations that would even better mimic physiological concentrations of insulin, both in fasting state and after eating a meal, i.e. basic (basal) and prandial (bolus) insulin secretion, compared with currently available preparations (Figure 1). On the one hand, studies are in progress to find insulins with even faster and shorter action than known short-acting analogs (ultra-rapid insulins), and on the other hand, researches are trying to develop longer and more stable basal insulins. The expected effect of using such preparations is to improve the metabolic control in diabetes and, at the same time, provide a greater comfort and safety of patients.

New fast-acting insulin produced by Novo Nordisk under the trade name Fiasp® seems to be a product that can meet one of those expectations.

It should be mentioned that two phase 3 clinical trials with another new insulin carried out by Lilly have been recently completed. Their results will be available at the beginning of 2019 [1].

Table 1 summarizes the pharmacological parameters of commercially available fast-acting insulin analogs.

Pharmacokinetic properties of Fiasp®

Fiasp® (Faster-acting Insulin Aspart) is an Aspart insulin formulation that has been enriched with niacinamide (vitamin B3 amide) and amino acid L-arginine. Niacinamide was added to increase the absorption of insulin after subcutaneous administration, and the addition of L-arginine resulted in stabilization of the whole molecule [5].

These two excipients are well known; they are both included in the American FDA list of inactive ingredient that have an neutral effect on the human body and, therefore, can be used for the production of injectables (Inactive Ingredient Search for Approved Drug Products). The concentrations of these substances used for the production of Fiasp® are small — lower than those used for the production of other drugs. These substances are also approved for use during pregnancy [6].

In vitro studies in an experimental model using vascular endothelial cell lines confirmed that the presence of niacinamide increases the absorption of insulin Aspart monomers by increasing endothelial permeability, which is a key mechanism changing the properties of insulin Aspart [7].

In 2014–2017 a number of studies were carried out aimed at assessing the pharmacokinetic profile, pharmacodynamic properties and the safety of Fiasp®. These trials resulted in approval of Fiasp® by the FDA and EMA.

The results of six single-center, randomized, double-blind, cross-over, phase 1 trials that evaluated the pharmacological properties of Fiasp® in adult patients with type 1 diabetes were summarized by Heise et al. [8–11]. A total of 218 patients aged 18–64 years were randomized to subcutaneous insulin Fiasp® or Novorapid at a dose of 0.2 U/kg body weight in order to compare the pharmacokinetic parameters of both insulins. In some of the participants, metabolic clamp studies were performed [5, 12].

Based on the results of the above studies, it was found that blood Fiasp® concentration-time curve was shifted to the left in relation to blood Novorapid concentration-time curve, indicating that both the time from

Table 1. Selected pharmacological parameters of commercially available insulin analogs

Generic name/Trade name/ /Manufacturer	Onset of action	Maximum glucose- -lowering effect	Duration of action	Dosing
Insulin Aspart/Novorapid/Novo Nordisk [2]	10–20 minutes	60 minutes–3 hours	3–5 hours	Immediately before or after a meal
Insulin Glulisine/Apidra/Sanofi [3]	10–20 minutes	55 minutes	4–5 hours	0–15 before or after a meal
Insulin Lispro/Humalog and Liprolog/Eli Lilly; Insulin Lispro/Sanofi [4]	15 minutes	30–70 minutes	2–5 hours	Immediately before or after a meal

Table 2. The results of the Onset trials comparing Fiasp® and Novorapid used for intensive insulin therapy in patients with type 1 diabetes

Name of the trial	Diabetes treatment	Number of patients/ /duration	Change in HbA_{1c}	Postprandial blood glucose Fiasp® *vs.* Novorapid	Hypoglycemic episodes
Onset 1 [15]	Insulin Levemir	1143/52 weeks	–0.08 *vs.* +0.01% $p < 0.0424$	Change in favor of Fiasp®: –14.3 *vs.* +2.5 $p < 0.005$	No difference
Onset 8 [16]	Basal insulin degludec	1025/26 weeks	Comparable	Confirmed better postprandial glycemic control in the Fiasp® group $p < 0.05$	No difference
Onset 4 [17]	Insulin pump	37/6 weeks	Comparable	A trend towards lower postprandial glucose levels in the Fiasp® group	No difference
Onset 5 [18]	Insulin pump (with CGM)	472/16 weeks	Non-inferior to insulin Aspart, but smaller HbA_{1c} reduction in the Fiasp® group	Confirmed better postprandial glycemic control in the Fiasp® group $p < 0.05$	No difference

insulin delivery to its maximum concentration in the blood (t_{max}) and the time to maximum glucose reduction (t_{GIRmax}) were shorter for Fiasp® compared to Novorapid (by 7 and 11 minutes, respectively). Time to 50% decrease from maximum concentration ($t_{early\ 50\%\ C\ max}$) was shorter by 10 minutes (decreased by 30%) with Fiasp® compared to Novorapid. In addition, the initial effect of Fiasp® occurred about 5 minutes earlier (*i.e.* twice as fast compared to Novorapid).

The pooled analysis showed that both the initial concentration of insulin in the blood and the early glucose-lowering effect were greater for Fiasp® compared to Novorapid within the first 2 hours after injection [12].

During the first 30 minutes after insulin injection, a two times higher availability ($AUC_{0–30\ min}$) and a 74% higher metabolic effect ($AUC_{GIR,\ 0–30\ min}$), measured by reduction in blood glucose, was found for Fiasp® compared with Novorapid [5, 12]. This corresponds to a reduction in blood glucose of 51 mg/kg with Fiasp® and 29 mg/kg with Novorapid (Fiasp®/Novorapid ratio: 1.74 [95% CI: 1.47–2.10]) [13]. After reaching the maximum concentration (C_{max}), the decrease in insulin concentration was observed earlier for Fiasp® than for Novorapid. The difference in time to 50% reduction from the maximum blood insulin concentration ($t_{late\ 50\%\ C\ max}$) between Fiasp® and Novorapid was 12.2 min. Similarly, the glucose lowering effect occurred earlier for Fiasp® compared to Novorapid (the difference in $t_{late\ 50\%\ GIR\ max}$ was 14.3 minutes) [12].

The maximum glucose-lowering effect occurred between 1 and 3 hours after the injection. The total glucose-lowering effect and maximum glucose-lowering effect (GIR_{max}) were comparable between both insulins. Fiasp® had a shorter duration of action compared to Novorapid insulin and it was 3–5 hours.

In the therapeutic dose range, a linear relationship between Fiasp® dose and glucose lowering effect was observed [13]. This insulin showed low daily intra-individual variability in reducing blood glucose for early ($AUC_{GIR,\ 0–1h}$, CV ~26%), total ($AUC_{GIR,\ 0–12h}$, CV ~18%), and the maximum glucose-lowering effect (GIR_{max}, CV ~19%) [9, 13]. There were no differences in the maximum glucose-lowering effect between patients of different ages [10]. Similar results in relation to postprandial glucose were also obtained in the Japanese study [14].

Clinical trials — assessment of clinical effectiveness

Clinical studies of Fiasp®, referred as the Onset trials, were carried out in various populations of patients with type 1 and type 2 diabetes. In total, these trials included over 3,000 patients. Table 2 presents the characteristics and main results of the Onset trials in the population of patients with type 1 diabetes mellitus (DM1).

The trials in DM1 patients showed comparable or better glycemic control in the Fiasp® groups compared with Novorapid groups, with significantly lower blood glucose levels in the early postprandial period. No increase in the number of hypoglycemic episodes was observed in the Fiasp® groups, and in the study with basal insulin degludec there were less episodes of late postprandial hypoglycemia. It is worth noting that administration of Fiasp® within 20 min of the beginning of the meal was associated with comparable results to those obtained with Novorapid given before meals

(Onset 8). The authors of the study conclude that the use of Fiasp® enables obtaining a glycemic profile that is closer to physiological [19].

Overall, Fiasp® was evaluated in 921 patients with type 2 diabetes mellitus (DM2). The Onset 2 trial compared two meal-time insulins, Fiasp® or Novorapid, in patients previously treated with metformin and basal insulin. There were no significant differences in diabetes control (noninferiority trial), although Fiasp® caused a greater reduction in blood glucose 60 min after a meal compared to Novorapid (38.5 *vs.* 27.9, p = 0.019), no such difference was found within 2–4 hours after a meal [20]. The reduction in postprandial blood glucose and body weight as well as overall safety profile were similar in both groups, but the risk of early-postprandial hypoglycemia (0–2 h) was higher in patients using Fiasp®. If in patients with poorly controlled diabetes (HbA_{1c} 7.0–9.5% at baseline) on metformin and basal insulin (Onset 3) Fiasp® was added, while in the control group of patients previous treatment was maintained, a significantly higher reduction of HbA_{1c} was obtained (1.2 *vs.* 0.2%, p = 0.0001), as expected; however, at the cost of a greater number of hypoglycemic events (severe and confirmed hypoglycemia: 58.3 *vs*. 25.0%) [21].

No significant differences in the body weight of study participants were found in the studies mentioned above. In the Onset 5 trial, there were more skin reactions at the injection site in patients receiving Fiasp® by continuous subcutaneous insulin infusion. No other significant side effects were found.

Prescription form

Fiasp® is a clear, aqueous solution that can be administered subcutaneously and intravenously. Fiasp® is available as a 100 U/mL solution for injection in 3-mL penfill cartridges.

According to the manufacturer's recommendations, Fiasp® is a mealtime insulin that should be administered up to 2 minutes before the meal, but it can be taken up to 20 minutes after starting a meal. It is recommended that Fiasp® should be injected into the subcutaneous tissue of the abdomen or arm, which results in a faster onset of action [22].

The dosage of Fiasp®, like all other insulins, should be adjusted individually and determined in accordance with the patient's needs. The duration of action may vary depending on the dose, injection site, blood flow, body and ambient temperature, and the level of physical activity of the patient.

The potency of Fiasp® corresponds to 1 international unit of human insulin or 1 unit of another rapid-acting insulin analog; therefore, there is no need to modify the dose when changing from another rapid-acting insulin formulation, but obviously it may be necessary to adjust the doses and dosing time of concomitantly used medium- or long-acting insulins or adjustment of other antidiabetic treatment. Fiasp® has not been registered in patients < 18 years of age.

Summary

The authors of the studies performed conclude that Fiasp® allows for better mimicking of the physiological secretion of insulin compared with Novorapid [14, 15, 19]. Pharmacokinetic studies showed a twice rapid onset of action (4 *vs*. 9 min) and 2 times higher exposure to insulin at 30 min after its administration and 74% more hypoglycemic activity during the first 30 minutes following subcutaneous injection.

The results of the above-discussed trials including various groups of patients suggest that Fiasp® may be a good alternative for patients using functional, intensive insulin therapy, both multiple subcutaneous injections and CSII (insulin pump). Although this has not been directly demonstrated in clinical studies, Fiasp® can be particularly useful if patients' diet is rich in simple carbohydrates, or if used instead of regular analog for selected meals. It would be an alternative therapy for patients who are well-educated and actively involved in their own management. However, it can be expected that the largest group of patients using Fiasp® will be patients who are unable to keep, for various reasons (e.g., short breaks for meals at work and at school, hurry in eating meals, etc.), the time between insulin injections and meal intake, and those who are tired with constant time control. This group may include both very active and independent patients, and those dependent on caregivers, e.g. nursing home residents. Approval of Fiasp® for use in children can significantly improve their quality of life.

Although registered for use in Poland, Fiasp® is not yet widely available for patients due to the high price and the lack of reimbursement by the NFZ. It is expected that this insulin can potentially improve metabolic control in patients with diabetes, but only the widespread availability of Fiasp® will allow follow-up and more accurately defining groups of patients with diabetes who will benefit from its use.

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