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ORIGINAL ARTICLE

New Insulins and Insulin Therapy

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Introduction

THE QUEST FOR new ultra-long- and ultra-fast-acting insulin analogs with improved pharmacokinetic and pharmacodynamic profiles continues. Among the new generation of ultra-long-acting insulins, insulin degludec is the first to have reached the market, and data on efficacy and safety characteristics of this analog are accumulating. Glargine U300, which is a higher-strength formulation of insulin glargine resulting in a more gradual and protracted release, is presumably next in line of the prolonged-acting analogs to be approved. The third novel ultra-long-acting analog, LY2605541, is based on the polyethylene glycol(PEG)ylation principle, where insulin lispro has been linked to PEG. The so-formed, large-sized peglispro molecule retards insulin absorption and clearance, leading to a steady and extended action profile. Interestingly, experimental findings indicate an uneven tissue distribution of peglispro, with a preferential hepatoselective mode of action.

The mounting evidence for the deleterious effects of postprandial glucose excursions in type 1 and type 2 diabetes has also prompted more investment into ultra-rapid insulin formulations. However, while several approaches to accelerate postinjection insulin absorption are under development as evidenced from the companies' home pages, the published literature over the last year has been meager. Notably, at the annual meeting of the American Diabetes Association 2014 in San Francisco, Heise and coworkers reported on a phase I study with a novel faster-acting formulation of insulin aspart with promising findings. Furthermore, the American Food and Drug Administration (FDA) approved on June 27, 2014, the inhaled insulin Afrezza, also demonstrating a faster onset of action and shorter duration compared to a fast-acting analog (FDA Briefing Document—Endocrinologic and Metabolic Drug Advisory Committee, April 01, 2014). Finally, coformulation of insulins with hyaluronidase may be another clinically relevant solution for speeding up prandial insulin action.

INSULIN DEGLUDEC: FIRST APPROVED AND MARKETED ULTRA-LONG-ACTING INSULIN ANALOG

Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial

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Diabetes Obes Metab 2014; ***16:*** *922–30*

Background

To compare the efficacy and safety of basal insulin supplementation with insulin degludec (IDeg) and insulin detemir (IDet) in patients with type 1 diabetes mellitus (T1DM) over a 26-week period.

Methods

This multinational, open-label, parallel-group trial included adult patients with T1DM receiving any type of basal-bolus insulin regimen for at least 1 year, with HbA1c $< 10\%$, and body mass index ≤ 35.0 kg/m^2. The patients were randomized to once-daily administration of IDeg ($n = 302$) or IDet ($n = 153$) together with insulin aspart as meal-time insulin, using a treat-to-target titration algorithm.

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Results

At study end, HbA1c had decreased 0.73% with IDeg and 0.65% with IDet (estimated treatment difference [ETD] IDeg minus IDet −0.09% [95% CI −0.23 to 0.05]), confirming noninferiority. Mean fasting plasma glucose was lowered more with IDet than with IDeg (ETD IDeg minus IDet −1.66 mmol/l [95% CI −2.37 to −0.95], $p < 0.0001$). The total rate of confirmed hypoglycemia (plasma glucose <3.1 mmol/l) was comparable in the two groups (IDeg 45.83 and IDet 45.69 episodes per patient-year of exposure, respectively); the estimated rate ratio (RR) IDeg/IDet was 0.98 ([95% CI 0.80 to 1.20], $p = 0.86$). The rate of nocturnal confirmed hypoglycemia (between 00:01 and 05.59 hours) was lower with IDeg than with IDet (4.14 vs. 5.93 episodes per patient-year of exposure); RR IDeg/IDet = 0.66 [95% CI 0.49 to 0.88], $p = 0.0049$). Adverse event patterns were similar in the two treatment groups.

Conclusions

Basal insulin supplementation with IDeg once daily effectively improved glycemic control in patients with T1DM, with less risk of nocturnal hypoglycemia compared with IDet.

Insulin degludec's ultra-long pharmacokinetic properties observed in adults are retained in children and adolescents with type 1 diabetes

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*Pediatr Diabetes 2014; **15**: 27–33*

Background

To investigate the pharmacokinetic properties of insulin degludec (IDeg) in children and adolescents with type 1 diabetes mellitus (T1DM).

Methods

A single-center, randomized, double-blind, single-dose, two-period, cross-over study including 12 children (6–11 years), 13 adolescents (12–17 years), and 12 adults (18–65 years) with T1DM. A single subcutaneous injection of 0.4 U/kg of IDeg or insulin glargine (IGlar) was administered on two separate occasions, separated by a 7–21 days washout period. Pharmacokinetic blood sampling was performed up to 72 h after each insulin dose.

Results

Relative to adults, total exposure of IDeg after a single dose (area under the curve of serum IDeg concentration from time zero to infinity) was higher in children (estimated ratio children/adults 1.48 [95% CI 0.98 to 2.24]) and in adolescents (estimated ratio adolescents/adults 1.33 [95% CI 1.08 to 1.64]). There were no statistically significant differences in maximum IDeg concentrations between the three groups. Simulated mean steady-state IDeg pharmacokinetic profiles indicated a flat and stable distribution of exposure across a 24 h dosing interval. In all subjects, detectable IDeg concentrations were found at the end of the observation period (72 h) after the single dose.

Conclusions

The ultra-long pharmacokinetic properties of IDeg previously observed in adults seem to be analogous in children and adolescents with T1DM.

Insulin degludec is not associated with a delayed or diminished response to hypoglycemia compared with insulin glargine in type 1 diabetes: a double-blind randomized crossover study

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*Diabetologia 2014; **57**: 40–49*

Background

To compare the acute responses to hypoglycemia elicited by insulin degludec (IDeg) and insulin glargine (IGlar).

Methods

Twenty-eight adult patients with type 1 diabetes mellitus (HbA1c 7.8 ± 0.6%) with normal hypoglycemia awareness were randomly allocated (double-blind) to once-daily IDeg or IGlar basal insulin for 5 days in a two-period cross-over design (with a 13–21 washout period in between). Hypoglycemia was induced by giving three times the usual daily insulin dose subcutaneously at midnight on day 5. Thereafter, plasma glucose (PG) was controlled by a variable intravenous glucose infusion (glucose clamp), and set at 5.5 mmol/l overnight. The next morning, PG was lowered in a stepwise fashion to 3.5 mmol/l (which was kept for 30 min) and 2.5 mmol/l (maintained for 15 min). PG was then allowed to increase and plateaued at 3.9 mmol/l for 120 min; thereafter, it was increased to the baseline level. Hypoglycemic symptom score (HSS), hypoglycemia awareness, cognitive function, counter-regulatory hormonal responses, and vital signs were measured at each PG plateau.

Results

Rates of PG lowering and the PG concentrations at nadir were comparable with both insulins. No differences between IDeg and IGlar were detected with regard to HSS, cognitive function, or hypoglycemia awareness. Hypoglycemia-induced responses of growth hormone (GH) and cortisol

were more pronounced with IDeg than with IGlar (AUC IDeg/IGlar ratio 2.44 [95% CI 1.30 to 4.60], $p < 0.01$ for GH, and 1.23 [95% CI 1.01 to 1.50], $p < 0.05$ for cortisol), and the adrenaline response also tended to be greater with IDeg (AUC IDeg/IGlar ratio 1.40 [95% CI 0.96 to 2.04]). Similar rates of PG recovery after hypoglycemia were observed.

Conclusions

IDeg- and IGlar-induced hypoglycemia elicits comparable symptomatic and cognitive responses. IDeg may bring about a slightly more pronounced counter-regulatory hormonal response, but the rate of PG recovery after hypoglycemia is similar for IDeg and IGlar.

Comparison of insulin degludec with insulin glargine in insulin-naïve subjects with type 2 diabetes: a 2-year randomized, treat-to-target trial

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*Diabet Med 2013; **30**: 1298–304*

Background

To compare the long-term efficacy and safety of insulin degludec (IDeg) versus insulin glargine (IGlar) in insulin-naïve patients with type 2 diabetes mellitus (T2DM).

Methods

Parallel-group, randomized, open-label, treat-to-target trial including a 52-week core study followed by a 52-week extension period. Insulin-naïve patients with T2DM were allocated 3:1 to once-daily IDeg ($n = 773$) or IGlar ($n = 257$) as add-on to ongoing metformin ± dipeptidyl peptidase-4 (DPP4) inhibitors.

Results

At 104 weeks, mean HbA1c reductions were comparable for IDeg and IGlar (estimated treatment difference IDeg–IGlar 0.07% [95% CI −0.07 to 0.22]) in patients who completed the core study and continued into the extension trial (IDeg 551 patients and IGlar 174 patients, respectively). Data from the safety analysis set comprising all randomized patients showed similar rates of overall confirmed hypoglycemia (IDeg 1.72 and IGlar 2.05 episodes per patient-year), whereas the rates of nocturnal confirmed hypoglycemia (0.27 vs. 0.46 episodes per patient-year; $p = 0.002$) and severe hypoglycemia (0.006 vs. 0.021 episodes per patient-year) were significantly less frequent with IDeg. Rates of adverse events possibly or probably related to the trial insulin (0.19 events per patient-year in both groups), weight gain (2.7 vs. 2.4 kg), and mean insulin dose (0.63 U/kg in both groups) were comparable in the two treatment groups.

Conclusions

Insulin supplementation with insulin degludec as add-on to oral antidiabetic drugs safely and effectively improves long-term glycemic control in patients with T1DM, with significantly less risk of nocturnal hypoglycemia as compared with glargine.

Efficacy and safety of insulin degludec three times a week versus insulin glargine once a day in insulin-naïve patients with type 2 diabetes: results of two phase 3, 26 week, randomized, open-label, treat-to-target, non-inferiority trials

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*Lancet Diabetes Endocrinol 2013; **1**: 123–31*

Background

To compare the efficacy and safety of insulin degludec administered three times a week (IDeg 3TW) with once-daily insulin glargine (IGlar) in insulin-naïve patients with type 2 diabetes mellitus (T2DM).

Methods

Two phase 3, 26-week, multinational, randomized, open-label, parallel-group, noninferiority trials, where insulin-naïve patients with T2DM on oral antidiabetic agents (HbA1c 7.0–10.0%; body mass index ≤ 45 kg/m^2) were allocated to IDeg administered three times weekly (Monday, Wednesday and Friday) or once-daily IGlar; all patients continued oral therapy with metformin ± dipeptidyl-peptidase-4 (DPP4) inhibitors. In one trial, IDeg was given before breakfast (IDeg 3TW$_{AM}$, $n = 230$; IGlar, $n = 230$), and in the other, together with the evening meal (IDeg 3TW$_{PM}$, $n = 233$; IGlar, $n = 234$). Insulin doses were titrated according to a treat-to-target algorithm. The primary end point was noninferiority of IDeg versus IGlar in terms of HbA1c reduction from baseline to 26 weeks (noninferiority limit 0.4%).

Results

At study end, mean HbA1c reductions in the AM trial were 0.9% with IDeg and 1.3% with IGlar; in the PM trial, the corresponding figures were 0.9% and 1.4%, respectively. Noninferiority was not confirmed in either trial, with the

estimated treatment difference between IDeg 3TW and IGlar being 0.34% [95% CI 0.18 to 0.51] in the AM trial and 0.26% [95% CI 0.11 to 0.41] in the PM trial. In the two trials, rates of confirmed hypoglycemia or severe hypoglycemia ranged between 1.0 and 1.6 episodes per patient-year; comparable rates were found between IDeg 3TW and IGlar in the AM trial (estimated rate ratio [ERR] IDeg $3TW_{AM}$/IGlar 1.04 [95% CI 0.69 to 1.55]), but in the PM trial, significantly higher rates were observed with IDeg 3TW than IGlar (ERR 1.58 [95% CI 1.03 to 2.43]). As compared with IGlar, the rate of nocturnal confirmed hypoglycemia was significantly higher for IDeg $3TW_{AM}$ (ERR 2.12 [95% CI 1.08 to 4.16]), whereas it was comparable for IDeg $3TW_{PM}$ (ERR 0.60 [95% CI 0.21 to 1.69]).

Conclusions

Compared with IGlar once daily, IDeg administered three times a week showed inferior glycemic control and higher risk of hypoglycemia. Consequently, the observed findings do not support a three-times-weekly dosing regimen with IDeg.

Comment

Insulin degludec (Tresiba®) is approved and marketed in Europe and several other countries around the globe, but still awaits the results of a cardiovascular outcome trial to be finally considered for approval by the FDA.

In earlier yearbooks, we have described the molecular structure of insulin degludec and the pharmacokinetic and pharmacodynamic properties of this prolonged-acting insulin analog. Briefly, its prolonged action profile is mainly the result of a slow and stable release of insulin degludec monomers from soluble multihexamers that form after subcutaneous administration. We have previously also summarized the findings of several clinical phase II–III trials, where the efficacy and safety of insulin degludec had been assessed in treat-to-target designed studies in adult patients with T1DM and T2DM, almost invariably with insulin glargine as comparator. The most consistent finding from these studies is that at comparable improvements in glycemic control (i.e., reductions in A1C), the rate of confirmed nocturnal hypoglycemic events is reduced in both T1DM and T2DM with degludec, whereas its effect on confirmed overall rates of hypoglycemia has been more varying and mostly restricted to patients with T2DM. It has been inferred that the observed effect of degludec on nocturnal hypoglycemia in these clinical trials might have been amplified owing to methodological issues such as patient selection, definition of hypoglycemia (i.e., plasma glucose cutoff), selected time limits for the nocturnal observation period, timing of insulin administration for the comparator, and so on (1). Yet, from the results of the accumulating body of evidence, including the presently referenced trials in both T1DM and T2DM, it would seem that degludec preferentially lowers the risk of nocturnal hypoglycemia but not overall rates of hypoglycemia; evidently, the same is found also when insulin detemir (once or twice daily) is used as comparator. Accordingly, insulin degludec appears to be especially suitable for patients with unstable glycemic control and documented nocturnal hypoglycemia despite other educational and treatment efforts. Therefore, it is reassuring that the physiological and cognitive responses to—and the recovery from—degludec-induced hypoglycemia are not deprived, as shown by Koehler and coworkers.

The clinical trial program has confirmed the safety and efficacy of degludec in adults of several ethnic origins. The report by Biester et al. showed—perhaps not surprisingly—that the pharmacokinetic properties of insulin degludec are retained also in children and adolescents, which warrants clinical trials in pediatric subjects.

The ultra-long-action profile of degludec allows more flexible timing of basal insulin administration from day to day, as has previously been shown in both T1DM and T2DM (2,3). Earlier findings from a short-term, phase II trial even suggested the possibility of administering degludec only three times a week without compromising safety or glycemic control in patients with T2DM (4). The more recent, longer-term study by Zinman and coworkers, however, clearly demonstrates that this treatment regimen is associated with inferior glycemic control and markedly increased risk of hypoglycemia. Consequently, their data support the notion that insulin degludec should only be used in a once-daily dosing regimen.

NEW INSULIN GLARGINE U300: NEXT ULTRA-LONG-ACTING INSULIN TO BE APPROVED?

Investigational new insulin glargine 300 U/ml has the same metabolism as glargine 100 U/ml

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Diabetes Obes Metab 2014; ***16:*** *873–6*

Background

To compare the metabolism and metabolite pharmacokintetics of insulin glargine 300 U/ml and glargine 100 U/ml in patients with type 1 diabetes mellitus (T1DM).

Methods

In a double-blind, randomized, cross-over study, 30 T1DM patients were administered once-daily (evening) subcutaneous doses of either 0.4 ($n = 18$) or 0.6 U/kg ($n = 12$) of glargine 300 U/ml for 8 days in one treatment period, and 0.4 U/kg of glargine 100 U/ml for 8 days in the other, with a 5–19 washout period in between. After each treatment period, on day 8, a 36 h euglycemic clamp was performed. M0, M1, and M2 metabolites were quantified using immunoaffinity enrichment and liquid chromatography tandem mass spectrometry.

Results

The metabolism was the same for both glargine preparations, with M1 as the principal active circulating moiety.

Steady-state concentrations of M1 were observed after 2 and 4 days with glargine 100 U/ml and glargine 300 U/ml, respectively, with the pharmacokinetic profile being prolonged and even flatter with the 300 U/ml preparation.

Conclusions

Insulin glargine metabolism in patients with T1DM is the same for glargine 300 U/ml and glargine 100 U/ml, with M1 being the main active moiety in circulating blood.

Comment

Glargine U300 is a new formulation that contains insulin glargine at a higher concentration (300 U/ml) than the original one (100 U/ml). With this higher-strength formulation, glargine U300 forms a denser subcutaneous depot with a smaller surface area, resulting in a more gradual and prolonged release relative to the U100 formulation. Accordingly, glargine 300 has a flatter pharmacokinetic and pharmacodynamic profile than glargine U100, with a prolonged duration of action (> 24 h). As shown in the article by Steinstraesser *et al.*, the metabolism of glargine 300 is the same as for glargine U100, with the M1 metabolite (21^{A}-Gly-human insulin) being the principal active moiety circulating in blood. This is important as the M1 metabolite does not exhibit an increased affinity for the IGF-1 receptor or enhanced mitogenicity compared with human insulin.

Recently, the European Medicines Agency (EMA) accepted to review Sanofi's marketing dossier for insulin glargine U300 (intended trade name Toujeo®) for the European countries; in the United States, it has been submitted to the FDA and their formal acceptance of the submission is pending. However, results from the clinical trials with glargine U300 are still to be published. Preliminary data from treat-to-target studies in patients with T2DM with glargine U100 as comparator indicate similar improvement in glycemic control (HbA1c) but less risk of hypoglycemia—in particular nocturnal hypoglycemia—in glargine U300-treated patients. In patients with T1DM, basal insulin supplementation with glargine U300 seems to allow more flexible timing of the once-daily administration, whereas its effect on rates of hypoglycemia appears less clear. Hopefully, the clinical benefits of glargine U300 will be clarified in more detail in the near future.

PEGLISPRO: AN ULTRA-LONG-ACTING INSULIN ANALOG WITH PREFERENTIAL HEPATIC ACTION?

Steady-state, pharmacokinetics and glucodynamics of the novel, long-acting basal insulin LY2605541 dosed once-daily in patients with type 2 diabetes mellitus

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*Diabetes Obes Metab 2014; **16**: 344–50*

Background

To investigate the pharmacokinetics and glucodynamics of LY2605541 after single- and multiple-dose administration in patients with type 2 diabetes mellitus (T2DM).

Methods

Parallel-group, open-label, multiple-ascending dose study where 32 insulin-treated (basal-bolus) T2DM patients were randomized into four parallel groups to receive a fixed dose of insulin LY2605541 once daily (in the morning) in doses ranging from 0.33 to 1.00 U/kg for 14 days. A 24 h euglycemic clamp was carried out after the first (day 1) and last dose (day 14).

Results

Steady-state pharmacokinetics were observed within 7–10 days, with an essentially peakless glucose infusion rate (GIR) profile and a duration of action of at least 24 h. Across the different dose groups $t_{1/2}$ ranged from about 45 to 75 h. When steady state had been achieved, there were dose-dependent decreases in prandial insulin doses and in fasting blood glucose (decreased to 60–100 mg/dl). Within-patient variability was < 14% when determined by the area under the concentration versus time curve (AUC) for an 8-point blood glucose profile, and < 26% based on the fasting blood glucose concentration. Mild hypoglycemia was the most common adverse event (44 events in 38% of the patients).

Conclusions

Basal insulin supplementation with fixed LY2605541 doses resulted in flat pharmacokinetic and glucodynamic profiles, improved glucose control, reduction in prandial insulin demand, and no severe hypoglycemia.

Lower glucose variability and hypoglycemia measured by continuous glucose monitoring with novel long-acting insulin LY2605541 versus insulin glargine

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*Diabetes Care 2014; **37**: 659–65*

Background

To assess the effect of insulin LY2605541 on hypoglycemia and glycemic variability in patients with type 2 diabetes mellitus (T2DM), using continuous glucose monitoring (CGM).

Methods

CGM recordings of subcutaneous interstitial glucose (IG) were performed in a subset of 76 patients with T2DM participating in a phase 2, randomized, open-label, parallel-group trial comparing basal insulin supplementation with insulin

LY2605541 ($n=51$) and insulin glargine ($n=25$). Blinded CGM was carried out on three consecutive days (72–84 h) during the week before week 0, 6, and 12 (study end) visits.

Results

According to the 3-day CGM recordings at study end, fewer patients on LY2605541 than on insulin glargine experienced hypoglycemic episodes (defined as IG < 70 mg/dl) overall (50.0% vs. 78.3%; $p=0.036$) and during nighttime (20.5% vs. 47.8%; $p=0.027$). LY2605541-treated patients also spent less time with IG < 70 mg/dl than glargine-treated patients (25 ± 6 vs. 83 ± 16 min/24 h; $p=0.012$ and 11 ± 5 vs. 38 ± 13 min/during nighttime $p=0.024$), whereas the average duration of individual hypoglycemic events was comparable (57.2 ± 5.4 vs. 69.9 ± 10.2 min/episode; $p=$ NS). In addition, within-day glucose variability (SD) for both 24 h and nocturnal periods was lower in the LY2605541-treated patients.

Conclusions

When compared with insulin glargine, basal insulin therapy with LY2605541 resulted in less risk of overall and nocturnal hypoglycemic events, less time spent in the hypoglycemic range, and was not associated with protracted or severe hypoglycemia.

Basal insulin peglispro demonstrates preferential hepatic versus peripheral action relative to insulin glargine in healthy subjects

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*Diabetes Care 2014; **37:** 2609–15*

Background

To investigate and compare the effects of insulin peglispro and insulin glargine on endogenous glucose production (EGP) and glucose disposal rates (GDR) in healthy subjects.

Methods

Single-center, randomized, open-label, four-period, incomplete-block, cross-over study design. Healthy male subjects ($n=8$) were randomly allocated to two parallel groups, and underwent 8 h euglycemic clamps on three occasions with primed, continuous intravenous infusions of different doses of peglispro (ranging from 5.1 to 74.1 mU/min) and a fourth clamp with insulin glargine (20 or 30 mU/m^2/min), targeted to result in 50–100% suppression of EGP. D-[3-^{3}H]-glucose was infused to measure rates of glucose appearance and disappearance.

Results

Average serum peglispro and glargine concentrations (which were targeted to reflect their differences in intrinsic affinities) ranged from 824 to 11400 pmol/l, and from 212 to 290 pmol/l, respectively, and increased in a dose-dependent way. Lowering of EGP and stimulation of GDR was seen with increasing circulating levels of both insulins. At insulin concentrations where EGP was significantly suppressed, glargine increased GDR substantially. At similar reduction of EGP, peglispro at lower concentrations had marginal GDR-stimulating effects, and at higher doses it provided markedly less effect on GDR than that observed with glargine.

Conclusions

Compared with insulin glargine, the novel insulin peglispro shows preferential hepatic action and lesser peripheral action in healthy subjects.

Comment

LY2605541 is a long-acting insulin analog that consists of insulin lispro with a 20 kDA polyethylene glycol (PEG) unit covalently attached to lysine at position B28 via a urethane bond. The large hydrodynamic size results in delayed insulin absorption from the subcutaneous depot and reduced renal clearance and hence prolonged duration of action, as was shown by Sinha et al. Findings from published phase II trials with LY2605541 in T1DM (5) and T2DM (6) that we reviewed a year ago indicated similar or better glycemic control, lower glucose variability, and lower rates of nocturnal hypoglycemia, as compared with insulin glargine. Using CGM recordings in a subset of patients from the latter trial to assess glucose control in greater detail, Bergenstal and co-workers indeed demonstrated less propensity for hypoglycemia (overall and nocturnal) and lower variability in glucose control in LY2605541-treated patients.

It has been speculated that the large functional size of the peglispro-molecule might influence the tissue distribution between the liver and the peripheral insulin-sensitive tissues, leading to a more hepatoselective mode of action. This notion was recently confirmed experimentally in the conscious dog model where peglispro was compared with human insulin in a euglycemic clamp study (7). During intravenous infusion of LY2605541, there was a shift from net hepatic glucose output to uptake, and nonhepatic glucose uptake was stimulated less than in control experiments with human insulin, suggesting a preferential hepatoselectivity. This may mirror normal physiology where the liver is exposed to higher concentrations of insulin than the peripheral tissues. The present study by Henry et al. suggests that the relative hepatoselective effect of peglispro is retained also in humans, and is mainly due to decreased peripheral effectiveness rather than increased hepatic action. It remains to be established whether this is maintained during long-term subcutaneous administration of peglispro. Moreover, effects on, for example, hypoglycemia counter-regulation, lipid metabolism, and hepatic lipid content need to be explored in more detail, to fully disclose the potential clinical benefits of the peglispro analog.

ULTRA-FAST INSULINS FOR OPTIMUM MEAL-TIME INSULIN SUPPLEMENTATION

Subcutaneous injection of hyaluronidase with recombinant human insulin compared with insulin lispro in type 1 diabetes

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Aims

Subcutaneous treatment with human regular insulin for covering meals in people with diabetes may result in early postprandial hyperglycemia and late hypoglycemia due to its slow onset and long duration of action. This study compared safety and efficacy of recombinant human insulin (rHI) formulated with recombinant human hyaluronidase [rHuPH20] (INSULIN-PH20) to insulin lispro for covering meals in subjects with T1D.

Methods

During a 1-month run-in period participants were using twice-daily insulin glargine (or usual basal insulin therapy for pump users) with preprandial lispro. At baseline, 46 subjects with T1D (42 ± 13 years; body mass index: 26 ± 4 kg/m^2; HbA1c 6.8 ± 0.5%) were randomized to either INSULIN-PH20 (excipient rHuPH20 5 μg/ml) or lispro for two consecutive 12-week periods as the preprandial insulin in a basal-bolus treatment regimen. The primary efficacy end point was 2 h postprandial blood glucose increase (from preprandial glucose value) averaged over nine meals during the last 2 weeks of each treatment period. Rates of hypoglycemia (blood glucose value of ≤ 3.9 mmol/l); severe hypoglycemia, which required assistance from another individual to actively administer carbohydrate, glucagon, or other resuscitative action; the percentage of time in range (3.9 and 7.8 mmol/l) during a 72 h period near the end of each treatment cycle; levels of 1,5-AG; insulin use during the last week of each treatment cycle; and variability of glucose values were secondary endpoints. Adverse events (AEs), laboratory data, vital signs, physical examinations, and concomitant medications were analyzed in the safety analysis.

Results

The mean glycemic excursion for INSULIN-PH20 (0.96 ± 2.00 mmol/l) was comparable ($p = 0.322$) to lispro (0.80 ± 1.95 mmol/l), and the prespecified noninferiority margin of 1.2 mmol/l for the difference between treatments was met. The 8-point self-monitored blood glucose profiles were also comparable in the two groups. Good glycemic control (A1c) was maintained for both treatments at 12 weeks (INSULIN-PH20: 7.0 ± 0.5%; lispro: 6.9 ± 0.6%). Overall rates of hypoglycemia (≤ 3.9 mmol/l) were 24 events per patient per 4 weeks for INSULIN-PH20 and 22 events for lispro. There were no significant differences in adverse events or immunogenicity between treatments, and both treatments were well tolerated. The difference in CGM (at least 1 day of data) mean glucose ± SE of 0.57 ± 0.26 mmol/l favored insulin lispro with a one-sided 95% CI of 1.01 mmol/l ($p = 0.018$). The difference in CGM mean hyperglycemia (AUC above 7.8 mmol/l) of 8.29 ± 4.91 mmol/(l·h) also favored insulin lispro with a one-sided 95% CI of 16.57 mmol/(l·h) ($p = 0.0499$). The AUC ≤ 3.9 mmol/l favored INSULIN-PH20 (2.10 ± 1.88 vs. 2.63 ± 2.35 mmol/(l·h), $p = 0.049$).

Conclusions

A formulation of rHI with rHuPH20 was comparable to lispro for postprandial glucose excursions in a basal-bolus treatment regimen for T1D patients. Glycemic control, safety, and tolerability profiles were comparable for both treatments.

Comment

Data produced in this trial may be an important step toward an ultra-rapid insulin formulation, which is clearly needed for several clinical scenarios: prandial boluses, especially for low glycemic index food, correction boluses, and notably for the closed-loop insulin delivery where covering meals remains a major challenge. As postprandial glycemic excursions may cause oxidative stress, novel ultra-rapid-acting analog formulations may also reduce long-term complications. Non inferiority of a co-formulation of regular human insulin with recombinant hyaluronidase rHuPH20 (each separately FDA approved) to a standard rapid-acting analog in patients with T1D may indicate that a coformulation of a rapid-acting analog with recombinant hyaluronidase rHuPH20 may indeed deliver a much needed ultra-rapid-acting insulin formulation, as already successfully tested in healthy volunteers (8).

Adding excipients into the insulin formulation that enhances the appearance of monomeric insulin after injection is another approach to speed up the absorption of insulin. Faster-acting insulin aspart (FIAsp) is based on this concept, and in a preliminary report (9), Heise *et al.* indeed demonstrated a faster onset of appearance (median diff. [95% CI]: −6.6 min [−8.0; −5.0]) and greater exposure during the first 2 h with the largest difference in the first 15 min (mean ratio [95% CI] AUC0-15 min: 3.14 [2.59; 3.80]; AUC0-30 min: 1.93 [1.64; 2.26]; AUC0-1h: 1.30 [1.15; 1.46]; AUC0-2h: 1.13 [1.03; 1.24]; AUC0-10h: 0.99 [0.93; 1.06]) as compared with the original insulin aspart formulation in patients with T1DM. This led to a greater reduction in postprandial BG with FIAsp versus IAsp, indicated by lower postmeal AUC-BG over 2 and 6 h (reduction by 26% and 33%, respectively), and by lower BG values 1 and 2 h postprandially (mean diff. [95% CI] BG1h: −22.3 mg/dL [−36.2; −8.3]; BG2h: −26.1 mg/dL [−44.9; −7.6]). More data from the extensive on-going phase III program with this novel rapid-acting insulin formulation are much awaited.

Author Disclosure Statement

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