The Ultra-Rapid BioChaperone® Lispro shows a Faster Onset of Action and Stronger Early Metabolic Effect than Humalog®

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Abstract

In this double-blind, crossover study we investigated the pharmacodynamic characteristics of BC LIS, a novel insulin lispro (LIS) formulation with BioChaperone aimed at accelerating the absorption from the subcutaneous tissue. Thirty-six people with type 1 diabetes completed this study and received 0.2 U/kg of BC LIS or LIS under automated euglycemic clamp conditions (ClampArt®, target blood glucose 100 mg/dL, clamp duration 6h post-dosing). Mean glucose infusion rates (GIR) are given in the figure. Compared with LIS, BC LIS showed ultra-rapid properties with a faster onset of action (23.1±7.0 (mean±SD) vs. 34.4±15.3 min, p<0.0001), an earlier maximum effect (TGIR max 99±42 vs. 133±45 min, p=0.0002) and a stronger early metabolic effect in the first hour (AUCGIR 0-1h 218±88 vs. 129±63 mg/kg, p<0.0001) and first 2 hours (AUCGIR 0-2h 627±235 vs. 525±214 mg/kg, p=0.0041). Total (AUCGIR 0-6h 1409±494 vs. 1434±506 mg/kg, p=0.72) and maximum metabolic effect (GIRmax 7.85±2.87 vs. 7.96±2.81 mg/kg/min, p=0.76) were comparable. Both insulin formulations were well tolerated. In conclusion, BC LIS shows a faster onset of action, an earlier maximum action and stronger metabolic effect in the first 2 hours than native insulin lispro. BC LIS has the characteristics of an ultra-fast acting insulin with the potential to be injected at mealtime with excellent glycemic control.

Aim

- To compare the pharmacokinetic (PK) profile of BioChaperone Lispro and Humalog after administration of a single dose during euglycemic clamps in patients with type 1 diabetes

Introduction

- Rapid-acting insulin analogs show a faster absorption than regular human insulin leading to an earlier onset of action and consequently to lower postprandial glucose excursions.
- However, even rapid-acting insulin analogs are not acting fast enough and still have a too late onset and offset of action to replicate the physiological first-phase and second-phase insulin release observed in healthy subjects after meal intake.
- Thus, there is a medical need for a prandial insulin with an even earlier metabolic effect with the potential to improve postprandial glycemic excursions and reduce the incidence of late postprandial hypoglycemia.
- In this study, we compared the pharmacokinetics (PK), pharmacodynamics (PD) and safety of BioChaperone Lispro, an ultrafast insulin lispro formulation with Adocia's BioChaperone technology, with those of insulin lispro (Humalog) in people with type 1 diabetes.

BioChaperone Lispro

- Adocia's proprietary technology platform BioChaperone is applied to insulins to develop second-generation, best–in-class products.
- In the case of prandial insulins, BioChaperone enhances their diffusion, thereby facilitating their absorption into the blood circulation after a subcutaneous injection. BioChaperone Lispro is an innovative, ultra-fast formulation of insulin lispro (100IU) using BioChaperone.
- The use of BioChaperone does not modify the physical, chemical and biological integrity of insulin lispro.

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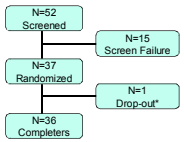
Methods

- This was a randomized, single-center, double-blind, two-way crossover glucose clamp study
- Eligible study participants were male subjects with type 1 diabetes mellitus (T1DM) for at least a year, age between 18 and 64 years, body mass index (BMI) 18.5-28.0 kg/m², HbA1c ≤ 9.0 %, treated with multiple daily insulin injections or insulin pump, total daily insulin dose < 1.2 U/kg/day, fasting C-peptide < 0.30 nmol/l
- Patients were randomly assigned to two single-dose administrations of 0.2 U/kg BioChaperone Lispro or Humalog at two separate visits. Each euglycemic glucose clamp experiments lasted 6 hours
- After an overnight fast, patients were connected in the morning to ClampArt® (a modern clamp device developed by Profil, Neuss, Germany). A variable intravenous infusion of insulin aspart was started to reach a target blood glucose level (BG) of 100 mg/dl (run-in)
- Glucose infusion rates (GIR) were automatically adjusted by ClampArt® to maintain BG close to target for 6 hours post-dosing. The damp experiment was stopped earlier if BG increased to > 200 mg/dl without any glucose infusion in the last 30 min
- Blood samples for determination of pharmacokinetics (PK) were drawn at pre-dose and in regular intervals until 6 h post-dose
- Serum insulin lispro concentrations were determined with an immunoradiometric sandwich assay (BI-INSULIN-IRMA, Cisbio Bioassays; detection Limit: 0.2 µU/ml (8 pg/ml); measurement range: 0.2-500 µU/ml)

Statistical analysis

- Glucose infusion rate profiles were smoothed using a local weighted regression technique (LOESS, smoothing factor 0.25). Time-related parameters were derived from the smoothed curves, AUCs from the unsmoothed data.
- PK-values were adjusted for baseline values.
- The primary endpoint was the insulin lispro AUC from t=0 to 30 minutes.
- PK and PD endpoints were analyzed using a mixed effect linear model with treatment, period and sequence as fixed effects and subjects within sequence as random effect. Not normally or log-normally distributed data and time-related PK/PD-endpoints (e.g. tmax) were analyzed non-parametrically using Wilcoxon Signed Rank Test.

Table 1: Subject Disposition and Demographics



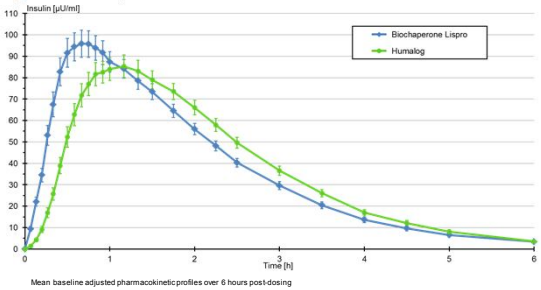
Parameter	Mean (SD)
Age (years)	42.8 (13.0)
Height (m)	1.82 (6.74)
Weight (kg)	81.6 (7.5)
BMI (kg/m²)	24.7 (1.7)
Diabetes duration (years)	20.3 (12.5)
HbA1c (%)	7.6 (0.6)

*1 subject was excluded after presenting with a peritonsillar abscess after first dosing with Humalog®.

Efficacy Results

- BioChaperone Lispro had a greater early PK exposure (significantly higher $AUC_{LIS\ 0\text{-}30min}$), a faster appearance (earlier reach of 10% and 50% maximum values, earlier $t_{max\ LIS}$) and an earlier return to baseline (earlier reach of late half-maximum values) than Humalog (Table 2, Figure 1, Figure 3).
- Likewise, AUC_{LIS} values from 15 minutes to 2 hours were significantly higher for BioChaperone Lispro.
- In line with the PK results, BioChaperone Lispro also showed an earlier onset of action which occurred about 33% faster than with Humalog. Time to 10% and 50% maximum GIR were significantly shorter with BioChaperone Lispro as was time to maximum action (Table 2, Figure 2).
- Late PK exposure was significantly lower for BioChaperone Lispro than for Humalog ($AUC_{LIS3\text{-}6h}$ Table 2).
- $AUC_{GIR3\text{-}6h}$ showed a significantly lower late metabolic effect for Biochaperone Lispro than for Humalog.

Figure 1: Mean PK profiles



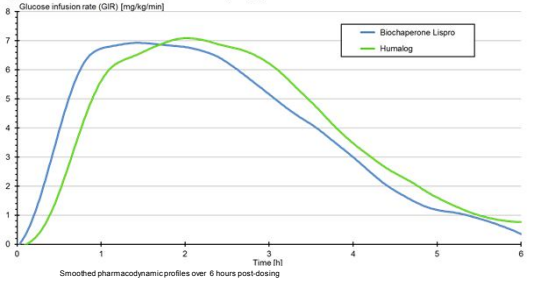
Mean baseline adjusted pharmacokinetic profiles over 6 hours post-dosing

Table 2: PK/PD Parameters

	BioChaperone Lispro	Humalog	p-value
Pharmacokinetic (PK) parameters, based on insulin lispro (Lis) concentrations			
$AUC_{LIS\ 0\text{-}30\ min}$ [mU*h/l]	23.7 (48.1)	9.5 (65.4)	**<0.0001**
$AUC_{LIS\ 3\text{-}6h}$ [mU*h/L]	**34.8 (1.4-77.5)**	45.9 (11.4-81.3)	**0.0109**
$AUC_{LIS\ 0\text{-}6h}$ [mU*h/l]	215 (73.2-364.4)	203 (114.9-370.1)	0.8535
$C_{max\ LIS}$ [mU/l]	103 (37.7)	90 (36.1)	**0.0129**
$t_{max\ LIS}$ [min]	40 (25.2-70.2)	70 (40-120)	**<0.0001**
Pharmacodynamic (PD) parameters, based on glucose infusion rates (GIR)			
$AUC_{GIR\ 0\text{-}1h}$ [mg/kg]	218 (40.6)	129 (49.3)	**<0.0001**
$AUC_{GIR\ 3\text{-}6h}$ [mU*h/L]	**413 (53.9)**	504 (46.7)	**0.0115**
$AUC_{GIR\ 0\text{-}6h}$ [mg/kg]	1409 (35)	1434 (35)	0.7249
GIR_{max} [mg/kg/min]	7.9 (36.6)	8.0 (35.3)	0.7617
$t_{GIR\ max}$ [min]	98.8 (42.9)	133.2 (33.6)	**0.0002**
Onset of action [min]	23 (30.1)	34 (44.5)	**0.0003**

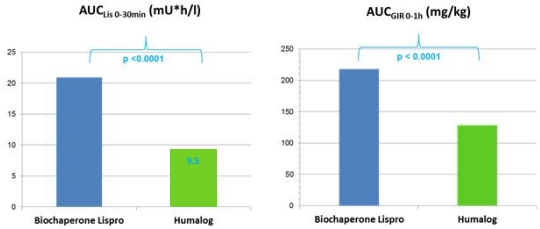
Table shows arithmetic means (CV%) or median (min-max) for tmax (insulin and GIR) with corresponding p-values. P-values are based on parametric and non-parametric analyses. P-values <0.05 are marked in bold.

Figure 2: Mean glucose infusion rate (GIR) profiles



Smoothed pharmacodynamic profiles over 6 hours post-dosing

Figure 3: Differences in early exposure and early metabolic effect



Safety Results

- Both insulins were well tolerated and no injection site reactions occurred.
- One serious adverse event occurred (peritonsillar abscess) which was judged to be unlikely associated with the study drug. All other eight treatment emergent adverse events were either mild (50% of cases) or moderate (50%) and had a similar incidence between treatments (4 occurring after BioChaperone Lispro and 4 after Humalog).

Conclusions

- BioChaperone Lispro shows an earlier onset of action, a stronger metabolic effect and a greater insulin lispro exposure in the first 2 hours than Humalog.
- BioChaperone Lispro shows significantly lower exposure and metabolic effect after 3 hours than Humalog.
- BioChaperone Lispro has the characteristics of an ultra-fast acting insulin with the potential to be injected at mealtime or post-prandially and improving post-prandial glycemic control compared with available bolus insulins.