Preclinical efficacy of a stable aqueous formulation of human glucagon with BioChaperone® technology

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Abstract

Human glucagon is an emergency drug used to rescue people with diabetes from severe hypoglycemia. Dual hormone artificial pancreas (DHAP) is designed to better mimic normal physiology by automatically infusing both insulin and glucagon as required. However, due to the poor solubility and stability of glucagon in solution, no commercial ready-to-use liquid formulation is available for rescue or for pump use in DHAP. BioChaperone® Glucagon (BC GLU) is a stable, ready-to-use, neutral pH, aqueous formulation of glucagon based on BioChaperone® (BC) technology. Two formulations are developed for two uses: rescue and dual-hormone artificial pancreas, at 1 and 2 mg/mL.

We investigated the pharmacokinetics and the pharmacodynamics of a single subcutaneous dose (1 µg/kg) of BC GLU (1 mg/mL) and BC GLU (2 mg/mL) against the freshly reconstituted commercial glucagon in 12 octreotide treated pigs.

BC GLU (1 mg/mL) and glucagon displayed a similarly rapid absorption (time to early 50% t_{max}: 5 and 3 min respectively) resulting in similar incremental blood glucose levels, especially during the first 15 min after injection (mean ratio [95%CI] ΔBG15min: 1.16 [0.93; 1.45], ΔBG30min: 1.16 [0.85; 1.57], ΔAUCBG0-15min:1.25 [0.81; 1.92], ΔAUCBG0-30min: 1.14 [0.89; 1.47]). Similar results were obtained for BC GLU at 2 mg/mL.

In conclusion, the preclinical PKPD properties of BC GLU support its clinical development for both severe hypoglycemia rescue and DHAP applications.

Introduction & Background

- Glucagon is a pancreatic hormone produced by α-cells to help maintain euglycemia by stimulating the release of endogenous glucose in the fasting state. It stimulates the breakdown of stored liver glycogen and promotes hepatic gluconeogenesis and ketogenesis.
- Glucagon is currently commercialized in "rescue" kits to treat severe hypoglycemia. However, due to its low solubility at neutral pH (0.2-0.3 mg/mL) and its poor stability in solution, glucagon is only available as a lyophilizate that needs to be reconstituted immediately prior injection. Once in aqueous solution, glucagon rapidly fibrillates and chemically degrades.
- Usability of the emergency kit is limited due to the complexity of the reconstitution and administration process, especially in stressful circumstances.
- A stable ready-to-use liquid formulation of glucagon could improve its use in a rescue setting, as well as enable its use in other indications, such as dual hormone artificial pancreas (i.e. closed-loop pumps injecting both insulin and glucagon as a function of real-time glycaemia).
- Adocia proprietary BioChaperone® (BC) technology is a library of chemical compounds designed to form reversible physical complexes with proteins in order to improve their physico-chemical properties. BC technology allows the solubilization and stabilization of glucagon at neutral pH.
- BC Glucagon (BC GLU) is a homogeneous, limpid, aqueous formulation at pH 7. It is a ready-to-use solution to treat severe hypoglycemia that could also be used in DHAP for tighter and safer control of glycaemia.

Aims of the study

- To evaluate the pharmacokinetic and pharmacodynamic profiles of BC GLU (1 mg/mL and 2 mg/mL) compared to freshly reconstituted commercial glucagon kit (GLU, GlucaGen® HypoKit®, Novo Nordisk, 1 mg/mL) in a pig model.

Methods

- In two separate experiments, pharmacokinetic and pharmacodynamic profiles for BC GLU 1 mg/mL and BC GLU 2 mg/mL were evaluated in domestic pigs through a sequential design against GlucaGen HypoKit (GLU, glucagon lyophilizate for reconstitution, Novo Nordisk, freshly reconstituted as 1 mg/mL solution).
- In each experiment, 12 pigs were pre-treated with subcutaneous octreotide prior to BC GLU or GlucaGen solution administration, in order to inhibit any endogenous counter-regulation induced by administered glucagon. Each animal received a single subcutaneous dose of 1 µg/kg of BC GLU and GLU.
- Plasma glucagon concentrations and glycaemia were measured by ELISA (Mercodia Glucagon ELISA kit) and blood glucose sensor (Accu-chek Performa®, Roche), respectively.
- A linear mixed model was used with treatment as fixed effects for BC GLU 2 mg/mL only with a 5% level of significance.

Pharmacokinetics and Pharmacodynamic results

Pharmacokinetics

- Early exposure ($\Delta AUC_{0\text{-}20min}$) for either formulation of BC GLU (1 and 2 mg/mL) was comparable to that of GLU despite a slight delay in the time to early half tmax (Figure 1A and 1B respectively and Table 1).
- Total exposure (AUC_{last}) for either formulation of BC GLU (1 and 2 mg/mL) was comparable to that of GLU, indicating similar bioavailability. GLU (no statistically significant difference, Figure 1A and 1B respectively and Table 1).

Figure 1: Median baseline adjusted blood glucagon profiles (0-180 min) of BC GLU at 1 mg/mL and 2 mg/mL

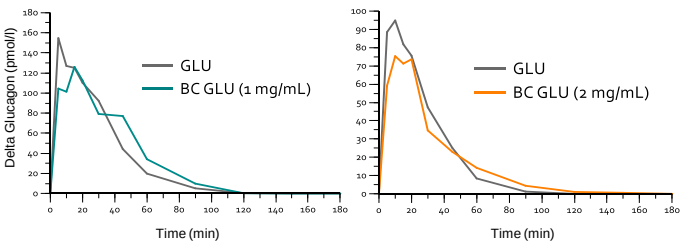

Table 1: PK parameters based on baseline adjusted blood glucagon

	BC GLU 1 mg/mL	GLU	Difference * / Ratio# between BC GLU and GLU
$T_{50\% early}$ (min)	4.5	2.8	1.7* [0.4 – 3.0]
$\Delta AUC_{0\text{-}20min}$ (pmol/L.min)	1822.55	2180.41	0.84# [0.56 – 1.25]
AUC_{last} (pmol/L.min)	5740.67	5113.72	1.12# [0.70 – 1.8]
	BC GLU 2 mg/mL	**GLU**	**Difference*/ Ratio# between BC GLU and GLU**
$T_{50\% early}$ (min)	5.0	3.0	2.0* [0.8 – 3.3]
$\Delta AUC_{0\text{-}20min}$	1176.03	1725.75	0.68# [0.37 - 1.24]
AUC_{last} (pmol/L.min)	3232.48	3834.18	0.84# [0.46 – 1.53]

Differences and ratios were based on least squares means differences for $T_{50\% early}$ and geometric means, respectively, with 95 % confidence intervals.
BC GLU and GLU time-related parameters were expressed as least square means, and geometric least squares mean for other parameters.

Pharmacodynamics

- Both formulation of BC GLU (1 and 2 mg/mL) showed comparable early glucose response (ΔBG_{15min} ; ΔBG_{30min} ; $\Delta AUC_{0\text{-}15min}$; $\Delta AUC_{0\text{-}30min}$) to that of GLU (no statistically significant difference, Figure 2A and 2B respectively and Table 2).
- BC GLU onset of action at 1 mg/mL and 2 mg/ml was comparable to GLU (no statistically significant difference, Table 2).

Figure 2: Mean baseline adjusted blood glucose ±SE profiles (0-180 min) of BC GLU at 1 and 2 mg/mL

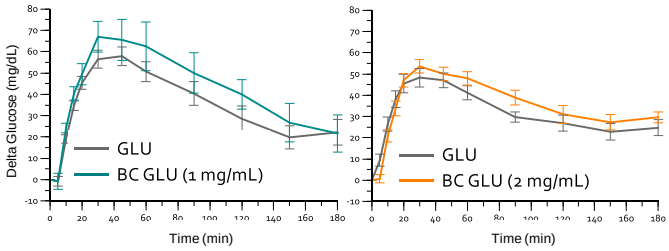

Table 2: PD parameters based on baseline adjusted blood glucose

	BC/GLU 1 mg/mL	GLU	Difference*/Ratio# between BC GLU and GLU
$T_{onset\ 20\ mg/dL}$ (min)	9.4	10.7	-1.3* [- 2.5 – - 0.01]
ΔBG_{15min} (mg/dL)	39.46	33.90	1.16# [0.93 - 1.45]
ΔBG_{30min} (mg/dL)	63.34	54.73	1.16# [0.85 – 1.57]
$\Delta AUC_{0\text{-}15min}$ (mg/dL.min)	203.38	162.67	1.25# [0.81 – 1.92]
$\Delta AUC_{0\text{-}30min}$ (mg/dL.min)	988.41	864.90	1.14# [0.89 – 1.47]
	BC GLU 2 mg/mL	**GLU**	**Difference*/Ratio# between BC GLU and GLU**
$T_{onset\ 20\ mg/dL}$ (min)	10.6	9.7	0.9* [-2.0 - 3.8]
ΔBG_{15min} (mg/dL)	32.13	35.42	0.91# [0.67 - 1.24]
ΔBG_{30min}(mg/dL)	52.56	45.55	1.15# [0.91 - 1.47]
$\Delta AUC_{0\text{-}15min}$ (mg/dL.min)	157.50	235.56	0.67# [0.39 – 1.14]
$\Delta AUC_{0\text{-}30min}$ (mg/dL.min)	868.10	877.59	0.99# [0.74 - 1.32]

Differences and ratios were based on least squares means differences for $T_{onset\ 20\ mg/dL}$ and geometric means respectively with 95 % confidence intervals.
BC GLU and GLU time related parameters were expressed as least square means, and geometric least squares mean otherwise.

Conclusions

- ✓BC GLU pharmacokinetic and pharmacodynamic profiles were comparable to those of GLU (1 mg/mL) at either tested concentration (1 mg/mL and 2 mg/mL). In particular, the early metabolic response observed with either BC GLU (1mg/mL) or BC GLU (2 mg/mL) at 15 min and 30 min was comparable to that of GLU (1 mg/mL).
- ✓A Phase 1 clinical study of BC GLU (1 mg/mL) in people with type 1 diabetes was initiated in May 2017

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