A Randomized, Single Center, Three-period Trial to Compare the Relative Pharmacodynamic and Pharmacokinetic Properties of Different Glucagon Dosages at Four Different Blood Glucose Concentrations

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Introduction

Bihormonal closed-loop systems deploy the administration of glucagon in case of imminent or actual hypoglycemia. The administration of glucagon in such a closed-loop system will not necessarily be limited to hypoglycemia, but can also be done preemptively, trying to avoid hypoglycemia. Available published knowledge on the pharmacokinetic and pharmacodynamic properties of glucagon is very limited.

Thus more information is needed about the pharmacodynamic effects of small doses of glucagon, also at non-hypoglycemic blood glucose (BG) levels. We evaluated the pharmacokinetics and pharmacodynamics of different dosages of s.c. glucagon at different BG levels.

Study Objectives

Primary objective:

- To compare the pharmacodynamic properties (PD) of different glucagon dosages given s.c.

Secondary Objective

- To assess the pharmacokinetic (PK) and pharmacodynamic (PD) of glucagon at different levels of blood glucose
- To assess the single and repeat dose safety and local tolerability of glucagon

Inclusion Criteria

Trial Population (n=6)

- Male or female subjects with type 1 diabetes
- Diabetes duration ≥ 10 years
- No serious concomitant diseases other than diabetes
- HbA1c ≤9.0 %
- Age 18 - 65 years
- Body mass index 18.0 - 30.0 kg/m^2
- Stable therapy with insulin glargine and prandial bolus insulin, or subjects on insulin pumps

Study Protocol

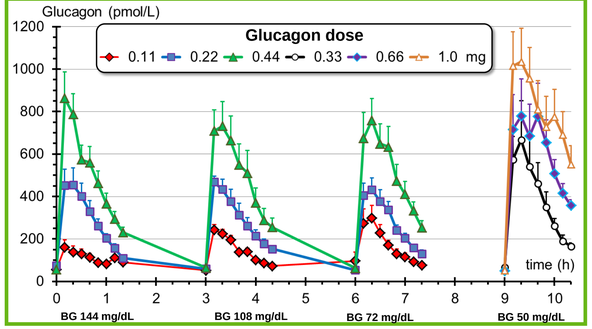
- 3 Period Cross-Over Glucose clamp study
- 3 dosing visits with four glucagon dosings each
- BG levels of 8, 6, 4 and 2.8 mmol/l were established by means of a glucose clamp
- 3 sequences of glucagon doses were defined and used in random order:

Sequence	Clamp Step 1		Clamp Step 2		Clamp Step 3		Clamp Step 4	
	BG (mmol/L)	Glucagon dose (mg)	BG (mmol/l)	Glucagon dose (mg)	BG (mmol/l)	Glucagon dose (mg)	BG (mmol/l)	Glucagon dose (mg)
A	8 [144 mg/dL]	0.11	6 [108 mg/dL]	0.11	4 [72 mg/dL]	0.11	2.8 [50 mg/dl]	1.0
B	8 [144 mg/dL]	0.22	6 [108 mg/dL]	0.22	4 [72 mg/dL]	0.22	2.8 [50 mg/dl]	0.66
C	8 [144 mg/dL]	0.44	6 [108 mg/dL]	0.44	4 [72 mg/dL]	0.44	2.8 [50 mg/dl]	0.33

Glucose clamp procedure (Visits 2-4):

- Manual clamp to reach target blood glucose level
- 30 min stable blood glucose in target zone
- Dosing of glucagon (GlucaGen HypoKit, Novo Nordisk)
- Sampling for 90 min post-dosing:
  - BG every 5 min
  - Glucagon every 10 min
  - Insulin before dosing and after 90 min
- Manual Clamp phase to reach next blood glucose target level

Pharmacokinetics of Glucagon

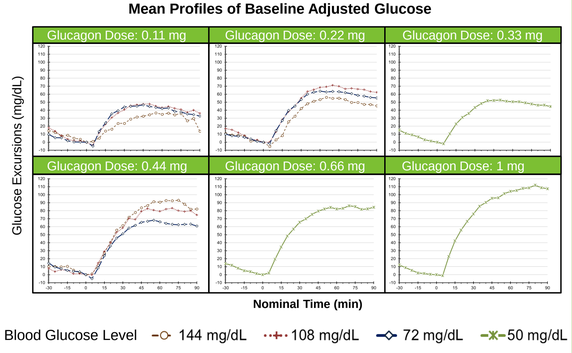


Pharmacokinetics of Glucagon

Glucose Level (mmol/L)	Glucagon Dose (mg)	$AUC_{Glucagon.0\text{-}end\ of\ action}$ (pmol*h/L)	$t_{max\ Glucagon}$ (min)	$C_{glucagon\ .max}$ (pmol/L)
8	0.11	147±64	26.3±23.3	175±90
(144 mg/dl)	0.22	388±131	13.3±5.1	476 ±189
	0.44	675±172	11.7±4.0	885±298
6	0.11	198±41	11.7±4.0	246±59
(108 mg/dl)	0.22	391±112	13.3±8.1	480±86
	0.44	663±258	15.0±5.4	781±267
4	0.11	230±72	11.7±7.5	327 ±129
(72 mg/dl)	0.22	374±100	16.7±5.1	448±147
	0.44	672±241	16.7±5.1	780±270
2.8	0.33	526±247	16.0±5.4	696±385
(50 mg/dl)	0.66	790±266	25.0±16.4	1005±420
	1.00	1052±308	23.3±19.6	1231±236

Values given in mean ± SD

Pharmacodynamics of Glucagon: Glucose



Safety

Local tolerability: no adverse events

One subject experienced mild nausea for 1-2 h on two of three days after the last dosing

No other dosing related adverse events were noted.

Pharmacodynamic parameters (Glucose)

Glucose Level (mmol/L)	Glucagon Dose (mg)	$AUC_{Glucose.0\text{-}30min}$ (mg*h/L)	$AUC_{Glucose.0\text{-}end\ of\ action}$ (mg*h/L)	$t_{max\ Glucose}$ (min)	$C_{glucose\ .max}$ (mg/L)
8	0.11	5.9±6.9	45±40	41.3±32.0	48.7±43.2
(144 mg/dl)	0.22	7.5±8.9	57±33	58.2±17.2	60.8±29.5
	0.44	14.0±2.6	97±27	60.8±12.4	97.3±33.1
6	0.11	9.8±5.5	52±24	60.8±21.1	52.2±22.4
(108 mg/dl)	0.22	12.7±2.2	77±21	56.5±16.5	75.8±24.6
	0.44	13.8±4.8	90±26	69.0±16.6	87.5±24.4
4	0.11	10.8±5.8	51±25	45.8±20.1	48.8±23.4
(72 mg/dl)	0.22	12.6±5.5	72±27	55.0±13.8	66.5±24.8
	0.44	11.2±4.8	73±28	55.0±18.7	71.0±26.9
2.8	0.33	10.0±4.8	59±25	45.0±11.7	55.6±22.6
(50 mg/dl)	0.66	16.2±7.3	95±39	64.2±14.9	88.3±37.6
	1.00	18.7±3.7	119±28	79.2±8.6	111.0±28.3

Values given in mean ± SD

Conclusion

- Glucagon raised blood glucose in a dose-dependent fashion at all blood glucose levels.
- Thus, s.c. administered glucagon produces a predictable pharmacokinetic and pharmacodynamic response at lower doses than the usual rescue dose and across a range of hypo- to hyperglycemic BG levels.
- This information can be used to further optimize the control algorithms of bihormonal closed-loop systems.

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