ATTD7-0076

EFFECTS OF NASAL CONGESTION FROM COMMON COLD ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF NASAL GLUCAGON

Hélène Dulude[1], Éric Sicard[2], Marianne Rufiange[2], Aziz A. Sadoune[2], Dolores Carballo[1], Myriam Triest[1], Maryam Tafreshi[3], Emmanouil Rampakakis[3], Claude A. Piché[1], Xiaotian Michelle Zhang[4], Cristina B. Guzman[5]

[1]Locemia Solutions, Montreal, Quebec, Canada; [2]Altasciences/Algorithme Pharma, Montreal, Quebec, Canada; [3]JSS Medical Research, Montreal, Quebec, Canada; [4]Eli Lilly Canada Inc., Toronto, Ontario, Canada; [5]Eli Lilly and Company, Indianapolis, IN, USA

ABSTRACT

Background: Nasal glucagon (NG), a needle-free glucagon that is absorbed through the nasal mucosa, is being developed to treat severe hypoglycemia. This single center, open-label study evaluated the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of NG in 36 otherwise healthy subjects with nasal congestion from common cold with or without concomitant nasal decongestant.

Methods: Cohort 1 (N=18) received 2 NG doses: a 3 mg dose while suffering from common cold and a second 3 mg dose after return to normal health. Cohort 2 (N=18) received a single 3 mg dose of NG 2 hours after receiving the nasal decongestant oxymetazoline while suffering from common cold.

Results: There were no serious adverse events (AEs); the most common AEs were transient lacrimation, nasal discomfort, rhinorrhea, and nausea, with reduced nasal symptoms and nausea in participants with normal health versus those with cold symptoms, with or without decongestant. Glucagon and glucose levels increased rapidly after treatment to peak glucagon levels at 20 minutes post dose and peak glucose levels at 30 to 40 minutes post dose for all groups.

Conclusions: Nasal congestion, with or without concomitant use of a nasal decongestant, did not significantly affect the PK and PD of NG although transient AEs were more frequent in participants with common cold than in healthy participants. These data suggest that NG can be used to treat severe hypoglycemia in patients with nasal congestion.

BACKGROUND

- Currently, treatment of severe hypoglycemia outside of a hospital setting is limited to injectable glucagon
- Injectable glucagon administration requires several steps, including reconstitution and is prone to error. Needle-free nasal glucagon has been shown to be more easily and successfully administered by trained and untrained caregivers[1]
- Previous studies in adults and children demonstrated that nasal glucagon may be a viable alternative to injectable glucagon[2,3]
- This study assessed the pharmacokinetics (PK), pharmacodynamics (PD), and safety characteristics of nasally-administered glucagon in men and women with and without:
  - nasal congestion and/or nasal discharge associated with common cold
  - concomitant administration of nasal decongestant

METHODS

- Single-center, single-dose, open-label, repeated-measures, parallel-design phase 1 study
- Participants were otherwise healthy men and women, aged 18 to 50 years
  - Light-, non-, or ex-smokers
  - Had body mass index ≥18.50 and <30.00 kg/m^2
  - Had nasal congestion and/or nasal discharge associated with common cold (confirmed using the 8-item Jackson Cold Scale[4] and congestion confirmed by measuring peak nasal inspiratory flow before each treatment)
- Participants were divided into 2 cohorts:
  - Cohort 1 received nasal glucagon twice
    - At first administration, the participants had nasal congestion and/or nasal discharge
    - At second administration (7-28 days later), participants had been symptom-free ≥2 days
  - Cohort 2 received nasal glucagon only once
    - Participants had nasal congestion and/or nasal discharge
    - Participants received the nasal decongestant oxymetazoline (Dristan® Long Lasting Nasal Mist 0.05%) 2 hours before nasal glucagon was administered
- All participants fasted overnight (10 hours)
- The next morning they received a single 3 mg dose of nasal glucagon

NG Administration Period	Cohort 1 (N=18) [Received NG Twice]	Cohort 2 (N=18) [Received NG Only Once]
First NG administration (Period 1)	Participants had common cold*; received no treatment for cold symptoms	Participants had common cold*; received nasal decongestant
Second NG administration (Period 2)	Participants were symptom-free for ≥2 days	Not applicable

**Verified by Jackson Cold Scale; NG=Nasal Glucagon*

Safety and Tolerability

- Safety and tolerability were evaluated through the assessment of adverse events (AEs), physical examination, nasal examination, bilateral anterior rhinoscopy, standard laboratory evaluations, vital signs, glycemia measurements, ECG, and nasal and non-nasal symptoms scores
- AEs were classified by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities version 13.1

Analytical Methods

- Plasma glucagon levels were measured using a radioimmunoassay with a limit of quantification of 20 pg/mL. Plasma glucose was measured using a Synchron® System, which determines GLUCm concentration by an oxygen rate method employing a Beckman Coulter oxygen electrode
- PK and PD parameters of glucagon were derived using non-compartmental analysis based on raw concentrations (area under the curve $[AUC]_{0\text{-}3h}$ [PK], area under the effect curve $[AUEC]_{0\text{-}3h}$ [PD], maximum concentration [C_{max}], and time to maximum concentration [T_{max}])

Table 1. Demographic and Baseline Characteristics

	Cohort 1 (N=18)	Cohort 2 (N=18)
Age, years, mean (SD)	32 (9)	29 (8)
Women, n (%)	9 (50.0)	10 (55.6)
Race, n (%)		
White	16 (88.9)	14 (77.8)
Black	2 (11.1)	3 (16.7)
Other	0 (0.0)	1 (5.6)
Weight, kg, mean (SD)	69.7 (9.3)	68.5 (14.1)
Height, cm, mean (SD)	170.8 (7.5)	169.9 (10.3)
BMI, kg/m^2, mean (SD)	23.9 (2.7)	23.6 (3.5)

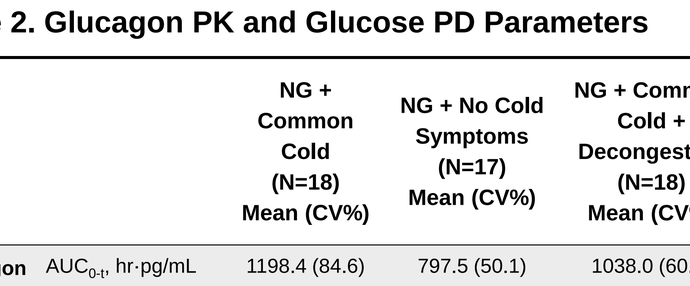
BMI=body mass index; SD=standard deviation
One subject in Cohort 1 withdrew consent before second visit; all subjects in Cohort 2 completed the study

Table 2. Glucagon PK and Glucose PD Parameters

		NG + Common Cold (N=18) Mean (CV%)	NG + No Cold Symptoms (N=17) Mean (CV%)	NG + Common Cold + Decongestant (N=18) Mean (CV%)
Glucagon	$AUC_{0\text{-}t}$, hr·pg/mL	1198.4 (84.6)	797.5 (50.1)	1038.0 (60.7)
	C_{max}, pg/mL	1198.4 (83.0)	801.5 (68.2)	868.0 (68.8)
	T_{max}, hours[a]	0.3 (0.08, 1.50)	0.3 (0.25, 0.67)	0.3 (0.17, 1.00)
Glucose	$AUEC_{0\text{-}t}$, hr·mmol/L	17.0 (16.9)	16.4 (13.4)	19.0 (14.3)
	C_{max}, mmol/L	8.0 (22.9)	7.7 (19.4)	8.8 (17.7)
	T_{max}, hours[a]	0.5 (0.25, 1.00)	0.6 (0.33, 1.00)	0.7 (0.33, 1.00)

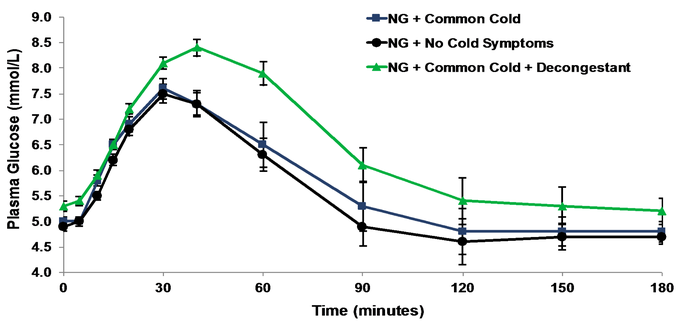
NG=nasal glucagon; CV=coefficient of variation; $AUC_{0\text{-}t}$=area under the curve from time zero; $AUEC_{0\text{-}t}$=area under the effect curve from time zero; C_{max}=maximum concentration; T_{max}=time to maximum concentration; for glucose, 1 mmol/L=18 mg/dL
[a]Median (minimum, maximum)

Figure 1. Mean Plasma Glucagon Concentration Following Treatment



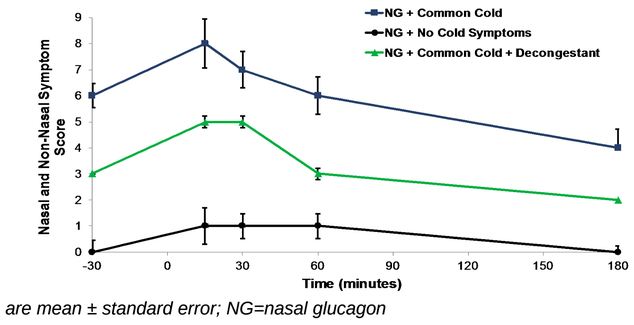
Values are mean (adjusted for baseline glucagon concentration) ± standard error; NG=nasal glucagon

Figure 2. Mean Plasma Glucose Concentration Following Treatment



Values are mean ± standard error; NG=nasal glucagon; 1 mmol/L=18 mg/dL

Figure 3. Nasal and Non-Nasal Symptom Score Over Time



Values are mean ± standard error; NG=nasal glucagon

Figure 4. Participants With Total Nasal/Non-Nasal Symptom Score ≥2

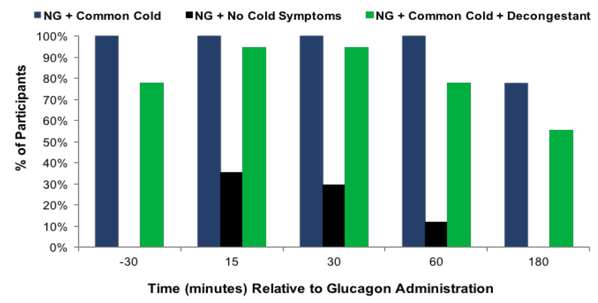


Table 3. Most Commonly Reported Adverse Events

		Cohort 1		Cohort 2
		Period 1 (N=18)	Period 2 (N=17)	Period 1 (N=18)
System Organ	**Class**	n (%)	n (%)	n (%)
Ocular	Increased lacrimation	13 (72.2)	12 (70.6)	12 (66.7)
	Ocular hyperemia	7 (38.9)	7 (41.2)	8 (44.4)
	Eye pruritus	5 (27.8)	0	5 (27.8)
Respiratory	Nasal discomfort	12 (66.7)	7 (41.2)	15 (83.3)
	Rhinorrhea	10 (55.6)	5 (29.4)	14 (77.8)
	Nasal congestion	5 (27.8)	3 (17.6)	4 (22.2)
	Sneezing	5 (27.8)	3 (17.6)	3 (16.7)
Nervous	Dizziness	4 (22.2)	5 (29.4)	5 (27.8)
	Headache	4 (22.2)	3 (17.6)	5 (27.8)
	Somnolence	6 (33.3)	3 (17.6)	1 (5.6)
Gastrointestinal	Nausea	8 (44.4)	2 (11.8)	7 (38.9)
	Vomiting	1 (5.6)	0	5 (27.8)

In Cohort 1, 112 and 64 adverse events were reported in Period 1 and 2, respectively. In Cohort 2, 113 adverse events were reported

SUMMARY OF RESULTS

- Glucagon PK and glucose PD profiles were comparable with or without cold symptoms and decongestant use
- Blood glucose increased within 5 minutes after nasal glucagon administration in all groups, indicating that nasal congestion and/or concomitant decongestant use did not affect onset of the glycemic response
- Nasal glucagon was generally well tolerated
  - Incidence of AEs was higher when participants were suffering from common cold and did not appear to be affected by decongestant use
  - The most commonly reported AEs were transient increased lacrimation, nasal discomfort, rhinorrhea, and nausea/vomiting
- Nasal/non-nasal symptom scores indicate that:
  - Participants with common cold had elevated scores before treatment
  - Treatment with nasal glucagon resulted in a transient increase in symptom scores in all groups

CONCLUSIONS

The safety and PK and PD of nasal glucagon are not significantly affected by nasal congestion associated with common cold, with or without concomitant administration of nasal decongestant. These data suggest that nasal glucagon can be used to treat episodes of severe hypoglycemia in patients with nasal congestion.

Acknowledgements:

The authors would like to thank all the study participants. They also thank Dr. Sheetal Pradhan of Eli Lilly and Company for her assistance in preparation of this poster.

References:

1. Yale JF, et al. *Diabetologia* 2015;58(Suppl 1): S417
2. Rickels MR, et al. *Diabetes Care* 2016;39:264-270
3. Sherr JL, et al. *Diabetes Care* 2016;39:555-562
4. Jackson G, et al. *Ann Intern Med* 1960;53:719-738