ATTD7-0077

PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY FOLLOWING SINGLE OR REPEATED 3-MG NASAL GLUCAGON DOSES IN ADULTS WITH TYPE 1 OR TYPE 2 DIABETES

Hélène Dulude[1], Éric Sicard[2], Marianne Rufiange[2], Claude A. Piché[1], Cristina B. Guzman[3], Shuyu Zhang[3], Tong Shen[3], Jennie G. Jacobson[3], Xiaotian Michelle Zhang[4]

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

ABSTRACT

Objectives: Examine the pharmacokinetics (PK), pharmacodynamics (PD), and safety of single or repeated 3-mg nasal glucagon (NG) doses given in randomized sequence in a 4-period, cross-over study.

Methods: Subjects (insulin-using adults with type 1 or type 2 diabetes [T1D or T2D], BMI 18.5-35.0 kg/m^2) received 4 NG treatments (Trts) ≥1 wk apart. Trts were given 4 hrs after a low-carbohydrate breakfast. Trts were: 1) Single 3-mg NG; 2) 3-mg NG plus another 3-mg NG 15 minutes later (same nostril); 3) 3-mg NG plus another 3-mg NG 15 minutes later (opposite nostril); 4) 2 concurrent 3-mg NG doses (both nostrils).

Results: 32 subjects were enrolled (T1D: 23, T2D: 9). Number of subjects who received Trts 1, 2, 3, 4 were 27, 28, 25 and 29, respectively. Baseline (BL) blood glucose was 40-181 mg/dL. For Trts 1-4, PK parameters of change from BL for glucagon were mean area under the curve 0-3 hrs: 2471, 4097, 4639, and 3611 hr.pg/mL, median T_{max}: 0.17, 0.33, 0.50, and 0.33 hrs; PD parameters of change from BL for glucose were mean area under the effect concentration 0-3 hrs: 157, 168, 190, and 194 hr·mg/dL, median T_{max}: 0.75, 1.00, 1.00, and 1.00 hrs. Repeated NG doses resulted in higher glucagon concentrations, but gave glucose responses comparable to single dose. The only serious adverse event (AE; cellulitis) was not drug-related. Most drug-related AEs were transient and resolved within 2 hours.

Conclusions: Although repeat dosing resulted in greater systemic glucagon exposure, it did not result in additional clinically meaningful increase in observed glucose response. All NG treatments were well-tolerated.

BACKGROUND

- Nasal glucagon for severe hypoglycemia rescue
  - Needle-free
  - Nasal dry powder
  - Ready to use: no reconstitution
  - Compact, portable, single-use nasal dosing device
  - No need for the patient to inhale or breathe deeply

- A previous study demonstrated noninferiority of 3 mg nasal glucagon to 1 mg injectable glucagon in correcting insulin-induced hypoglycemia in adults with type 1 diabetes[1]

Study Objectives

To examine the pharmacokinetics, pharmacodynamics, and safety of single or repeated 3-mg doses of nasal glucagon given in randomized sequences in a 4-period, cross-over study in adults receiving insulin therapy for type 1 or type 2 diabetes.

METHODS

- The study subjects were insulin-using adults with T1D or T2D and BMI 18.5-35.0 kg/m^2
- Subjects received 4 different types of nasal glucagon treatment ≥1 week apart

  Treatment 1: Single dose, 3-mg nasal glucagon

  Treatment 2: Repeated dose, 3-mg nasal glucagon dose plus another 3-mg nasal glucagon dose 15 minutes later (same nostril)

  Treatment 3: Repeated dose, 3-mg nasal glucagon dose plus another 3-mg nasal glucagon dose 15 minutes later (opposite nostril)

  Treatment 4: Repeated dose, 2 concurrent 3-mg nasal glucagon doses (both nostrils)
- Subjects were randomly assigned to one of 4 sequence groups, which received the 4 treatments in the following order (Table 1):

Table 1. Treatment Group by Sequence Order

Group	Period 1	Period 2	Period 3	Period 4
A	Treatment 1	Treatment 2	Treatment 3	Treatment 4
B	Treatment 2	Treatment 3	Treatment 4	Treatment 1
C	Treatment 3	Treatment 4	Treatment 1	Treatment 2
D	Treatment 4	Treatment 1	Treatment 2	Treatment 3

- Treatment was given 4 hours after a low-carbohydrate breakfast; to maintain blood glucose levels between breakfast and initiation of treatment, subjects were to take:
  - 125 mL orange juice if blood glucose level was <72 mg/dL (4 mmol/L)
  - a bolus dose of short-acting insulin if blood glucose level was >180 mg/dL (10 mmol/L)
- Safety and tolerability were evaluated by physical examination, nasal examination, bilateral anterior rhinoscopy, standard laboratory evaluations, electrocardiogram, measurement of vital signs and glycemia, and collection of adverse event data (only adverse event results are discussed in this poster)
- Adverse events were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0
- Baseline glucose and glucagon concentrations were calculated as the means of the concentrations from samples obtained prior to dosing
- Plasma glucagon was measured using a radioimmunoassay with a limit of quantification of 20 pg/mL
- Plasma glucose was measured using hexokinase method (enzymatic method) on a Modular P analyzer
- Change in PK and PD parameters from baseline was derived using noncompartmental analysis based on raw concentrations (area under the curve $[AUC]_{0\text{-}1.5h}$, $[AUC]_{0\text{-}3h}$ [PK], area under the effect curve $[AUEC]_{0\text{-}1.5h}$, $[AUEC]_{0\text{-}3h}$ [PD], maximum concentration [C_{max}], and time to maximum concentration [T_{max}])

RESULTS

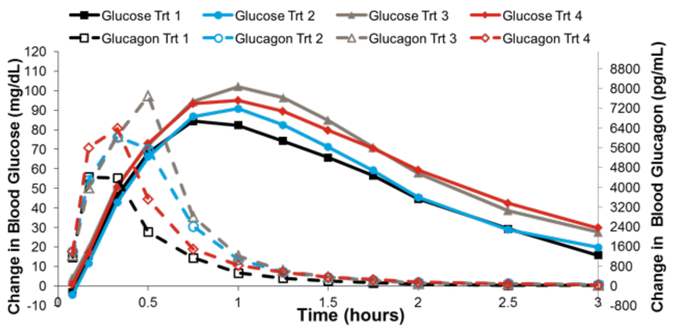
- Thirty-two subjects were enrolled; 8 subjects were randomly assigned to each treatment sequence (Tables 1 and 2)
- Seven subjects discontinued before end of study
  - 1 withdrew for safety reasons (investigator's decision)
  - 4 withdrew for personal reasons not related to clinical events
  - 2 withdrew for personal reasons related to clinical events
- The number of subjects treated with Treatments 1, 2, 3, and 4 were 27, 28, 25, and 29 respectively
- Baseline blood glucose range was 40-181 mg/dL
- All treatments resulted in similar blood glucagon levels within 10 minutes; with repeated dosing of nasal glucagon (Treatments 2-4), blood glucagon continued to increase through 20 or 30 minutes (Figure 1)
- Overall PK profiles for repeated dosing of nasal glucagon (Treatments 2-4) were significantly higher than the profile for a single 3-mg dose (Treatment 1)
- Plasma glucose profiles observed over time in all treatment groups were mostly similar irrespective of single or repeated glucagon dose
- Repeat dosing resulted in greater systemic glucagon exposure (Figure 1, Table 3), but not additional clinically meaningful increase in observed glucose response (Figure 1, Table 4) compared with single dosing
- Safety results
  - The majority of adverse events (88.3%) were mild; 11.3% were moderate, and 0.4% were severe
  - The only serious adverse event, cellulitis, was judged by the investigator as being unrelated to the study drug
  - Drug-related adverse events were reported by all subjects receiving Treatments 1 and 2, 96% of subjects receiving Treatment 3, and 93% of subjects receiving Treatment 4 (Table 5)
  - The most frequently reported drug-related adverse events were increased lacrimation, headache, nasal discomfort, and nausea (Table 5)
  - Most drug-related adverse events were transient and resolved within 2 hours (Table 6)

Table 2. Baseline Characteristics and Demographics

	All Subjects (N=32)
Type 1 diabetes, n (%)	23 (72)
Type 2 diabetes, n (%)	9 (28)
Age, years, mean (SD)	39 (12)
Men, n (%)	21 (65.6)
Race, n (%)	
White	28 (87.5)
Black	2 (6.3)
Asian	2 (6.3)
Weight, kg, mean (SD)	74.7 (13.9)
Height, cm, mean (SD)	169.3 (7.3)
BMI, kg/m^2, mean (SD)	25.96 (3.89)

BMI=body mass index; SD=standard deviation

Figure 1. Change in Blood Glucose and Blood Glucagon Levels Over Time



Values shown are arithmetic means; abbreviations: Trt, Treatment

Table 3. Change in Pharmacokinetic Parameters of Glucagon From Baseline

	Treatment 1 N=27	Treatment 2 N=28	Treatment 3 N=25	Treatment 4 N=29
$AUC_{0\text{-}1.5hr}$, hr.pg/mL[a]	2359 (74)	3878 (44)[b]	4440 (53)[b]	3381 (53)[b]
$AUC_{0\text{-}3hr}$, hr.pg/mL[a]	2471 (75)	4097 (43)[b]	4639 (52)[b]	3611 (52)[b]
C_{max}, pg/mL[a]	4958 (75)	7141 (46)[b]	8083 (52)[b]	6654 (55)[b]
T_{max}, hr[c]	0.17 (0.17, 0.75)	0.33 (0.17, 0.50)	0.50 (0.17, 0.50)	0.33 (0.17, 0.33)

[a]Mean (CV%); [b]Significantly different from single dosing (Treatment 1), p≤.043; [c]Median (minimum, maximum)
Note - Repeated measures ANOVA mixed models were used to compare Ln-transformed PK parameters of glucagon ($AUC_{0\text{-}1.5}$, $AUC_{0\text{-}3}$ and C_{max}) between treatments.
ANOVA=Analysis of variance; CV=coefficient of variation; $AUC_{0\text{-}1.5/3}$=area under the curve from time 0 to 1.5 or 3 hrs; C_{max}=maximum concentration; T_{max}=time to maximum concentration

Table 4. Change in Pharmacodynamic Parameters of Glucose From Baseline

	Treatment 1 N=27	Treatment 2 N=28	Treatment 3 N=25	Treatment 4 N=29
$AUEC_{0\text{-}1.5hr}$,mg/dL*hr[a]	93 (46)	97 (45)	111 (37)	106 (46)
$AUEC_{0\text{-}3hr}$,mg/dL*hr[a]	157 (61)	168 (59)	190 (50)	194 (60)
C_{max}, mg/dL[a]	90 (41)	98 (40)	108 (34)[b]	105 (42)
T_{max},hr[c]	0.75 (0.50, 1.50)	1.00 (0.50, 2.50)	1.00 (0.75, 1.75)	1.00 (0.50, 2.50)

[a]Geometric means (CV%); [b]Significantly different from single dosing (Treatment 1), p=.049; [c]Median (minimum, maximum)
Note - ANOVA mixed models were used to compare Ln-transformed PD parameters of glucose ($AUEC_{0\text{-}1.5}$, $AUEC_{0\text{-}3}$ and C_{max}) between treatments.
ANOVA=Analysis of variance; CV=coefficient of variation; $AUEC_{0\text{-}1.5/3}$=area under the effect curve from time 0 to 1.5 or 3 hrs; C_{max}=maximum concentration; T_{max}=time to maximum concentration

Table 5. Most Reported Drug-Related Adverse Events

MedDRA SOC and Preferred Term	Treatment 1 (N=27)	Treatment 2 (N=28)	Treatment 3 (N=25)	Treatment 4 (N=29)
Subjects with ≥1 serious AE, n	0	0	0	0
Deaths, n	0	0	0	0
Subjects with ≥1 AE[a]	27 (100)	28 (100)	24 (96)	27 (93)
Eye disorders	25 (93)	25 (89)	23 (92)	25 (86)
•Lacrimation Increased[a]	25 (93)	25 (89)	23 (92)	25 (86)
Nervous system disorders[a]	10 (37)	19 (68)	15 (60)	14 (48)
•Headache[a]	7 (26)	14 (50)	10 (40)	11 (38)
Respiratory, thoracic, and mediastinal disorders[a]	11 (41)	16 (57)	12 (48)	18 (62)
•Nasal discomfort[a]	9 (33)	7 (25)	6 (24)	10 (35)
Gastrointestinal disorders[a]	5 (19)	14 (50)	7 (28)	8 (28)
•Nausea[a]	4 (15)	9 (32)	5 (20)	7 (24)
•Vomiting[a]	0	7 (25)	3 (12)	2 (7)

[a]All values are expressed as n (%) (% is calculated as the number of subjects with the event in each treatment arm divided by the number of subjects who received that treatment)
Note – "Most reported" is defined as reported by ≥25% subjects in any treatment arm. Each adverse event is counted only once for each subject within each System Organ Class and Preferred Term
AE=adverse event; SOC=System, Organ, Class

Table 6. Time to Resolution of Drug-Related Adverse Events

	Treatment 1 (N=27)	Treatment 2 (N=28)	Treatment 3 (N=25)	Treatment 4 (N=29)	All Subjects (N=32)
All drug-related adverse events reported	73 (18)	140 (34)	102 (24)	102 (24)	417 (100)
Time to resolution:					
<5 minutes	31 (42)	39 (28)	39 (38)	29 (28)	138 (33)
6-15 minutes	7 (10)	14 (10)	8 (8)	12 (12)	41 (10)
16-30 minutes	3 (4)	15 (11)	7 (7)	9 (9)	34 (8)
31-60 minutes	6 (8)	15 (11)	7 (7)	3 (3)	31 (7)
61-120 minutes	4 (6)	12 (9)	10 (10)	10 (10)	36 (9)
121-180 minutes	5 (7)	19 (14)	14 (14)	11 (11)	49 (12)
≥181 minutes	17 (23)	26 (19)	17 (17)	28 (28)	88 (21)

All values are expressed as n (%)
- *For the first row (all drug-related adverse events reported), % is calculated as the number of events from subjects in each specific treatment arm divided by the number of events from all subjects*
- *For the section on "Time to Resolution", % is calculated as the number of events resolved in each time interval divided by the number of events from subjects in that specific treatment arm*

CONCLUSIONS

- Although repeat dosing resulted in greater systemic glucagon exposure, it did not result in additional clinically meaningful increase in observed glucose response
- All nasal glucagon treatments were well tolerated
- Most drug-related adverse events were transient and resolved within 2 hours

Acknowledgments

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

References:

1. Rickels et al. *Diabetes Care* 2016;39:264-270

Privacy Notice Regarding the Collection of Personal Information
By scanning this QR code, you are consenting to have your IP address and, if you choose, email address temporarily retained in a secured computer system and used only for counting purposes, performing file download, and sending you an email. Your information will not be shared for any other purpose, unless required by law. You will not receive any future communications from Eli Lilly and Company based on the system-retained information. Contact information at: http://www.lilly.com/Pages/contact.aspx

ATTD 2017 Eli Lilly and Company
ATTD7-0077