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Brief Report

Nasal Glucagon Reverses Insulin-induced Hypoglycemia With Less Rebound Hyperglycemia: Pooled Analysis of Clinical Trials

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Abstract

Background: Rebound hyperglycemia may occur following glucagon treatment for severe hypoglycemia. We assessed rebound hyperglycemia occurrence after nasal glucagon (NG) or injectable glucagon (IG) administration in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D).

Methods: This was a pooled analysis of 3 multicenter, randomized, open-label studies (NCT03339453, NCT03421379, NCT01994746) in patients ≥18 years with T1D or T2D with induced hypoglycemia. Proportions of patients achieving treatment success [blood glucose (BG) increase to ≥70 mg/dL or increase of ≥20 mg/dL from nadir within 15 and 30 minutes]; BG ≥70 mg/dL within 15 minutes; in-range BG (70-180 mg/dL) 1 to 2 and 1 to 4 hours postdose; and BG >180 mg/dL 1 to 2 and 1 to 4 hours postdose were compared. Incremental area under curve (iAUC) of BG >180 mg/dL and area under curve (AUC) of observed BG values postdose were analyzed. Safety was assessed in all studies.

Results: Higher proportions of patients had in-range BG with NG vs IG (1-2 hours: $P = .0047$; 1-4 hours: $P = .0034$). Lower proportions of patients had at least 1 BG value >180 mg/dL with NG vs IG (1-2 hours: $P = .0034$; 1-4 hours: $P = .0068$). iAUC and AUC were lower with NG vs IG ($P = .025$ and $P < .0001$). As expected, similar proportions of patients receiving NG or IG achieved treatment success at 15 and 30 minutes (97-100%). Most patients had BG ≥70 mg/dL within 15 minutes (93-96%). The safety profile was consistent with previous studies.

Conclusion: This study demonstrated lower rebound hyperglycemia risk after NG treatment compared with IG.

Clinical Trial Registration: NCT03421379, NCT03339453, NCT01994746

Key Words: hypoglycemia, nasal glucagon, rebound hyperglycemia, type 1 and 2 diabetes

Introduction

Hypoglycemia is a major limiting factor in optimal glycemic management among patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) throughout the spectrum of the disease. Treatment with exogenous insulin is often associated with an increased risk of hypoglycemia [1, 2]. Patients treated with insulin experience 1 severe hypoglycemic event per year on average or about 4.9 and 2.5 events/patient-year for T1D and T2D, respectively [1, 2]. Current guidelines, including those from the American Diabetes Association, Diabetes Canada, International Society for Pediatric and Adolescent Diabetes, European Association for the Study of Diabetes, and International Hypoglycaemia Study Group, among others [3-7], recommend treatment with glucagon for patients with diabetes who experience severe hypoglycemia and are unable or unwilling to consume oral carbohydrates. Furthermore, guidelines suggest that glucagon be prescribed for all individuals at increased risk of level 2 or 3 hypoglycemia, so it is available when needed [4, 6].

Before ready-to-use glucagon became available, treatment options for severe hypoglycemia included glucose and reconstituted injectable glucagon (IG). IG requires a multistep reconstitution process that is challenging and often leads to administration failures as demonstrated through simulated rescue studies [8, 9]. Settles et al demonstrated that the administration success rate for IG was 7.9%, with or without training [8]. Yale et al found that 13% of caregivers and none of the acquaintances of patients with diabetes were able to deliver full doses of IG [9]. Advances in glucagon therapies have led to the development of ready-to-use glucagon treatment options that do not require reconstitution. These include nasal glucagon (NG; Eli Lilly and Company, Indianapolis, IN, USA), glucagon injection (Xeris Pharmaceuticals, Inc.), and dasiglucagon (Zealand Pharma). NG, which contains a 3-mg dose of glucagon in a dry powder formulation, was

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developed for the treatment of severe hypoglycemia and is absorbed passively through the nasal mucosa [10].

Despite advances in the treatment of severe hypoglycemia, glucagon and glucose treatment may be accompanied by a secondary effect of rebound hyperglycemia or, less commonly, rebound hypoglycemia in the setting of insulinoma [11]. Acute hyperglycemia has been shown to reduce spatial working memory capacity in adolescents with T1D [12] and to slow information processing, working memory, and affect aspects of attention and mood in older adults with T2D [13]. Posthypoglycemic hyperglycemia is associated with endothelial dysfunction, oxidative stress, and inflammation and has been shown to worsen thrombosis activation and endothelial damage in patients with T1D [14, 15]. In view of this, Diabetes Canada clinical practice guidelines state that it is important to avoid overtreatment of hypoglycemia "since this can result in rebound hyperglycemia" [5]. Ideally, a glucagon therapy that lowers the risk of rebound hyperglycemia would therefore be beneficial.

We conducted a pooled analysis of NG clinical trials to determine the occurrence of rebound hyperglycemia after NG administration in comparison with reconstituted IG in patients with T1D and T2D. This is the first analysis evaluating rebound hyperglycemia with a ready-to-use glucagon treatment option.

Materials and Methods

Study Design

This was a pooled analysis of 3 multicenter, randomized, open-label, single-dose, 2-period, 2-treatment, crossover studies in patients with T1D or T2D with induced hypoglycemia [16-18]. All 3 studies had a similar study design with the same objective to assess the efficacy and safety of NG (BAQSIMI® 3 mg; Eli Lilly and Company) compared with that of IG (GlucaGen® 1 mg; Novo Nordisk, Bagsværd, Denmark). The studies were registered at www.clinicaltrials.gov (study 1: NCT03339453, study 2: NCT03421379, and study 3: NCT01994746) [16-18].

Study Population

Eligible participants for the 3 studies were male or female adults (≥18 years) with T1D or T2D who used insulin therapy. Patients in each study were randomized to receive a single dose of either NG or IG in the first dosing period, followed by the alternate treatment in the second dosing period.

General Treatment Protocol

Details of the procedures have been published previously for each study [16-18]. Briefly, patients discontinued their basal insulin treatment and were in a fasting state before hypoglycemia was induced. An insulin infusion (human regular insulin, 100 U/mL in all 3 studies) was initiated to lower patients' plasma glucose level to <60 mg/dL, and the infusion was stopped once this level was reached. The glucagon (NG or IG) was administered approximately 5 minutes after the insulin infusion was stopped. Bedside plasma glucose was measured frequently for safety. Safety and tolerability were assessed throughout the studies by the record of adverse events, vital signs, and clinical laboratory tests.

Venous blood samples for glucagon and glucose measurements were collected 5 minutes before glucagon administration and at 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes (studies 1 [17] and 3 [16]) or at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, and 240 minutes (study 2 [18]) after glucagon administration.

Pooled Analysis Cohorts

Patients from studies 1 [17] and 2 [18], which used the commercial-equivalent NG drug product, were included in the efficacy cohort. These 2 studies included data beyond 60 minutes, which was required for the analysis of rebound hyperglycemia. Patients from study 3 [16], which used a clinical trial NG drug product, were included in the safety cohort along with patients from studies 1 and 2. Data from the efficacy cohort were used to assess treatment success and the risk of rebound hyperglycemia after NG vs IG administration. Data from the safety cohort were used to assess the safety and tolerability of NG vs IG administration.

Outcome Measures

Pharmacodynamic profiles

1. Treatment success was defined as an increase in blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from nadir within 15 and 30 minutes. The proportion of patients in the efficacy cohort who achieved treatment success was measured.
2. The proportion of patients with a blood glucose level that returned to ≥70 mg/dL within 15 minutes was measured.

Treatment success was also evaluated based on Ademolus Classification of Hypoglycemia [19].

Rebound hyperglycemia

Rebound hyperglycemia was defined as a blood glucose level >180 mg/dL between 1 and 4 hours after glucagon administration. The blood glucose threshold for hyperglycemia was based on the American Diabetes Association and American Association of Clinical Endocrinology guidelines and the consensus time-in-range metrics [20]. The following parameters were used to examine rebound hyperglycemia:

1. Proportion of patients with an in-range blood glucose level (70-180 mg/dL) at 1 to 2 hours after glucagon administration
2. Proportion of patients with a blood glucose level >180 mg/dL (hyperglycemia) between 1 and 2 hours after glucagon administration
3. Proportion of patients with an in-range blood glucose level (70-180 mg/dL) at 1 to 4 hours after glucagon administration
4. Proportion of patients with a blood glucose level >180 mg/dL (hyperglycemia) between 1 and 4 hours after glucagon administration
5. Incremental area under the curve (iAUC) of blood glucose >180 mg/dL between 1 and 4 hours after glucagon administration
6. Area under the curve (AUC) of observed blood glucose values at 0 to 2 hours, 1 to 2 hours, and 1 to 4 hours after glucagon administration

Safety Analysis

Safety and tolerability were assessed throughout the studies.

Table 1. Baseline characteristics of patients across the 3 trials

	Efficacy cohort			Safety cohort		
	Overall (N = 142)	T1D (n = 103)	T2D (n = 39)	Overall (N = 225)	T1D (n = 180)	T2D (n = 45)
Age, y, mean (SD)	46.0 (13.5)	41.7 (12.3)	57.5 (9.2)	41.6 (14.5)	37.9 (13.0)	56.2 (10.4)
Sex, n (%)						
Male	93 (65.5)	63 (61.2)	30 (76.9)	127 (56.4)	95 (52.8)	32 (71.1)
Female	49 (34.5)	40 (38.8)	9 (23.1)	98 (43.6)	85 (47.2)	13 (28.9)
Weight, kg, mean (SD)	73.0 (13.4)	73.5 (14.3)	71.7 (10.7)	74.2 (14.6)	74.2 (14.8)	74.2 (13.7)
BMI, kg/m^2, mean (SD)	24.8 (3.2)	24.6 (3.1)	25.5 (3.1)	25.3 (3.6)	25.1 (3.5)	26.3 (4.0)
Diabetes duration, y, mean (SD)	17.1 (10.6)	17.8 (11.1)	15.3 (9.4)	17.5 (10.7)	17.9 (11.1)	15.8 (9.2)
HbA1c, %, mean (SD)	7.64 (1.0)	7.46 (0.9)	8.13 (0.9)	7.74 (1.2)	7.66 (1.3)	8.07 (0.9)

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; n, number of patients; N, total number of patients; T1D, type 1 diabetes, T2D, type 2 diabetes; y, year.

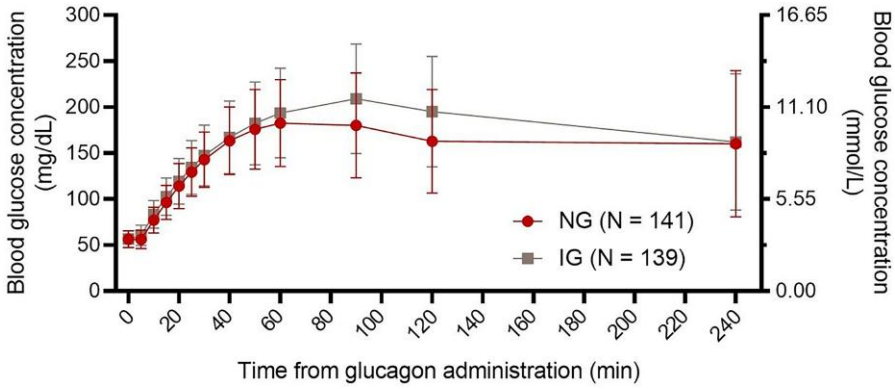

Figure 1. Mean (SD) blood glucose concentration vs time from glucagon administration. The efficacy cohort comprised all patients who completed both treatment visits and had evaluable data for efficacy analyses. Abbreviations: IG, injectable glucagon; N, number of patients; NG, nasal glucagon.

Statistical Analysis

The 2-sided Wald test with 95% confidence intervals using continuity correction was conducted for the differences in the proportion of patients who achieved treatment success with NG and IG. A linear mixed-effects model was used to analyze the iAUC of blood glucose >180 mg/dL (hyperglycemia) between 1 and 4 hours after glucagon administration and the AUCs of observed blood glucose values from 0 to 2, 1 to 2, and 1 to 4 hours after glucagon administration. The model was fitted to the log-transformed data, with treatment, period, and sequence as fixed effects and patient as a random effect. The 2-proportion z test with continuity correction was used to compare NG and IG for the proportion of patients with an in-range blood glucose reading (70-180 mg/dL) and the proportion of patients with at least 1 blood glucose value >180 mg/dL (hyperglycemia). This analysis was conducted separately for the blood glucose values from 1 to 2 hours and 1 to 4 hours after glucagon administration.

Results

Demographic and Baseline Characteristics

A total of 142 adult patients [T1D, n = 103 (age range, 20-64 years); T2D, n = 39 (age range, 35-to 70 years)] were included in the efficacy cohort (Table 1). The safety cohort included 225 adult patients [T1D, n = 180 (age range, 18-64 years); T2D, n = 45 (age range, 22-70 years)].

Pharmacodynamic Summary

Consistent with individual study results, the early effects of increased blood glucose levels after glucagon administration were similar between NG and IG in the pooled population (Fig. 1). All patients in the efficacy cohort achieved treatment success within 30 minutes of receiving NG or IG (Table 2). This included all patients who had a nadir blood glucose <54 mg/dL (level 2 hypoglycemia). The proportion of patients who achieved treatment success within 15 minutes was similar across treatments [NG (98%) and IG (97%)]. Comparable proportions of patients who received NG (93%) and IG (96%) had blood glucose levels return to ≥70 mg/dL within 15 minutes. The mean (SD) time to achieve treatment success (not including preparation time) was 11.7 (3.0) minutes with NG and 10.5 (3.2) minutes with IG. The median time from glucagon administration to treatment success was 10 minutes for both treatments.

Analysis of treatment success based on Ademolus Classification of Hypoglycemia showed similar results (Supplementary Table S1) [21].

Rebound Hyperglycemia

The proportion of patients with an in-range blood glucose reading (70-180 mg/dL) between 1 and 2 hours after glucagon administration was significantly ($P = .0047$) higher with NG

Table 2. Treatment success

	30-minute treatment success						15-minute treatment success					
	Pooled		T1D		T2D		Pooled		T1D		T2D	
	nG (n = 134)	IG (n = 134)	nG (n = 98)	IG (n = 98)	nG (n = 36)	IG (n = 36)	nG (n = 134)	IG (n = 134)	nG (n = 98)	IG (n = 98)	nG (n = 36)	IG (n = 36)
Treatment success, n (%)[a]	134 (100)	134 (100)	98 (100)	98 (100)	36 (100)	36 (100)	131 (97.8)	130 (97.0)	95 (96.9)	97 (99.0)	36 (100)	33 (91.7)
Treatment difference, % (2-sided 95% CL)[b]	0.00 (−0.7, 0.7)		0.00 (−1.0, 1.0)		0.0 (−2.8, 2.8)		−0.75 (−5.3, 3.8)		2.04 (−2.9, 7.0)		−8.33 (−20.1, 3.5)	
Glucose criterion met, n (%)												
(i) ≥ 70 mg/dL	134 (100)	134 (100)	98 (100)	98 (100)	36 (100)	36 (100)	124 (92.5)	128 (95.5)	93 (94.9)	97 (99.0)	31 (86.1)	31 (86.1)
(ii) Increase by ≥20 mg/dL	134 (100)	134 (100)	98 (100)	98 (100)	36 (100)	36 (100)	129 (96.3)	130 (97.0)	94 (95.9)	97 (99.0)	35 (97.2)	33 (91.7)
Both (i) and (ii)	134 (100)	134 (100)	98 (100)	98 (100)	36 (100)	36 (100)	122 (91.0)	128 (95.5)	92 (93.9)	97 (99.0)	30 (83.3)	31 (86.1)

Abbreviations: CL, confidence limit; IG, injectable glucagon; n, number of patients; n, total number of patients; NG, nasal glucagon; T1D, type 1 diabetes, T2D, type 2 diabetes.
The efficacy cohort comprised all patients who completed both treatment visits and had evaluable data for efficacy analyses.
[a]Treatment success was defined as an increase in blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from nadir within 15 or 30 minutes after receiving glucagon.
[b]Treatment difference was calculated as (percentage with success in IG) − (percentage with success in NG).

Table 3. Proportion of patients who reached BG targets

	Treatment	N	n (%)	*P*-value
Proportion of patients with all BG values within range (70-180 mg/dL) between 1 and 2 hours	NG IG	141 139	69 (49) 44 (32)	.0047
Proportion of patients with ≥1 hyperglycemic BG value (>180 mg/dL) between 1 and 2 hours	NG IG	141 139	70 (50) 94 (68)	.0034
Proportion of patients with all BG values within range (70-180 mg/dL) between 1 and 4 hours	NG IG	141 139	61 (43) 36 (26)	.0034
Proportion of patients with ≥1 hyperglycemic BG value (>180 mg/dL) between 1 and 4 hours	NG IG	141 139	73 (52) 95 (68)	.0068

Abbreviations: BG, blood glucose; IG, injectable glucagon; n, number of patients; n, total number of patients; NG, nasal glucagon.
BG values were measured 60, 90, 120, and 240 minutes after glucagon administration.

Table 4. Area under the blood glucose curve

	Treatment	n	Geometric LSM	Ratio (NG:IG) of geometric LSM (95% CI)	*P*-value
$AUC_{0\text{-}2}$, mg*h/dL	NG IG	141 139	299.08 328.19	0.91 (0.88-0.94)	<.0001
$AUC_{1\text{-}2}$, mg*h/dL	NG IG	141 139	168.55 193.23	0.87 (0.84-0.91)	<.0001
$AUC_{1\text{-}4}$, mg*h/dL	NG IG	141 139	469.92 528.42	0.89 (0.85-0.93)	<.0001

Abbreviations: $AUC_{0\text{-}2}$, area under the curve 0 to 2 hours after glucagon administration; $AUC_{1\text{-}2}$, area under the curve 1 to 2 hours after glucagon administration; $AUC_{1\text{-}4}$, area under the curve 1 to 4 hours after glucagon administration; CI, confidence interval; LSM, least squares mean; IG, injectable glucagon; NG, nasal glucagon.

(49%) compared with IG (32%) (Table 3). In contrast, a lower proportion of patients achieved at least 1 blood glucose value >180 mg/dL (hyperglycemia) between 1 and 2 hours after glucagon administration with NG (50%) compared with IG (68%; $P = .0034$). Similarly, the proportion of patients with an in-range blood glucose reading (70-180 mg/dL) between 1 and 4 hours after glucagon administration was also significantly ($P = .0034$) higher with NG (43%) compared with IG (26%), while a higher proportion of patients achieved at least 1 blood glucose value >180 mg/dL between 1 and 4 hours after glucagon administration with IG (68%) compared with NG (52%; $P = .0068$).

The iAUC of blood glucose >180 mg/dL between 1 and 4 hours postdose was lower with NG (26.4 mg*h/dL) compared with IG (43.3 mg*h/dL; $P = .025$). Furthermore, the AUCs of observed blood glucose values (geometric least squares mean) between 0 and 2 hours, 1 and 2 hours, and 1 and 4 hours after glucagon administration were significantly ($P < .0001$) lower with NG compared to IG (Table 4).

Safety Analyses

The safety profile of this pooled population was consistent with individual studies and with the IG profile (Table 5), with NG having additional local side effects associated with the nasal administration route.

Discussion

This pooled post hoc analysis of 3 clinical trials provides the first assessment of rebound hyperglycemia with a ready-to-use

Table 5. Safety summary

TEAE, n (%)	NG (n = 224)	IG (n = 221)
Patients with ≥1 TEAE	95 (42.4)	85 (38.5)
Nausea	45 (20.1)	62 (28.1)
Vomiting	25 (11.2)	25 (11.3)
Headache	28 (12.5)	15 (6.8)

Abbreviations: IG, injectable glucagon; n, total number of patients; NG; nasal glucagon; TEAE, treatment-emergent adverse event.
Data include TEAEs that were reported in >5% of patients in either arm.

glucagon treatment option relative to IG. The results indicate that NG has a lower risk of rebound hyperglycemia compared with that of IG. The proportion of patients who had a blood glucose level in the hyperglycemic range, along with the blood glucose AUCs, indicate a lower risk of rebound hyperglycemia with NG. Finally, NG resulted in a higher proportion of patients with blood glucose values within the target range (70-180 mg/dL) from 1 to 2 hours and 1 to 4 hours after glucagon administration.

Rebound hyperglycemia may contribute to transient cognitive impairment and may exacerbate pathogenic factors associated with cardiovascular disease [12-15]. Our findings suggest that the use of NG as a treatment for severe hypoglycemia could possibly be associated with fewer hyperglycemia-induced complications than would be seen with IG treatment.

This pooled analysis included 3 studies with similar methodology and data collection methods, enabling the analysis of a larger and a more diverse population including patients with T2D. This analysis included studies that were conducted in a controlled hospital setting, which eliminated the challenges of IG reconstitution and administration that trained or untrained users may face. Therefore, these findings may not directly translate into a complex real-world environment. Furthermore, an intravenous insulin infusion was used to induce hypoglycemia in all 3 studies. This may complicate the interpretation of the in-range blood glucose data, considering that intravenous insulin is cleared faster from the body than subcutaneous insulin.

Conclusion

Overall, this pooled analysis demonstrated that NG has a lower risk of rebound hyperglycemia and a higher rate of euglycemia after treatment compared to reconstituted IG. The findings of this analysis support NG as a beneficial treatment for insulin-induced hypoglycemia in adults with T1D or T2D.

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Author Contributions

All authors participated in the interpretation of study results and in the drafting, critical revision, and approval of the final version of the manuscript. E.S., Y.Y., and C.Y.K. were involved in the study design and data analyses, and C.Y.K. conducted the statistical analysis.

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Data Availability

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available from the corresponding author upon reasonable request.

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