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Safety and Treatment Success or Failure of Nasal Glucagon for Children and Adolescents with Diabetes in Japan： A Post-marketing Surveillance Study

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Abstract

Background and objective：Nasal glucagon is a dry powder glucagon formulation approved in Japan as rescue treatment for hypoglycemia in patients with diabetes. This study evaluated safety, treatment success or failure, and characteristics of patients prescribed nasal glucagon among pediatric patients with diabetes under routine clinical practice in Japan.

Methods：This single-arm, multicenter, observational post-marketing surveillance study was conducted from November 2020 to February 2024 at 11 study sites. Included patients had diabetes and were ＜17 years old at first prescription of nasal glucagon. Case report forms were used to collect patient characteristics, details of hypoglycemia events and nasal glucagon use, and adverse events（AEs）and adverse drug reactions（ADRs）within 1 day of nasal glucagon use.

Results：Nasal glucagon was prescribed to 102 patients with type 1 diabetes and administered to 13 patients during 16 hypoglycemia events. Six out of 13 patients had ≥1 AE and ≥1 ADR within 1 day of administration of nasal glucagon. No serious AEs or ADRs were observed. Gastrointestinal AEs/ADRs were the most common（5/13 patients；4/13 patients experienced vomiting）. Most hypoglycemia events happened at home（12/16 events）and nasal glucagon was most commonly administered by a

Key words：children, diabetes mellitus, hypoglycemia, intranasal glucagon, post-marketing surveillance

caregiver（12/16 events）. All patients treated with nasal glucagon recovered from hypoglycemia；10/16 events were resolved in ≤15 minutes.

Conclusion：In children and adolescents with diabetes in Japan, the observed safety profile of nasal glucagon as a rescue treatment for hypoglycemia in a real-world setting was consistent with the established safety profile identified from clinical trials.

Introduction

Type 1 diabetes（T1D）is an autoimmune disease characterized by immune-mediated destruction of pancreatic beta cells, impaired glucose tolerance, and subsequent dependence on exogenous insulin[1]. Type 2 diabetes（T2D）is characterized by tissue insulin resistance and relative insulin deficiency due to impaired function of the pancreatic beta cells[2)3)]. The incidences of both T1D and T2D in children have been increasing in many countries in recent decades[2)4)]. In Japan, results from the National Diabetes Survey（1997-2007）showed that the incidence of T1D and T2D in children（per 100000 person-years）was 1.5-2.5 and 0.75-6.73, respectively[5]. Management of both T1D and T2D requires strict glycemic control[6]. However, intensive glycemic control may be associated with an increased risk of hypoglycemia in patients with T1D[7]. Furthermore, children and adolescents with T1D are at greater risk of hypoglycemia than adults[7].

Severe hypoglycemia events are potentially life-threatening, particularly for children, and can be a scary experience for both patients and caregivers[7]. Rescue treatment for hypoglycemia requires administration of carbohydrate（e.g. oral glucose）[8]. In cases of severe hypoglycemia, intravenous（Ⅳ）glucose, administration of intramuscular glucagon, or other resuscitative actions are also required[8]. In Japan, Ⅳ glucose is administered in hospitals and glucagon injection is used as an emergency treatment when no medical staff are available. Glucagon emergency kits or glucagon injection vials are commercially available in many countries for rescue treatment of severe hypoglycemia, including in Japan. However, glucagon typically needs to be reconstituted before it can be administered, by either intramuscular or subcutaneous injection[9]. Nasal glucagon（Baqsimi®, Eli Lilly and Company at the time of launch；acquired by Amphastar Pharmaceuticals, Inc. in 2023）is a dry powder formulation of glucagon that does not require reconstitution, is provided in a single-use device, and is absorbed passively through the nasal mucosa[7)8)]. Japanese regulatory approval of nasal glucagon as rescue treatment for hypoglycemia in patients ≥4 years old was granted in March 2020[10], and both the usability of the administration device and the rationale for the pediatric dose of 3 mg have been supported by modelling and simulation studies[11)12)]. Nasal glucagon has been demonstrated to be effective and non-inferior to intramuscular glucagon as a rescue treatment for hypoglycemia in adults and children[7)8)13)-16)]. However, these recent trials of nasal glucagon did not include Japanese pediatric and adolescent patients with

diabetes[7)8)13)-16)].

This single-arm, multicenter, observational post-marketing surveillance study was conducted as part of the pharmacovigilance activity required by Japanese regulators. The objectives were to collect all adverse events (AEs) observed within 1 day of nasal glucagon used as a rescue treatment for hypoglycemia among children and adolescents with diabetes, to collect data for either treatment success or treatment failure in routine clinical practice in Japan, and to describe the characteristics of patients who were prescribed nasal glucagon in routine clinical practice, including those who did not use the drug.

Ⅰ Materials and methods

1. Study design

This was a single-arm, multicenter, observational study of children and adolescents with diabetes prescribed nasal glucagon as rescue treatment for hypoglycemia in routine clinical practice in Japan. Data were collected from November 2020 to February 2024, with final database lock in April 2024.

Eleven sites were included in this study, selected from hospitals throughout Japan that treat children and adolescents with diabetes. Patients were enrolled using a centralized registration system. The treating doctor completed the registration form and sent it to the patient enrolment center. Baseline and follow-up data were then obtained using case report forms (CRFs) completed by treating doctors. Observations and investigations were performed at the discretion of the treating doctors in routine clinical practice.

2. Study population, ethics, and consent

Patients were included in the study if they (1) had diabetes (either T1D or T2D) and were prescribed nasal glucagon, and (2) were <17 years old at the time of first prescription of nasal glucagon. Patients were excluded from the study if they were contraindicated for prescription of nasal glucagon according to the label in Japan (patients with pheochromocytoma or medical history of hypersensitivity to nasal glucagon).

This study was conducted in compliance with the Japan Ethical Guidelines for Medical and Biological Research Involving Human Subjects set out by the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labour and Welfare, and the Ministry of Economy, Trade and Industry (enforced on March 23, 2021; partially revised on March 27, 2023).

Based on the pharmaceutical affairs law in Japan, institutional review board approval and informed consent to participate are not required for post-marketing safety studies. However, patients or their caregivers were asked to provide written consent for scientific publication. The data presented in this article are only from patients for whom written informed consent for publication was obtained.

3. Data collection

CRFs were completed by the treating doctor at the initial prescription of nasal glucagon and every 6 months thereafter until the completion of the study. CRFs were also completed for each administration of nasal glucagon. Information collected on these CRFs, if available, included patient characteristics and medical history; concomitant drugs; height, body weight,

vital signs, and laboratory data；records of severe hypoglycemia event(s) and nasal glucagon use（on 6-monthly CRFs only）；detailed information on the situation in which the nasal glucagon was used（on post-administration CRFs only）；and AEs and adverse drug reactions（ADRs）(on post-administration CRFs only).

4. Outcome measures

1）Characteristics of patients prescribed nasal glucagon

Data collected in the CRFs were used to describe the characteristics of patients with diabetes who were prescribed nasal glucagon, including those who did not use the drug.

2）Safety of nasal glucagon as rescue treatment

Safety data（AEs, serious AEs, ADRs, and serious ADRs）were collected for all patients who were administered nasal glucagon as a rescue treatment for hypoglycemia. An AE was defined as an untoward medical occurrence in a patient within 1 day of the administration of nasal glucagon as a rescue treatment for hypoglycemia. An AE was defined as an ADR if the treating doctor judged the event to be related to nasal glucagon. AEs and ADRs were reported by treating physicians using their professional judgment.

3）Nasal glucagon treatment events

Details of hypoglycemia events in patients who were administered nasal glucagon were described, including the following：age and sex of patients who were administered nasal glucagon；place and time that the hypoglycemia event occurred；whether the hypoglycemia event was judged as severe, in accordance with the definitions of the American Diabetes Association[6] and the International Society for Pediatric and Adolescent Diabetes[17]；who administered the nasal glucagon（caregiver, patient, medical personnel, or other）；treatment success or failure；time to recovery；whether a concomitant treatment for hypoglycemia was given（e.g. muscle injection or oral glucose）；and whether a hospital outpatient visit occurred after the hypoglycemia event.

Severity of the hypoglycemia event was assessed by the treating doctor based on patient-/caregiver-provided information about patient consciousness during the event, presence/absence of convulsions, and the degree of assistance required by the patient. A patient was considered recovered if they recovered from a convulsion, regained consciousness, or were able to self-administer oral glucose.

5. Statistical analysis

The sample size was based on the expected incidence of severe hypoglycemia for Japanese children and adolescent patients with T1D (4.4 events per 100 person-years)[18]. The original study design ended the observation period for a patient after the first use of nasal glucagon for the treatment of hypoglycemia, so the planned sample size assumed that each patient would experience severe hypoglycemia no more than once. Therefore, in order to capture ≥3 severe hypoglycemia episodes with ≥90% probability, the study needed 79 patients prescribed nasal glucagon with a follow-up period of 1.5 years (the minimum follow-up for this study). However, given recent decreases in severe hypoglycemia events due to improvements in insulin treatments[19], and the likely dropout rate, the minimum sample size was set at 100 patients. To maximize the sample of patients

using nasal glucagon, enrolment of eligible patients was allowed to exceed the minimum sample size during the enrolment period. In subsequent protocol amendments, the observation period was adjusted such that multiple hypoglycemia events could be recorded for a single patient.

Descriptive analysis was performed on 2 analysis sets. Patient characteristics were described using the CRFs Collected Set (with consent for publication), consisting of all patients who were prescribed nasal glucagon and provided consent to publish their data. AEs, ADRs, and details of hypoglycemia events were described using the Safety Analysis Set (with consent for publication), consisting of all patients who used nasal glucagon and provided consent to publish their data.

Categorical variables were summarized as counts and percentages, and continuous variables were summarized using mean, median, standard deviation (S.D.), minimum, and maximum. Patients who were administered nasal glucagon were grouped into five age categories based on their age at baseline : <6 years, ≥6 to <9 years, ≥9 to <12 years, ≥12 to <15 years, and ≥15 years. Partial missing dates were imputed as the 15th of the month for unknown day and as July 1st for unknown month and day ; other missing values were not imputed. The software used for statistical analysis was SAS 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

Ⅱ Results

1. Characteristics of patients prescribed nasal glucagon

There were 102 pediatric patients who were prescribed nasal glucagon, had CRFs collected, and provided consent to publish (**Figure 1**). Of these, 13 patients were administered nasal glucagon during the study period. The mean (S.D.) ages at baseline of patients who were prescribed nasal glucagon and who used nasal glucagon were 11.0 (3.3) years and 10.4 (4.3) years, respectively (**Table 1**). All of the patients prescribed nasal glucagon had T1D, with a median duration of the disease of 58.0 months (range, 0-151). The median glycosylated hemoglobin A1c (HbA1c) of these patients was 7.8% (range, 5.9-12.0%). For the patients who were administered nasal glucagon, the median duration of diabetes was 41.0 months (range, 0-121), and the median HbA1c was 8.2% (range, 6.3-12.0%).

Among the 102 patients prescribed nasal glucagon, 16 patients (15.7%) had a history of any severe hypoglycemia events, and 9 patients (8.8%) had a history of asymptomatic hypoglycemia. At least 80 patients (78.4%) possessed oral glucose that was available ≥3 days per week. Among the 13 patients who used nasal glucagon, 6 patients (46.2%) had a history of severe hypoglycemia events, and 5 patients (38.5%) had a history of asymptomatic hypoglycemia. At least 10 patients (76.9%) possessed oral glucose that was available ≥ 3 days per week. One (1.0%) of the patients prescribed nasal glucagon had previous experience in administering a glucagon muscle injection, and none of the patients

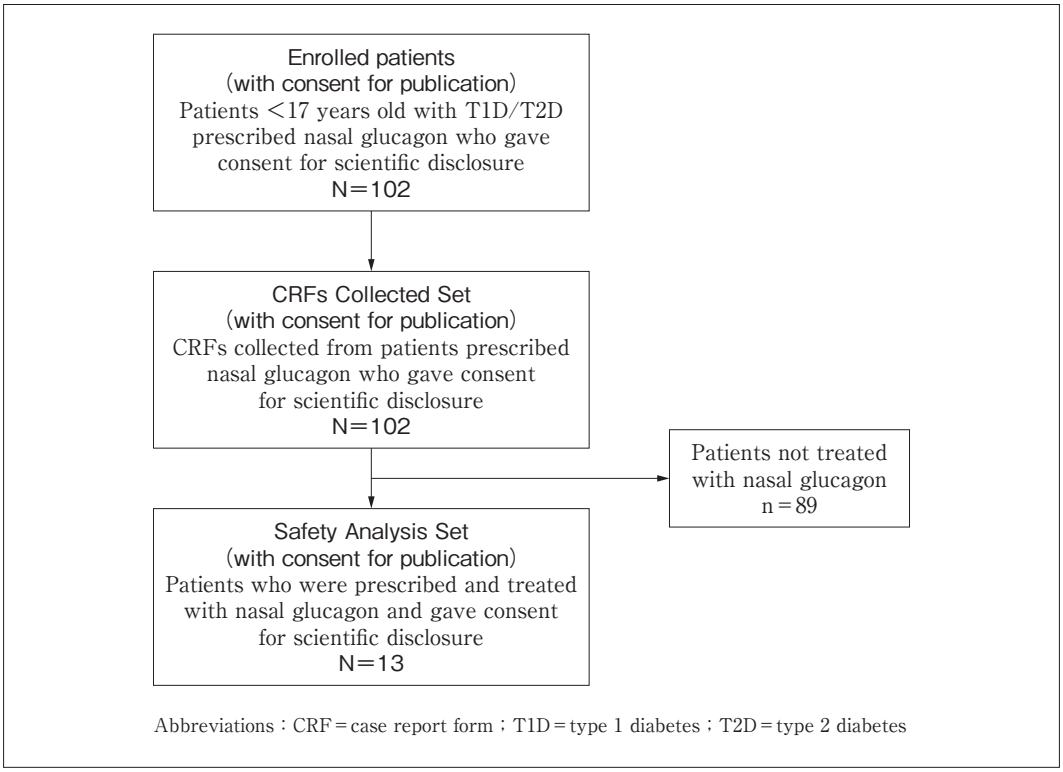


Figure 1 Patient flow diagram

had previous experience with administering nasal glucagon.

2. Safety of nasal glucagon as rescue treatment

Among the 13 patients who used nasal glucagon (Safety Analysis Set [with consent for publication]), there were 6 patients (46.2%) with ≥1 AE observed within 1 day of administration of nasal glucagon (**Table 2**). All of these patients were also judged to have experienced ADRs, i.e., the events were judged to be related to nasal glucagon treatment. None of the patients experienced serious AEs or serious ADRs.

The most commonly experienced AEs and ADRs were gastrointestinal disorders (5 patients), specifically vomiting (4 patients).

3. Nasal glucagon treatment events

In total, there were 16 hypoglycemia events experienced by the 13 patients in whom nasal glucagon was administered as a rescue treatment (**Table 3**). Patients in all age categories experienced hypoglycemia events, and some patients (Patients A, B, and C) experienced multiple events during the observation period.

Most hypoglycemia events happened at home (12/16 events ; **Table 3**). In 12 out of 16 events (75.0%), the patient's caregiver administered the nasal glucagon (**Figure 2**-a). All hypoglycemia events treated with nasal glucagon resulted in patients recovering from hypoglycemia symptoms. For most hypoglycemia events (10/16 ; 62.5%), the time to recovery was ≤15

Table 1 Patient demographics and clinical characteristics at initial prescription of nasal glucagon

Variable	Patients prescribed nasal glucagon[a] (N = 102)	Patients who used nasal glucagon[b] (N = 13)
Age, years		
Mean (S.D.)	11.0 (3.3)	10.4 (4.3)
Median (min, max)	11.00 (3.3, 17.0)	10.70 (3.8, 16.0)
Sex, male	42 (41.2)	7 (53.8)
Height, cm	n = 100	n = 12
Mean (S.D.)	139.2 (17.3)	131.4 (22.4)
Median (min, max)	141.7 (92.1, 175.4)	138.5 (92.1, 158.5)
Weight, kg	n = 100	n = 12
Mean (S.D.)	38.3 (13.3)	34.6 (13.5)
Median (min, max)	36.0 (14.0, 75.4)	33.3 (14.8, 53.3)
Type of diabetes		
Type 1	102 (100.0)	13 (100.0)
Type 2	0	0
Duration of diabetes, months	n = 101	
Mean (S.D.)	63.4 (39.1)	53.4 (36.7)
Median (min, max)	58.0 (0, 151)	41.0 (0, 121)
Prescribed concomitant drugs for diabetes[c]	102 (100.0)	13 (100.0)
HbA1c, %		
Mean (S.D.)	8.0 (1.1)	8.5 (1.5)
Median (min, max)	7.8 (5.9, 12.0)	8.2 (6.3, 12.0)
Fasting blood glucose, mg/dL	n = 39	n = 7
Mean (S.D.)	164.7 (66.1)	227.4 (72.0)
Median (min, max)	152.0 (65, 336)	211.0 (133, 336)
History of any severe hypoglycemia events		
Yes	16 (15.7)	6 (46.2)
No	86 (84.3)	7 (53.8)
Number of severe hypoglycemia events in previous year[d]		
Mean (S.D.)	0.2 (1.5)	1.5 (4.1)
Median (min, max)	0.0 (0, 15)	0.0 (0, 15)
History of asymptomatic hypoglycemia		
Yes	9 (8.8)	5 (38.5)
No	88 (86.3)	7 (53.8)
Unknown	5 (4.9)	1 (7.7)

(continued)

(continued)

Variable	Patients prescribed nasal glucagon[a] (N＝102)	Patients who used nasal glucagon[b] (N＝13)
Administration experience with glucagon muscle injection		
Yes	1 (1.0)	0 (0.0)
No	101 (99.0)	13 (100.0)
Administration experience with nasal glucagon		
Yes	0 (0.0)	0 (0.0)
No	102 (100.0)	13 (100.0)
Possession of oral glucose		
Yes	92 (90.2)	13 (100.0)
No	9 (8.8)	0 (0.0)
Unknown	1 (1.0)	0 (0.0)
Availability of oral glucose, days per week	n＝92	
≥6	68 (73.9)	8 (61.5)
≥3 to ≤5	12 (13.0)	2 (15.4)
≤2	1 (1.1)	0 (0.0)
Unknown	11 (12.0)	3 (23.1)
Drug allergy		
Yes	1 (1.0)	0 (0.0)
No	101 (99.0)	13 (100.0)
Renal disorder		
Yes	0 (0.0)	0 (0.0)
No	102 (100.0)	13 (100.0)
Hepatic disorder		
Yes	1 (1.0)	0 (0.0)
No	101 (99.0)	13 (100.0)
Follow-up period, days		
Mean (S.D.)	1008.6 (301.4)	1138.7 (135.3)
Median (min, max)	1168.0 (239, 1246)	1199.0 (814, 1246)

Data are n (%) unless otherwise stated.
[a]：And provided consent to publish their data, i.e. CRFs Collected Set (with consent for publication).
[b]：And provided consent to publish their data, i.e. Safety Analysis Set (with consent for publication).
[c]：Including insulin.
[d]：Prior to prescription of nasal glucagon.

Abbreviations：CRF＝case report form；HbA1c＝glycosylated hemoglobin A1c；max＝maximum；min＝minimum；S.D.＝standard deviation

Table 2 Summary of nasal glucagon safety (Safety Analysis Set [with consent for publication], N = 13)

Variable	Patients, n (%)	
Patients with ≥1 AE	6 (46.2)	
Patients with ≥1 SAE	0 (0.0)	
Patients with ≥1 ADR	6 (46.2)	
Patients with ≥1 SADR	0 (0.0)	
Type of AE or ADR[a], SOC PT	AEs (n[b], %)	ADRs (n[b], %)
Gastrointestinal disorders	5 (38.5)	5 (38.5)
Vomiting	4 (30.8)	4 (30.8)
Nausea	1 (7.7)	1 (7.7)
Nervous system disorders	1 (7.7)	1 (7.7)
Headache	1 (7.7)	1 (7.7)
Respiratory, thoracic, and mediastinal disorders	1 (7.7)	1 (7.7)
Rhinalgia	1 (7.7)	1 (7.7)

[a] : From MedDRA/J version 26.1.
[b] : Number of patients with ≥1 event per SOC/PT. If a patient experienced multiple events with different SOC/PT, the patient was counted more than once.

Abbreviations : ADR = adverse drug reaction ; AE = adverse event ; MedDRA/J = Medical Dictionary for Regulatory Activities/Japan ; PT = preferred term ; SADR = serious adverse drug reaction ; SAE = serious adverse event ; SOC = system organ class

minutes ; for an additional 3 events (18.8%), the time to recovery was >15 to ≤30 minutes (**Figure 2**-b). A hospital outpatient visit occurred after 6 out of 16 (37.5%) hypoglycemia events (**Figure 2**-c).

During most hypoglycemia events (10/16 ; 62.5%), a concomitant treatment for hypoglycemia was also administered (**Table 3**, **Figure 2**-d). None of the patients used intramuscular glucagon in addition to nasal glucagon. One patient received Ⅳ glucose. The most common concomitant treatments were oral glucose (5/16 events ; 31.3%) and juice (5/16 events ; 31.3%). Many patients used multiple concomitant treatments, e.g. oral glucose and juice combined. Other treatments administered included honey, jelly, candy, and sweet potato.

Ⅲ Discussion

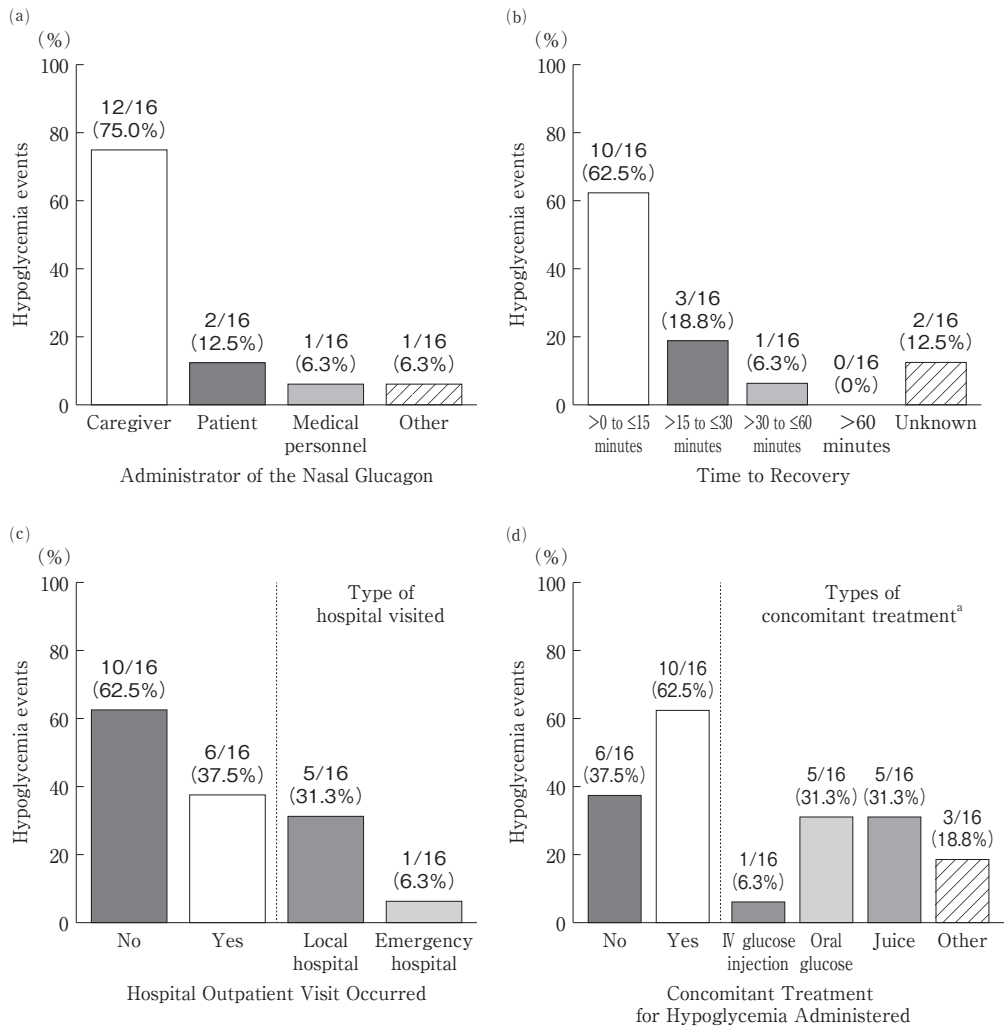
This single-arm, multicenter, observational post-marketing surveillance study is the first study to describe the safety profile of nasal glucagon in children and adolescents with diabetes in Japan in real-world clinical practice. During the post-marketing surveillance, 102 patients were prescribed nasal glucagon and 13 patients used nasal glucagon as a rescue treatment for 16 hypoglycemia events. No serious AEs were reported in patients who used nasal glucagon

Table 3 Summary of hypoglycemia events (Safety Analysis Set [with consent for publication], N = 16 events)

Patient details				Details of the hypoglycemia event				
Patient ID	Age, years[a]	Sex	Medication for diabetes[b]	Time at which the event occurred	Place at which the event occurred	Concomitant treatment required at the time of event[c]	Type (s) of concomitant treatment administered	Judged to be severe[d]
A[e]	<6	M	RAIA	22：30	Other	Yes	Oral glucose, juice	No
A[e]	<6	M	RAIA	18：12	Home	Yes	Oral glucose	Yes
B[e]	<6	M	RAIA	21：UN	Home	Yes	Oral glucose, juice	No
B[e]	<6	M	RAIA	21：28	Home	Yes	Oral glucose, juice	No
C[e]	<6	F	LAIA＋RAIA	18：30	Home	Yes	Ⅳ glucose injection	Yes
C[e]	<6	F	LAIA＋RAIA	UN：UN	Other	No	−	No
D	≥6 to<9	M	RAIA	05：30	Home	Yes	Other (jelly)	Yes
E	≥6 to<9	M	LAIA＋RAIA	18：50	Home	Yes	Other (honey)	Yes
F	≥9 to<12	M	RAIA	16：52	Home	Yes	Oral glucose, juice	Yes
G	≥9 to<12	M	LAIA＋RAIA	11：00	School	No	−	No
H	≥9 to<12	F	LAIA＋RAIA＋OAM	11：30	School	No	−	Yes
I	≥12 to<15	F	LAIA＋RAIA	06：30	Home	No	−	Yes
J	≥12 to<15	F	LAIA＋RAIA	15：30	Home	No	−	Yes
K	≥15	M	LAIA＋RAIA	06：UN	Home	No	−	Yes
L	≥15	F	RAIA	21：00	Home	Yes	Other (sweet potato, candy, 2 bottles of probiotic drink)	Yes
M	≥15	F	LAIA＋RAIA	05：30	Home	Yes	Juice	Yes

[a]：Age at baseline was categorized as follows：<6 years, ≥6 to<9 years, ≥9 to<12 years, ≥12 to<15 years, ≥15 years.
[b]：Information collected at baseline.
[c]：Concomitant treatment was defined as any other rescue treatment for hypoglycemia besides nasal glucagon.
[d]：Severity of the hypoglycemia event was judged by the treating doctor, based on patient/caregiver-provided information about patient consciousness during the event, presence/absence of convulsions, and the degree of assistance required by the patient.
[e]：Patients A, B, and C experienced multiple hypoglycemia events.

Abbreviations：F＝female；Ⅳ＝intravenous；LAIA＝long-acting insulin analog；M＝male；OAM＝oral anti-hyperglycemic medication；RAIA＝rapid-acting insulin analog；UN＝unknown



There were 16 hypoglycemia events across 13 patients who were treated with nasal glucagon ; the denominator for percentages is the N = 16 events. (a)Administrator of the nasal glucagon ; (b)Time to recovery ; (c)Percentage of events for which a hospital outpatient visit occurred ; (d)Percentage of events requiring concomitant treatment for hypoglycemia.

[a] : Concomitant treatment was defined as any other rescue treatment for hypoglycemia besides nasal glucagon (e.g., muscle injection or oral glucose) ; multiple concomitant treatments were administered during some events (see Table 3).

Figure 2 Outcomes of treatment of hypoglycemia with nasal glucagon

and no new safety concerns were revealed. All patients who used nasal glucagon recovered from their hypoglycemia symptoms.

The characteristics of the patients who were prescribed nasal glucagon generally reflected the characteristics of children and adolescents with T1D in Japan. For example, mean age and mean duration of diabetes

were similar to those of patients in a study of insulin detemir in Japanese children with T1D[18]. Furthermore, characteristics of the patients who used nasal glucagon, including age and duration of diabetes, were similar to patient characteristics in a phase 3 open-label study of nasal glucagon in children with T1D[7]. Therefore, despite the relatively small number of patients included in this study, the patients appear to be reasonably representative of both children and adolescents with T1D in Japan and of children and adolescents with T1D who require nasal glucagon.

The most common AEs experienced by patients who used nasal glucagon in this study were gastrointestinal disorders (vomiting and nausea). Gastrointestinal AEs were also common both in previous clinical trials of nasal glucagon in children[7)13)] and in a real-world cohort study of nasal glucagon use in Italian children and adolescents with T1D[16]. Headache and rhinalgia were also reported by patients in the present study and have been reported in previous studies[7)13)16)]. Adults also report gastrointestinal AEs and transient head or facial discomfort after nasal glucagon administration[8)14)15)]. Therefore, no changes were made to the risk profile of nasal glucagon based on the results of this study.

All of the hypoglycemia events treated with nasal glucagon reported in this study resulted in the patients recovering from their hypoglycemia symptoms, and most hypoglycemia events (81.3%) were resolved in ≤30 minutes. This is consistent with the earlier Italian real-world prospective cohort study, in which 95% of hypoglycemia events were resolved using nasal glucagon, and 92.3% were resolved in ≤30 minutes[16]. In the present study, during most hypoglycemia events (12/16), nasal glucagon was administered by caregivers, who had no prior experience in administering nasal glucagon. This frequent administration by caregivers with no prior experience is consistent with an earlier study in which caregivers reported that nasal glucagon administration was easy or very easy in 93.9% of hypoglycemic events[7].

The single-arm, observational design of this study had a practical advantage for monitoring the real-world clinical use of nasal glucagon in children and adolescents with diabetes in Japan. The prospective design of the study may have limited reporting bias. The design of the study also enabled description of actual nasal glucagon use in the real world, e.g. whether it was used for severe hypoglycemia or hypoglycemia, who administered it, etc. However, the descriptive nature of the study limited the use of statistical analyses, and the study was not designed to evaluate relationships between reported AEs and nasal glucagon use. In addition, the small number of participants limited statistical estimation of the incidence of AEs related to nasal glucagon use in the population where nasal glucagon was prescribed. The number of patients was limited due to the relatively low incidence of T1D in Japan[5], and the number may also have been limited because recent improvements in insulin therapies have resulted in reductions in the number of children and adolescents with T1D who experience hypoglycemia[19]. The small sample size may also affect the generalizability of this study.

In conclusion, in children and adolescents with diabetes in Japan, the observed safety profile of nasal glucagon as a rescue treatment for hypoglycemia in a real-world setting was consistent with the established safety profile identified from clinical trials. There were no new safety concerns identified in Japanese children and adolescents treated with nasal glucagon in routine clinical practice.

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Role of the sponsor

Eli Lilly Japan K.K. was involved in the study design, data collection, data analysis, and preparation of the manuscript.

Ethics statement

The study reported here was conducted in compliance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects set out by the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labour and Welfare, and the Ministry of Economy, Trade and Industry（enforced on March 23, 2021；partially revised on March 27, 2023）. Approval by an ethics committee was not required for this post-marketing surveillance study. Written informed consent was obtained for scientific disclosure from patients or their caregivers.

Data sharing

The datasets generated and analyzed during the current study are not publicly available as consent for data sharing was not collected from participants or caregivers.

Conflicts of interest

Rina Chin, Seiko Mizuno, and Hideaki Furuhama are employees of Eli Lilly Japan K.K. and are minor shareholders of Eli Lilly and Company. Makoto Imori is a former employee of Eli Lilly Japan K.K. and a minor shareholder of Eli Lilly and Company.

Role of contributors

All authors participated in the drafting, critical revision, and approval of the final version of the manuscript. Seiko Mizuno, Makoto Imori, and Rina Chin participated in the interpretation of study results, and Hideaki Furuhama conducted the statistical analysis.

Other contributors/acknowledgments

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原著

日本における糖尿病を有する小児・青年での点鼻グルカゴンの安全性および治療の成否：特定使用成績調査の結果から

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要　旨

背景・目的：点鼻グルカゴン（NG）は，糖尿病患者の低血糖救急処置薬として日本で承認されている粉末製剤である。日本の日常臨床下，小児糖尿病患者でのNGの安全性ならびに治療の成否を評価した。

方法：本製造販売後調査は多施設共同単群の観察研究で，2020年11月～2024年2月に11医療機関で実施された。初回処方時に17歳未満の糖尿病患者を対象とし，患者特性，低血糖の詳細，NG使用状況，NG使用後1日以内に発現した有害事象（AE）と副作用（ADR）を症例報告書で収集した。

結果：1型糖尿病患者102名にNGが処方され，13名16件の低血糖でNGが使用された。13名中6名でNG使用後1日以内にAE・ADRが認められた。重篤なものは認められなかった。最も多く認められたAE・ADRは消化器関連（5/13名，4名で嘔吐）であった。16件中12件は自宅で低血糖を発現した。また，NG投与者は12件で保護者であった。NGを使用した全ての患者で低血糖は回復した（16件中10件は15分以内に回復）。

結論：日本の実臨床下において，NGを使用した糖尿病小児・青年患者安全性プロファイルは，臨床試験と一致していた。

キーワード：小児，糖尿病，低血糖症，点鼻グルカゴン，製造販売後調査

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