

# Nasal Glucagon: A Promising New Way to Treat Severe Hypoglycemia

Lynn H. Nguyen and John R. White, Jr.

## Introduction

**H**ypoglycemia is a common side effect of diabetes treatment. Severe hypoglycemia is both potentially dangerous and costly to patients and the health care system. It occurs frequently in patients treated with intensive insulin therapy but can also occur in anyone treated with other hypoglycemic agents.

Glucagon is a polypeptide produced by the  $\alpha$ -cells in pancreatic islets (1). It stimulates the breakdown of glycogen in the liver with the resultant liberation of glucose, which increases the plasma glucose concentration. Currently, the only available glucagon formulation on the market for the treatment of severe hypoglycemia is injectable glucagon (subcutaneous, intramuscular). However, glucagon is unstable when in solution and so requires reconstitution before administration. This process can be stressful for both patients and caregivers during hypoglycemic emergencies.

Nasal glucagon has been shown to be as efficacious as the intramuscular glucagon formulation. Recently, Eli Lilly submitted a new drug application seeking approval of nasal glucagon from the U.S. Food and Drug Administration and the European Medicines Agency. If approved, this agent will be the first nasal glucagon preparation on the market to treat severe hypoglycemia.

## Indication

Nasal glucagon is intended for the treatment of severe hypoglycemia in

people with diabetes who are treated with insulin.

## Mechanism

Intranasal glucagon contains the 29–amino acid polypeptide identical to the human recombinant DNA-derived glucagon used in the currently available injectable emergency kit. Glucagon acts on liver glycogen, converting it to glucose and thus increasing the blood glucose concentration (2).

Dry-powder glucagon is packaged in an easy-to-use intranasal dispenser. The intranasal glucagon formulation consists of 3 mg glucagon, the phospholipid dodecylphosphocholine as an absorption enhancer, and cyclodextrin as a bulking agent in a total dose mass of 30 mg contained in a single-use one-step dispensing device (3). The molecule can passively cross the moist membrane of the nasal mucosa and enter the bloodstream without active inhalation from the patient.

## Potential Advantages

One significant advantage nasal glucagon offers over intramuscular glucagon is its ease of use. The intranasal glucagon product, which was initially developed by Locemia Solution, delivers glucagon with a one-step dispensing device. To use the device, the patient or caretaker inserts the tip of the device into one nostril and depresses the plunger, which is connected to a piston that discharges the powder. In all published studies, an increase of

---

Washington State University College of Pharmacy and Pharmaceutical Sciences, Spokane, WA

Corresponding author: John R. White, Jr., [whitej@wsu.edu](mailto:whitej@wsu.edu)

<https://doi.org/10.2337/cd19-0013>

©2019 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See [www.diabetesjournals.org/content/license](http://www.diabetesjournals.org/content/license) for details.

>20 mg/dL in plasma glucose can be expected (4).

A phase 1 study showed that nasal congestion, with or without concomitant use of a decongestant, did not adversely affect glucagon pharmacokinetics or glycemic response in otherwise healthy subjects given the 3-mg dose of nasal glucagon during and after recovery from a common cold (5).

Nasal glucagon also potentially causes less nausea and vomiting compared to the traditional intramuscular glucagon product. In one study, nausea with or without vomiting occurred in 67% of participants receiving intramuscular glucagon compared to 43% of participants receiving intranasal glucagon (4).

Intranasal glucagon also eliminates the need for weight-adjusted doses. The plasma glucose responses to the 2- and 3-mg intranasal doses are similar in all patients.

**Potential Disadvantages**

In one trial, a 6-year-old boy blew his nose immediately after administration of the 2-mg intranasal dose, resulting in a glucagon level 10-fold less than the dose administered to other participants (4). However, in the majority of real-life situations, it is unlikely that a patient with severe hypoglycemia will encounter this problem.

Some other side effects are seen more in nasal glucagon compared to intramuscular glucagon. Subjects receiving nasal glucagon experienced head and facial discomfort (24%),

increased lacrimation (13%), and nasal discomfort (15%).

**Cost**

Because nasal glucagon is not approved yet, there is no information regarding the potential cost of nasal glucagon kits. However, one study did model the cost of emergency treatment for severe hypoglycemia and found that the per-event cost of treatment with intramuscular glucagon was \$1,459 compared to \$970 for treatment with nasal glucagon (6). Patients are more likely to receive successful treatment from nasal glucagon and avoid the need for emergency services, which would explain this cost difference.

**Comments**

If approved, nasal glucagon will be the first nasal spray for severe hypoglycemia on the market. Multiple trials have proven the efficacy of nasal glucagon and suggested that it is comparable to intramuscular glucagon. Use of the nasal formulation would remove the stress of mixing and administering intramuscular glucagon in an emergency situation.

**Bottom Line**

Nasal glucagon is equally as efficacious as intramuscular glucagon for treatment of insulin-induced hypoglycemia in adults and children. Additionally, it is easier to use and does not require reconstitution before use. Finally, it may potentially offer a cost advantage when compared to injectable glucagon.

**Duality of Interest**

No potential conflicts of interest relevant to this article were reported.

**Author Contributions**

Both authors contributed to and were involved in the research, writing, and editing of this article. J.R.W. is the guarantor of this work and, as such, had full access to all of the references cited and takes responsibility for the accuracy of the content.

**References**

1. Barret KE, Barman SM, Boitano S, Brooks H. Endocrine functions of the pancreas and regulation of carbohydrate metabolism. In *Ganong's Review of Medical Physiology*. 23rd ed. McGraw Hill, New York, N.Y., 2009, p. 315–336
2. Eli Lilly and Company. Glucagon injection product information. Indianapolis, Ind., Eli Lilly and Company, 2005
3. Rickels MR, Ruedy KJ, Foster NC, et al. Intranasal glucagon for treatment of insulin-induced hypoglycemia in adults with type 1 diabetes: a randomized crossover noninferiority study. *Diabetes Care* 2016;39:264–270
4. Sherr JL, Ruedy KJ, Foster NC, et al. Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. *Diabetes Care* 2016;39:555–562
5. Guzman CB, Dulude H, Piché C, et al. Effects of common cold and concomitant administration of nasal decongestant on the pharmacokinetics and pharmacodynamics of nasal glucagon in otherwise healthy participants: a randomized clinical trial. *Diabetes Obes Metab* 2018;20:646–653
6. Bajpai S, Poehlmann J, Osumili B, Mitchell B, Valentine W. Nasal glucagon saves professional emergency medical (EM) costs versus intramuscular glucagon: a U.S.-based cost-offset model. *Value Health* 2018;21(Suppl. 1):S76