Glucagon Therapy: A Comparison of Current and Novel Treatments

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Hypoglycemia has been a barrier to A1C attainment in people with diabetes (1). It is well known that a glucocentric approach with intensive control reduces microvascular complications, but at what cost? Worse clinical outcomes, increased risk of severe hypoglycemia, and heavier treatment burden can result from aggressive efforts to lower A1C (2). People with diabetes also tend to experience more stress as a result of fear of hypoglycemia, higher costs of care, and increased prevalence of polypharmacy—especially for those with type 2 diabetes of longer duration. New medication classes (e.g., sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists) are providing impetus for replacing the glucocentric treatment paradigm with an individualized multifactorial approach (2).

Traditional glucagon kits have long been available for the ambulatory treatment of patients with hypoglycemia. However, these kits have disadvantages. Their complicated multistep injection procedure can be difficult to perform. Additionally, the use of glucagon must be taught to the family members, friends, or caregivers because it is administered by someone else when a person with diabetes is unconscious or otherwise incapacitated by severe hypoglycemia (3). For these reasons, glucagon is undertaught and underutilized (3).

Two new glucagon formulations offer potentially easier delivery. The purpose of this article is to review all available glucagon formulations, discussing the associated literature and possible new directions for the treatment of hypoglycemia.

Consequences and Treatment of Hypoglycemia

The American Diabetes Association has adopted a three-level classification of hypoglycemia. Level 1 is a glucose concentration <70 and ≥ 54 mg/dL; level 2 is glucose <54 mg/dL; and level 3 is defined as a severe event characterized by altered mental and/or physical status requiring assistance (1). Symptoms include dizziness, shakiness, sweating, intense hunger or thirst, irritability, and anxiety.

Although many patients experience symptoms, possible impaired counterregulatory responses necessitate adherence to glucose concentrations as clinical indicators. Patients may adopt behaviors to avoid hypoglycemia in the short term; however, frequent hypoglycemia over the long term can have significant consequences (1). Young children with type 1 diabetes and elderly people with diabetes may have reduced recognizable symptoms and are particularly vulnerable (4,5). A history of level 3 hypoglycemia in older adults with type 2 diabetes may be correlated with increased dementia risk (4). Thus, fear of hypoglycemia can be a significant barrier to the attainment of glycemic targets.

Hypoglycemia treatment involves the ingestion of fast-acting carbohydrates when blood glucose is ≤ 70 mg/dL (1). Although pure glucose is the preferred treatment, any carbohydrate form containing glucose will suffice. For unconscious patients and those unable to ingest oral glucose, glucagon in the ambulatory setting or intravenous (IV) glucose or dextrose in the hospital setting is indicated.

Traditional Glucagon Kits

The two traditional glucagon kits available in the United States are the Glucagon Emergency Kit (Eli Lilly) and the GlucaGen HypoKit (Novo Nordisk). Both were approved by the U.S. Food and Drug Administration (FDA) in 1998 for severe hypoglycemia, with no age limitations (6,7). They are structurally identical to the 29–amino acid human glucagon, with no clinically significant difference in terms of pharmacology, efficacy, or safety (8).

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Whether given intramuscularly or subcutaneously, plasma glucose concentrations should increase within ~10 minutes. The dose for adults and children weighing >55 lb (>6 years of age if weight is unknown) is 1 mg, reconstituted with the 1 mL diluent included in the kit. The dose is 0.5 mg for children <55 lb or <6 years of age. Glucagon should be administered immediately after reconstitution, and oral carbohydrate should be given after the patient regains consciousness and is able to swallow. Medical help should be sought if the patient does not respond to glucagon, with IV glucose or dextrose administered as soon as possible (8).

Both kits have instructions on the case. A brightly colored case contains a vial of glucagon powder and a prefilled syringe to provide a 1-mg/1-mL injection. Each kit includes specific directions (9). The user breaks off the plastic cap from the vial, and the diluent is injected into the vial. The contents are shaken until the reconstituted solution is clear and void of particulate matter. The solution is then drawn into the syringe and immediately injected into the unconscious patient's thigh or abdomen. The patient is rolled over onto his or her side during recovery in case of vomiting.

Glucagon is contraindicated for people with a known hypersensitivity or pheochromocytoma, which could cause secondary hypoglycemia from catecholamine release after glucagon administration (6,7). The adverse reactions most often reported with glucagon have been nausea and vomiting. Glucagon given extraneously can interact with β-blockers (leading to increased pulse and blood pressure), indomethacin (possibly rendering the glucagon unable to raise blood glucose levels), anticholinergics (causing increased gastrointestinal side effects), and warfarin (possibly increasing its anticoagulant effect) (6,7).

New FDA-Approved Formulations

Nasal Glucagon

Baqsimi Nasal Powder (Eli Lilly) is a nasal glucagon formulation that was approved by the FDA on 25 July 2019. It is a fixed dosage of 3 mg for the treatment of severe hypoglycemia in individuals who are ≥4 years of age (10). The portable, dry nasal spray needs no reconstitution or priming. This product can be stored at temperatures up to 86°F.

Longer-molecule hormones such as glucagon need a promoter (e.g., β-cyclodextrin plus dodecylphosphocholine) for intranasal administration (11). The bioavailability of intranasal glucagon generally is less than that of the traditional formulations, resulting in lower peak plasma concentrations. However, the clinical efficacy of intranasal glucagon is comparable to that of injectable formulations. The nasal powder is dispensed ready to use in a single-dose dispenser (12). Instructions are printed on the shrink-wrapped tube label. The tip is inserted into one nostril and the plunger is pressed all the way until the green line is no longer showing. Inhalation is not required. A response should occur within 15 minutes. If no response occurs, an additional 3-mg dose from another dispenser may be administered. Regardless of response, emergency medical services should be called immediately after dose administration. Oral carbohydrates should be given when the patient responds.

Contraindications, warnings, precautions, and drug interactions are the same as with the traditionally available kits. The most common adverse reactions include nausea, vomiting, headache, upper respiratory tract irritation, watery eyes, redness of eyes, and itchy nose, throat, and eyes (12). Of note, one study compared the efficacy of the nasal powder in patients with nasal congestion and after recovery from cold symptoms and found no difference in blood glucagon or glucose concentrations, even before and after giving a nasal decongestant (13).

Two noninferiority clinical studies were conducted in adult patients, both as randomized, multicenter, open-label, crossover trials comparing a 3-mg dose of the nasal formulation with a 1-mg dose of glucagon for injection (14,15). The first study included 70 adults with type 1 diabetes, and the second included 83 adults with either type 1 or type 2 diabetes. Both groups achieved 100% treatment success in the first study, and, in the second study, success levels were 98.8 and 100% for intranasal administration and injection, respectively. Treatment success was defined as an increase in plasma glucose levels to ≥70 mg/dL or an increase of ≥20 mg/dL in plasma glucose from the nadir within 30 minutes of glucagon administration.

A total of 48 children and adolescents with type 1 diabetes ranging in age from 4 to 17 years were evaluated in one multicenter trial (16). After hypoglycemia was induced, children aged 4–8 years and those aged 8–12 years were randomized to receive either 2 or 3 mg at the first visit and the alternative dose at the second visit. Weight-based injectable glucagon was used as the comparator. For participants who were 12–17 years of age, 1 mg intramuscular glucagon and 3 mg intranasal glucagon were given in alternate visits. The primary outcome, an increase in glucose levels of ≥25 mg/dL from nadir, was achieved in all groups within 30 minutes of dosing, with no statistically significant differences among groups.

Liquid-Stable Glucagon

The Gvoke HypoPen (Xeris Pharmaceuticals) is a liquid-stable formulation (delivered via autoinjector) that was

approved on 10 September 2019 for the treatment of severe hypoglycemia (17). Gvoke PFS, a prefilled syringe containing the same liquid glucagon formulation, was approved simultaneously. Both are approved for pediatric and adult patients with diabetes who are ≥2 years of age.

The main problem in the past with developing a stable liquid formulation that does not have to be mixed before administration was that amyloid-like fibrils form in aqueous solution (18). Both Gvoke formulations use a native human glucagon protein dissolved in an aprotic polar solvent, dimethyl sulfoxide (DMSO). Other FDA-approved injectable medications have used DMSO to promote stable liquid formulations (19).

Dose administration is weight dependent for pediatric patients aged 2 to <12 years (17). For those <45 kg, the recommended dose is 0.5 mg/0.1 mL. For those whose weight is ≥45 kg, the recommended dose is 1 mg/0.2 mL.

These products come packaged in a foil pouch with instructions. Before administration, the autoinjector or prefilled syringe should be inspected to ensure that the solution is clear and colorless and free of particulate matter. Injection with the autoinjector is intended to be similar to using an EpiPen, which injects when pressed against the body (17). Both products require subcutaneous injection in the lower abdomen, outer thigh, or upper arm. Emergency services should be contacted immediately after administration, and oral carbohydrates should be given when the patient is responsive. If response does not occur within 15 minutes, an additional dose from a new dispenser may be delivered.

Contraindications, warnings, precautions, and drug interactions are the same as with traditional kits, with one exception. The package inserts note that a skin rash, known as necrolytic migratory erythema, has been reported but is resolved with glucagon discontinuation (20). The most common adverse reactions for adults include nausea, vomiting, and injection site edema; hypoglycemia, headache, abdominal pain, hyperglycemia, injection site reactions, and urticaria additionally have been reported for pediatric patients. Drug interactions are similar to those of other glucagon products.

Clinical studies leading to FDA approval included two multicenter crossover trials with adults and one with pediatric participants, all with type 1 diabetes (20–22). The two studies in adults involved a total of 161 patients aged 18–74 years with two clinic visits 7 to 28 days apart. Random assignment of either the autoinjector or a traditional glucagon kit was administered on alternate clinic visits for patients with a mean plasma glucose manipulated to <45.2 mg/dL. Treatment success, as the primary end point, was defined as mean plasma glucose increased to >70 mg/dL or a relative increase of ≥20 mg/dL 30 minutes after glucagon administration. Treatment success rates were 98.7 and 100%, respectively, in the autoinjector and traditional glucagon kit groups and demonstrated noninferiority for the auto-injector. The median times to blood glucose elevation for treatment success were 13.8 and 10 minutes, respectively. In the study that included 31 pediatric patients, those who were 2–12 years of age were given a 0.5-mg dose, and those who were >12 years of age received 1 mg (or 0.5 mg, depending on weight). All pediatric patients were given the autoinjector and achieved a plasma glucose increase of ≥25 mg/dL.

Advantages and Disadvantages of the New Formulations

As previously mentioned, fear of hypoglycemia is a significant barrier to achieving therapeutic A1C targets (23). Hypoglycemia symptoms can be uncomfortable and can lead to death in worse-case scenarios. Patients often adopt behaviors to avoid hypoglycemia. In older adults, especially those with frequent hypoglycemia, it can lead to substantial complications (24). Lowered adaptive physiologic responses to hypoglycemia can be accompanied by cognitive and functional loss over time. Thus, the availability of more ways to use glucagon as a counteractive measure to hypoglycemia may be of benefit for people with diabetes (10,17).

Simulation studies have compared the ease of use and patient and caregiver perceptions of traditional glucagon kits versus nasal and autoinjector formulations. One study comparing the nasal formulation to a traditional glucagon kit found that 90 and 13% of caregivers delivered full doses with the nasal and traditional formulations, respectively (25). A usability study with adult caregivers and first responders experienced with glucagon administration was also completed. Whereas 88% administered the autoinjector glucagon successfully, only 31% were successful with a traditional glucagon kit (26). Another study used telephone interviews to qualitatively compare nasal- versus autoinjector-delivered (27). Patients, caregivers, and acquaintances commented favorably regarding nasal glucagon, noting that that it appeared easy to carry and use, lacked a needle, and did not require removal of clothing and that others would most likely feel comfortable using it. Overall, the new glucagon formulations appear acceptable by patients and may offer improved ease of use compared with traditional injections.

New Directions for Therapy

Two mechanisms for developing stable, aqueous glucagon formulations are being studied: 1) using amino acid

substitution in comparison with native glucagon and 2) using biochaperones (polymers, oligomers, and organic compounds) that form a complex with glucagon (18). Both methods protect against degradation and fibril formation. Dasiglucagon is an analog with seven substituted amino acids. The autoinjector and prefilled syringe for this investigatory agent currently uses a DMSO solvent for stabilization, as previously described, and other biochaperones are being studied (8).

Tight glycemic control reduces the risk of long-term microvascular complications of diabetes. However, attaining such control carries an increased risk of levels 1–3 hypoglycemic episodes. Even with levels 1 and 2, oral carbohydrate intake can be prohibitive when a patient is unwilling to ingest carbohydrates or unable to do so because of vomiting or nausea. Mini-dose glucagon, which involves giving a small dose of glucagon to raise blood glucose, has been used as an approach for such cases. The amount of glucagon used in this strategy is 1 unit per year of patient age. Blood glucose should be checked every 15 minutes, and the mini-dose should be repeated if blood glucose has not started to rise after 15 minutes or has not risen to >80 mg/dL within 30 minutes. Mini-dose glucagon has been studied for hypoglycemia in children and adults with type 1 diabetes and to prevent exercise-related hypoglycemia (28–30). The advantages of using mini-dose glucagon are that patients and caregivers are already familiar with syringes and that this approach could reduce patients' fear of hypoglycemia. However, the price of glucagon dosing may be a disadvantage that could necessitate a novel formulation for widespread use of mini-dosing in the future (18).

Conclusion

New nasal and liquid-stable glucagon formulations offer the potential to optimize treatment during hypoglycemia episodes when patients are unresponsive or cannot ingest oral carbohydrates.

DUALITY OF INTEREST

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

AUTHOR CONTRIBUTIONS

Both authors researched the data and wrote the manuscript. J.J.S. is the guarantor of this work and, as such, takes responsibility for the integrity of the data reported and the accuracy of the analysis.

REFERENCES

1. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S61–S70
2. Rodriguez-Gutierrez R, Gonzalez-Gonzalez JG, Zuñiga-Hernandez JA, McCoy RG. Benefits and harms of intensive glycemic control in patients with type 2 diabetes. BMJ 2019;367:l5887
3. Pearson T. Glucagon as a treatment of severe hypoglycemia: safe and efficacious but underutilized. Diabetes Educ 2008;34:128–134
4. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009;301:1565–1572
5. DuBose SN, Weinstock RS, Beck RW, et al. Hypoglycemia in older adults with type 1 diabetes. Diabetes Technol Ther 2016;18:765–771
6. Glucagon for Injection [package insert]. Indianapolis, IN, Eli Lilly & Co., 1999
7. GlucaGen [package insert]. Plainsboro, NJ, Novo Nordisk, 1999
8. Hawkes CP, De Leon DD, Rickels MR. Novel preparations of glucagon for the prevention and treatment of hypoglycemia. Curr Diab Rep 2019;19:97–107
9. Kedia N. Treatment of severe diabetic hypoglycemia with glucagon: an underutilized therapeutic approach. Diabetes Metab Syndr Obes 2011;4:337–346
10. Eli Lilly and Company. BAQSIMI (glucagon) nasal powder 3 mg, the first and only nasally administered glucagon to treat severe hypoglycemia in adults and children with diabetes ages four years and older, approved by FDA. Available from https://investor.lilly.com/news-releases/news-release-details/baqsimitm-glucagon-nasal-powder-3-mg-first-and-only-nasally. Accessed 10 November 2019
11. Pontiroli AE, Ceriani V. Intranasal glucagon for hypoglycaemia in diabetic patients: an old dream is becoming reality? Diabetes Obes Metab 2018;20:1812–1816
12. BAQSIMI [package insert]. Indianapolis, IN, Eli Lilly & Co., 2019
13. 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
14. Rickels MR, Ruedy KJ, Foster NC, et al.; T1D Exchange Intranasal Glucagon Investigators. 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
15. Elliott W, Chan J. Pharmacology update: glucagon nasal powder (Baqsimi). Available from https://www.reliasmedia.com/articles/144967-glucagon-nasal-powder-baqsimi. Accessed 11 November 2019
16. Sherr JL, Ruedy KJ, Foster NC, et al.; T1D Exchange Intranasal Glucagon Investigators. Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. Diabetes Care 2016;39:555–562
17. Beyond Type 1 Editorial Team. FDA approves first ready-to-use liquid stable glucagon Gvoke. Available from https://beyondtype1.org/gvoke-hypopen-fda-approval. Accessed 13 November 2019
18. Wilson LM, Castle JR. Stable liquid glucagon: beyond emergency hypoglycemia rescue. J Diabetes Sci Technol 2018;12:847–853
19. Haymond MW, DuBose SN, Rickels MR, et al.; T1D Exchange Mini-Dose Glucagon Study Group. Efficacy and safety of mini-dose glucagon for treatment of nonsevere hypoglycemia in adults with type 1 diabetes. J Clin Endocrinol Metab 2017;102:2994–3001
20. Gvoke (glucagon) injection [package insert]. Chicago, IL, Xeris Pharmaceuticals, 2019
21. Christiansen MP. A phase 3 comparison of a novel liquid glucagon autoinjector to glucagon emergency kit for the symptomatic relief of severe hypoglycemia. Presented at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018
22. Christiansen MP. A phase 3 comparison of a novel liquid glucagon autoinjector to glucagon emergency kit for the treatment of severe

hypoglycemia. Presented at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018

23. Rossi MC, Nicolucci A, Ozzello A, et al.; HYPOS-1 Study Group of AMD. Impact of severe and symptomatic hypoglycemia on quality of life and fear of hypoglycemia in type 1 and type 2 diabetes: results of the Hypos-1 observational study. Nutr Metab Cardiovasc Dis 2019;29:736–743
24. Sircar M, Bhatia A, Munshi M. Review of hypoglycemia in the older adult: clinical implications and management. Can J Diabetes 2016;40:66–72
25. Yale JF, Dulude H, Egeth M, et al. Faster use and fewer failures with needle-free nasal glucagon versus injectable glucagon in severe hypoglycemia rescue: a simulation study. Diabetes Technol Ther 2017;19:423–432
26. Valentine V, Newswanger B, Prestrelski S, Andre AD, Garibaldi M. Human factors usability and validation studies of a glucagon autoinjector in a simulated severe hypoglycemia rescue situation. Diabetes Technol Ther 2019;21:522–530
27. Bajpai SK, Cambron-Mellott MJ, Peck E, et al. Perceptions about glucagon delivery devices for severe hypoglycemia: qualitative research with patients, caregivers, and acquaintances. Clin Ther 2019;41:2073–2089.e6
28. Haymond MW, Redondo MJ, McKay S, et al. Nonaqueous, mini-dose glucagon for treatment of mild hypoglycemia in adults with type 1 diabetes: a dose-seeking study. Diabetes Care 2016;39:465–468
29. Rickels MR, DuBose SN, Toschi E, et al.; T1D Exchange Mini-Dose Glucagon Exercise Study Group. Mini-dose glucagon as a novel approach to prevent exercise-induced hypoglycemia in type 1 diabetes. Diabetes Care 2018;41:1909–1916
30. Phillips B. Towards evidence based medicine for paediatricians. Arch Dis Child 2016;101:497–499