Glucagon and Its Underutilization in Diabetes Self-Management: A Teachable Moment

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A woman with type 1 diabetes of 14 years' duration is admitted to a noncritical care unit after presenting to the emergency center with hypoglycemia. According to her family member and emergency medical services personnel, the person's blood glucose was noted to be 28 mg/dL. Pharmacy records indicate that her treatment regimen before admission included insulin glargine 40 units subcutaneously in the morning and insulin lispro 5 units subcutaneously before each meal, with a correction factor of 24 (1 unit of insulin for every 24 mg/dL above target) and that she received enough blood glucose monitoring supplies to perform four checks per day. Normal organ function is noted, and her A1C is found to have decreased from 9 to 6.2% in the past 3 months. During her 4-day hospitalization, her insulin therapy included insulin glargine 20 units subcutaneously in the morning and insulin lispro with a correction scale of 0–8 units subcutaneously four times per day (before meals and at bedtime). Her point-of-care glucose levels ranged from 98 to 245 mg/dL. She will be discharged today.

According to the Centers for Disease Control and Prevention, hypoglycemia accounts for an estimated rate of 10.2 emergency department visits per 1,000 adults with diabetes (1). Hypoglycemia is common in people with type 1 or type 2 diabetes and is primarily a consequence of drug therapies used to manage diabetes—particularly insulin and sulfonylureas. Hypoglycemia remains a barrier to achieving recommended levels of glycemic control and is associated with an increased risk for adverse cardiovascular outcomes (2).

Hypoglycemia is classified into three levels based on blood glucose value and/or presence of severe symptoms such as altered mental status and seizures. The American Diabetes Association (ADA) defines level 1 hypoglycemia as a blood glucose level <70 mg/dL and ≥54 mg/dL, level 2 hypoglycemia as a blood glucose <54 mg/dL, and level 3 hypoglycemia as any instance of hypoglycemia characterized by altered mental status and/or physical status requiring assistance for treatment (3).

People with diabetes are educated to manage hypoglycemia with oral glucose products or carbohydrate-containing foods (3). However, some individuals may lose the ability to have adequate oral intake during a hypoglycemic event and therefore must rely on a caregiver or family member to administer glucagon.

Recently, new glucagon formulations have become available that are easier to administer than those in traditional glucagon emergency kits. Traditional glucagon emergency kits require reconstitution prior to administration (2). This reconstitution step means that thorough education is required for caregivers and family members to carry out correct and effective administration in an emergency. In contrast, intranasal glucagon powder (Baqsimi) and liquid-stable glucagon available in a subcutaneous autoinjector (Gvoke HypoPen) and a prefilled syringe (Gvoke PFS), both approved in late 2019, are ready to administer straight from the package (2). These products have simple administration instructions and require less education to caregivers and family members than traditional glucagon kits. Dasiglucagon (Zegalogue) is a glucagon receptor agonist that was also approved in 2021 and has a different mechanism of action from that of other glucagon products. It is available in a ready-to-use aqueous solution that does not require reconstitution and is delivered via a subcutaneous autoinjector or refilled syringe (2). Table 1 offers a detailed comparison of the glucagon products now available on the market (2).

Despite the technological advancements in its delivery, glucagon remains underutilized for the management of hypoglycemia; <10% of prescriptions were found to be filled after an emergency room visit (4). Approximately

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TABLE 1 Summary of Current Glucagon Products

Product	Route	Dose, mg	Administration	Clinical Pearls
Intranasal glucagon powder (Baqsimi)	IN	3	Insert the tip into one nostril and press the device plunger all the way in until the green line is no longer showing.	• Inhalation not required for the dose • Approval for people ≥4 years of age
Liquid-stable glucagon in a subcutaneous autoinjector (Gvoke HypoPen)	SQ	1	Pull red cap off and then push yellow end down completely on skin; hold for 5 s until window turns red.	• Administration in upper arm, stomach, or thigh • Approval for people ≥2 years of age
Liquid-stable glucagon in a prefilled syringe (Gvoke PFS)	SQ	1	Remove needle cap, pinch skin around injection site, and inject at a 90° angle, pushing the plunger down completely.	• Removal from foil pouch at time of administration • Administration in upper arm, stomach, or thigh • Approval for people ≥2 years of age
Dasiglucagon (Zegalogue) autoinjector as glucagon receptor agonist in aqueous solution	SQ	0.6	Remove gray cap and push down yellow needle guard until the first click. Hold down for 10 s until the check window is red and a second click is heard.	• Storage for up to 12 months at room temperature • Administration in upper arm, stomach, or thigh • Approval for people ≥6 years of age
Dasiglucagon (Zegalogue) prefilled syringe as glucagon receptor agonist in aqueous solution	SQ	0.6	Remove gray needle cap, pinch skin around injection site, and inject at a 45° angle, pushing the plunger down completely.	• Storage for up to 12 months at room temperature • Administration in upper arm, stomach, or thigh • Approval for people ≥6 years of age
Traditional glucagon emergency kits	SQ, IM, IV	1	Reconstitute vial with prefilled sterile water for injection syringe in kit.	• Administration in upper arm, thigh, or buttocks • Approval for people of all ages

IM, intramuscular; IN, intranasal; IV, intravenous; SQ, subcutaneous.

600,000 glucagon prescriptions are filled annually among 5.6 million insulin-treated people with diabetes (5).

Current ADA guidelines recommend that glucagon should be prescribed for all individuals at increased risk of level 2 or level 3 hypoglycemia so that it is available should it be needed (3). Glucagon administration is not limited to health care professionals; caregivers and family members are able to administer these rescue products in emergency situations (3). People with diabetes who have hypoglycemia unawareness or have had a hypoglycemic event during a hospital admission and who use insulin in the outpatient setting should be evaluated for the need for a glucagon prescription at discharge.

An important consideration when choosing a glucagon product is cost, and specifically insurance coverage. With the newer products, insurance companies may provide coverage or offer a copay card. Additionally, some plans may require prior authorization. Unfortunately, all available glucagon products remain high-cost medications, which limits access.

In the case described at the beginning of this article, the woman is a candidate for glucagon therapy at discharge for multiple reasons, including her reason for admission, severe hypoglycemia upon admission, and outpatient diabetes management with insulin therapy. Her insurance coverage and preference should be determined before a specific glucagon product is prescribed, and strategies such as copay cards may be used to reduce the cost of the selected product. She should receive thorough education on the role of glucagon, indications, adverse events, storage, expiration date, and cost. In addition, a family member or caregiver should be educated about the appropriate administration technique for the prescribed product.

DUALITY OF INTEREST

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

AUTHOR CONTRIBUTIONS

K.W. wrote and J.N.C. reviewed and edited the commentary.

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