Use of Glucagon in Patients With Type 1 Diabetes

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IN BRIEF Glucagon is an invaluable tool for patients with type 1 diabetes who experience severe hypoglycemia, but little is known about the actual use of rescue glucagon in this patient population. This survey study found that patients with type 1 diabetes were not adequately prescribed glucagon or educated about the use of glucagon, and patients reported various administration issues in using it. These results strongly suggest the need for standards of practice to increase the prescribing of glucagon and the provision of initial and ongoing education about its use and administration and the development of a glucagon rescue device or a glucagon product that would eliminate the complexity of its current formulation and packaging.

Glucagon is an insulin counterregulatory hormone secreted by the α-cells of the pancreas in response to hypoglycemia in individuals without type 1 diabetes (1). In individuals with type 1 diabetes, hypoglycemia fails to elicit a normal glucagon response, increasing the risk of severe hypoglycemia (2,3).

Commercial lyophilized recombinant glucagon has been available for several decades, and animal-derived glucagon was available before that. At the time of severe hypoglycemia, subcutaneous or intramuscular injections of 1 mg for adults/older adolescents or 0.5 mg for children of reconstituted glucagon increase the blood glucose concentration (4); such use is termed "rescue glucagon." Once glucagon is injected, the blood glucose begins to rise within 10–15 minutes, peaking at 45–60 minutes with a total duration of effect of ~1–2 hours (4,5). In the lyophilized form and when stored in the refrigerator or at room temperature, glucagon is stable for up to 2 years after packaging. However, it is recommended that, once reconstituted, any remaining glucagon solution should be discarded because native glucagon will spontaneously polymerize and form amyloid-like fibrils, making it less effective or totally ineffective (4,5).

Glucagon rescue kits are now carried by many emergency medical service (EMS) providers, as well as by patients, family members, and other nonmedical personnel such as school nurses, coaches, and teachers. Two commercial products are currently available: GlucaGen HypoKit (Novo Nordisk) and Glucagon for Injection (Eli Lilly). Each kit consists of a small vial of lyophilized glucagon and a diluent, either in a vial or in an included syringe with a 23-gauge needle.

To use these products at the time of an emergency, the rescuing individual must find the kit, draw up the diluent into the syringe (if the syringe is not prefilled), inject the diluent into the vial containing the glucagon, mix to dissolve the glucagon, draw up the diluent containing the glucagon, and inject either subcutaneously or intramuscularly into the individual experiencing severe hypoglycemia.

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After glucagon administration, the vast majority of individuals experiencing severe hypoglycemia will recover within 15–20 minutes.

Although glucagon is an effective treatment, the complexity of its preparation and administration is intimidating for untrained, nonmedical providers (i.e., family, friends, coaches, or teachers). Often, those involved in rescuing patients attempt to force oral carbohydrates into semiconscious or unconscious individuals or will rely on EMS personnel to administer glucagon or transport the patient to a hospital where IV glucose can be administered. All of these methods result in significant delay of appropriate treatment for people with severe hypoglycemia, increasing the risk of neurological damage from prolonged neuroglycopenia or hypoxia (as a result of aspiration in an individual with altered consciousness).

We know little about the actual use of rescue-dose glucagon or about health care providers' habits in prescribing it or practices in providing initial and ongoing patient education regarding its use. The goals of this study were to understand patients' perceptions of and past experiences with using available glucagon rescue kits and to identify factors that might increase the utility of glucagon in the management of type 1 diabetes.

Methods

Adults registered on the myGlu.org website or in the T1D Exchange registry who opted to receive emails about research opportunities were invited to participate in an online survey. Information about the study was also posted on myGlu.org for potentially interested participants. Qualifying participants were ≥18 years of age, spoke English, and were either a person living with type 1 diabetes or a caregiver of someone with type 1 diabetes. This study was approved by the Quorum Review institutional review board, and all participants provided electronic informed consent before responding to the survey.

The survey took ~30 minutes to complete. The first 200 respondents were remunerated $20 for their time; additional participants were informed before signing the consent form that they would not be remunerated. In total, this study enrolled 366 participants, and 44 participants were excluded due to excessive missing data or to living outside of the United States. Thus, the final analysis included 322 participants.

Statistical Analysis

All statistics were performed using R software, version 3.4.1 (R Core Team, Vienna, Austria) (6). Confidence intervals were calculated using OpenEpi (Emory University, Atlanta, Ga.) (7). Open-ended survey questions were coded manually and in ATLAS.ti 7 (Scientific Software Development GmbH, Berlin, Germany) (8) to summarize common themes.

Descriptive statistical analyses were performed on demographics, including age, education level, work status, and health insurance status, as well as diabetes-specific information, including age at diagnosis, insulin pump use, and type of health care provider for diabetes management. Descriptive statistics were also calculated for questions regarding prescription, education, storage, and usage of glucagon kits.

All of the above measures were compared using t tests or χ^2 tests between participants who had had a severe hypoglycemic event in the past versus those who had not and between participants who had received a glucagon injection versus those who had not.

Results

Respondents

Adult Patients With Type 1 Diabetes

Of the participants, 264 (82%) were adults with type 1 diabetes. They were, on average, 41.2 ± 15.5 years of age (median 37 years, range 18–84 years), had been diagnosed at the age of 18.4 ± 13.4 years (median age 14, range 1–62 years), and had lived with type 1 diabetes for 22.8 ± 14.8 years (median 21 years, range 0–65).

Sixty-nine percent of these participants had completed a bachelor's degree or higher. Eighty percent had private health insurance, and the remainder received health insurance coverage from a variety of sources. Only 2% did not have insurance coverage. Seventy-six percent were on insulin pumps.

Caregivers of Individuals With Type 1 Diabetes

Of the 58 caregivers, 55 were parents or guardians, 1 was a spouse, and 2 were grandparents of individuals with type 1 diabetes. The average age of the caregivers was 45.7 ± 7.7 years (median 46 years, range 19–66). The individuals with type 1 diabetes for whom they cared were 11.8 ± 3.7 years of age (median 12 years, range 4–19), were diagnosed at an average age of 7.0 ± 3.5 years (median 7 years, range 1–13), and had an average duration of diabetes of 4.8 ± 3.6 years (median 3 years, range 0–14). Eighty-one percent of the caregivers had a bachelor's or advanced degree. Of the individuals with type 1 diabetes for whom they cared, 90% had private insurance, 14% had government insurance, and 83% were on insulin pumps.

Prescription of Glucagon

Eighty-five percent of adults with type 1 diabetes (n = 225) reported that they had been prescribed an emergency glucagon kit. Of these individuals, 91% (n = 205) obtained their prescription from their endocrinologist or certified diabetes educator (CDE); 91% picked up their glucagon kit, whereas the remainder did not fill their prescriptions because it was too expensive (5%), they forgot to (1%), or they felt that they did not need it (4%).

In contrast, 100% (n = 58) of the caregivers stated that the individual with type 1 diabetes for whom they cared received a glucagon prescription, and 97% (n = 56) of them picked up the prescription. (One did not pick up the prescription because it expired,

and one did not pick it up because it was not covered by insurance.) Virtually all of these individuals had received their prescriptions from an endocrinologist or CDE (n = 57).

Education About the Use of Rescue Glucagon

Seventy-one percent (n = 188) of the adults with type 1 diabetes reported that their health care provider had educated them about the use of emergency glucagon.

Ninety percent (n = 52) of the caregivers reported receiving education from health care providers about the use of emergency glucagon, although only 67% of the caregivers reported that the person with type 1 diabetes for whom they cared had received education on the use of rescue glucagon.

Availability of Glucagon for Patients With Type 1 Diabetes

Of the 225 adult patients with type 1 diabetes who had been prescribed glucagon, only 154 (68%) had a current prescription. Reasons for not having a current prescription included cost (17%), the doctor never discussed the importance of glucagon (17%), they never used the kit (11%), or they did not have anyone to administer it (6%). Furthermore, of the adult patients with type 1 diabetes who had current glucagon prescriptions, only 55% (n = 85) indicated that they have more than one glucagon kit.

Of the 154 adult patients with type 1 diabetes who had a glucagon kit, the majority (86%) indicated that they kept their glucagon kits at home, 41% kept the kit with them in their bag or purse, and 19% kept a glucagon kit at work. Twelve percent of these individuals also specified that they kept their glucagon kit in a refrigerator. However, when asked how often they had their glucagon kit with them, only 29% of individuals stated that they always had the kit with them. An additional 40% said they often or sometimes had the kit with them, 20% stated that they rarely had a glucagon kit with them, and 12% said they never did.

All of the caregivers reported that the person they cared for had a current glucagon prescription, and 91% stated that they had more than one kit. The majority (81%) of caregivers indicated that the individual they cared for kept glucagon at home, 72% stated that glucagon was also kept at the individual's school, and 47% said they carried it in their bag, purse, or luggage. Caregivers reported that 47% of the individuals they cared for carried their glucagon with them at all times; progressively fewer reported having it with them part of the time or never.

Use of Rescue Glucagon With Severe Hypoglycemia

Caregivers of Individuals With Type 1 Diabetes

Ninety percent of caregivers (n = 52) stated that they had never given a glucagon injection. Of the 10% (n = 6) who did, all had given the injections at home, at a grandparent's house, or while on vacation. Because of the small number of caregivers who had experience using rescue glucagon, these data remain to be explored. The results provided below are derived from the adults with type 1 diabetes who responded.

Adult Respondents With Type 1 Diabetes

Of the 264 adult participants with type 1 diabetes, 65% (n = 172) indicated that they had experienced a severe hypoglycemic event, whereas 35% (n = 92) had never experienced one (Table 1). Those who had experienced a severe hypoglycemic episode were older (44 years [95% CI 42–46] vs. 36 years [95% CI 33–39], P <0.001), had diabetes longer (27 years [95% CI 25–30] vs. 14 [95% CI 12–16], P <0.001), and were diagnosed at an earlier age (17 years [95% CI 15–19] vs. 22 years [95% CI 19–25], P = 0.003). Also, within this group, more individuals were unemployed or retired (41% [95% CI 34–48%] vs. 15% [95% CI 9–24%], P <0.001), and more individuals were on government insurance (34% [95% CI 28–42%] vs. 14% [95% CI 8–23%], P = 0.008). There were, however, no statistically significant differences in education (68% [95% CI 60–74%] vs. 73% [95% CI 63–81%] with a bachelor's degree or higher), whether they had been prescribed glucagon rescue kits (83% [95% CI 77–88%] vs. 89% [95% CI 81–94%]), whether they had picked up the prescription (91% [95% CI 85–95%] vs. 90% [95% CI 82–95%]), who wrote the prescription (92% [95% CI 87–96%] vs. 89% [95% CI 80–94%] written by endocrinologist or CDE), whether they had a current glucagon prescription (68% [95% CI 60–75%] vs. 70% [95% CI 59–78%]), whether they had the kits with them always or often (47% [95% CI 38–57%] vs. 47% [95% CI 35–60%]), the current use of an insulin pump (78% [95% CI 71–84%] vs. 73% [95% CI 63–81%]), or whether they have been educated regarding rescue glucagon (69% [95% CI 62–76%] vs. 75% [95% CI 65–83%]) for those who had and had not experienced a severe hypoglycemic event, respectively.

For those who had experienced a severe hypoglycemic event, 90 (52%) were treated with glucagon, whereas 80 (47%) were not. Those treated with glucagon and those who were not treated did not differ significantly in terms of age (44 years [95% CI 41–47] vs. 44 years [95% CI 40–47]), duration of type 1 diabetes (28 years [95% CI 25–31] vs. 26 years [95% CI 23–30]), insurance (39% [95% CI 30–49%] vs. 30% [95% CI 21–41%] having government insurance), level of education (67% [95% CI 56–76%] vs. 69% [95% CI 58–78%] with a bachelor's degree or higher), use of insulin pump (79% [95% CI 69–86%] vs. 76% [95% CI 66–84%]), prescription of glucagon (84% [95% CI 76–91%] vs. 81% [95% CI 71–88%]), or education on glucagon use (72% [95% CI 62–80%] vs. 65% [95% CI 54–75%]). However, more individuals treated with glucagon

TABLE 1. Demographic Information for Adult Participants With Type 1 Diabetes and Occurrence of Severe Hypoglycemia

	Severe Hypoglycemic Events	No Severe Hypoglycemic Events	*P*
	172 (65.2)	92 (34.8)	
Age, years			<0.001
Mean (SD)	44.0 (15.4)	36.0 (14.5)	
Median (range)	41.5 (19–84)	30.5 (18–75)	
Age at diagnosis, years			0.003
Mean (SD)	16.6 (12.4)	22.0 (14.7)	
Median (range)	12.0 (1–62)	17.5 (2–59)	
Duration of type 1 diabetes			
Mean (SD)	27.4 (14.5)	14.0 (10.8)	<0.001
Median (range)	24 (0–65)	13 (0–56)	
Insurance, %*			0.008
Private	77.3	85.9	
Government	34.3	14.1	
Other†	2.9	4.3	
Education (degree), %			0.324
<Bachelor's	32.0	26.1	
Bachelor's	35.5	44.6	
Advanced or other	32.0	28.3	

Data shown as n *(%) unless otherwise noted. *Some subjects had both private and government insurance coverage. †None/unsure/single service plan.*

had a current prescription than those not treated (74% [95% CI 63–82%] vs. 60% [95% CI 48–71%], $P = 0.08$). The two groups did not significantly differ in calls to 911 (50% [95% CI 40–60%] vs. 44% [95% CI 33–55%]) or emergency room visits.

Of the 90 adults who received glucagon, only 18% ($n = 16$) reported having no problem during the procedure; the remainder reported a problem with mixing (8%), that the procedure was too complex (8%), a problem with dose delivery (3%), broken needles (3%), and various other issues such as bad reaction, expired kit, and fear of hyperglycemia.

Additionally, those who had experienced a severe hypoglycemic event in the past were asked whether they had ever experienced a severe hypoglycemic episode without receiving a glucagon injection despite having the kit in their proximity, to which 51% reported yes. The reasons for why glucagon was not given included that oral treatment was used instead (25%) or that the rescuing individual was not trained to use it (18%), thought it was unnecessary (16%), was not aware of it (16%), was not able to use the kit correctly (8%), called EMS instead (8%), was not able to locate the kit (8%), or was too afraid to use the kit (3%).

Discussion

Although glucagon rescue kits have been available for several decades, a surprising number of diabetes experts and organizations have not established clear and evidence-based guidelines on routinely prescribing and educating patients about the administration and utility of glucagon. As a drug, rescue glucagon (1 mg for adults and older adolescents or 0.5 mg for children) has a remarkable safety profile. The primary side effects are headaches, nausea, and vomiting (4), which are attributed to the neurological or gastrointestinal motility effects of glucagon. However, these same symptoms could occur with severe hypoglycemia in the absence of glucagon administration.

As recommendations and treatment goals intensify to maintain blood glucose in the euglycemic range (70–180 mg/dL), the risk for hypoglycemia and severe hypoglycemic episodes increases in patients with type 1 or type 2 diabetes receiving insulin or sulfonylurea medications. Therefore, routine prescribing and patient education regarding the utility and administration of glucagon are increasingly important.

Our patient population is not representative of the at-large population of individuals with type 1 diabetes. Our subjects were highly affluent and well-educated. Despite these characteristics, two-thirds of these subjects had experienced at least one severe hypoglycemic episode. Interestingly, three-fourths of the adult subjects were on insulin pumps, regardless

of whether they had had an episode of severe hypoglycemia, and an even higher proportion of the children whose caregivers participated were on pumps.

We have demonstrated in this highly resourced group of adults with type 1 diabetes that nearly one-third had not received or did not remember receiving education about the use of rescue glucagon in the event of severe hypoglycemia, and only 90% received or remembered receiving a prescription for glucagon (and only 68% had a current prescription). We speculate that in a less well-resourced patient population, these statistics would be substantially lower. It does appear reassuringly that, for the pediatric patients represented by the responses of the caregivers, 100% reported receiving a prescription for rescue glucagon, and 90% recalled being educated about the use of glucagon.

Within this patient population, significant differences were observed between those who had experienced severe hypoglycemic episodes and those who had not. Those individuals who were older, had a longer duration of diabetes, and were younger at diagnosis appeared at increased risk for severe hypoglycemia. This is important to note because 84% of the population living with type 1 diabetes are now adults and, with treatment advances, their life span is significantly longer than before and often longer than clinicians realize (9,10). In addition, older individuals with type 1 diabetes may be at increased risk for severe hypoglycemia as they age (11).

These data also demonstrate the significant underuse of glucagon in adults with type 1 diabetes at the time of severe hypoglycemia. This survey confirmed the known obstacles to appropriate use of a glucagon rescue kit (i.e., lack of knowledge, complexity of preparation and administration, and so forth) and highlighted the lack of routine prescribing of glucagon among providers. Using data from Medicare part D and the National EMS Information System, significant delays were reported in the immediate treatment of severe hypoglycemia while waiting for EMS or other trained individuals, prolonging the period of severe neuroglycopenia, increasing the risk of potential neurological harm, and increasing the frequency and cost of unnecessary emergency room visits and hospital admissions (12).

Regular education efforts directed at patients with type 1 diabetes and their supporters/caregivers must be made using methods to validate that they have achieved the skills necessary to administer or teach another individual the therapy (e.g., the teach-back method). Additionally, different strategies to prevent severe hypoglycemia are needed, including mini-dose glucagon, a stable formulation of glucagon that does not require reconstitution, and an easily administered rescue dose of glucagon in a device such as an auto-injector. These advances would assist health care providers with patient education and make it easier for patients or caregivers to carry glucagon and for nonmedical caregivers to use glucagon in treating episodes of severe hypoglycemia without adding additional stress to an already stressful situation.

These data strongly suggest the need for standards of practice that would increase the prescribing of glucagon, as well as initial and ongoing education on its use and the development of rescue glucagon kits that would reduce the complexity of its current formulation and packaging.

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Duality of Interest

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

Author Contributions

M.W.H. and A.H.M.-F. researched data, contributed to discussion, wrote the manuscript, and reviewed/edited the manuscript. J.L., J.B., and A.H. researched data and reviewed/edited the manuscript. A.H.M.-F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation

An abstract on the research reported in this article was presented as a poster at the American Diabetes Association 78th Scientific Sessions in Orlando, Fla., 22–26 June 2018

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