Successful Administration of Intranasal Glucagon in the Out-of-Hospital Environment

Ted Sibley, MD, Ryan Jacobsen, MD, EMT-P, Joseph Salomone, MD

Abstract

We present a case of successful prehospital treatment of hypoglycemia with intranasal (IN) glucagon. Episodes of hypoglycemia can be of varying severity and often requires quick reversal to prevent alteration in mental status or hypoglycemic coma. Glucagon has been shown to be as effective as glucose for the treatment of hypoglycemia. The inability to obtain intravenous (IV) access often impairs delivery of this peptide and is therefore frequently given via the intramuscular (IM) route. Intranasal administration of glucagon has been shown to be as effective as the IV route and may be used for rapid correction of hypoglycemic episodes where IV access is difficult or unavailable and IM administration is undesirable. We describe the first documentation in the peer-reviewed literature of the successful treatment and reversal of an insulin-induced hypoglycemic episode with IN glucagon in the prehospital setting. We also present a review of the literature regarding this novel medication administration route. **Key words:** hypoglycemia; intranasal glucagon; emergency medical services

PREHOSPITAL EMERGENCY CARE 2013;17:98–102

Case Report

Prehospital Course

Fire department dispatchers received a 9-1-1 call about a known insulin-dependent diabetic woman who was noted by her sister to be unconscious. An advanced life support unit was dispatched and emergently responded to the scene with red lights and siren. Upon arrival, a 39-year-old woman was found supine on the bedroom floor with her sister present. The sister was only aware of diabetes with regard to the patient's medical condition, and the patient's only known medications were insulin glulisine (Apidra) and insulin glargine (Lantus). The sister stated that the patient did not eat after her lunchtime dose of glulisine, but she did not know how long the patient had been unconscious or how long she had been down. The patient was noted to be in no acute distress at the scene and was responding only to pain. Her vital signs were blood pressure (BP) 120 mmHg by palpation, heart rate (HR) 90 bpm, and respiratory rate (RR) 16 breaths/min.

The patient had a patent airway and her breathing was noted to be normal. Her capillary refill time was less than 2 seconds, but her extremities were cool and she was diaphoretic. Her pupils were equal and reactive bilaterally, and no obvious signs of trauma were noted. Her neurologic examination revealed decreased responsiveness, and she was given a Glasgow Coma Scale score (GCS) of 7 (responding only to pain). The remainder of her physical examination was essentially normal. Blood glucose was obtained and revealed a blood sugar level of 21 mg/dL. After three failed attempts at gaining peripheral intravenous (IV) access, the patient was given 1 mg of intranasal (IN) glucagon per emergency medical services (EMS) protocol. The patient was noted to be more alert and communicative shortly after being given the glucagon and was eventually able to converse with her sister without difficulty. The patient was given juice at the scene, but had one episode of emesis, and the decision was made to transport her to a nearby hospital. No other complications were noted en route to the emergency department (ED).

Emergency Department Course

The patient arrived to the ED with a repeat blood sugar level of 116 mg/dL. Her vital signs were noted to be BP 131/83 mmHg, HR 79 bpm, and RR 16 breaths/min. The results of her physical examination, including a neurologic examination, were unremarkable. The nursing staff was able to establish a 22-gauge IV line in her left wrist, a basic metabolic panel was obtained, and 8 mg of IV ondansetron was administered for nausea. Prior records were reviewed, which showed that the patient had previous episodes of hypoglycemia that required visits to the ED.

Approximately 90 minutes after arrival, the laboratory called with a glucose level of 48 mg/dL. The patient was given 25 g of IV dextrose and reported feeling much better. She was able to tolerate food and juice without any further nausea or vomiting. Repeat blood sugar levels were obtained, and the patient was observed for an additional four hours, with her blood sugar level never dropping below 118 mg/dL. She was

Received April 30, 2012, from the Department of Emergency Medicine, Truman Medical Center, Kansas City, Missouri. Revision received June 4, 2012; accepted for publication June 7, 2012.

The authors report no conflicts of interest.

Address correspondence and reprint requests to: Ted Sibley, MD, Truman Medical Center, Emergency Department, 2301 Holmes Street, Kansas City, MO 64108. e-mail: ted.sibley@tmcmed.org

doi: 10.3109/10903127.2012.717171

noted to be feeling much improved and did not have any symptoms of hypoglycemia after being given the IV dextrose. She was discharged to home in stable condition with arrangements for outpatient diabetic education, given her frequent hypoglycemic episodes. Her total ED course was six hours.

DISCUSSION

Interest in IN delivery of medications continues to grow rapidly in the medical field. The advantages of a safe, effective, and noninvasive route to administer medications are beneficial in the emergency setting where IV access may not always be rapidly achieved and the IM route may not be desirable. Patients often need quick administration of a medication for reversal of a potential life-threatening situation, and having a safe alternative method for delivery of these medications is a distinct advantage.

The nasal mucosa offers numerous benefits as a target tissue for medication delivery, such as large surface area for delivery (150 cm^2 in humans), rapid drug onset, potential for central nervous system delivery, and no first-pass metabolism.[1,2] The epithelial tissue within the nasal cavity is highly vascularized, and thus provides a potential large conduit for drug delivery.[1] All of these factors may maximize patient convenience, comfort, and compliance, along with providing an alternative method for medication delivery in the emergency setting.

The concept of IN delivery has been applied to numerous other medications and has been proven to be an effective and safe means of administration. Prominent examples of this are IN naloxone,[3] fentanyl,[4] and midazolam,[5] which are widely used in the prehospital setting and have proven very efficacious. Medical personnel are easily trained on the administration via the IN route, which may reduce potential exposure to blood-borne pathogens resulting from needlesticks. Additional beneficial characteristics of IN administration is that there is no need for sterile preparation of the administration site, IN delivery does not require the use of needles, and IN medications are easily administered in an emergency setting.[2] Because of these advantageous characteristics, IN delivery of medications has become a highly pursued modality of medical management. Based on previous studies, IN glucagon is a safe and effective means for emergency personnel to treat symptomatic hypoglycemic patients and could potentially decrease the hazards of accidental needlesticks and body-fluid exposures.[1,2]

Human glucagon is a linear polypeptide produced by the alpha cells of the pancreatic islets in the upper gastrointestinal tract.[6] The polypeptide contains 29 amino acids and undergoes a complex process to stimulate hepatic cells to breakdown glycogen and therefore increase plasma glucose concentrations. Normal human physiology will stimulate glucagon production mainly by hypoglycemia to regulate normal homeostasis, but also with stimulation of sympathetic nerves to the pancreas—especially during exercise.[6] The half-life of the polypeptide is approximately 5–10 minutes and is utilized by many tissues, but is mainly degraded by the liver itself. Glucagon is thought to be the counterregulator of insulin to achieve a balance of plasma glucose concentration. While insulin is glycogenic and antigluconeogenic, glucagon is glycogenolytic and gluconeogenic and has been termed the "hormone of energy release."[6]

Intranasal glucagon administration has been characterized and studied as early as the 1980s. Pontiroli et al. (1983) established that the administration of IN glucagon in healthy volunteers sharply raised plasma glucagon concentration along with blood glucose levels.[7] In this study, seven volunteers had 1 mg of either IN or IM glucagon administered after an overnight fast with monitoring of blood glucose, glucagon, and insulin levels. This was the first study to evaluate the efficacy of IN glucagon. However, the IN route appeared to be inferior to the IM route. The glucose-raising ability of glucagon delivered via the IM route seemed to be twice as effective as that for the IN route, but this finding raised the potential for IN glucagon to be an effective means of treatment for hypoglycemia.[7]

In 1989, Pontiroli et al. again studied the effect of IN glucagon, comparing the effects between healthy fasting subjects and insulin-dependent diabetic subjects with insulin-induced hypoglycemia. In this study, IN glucagon increased the blood glucose levels in healthy volunteers, similar to the authors' previous 1983 study, but also increased the blood glucose levels in the insulin-dependent diabetic population.[8] For the first part of this study, healthy volunteers (on random mornings) received 1 mg of IN glucagon, 1 mg of IM glucagon, or 50 g of oral (PO) glucose. It was noted that the highest glucose level for IN and IM administration was achieved at approximately 24 minutes, compared with 50 minutes for PO glucose. From this, the authors concluded that the rise of glucose level occurred earlier with IN glucagon than with PO glucose; therefore, IN glucagon could be considered more effective than PO glucose in healthy subjects.[8]

For the second part of the study, both 1- and 2-mg doses of IN glucagon were administered to insulin-dependent diabetic subjects, and the rise of glucose was compared with that after administration of 1 mg of IM glucagon. The authors found that within the first 30 minutes of onset, the 2-mg IN dose was noted to be comparable to 1 mg of IM glucagon, with slight variation at the 45-minute interval.[8] This result suggested that IN glucagon was an effective alternative to IM glucagon in insulin-dependent diabetic individuals within the first 30 minutes after administration.

Freychet and colleagues performed a similar study in 1988 and found that IN administration of glucagon in hypoglycemic patients relieved symptoms within 7 minutes, and glucose levels were increased 100% approximately 26 minutes after patients had been given IN glucagon.[9]

Another study evaluating the efficacy of IN glucagon was done by Rosenfalck et al. in 1992.[10] This study compared the effects of IN-administered glucagon in doses of 1 and 2 mg versus the effect of 1 mg of IM-administered glucagon. This dosing was based on the previous study in 1983 by Pontiroli et al., which showed that the IM route had a 2:1 efficacy over the IN route. Twelve subjects were studied, all of whom had insulin-dependent diabetes. In this study, hypoglycemia was induced via IV insulin infusion and the subjects 1) were given either 1 or 2 mg of IN glucagon, 2) were given 1 mg of IM glucagon, or 3) were allowed to recover spontaneously. In this study, there was no difference between the 2-mg IN dose and the 1-mg IM dose of glucagon in terms of the blood glucose rise in the first 15 minutes, with both being superior to the 1-mg IN dose or spontaneous recovery.[10] The only side effects that were noted from this study were those of local irritation, rhinitis, or sneezing after the administration of IN glucagon. Because of the similarity of these data to those of previous studies, the authors proposed that the efficacy of IN glucagon was similar to that of the IM route if given in 2-mg doses.

Intranasal administration of glucagon has also been used in the pediatric population. In a study done in 1993 by Stenninger and Aman, IN glucagon was used to compare the rise in blood glucose levels versus that after subcutaneous (SC) administration glucagon. The subjects were 11 children who ranged from 7 to 12 years of age and all had type 1 insulin-dependent diabetes mellitus. Hypoglycemia was induced by continuous infusions and the child was then given 1 mg of IN or 0.5 mg of SC glucagon.[11] At 15 minutes, the blood glucose levels were again measured and the rise in the subjects who received SC glucagon matched that of the subjects who received IN glucagon. The authors of this study noted that the SC injections induced higher and more sustained blood glucose levels, but the children who received glucagon SC suffered from more nausea than did those who received IN glucagon.[11] In this paper, the authors suggested that IN administration of glucagon was an efficient and safe method for rapid correction of insulin-induced hypoglycemia in type 1 diabetic children.

Despite these promising studies showing the IN route of glucagon being similar in efficacy to the IM and SC routes, a paper produced by Hvidbeg et al. in 1994 showed a marginally significant difference in initial efficacy between the modalities of administration. In this study, 12 healthy subjects were made hypoglycemic with IV insulin boluses, and then given either 1 mg of IM or 2 mg IN glucagon (based on the previous study by Rosenfalck et al.[10]).[12]

In addition, somatostatin and propranolol were also given to block any endogenous glucose counterregulation. The glucose values were again measured at 15 minutes, along with an additional measurement at 5 minutes. From this study, the glucose level was noted to be significantly higher for the IM route at 5 minutes; however, at 15 minutes, the blood glucose levels did not appear to be statistically different.[12] The authors concluded from this study that although there appeared to be an initial difference at 5 minutes between the two modalities, this did not seem to be of major clinical importance. The lag time for the IN route was hypothesized to be due to slight differences in the speed of absorption between the nasal and muscle tissue, or that the device used by these authors to deliver the IN glucagon was different from that of the previous study.[12] Hvidberg et al. did note less sneezing and nasal irritation than Rosenfalck et al. did, and concluded that although IM administration raised the blood glucose level sooner than IN glucagon, both are adequate treatments for hypoglycemic patients.

The use of IM glucagon has been studied and established as an effective means for treating hypoglycemia in the prehospital literature. In 1991, Vukmir et al. studied the efficacy of either IM or SC glucagon administration for prehospital therapy of hypoglycemia. In this study, 50 patients were treated with either 1 mg (adults) or 0.5 mg (pediatric) of IM or SC glucagon if they were found to be hypoglycemic (glucose level less than 80 mg/dL). The authors measured not only the rise of blood sugar, but also the cognition and mental status of the patient. In this study, the authors found that there was a mean increase of 100.2 mg/dL in glucose concentration after administration of glucagon, and all of the patients were noted to have a mean ($\pm$ standard deviation) increase in mental status approximately 8.85 $\pm$ 4.37 minutes after being given glucagon.[13] Also of note, the authors divided up the patients into "responders" if their hospital diagnosis was primary hypoglycemia (insulin-dependent diabetic patients) and "non responders" if their secondary diagnosis was hypoglycemia caused by sepsis, a cerebrovascular accident, or another primary diagnosis that was not insulin-induced hypoglycemia. The authors found that regardless of the cause of the hypoglycemia, 49 of the 50 patients treated had an increase in glucose levels after glucagon administration.[13] Because of these results, the authors concluded that glucagon was a safe and effective therapy in the prehospital treatment of hypoglycemia.[13]

Another prehospital study done by Howell and Guly in 1997 compared the median times to full orientation in patients with insulin-induced hypoglycemia after being given either IM glucagon or IV glucose. This study was broken up into two phases. The first

phase consisted of nine hypoglycemic subjects who were given 1 mg of IM glucagon. These subjects were then timed until they had return of full orientation, defined as a GCS of 15. This group was found to have a median time to full orientation of approximately 28 minutes after medication administration.[14] The second phase consisted of an additional 19 patients who were given 25 g of IV dextrose and were again timed until they became fully oriented. The second group was found to have a median time to full orientation of approximately 11 minutes[14]; however, five of these patients were given 1 mg of IM glucagon because of failure to secure IV access. There was no recorded measurement of serum glucose values in either group studied. Because of these results, the authors concluded that although IV glucose is the first-line therapy in prehospital hypoglycemia, IM glucagon has several advantages and should be available to treat patients in which IV access cannot be secured.[14]

An additional study was done in 1998 by Carstens and Sprehn that again compared 1 mg of IM glucagon with 25 mg of IV dextrose in the prehospital setting. The authors found that although the time for patient recovery was 10–20 times longer in the glucagon group, there appeared to be more fluctuation of the blood glucose measurement in the IV dextrose group, including some subjects who had further episodes of hypoglycemia if PO glucose was not available.[15] The subjects who were treated with IM glucagon had a steady increase in blood glucose measurements. Again, these authors concluded that IM glucagon was a safe and effective treatment for hypoglycemic patients in the prehospital setting and that IM glucagon produced a predictable rise of blood glucose measurement after administration.[15]

Since these studies in the 1990s, there has not been much research in the advancement of IN glucagon administration for acute hypoglycemia. Most of the current studies for IN glucagon administration aim for long-term homeostasis in patients who have undergone pancreatectomies and are unable to maintain adequate blood glucose levels. However, these current studies cite the papers published in the 1980s and 1990s for references on IN administration and use them to support current research and data.[16] Despite no recent study since these original papers, the ease of delivery and the apparent similarities between different routes of administration have allowed IN administration to gain in popularity among EMS providers. The idea of being able to treat patients without exposure to potential hazardous needles or bodily fluids has allowed for more widespread adoption of IN use.[17]

One component of IN glucagon administration that may be problematic for EMS systems is the cost. Glucagon hydrochloride is currently manufactured by Eli Lilly and Company (Indianapolis, IN), and the current cost of a Glucagon Emergency Kit is $153.00 USD.[18] This is far more expensive than the 25 g of IV dextrose that can be purchased for approximately $2.00–$8.00 USD on average.[19] This disparity in the two medical treatments for hypoglycemia may pose a challenge to prehospital emergency services that would like to have glucagon in the EMS protocol but cannot afford the higher cost of this medication. However, the advantage of having glucagon for basic life support (BLS) ambulance services may be enough to justify the higher cost. Most BLS ambulance services allow for basic stabilization of patients in the prehospital setting, but do not allow BLS crews to establish IV access in these patients. This can be problematic for a BLS crew who are attending to a patient suffering from hypoglycemia and who, because of their scope of practice, are unable to obtain IV access. Therefore, some in the emergency medical technician (EMT) community have started to advocate for EMT-Basics and EMT-Intermediates to be able to measure glucose via glucometry and administer IN medications as necessary.[20] This would allow for a safe, and effective, means of treating a potentially life-threatening condition without the need for advanced training. This would also allow BLS providers to be able to treat patients who may be of great need in rural areas, where access to local hospitals is restricted.[20]

Along with emergency medical personnel, patients and the general public may also be able to administer IN glucagon in the emergent setting. In a 2005 study by Yanai et al., a questionnaire was sent out to patients who had insulin-dependent diabetes mellitus and investigated coping strategies for mild and severe episodes of hypoglycemia. Along with questioning the patient's knowledge of what to do in a hypoglycemic episode, they also questioned the use and comfort level of a glucagon emergency kit. In this study, 67% of the people surveyed said they would prefer the IN route if it were available and 82% of these people felt that persons surrounding them would prefer to administer the IN spray in an emergency situation.[21] The conclusion from this study was that the IN route would increase the use of glucagon and prevent some of the insulin-dependent diabetes mellitus patients from waiting for prehospital providers to treat the hypoglycemic episode. Family members could easily administer IN glucagon from an emergency kit, and it is regarded as safer to use than glucose in the unconscious patient.

CONCLUSION

Intranasal administration of glucagon has been of increasing interest because of its potential to treat emergent hypoglycemic episodes, along with the potential to reduce exposure of EMS providers to blood-borne pathogens resulting from needlesticks. The studies on IN glucagon were performed in the

1990s without any further evidence to discredit its effectiveness. From these studies, the authors have shown that 2 mg of IN glucagon is as effective as 1 mg of IM glucagon and has fewer side effects than SC administration. The idea of an IN administration has also been shown to be a more acceptable method of administration by the general populace and may decrease the potential hazards that come with IV, IM, or SC administration. We present a case of a symptomatic diabetic hypoglycemic patient who was successfully treated with IN glucagon in the prehospital setting without further side effects or complications. From our knowledge, this is the first reported successful prehospital treatment of hypoglycemia with IN glucagon, and this method of administration should be considered in any emergent hypoglycemic episode where IV access is unable to be obtained in a timely fashion.

References

1. Wolfe T, Barton E. Nasal drug delivery in EMS: reducing needle stick risk. JEMS. 2003;28(12):52–63.
2. Costantino HR, Ilum L, Brandt G, Johnson P, Quay S. Intranasal delivery: physiochemical and therapeutic aspects. Int J Pharm. 2007;337:1–24.
3. Barrett KE, Barman SM, Boitano S, Brooks H (eds). Endocrine functions of the pancreas & regulation of carbohydrate metabolism. In: Ganong's Review of Medical Physiology. 23rd edition. New York: McGraw-Hill, 2010, pp. 315–36.
4. Rickard C, O'Meara P, McGrail M, Garner D, McLean A, Le Lievre P. A randomized control trial of intranasal fentanyl versus intravenous morphine for analgesia in the prehospital setting. Am J Emerg Med. 2007;25:911–7.
5. Lahat E, Goldham M, Barr J, Bistritzer T, Berkovitch M. Intranasal midazolam for childhood seizures. Lancet. 1998;52:620.
6. Barton E, Colwell C, Wolfe T, et al. Efficacy of intransal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. J Emerg Med. 2005;29: 265–71.
7. Pontiroli AE, Alberetto M, Pozza G. Intranasal glucagon raises blood glucose in healthy volunteers. BMJ. 1983;287:462–3.
8. Pontiroli A, Calerara A, Pajetta E, Albertetto M, Pozza G. Intranasal glucagon as a remedy for hypoglycemia. Studies in healthy subjects and type 1 diabetic patients. Diabetes Care. 1989;12:604–8.
9. Freychet L, Rizkalla, Desplanque N, et al. Effect of intranasal glucagon on blood glucose in healthy subjects and hypoglycemic patients with insulin-dependent diabetes. Lancet. 1988;1:1364–6.
10. Rosenfalck AM, Bendtson I, Jørgensen S, Binder C. Nasal glucagon in the treatment of hypoglycemia in type 1 (insulin dependent) diabetic patients. Diabetes Res Clin Pract. 1992;17:43–50.
11. Stenninger E, Aman J. Intranasal glucagon treatment relieves hypoglycemia in children with type 1 (insulin dependent) diabetes mellitus. Diabetologia. 1993;36:931–5.
12. Hvidberg A, Djurup R, Hilsted J. Glucose recovery after intranasal glucagon during hypoglycemia in man. Clin Pharmacol. 1994;46:15–7.
13. Vukmir RB, Paris PM, Yealy DM. Glucagon: prehospital therapy for hypoglycemia. Ann Emerg Med. 1991;20:375–9.
14. Howell MA, Guly HR. A comparison of glucagon and glucose in prehospital hypoglycaemia. J Accid Emerg Med. 1997;14:30–2.
15. Carstens S, Sprehn M. Prehospital treatment of severe hypoglycemia: a comparison of intramuscular glucagon and intravenous glucose. Prehosp Disaster Med. 1998;13(2-4):44–50.
16. Teshima D, Yamauchi A, Makino K, et al. Nasal glucagon delivery using microcrystalline cellulose in healthy volunteers. Int J Pharm. 2002;233:61–6.
17. Collopy K, Snyder S. Intranasal drug administration: an innovative approach to traditional care. EMS World. 2011;40(5):45–50.
18. Glucagon Emergency Kit. In Micromedex (Healthcare Series) [Internet database]. Greenwood Village, CO: Thompson Reuters (Healthcare) Inc. Available at: http://thomsonhc.com. Accessed May 16, 2012.
19. Dextrose. In Micromedex (Healthcare Series) [Internet database]. Greenwood Village, CO: Thompson Reuters (Healthcare) Inc. Available at: http://www.thomsonhc.com. Accessed May 16, 2012.
20. Curran R. A milestone change in practice: a call for widespread application of intranasal delivery in the prehospital environment. Emerg Med Serv. 2007;36(4):40–1,43–6,48–9.
21. Yani O, Philip M, Eliztur-Lieberman E, Pilpel D. IDDM patients' opinions on the use of glucagon emergency kit in severe episodes of hypoglycemia. Pract Diabetes. 2005;14(2):40–2.