


Evaluating Ease of Use and Patient Safety of Dasiglucagon Hypo Pal Autoinjector for the Management of Hypoglycemia

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Introduction: Severe hypoglycemia is a medical emergency that must be treated promptly in order to prevent complications or death in a patient. Patients who have been diagnosed with Type 1 diabetes and treated with insulin have the potential to experience a severe hypoglycemia episode, or low blood sugar. When a patient is experiencing severe hypoglycemia, it is imperative for this patient to receive glucose quickly. However, patients who are experiencing low blood sugar may not be able to manage for themselves, take food or liquid orally or may be unconscious. Glucagon is a medication that reverses low blood sugar. Up until 2018, glucagon had to be reconstituted immediately before injection because of the medication's lack of stability after reconstitution. A medication recently approved for patients 6 years through adult is Dasiglucagon. This form of glucagon comes in a ready-to-administer, pre-filled syringe, making it easier for caretakers and bystanders to administer in an emergency situation due to the readiness of the medication.

Purpose: The purpose of the paper is to evaluate literature that pertains to the ease of use and patient safety of dasiglucagon HypoPal autoinjector for the management of severe hypoglycemia.

Keywords: glucagon, caregiver, bystander, emergency, safety, type 1 diabetes

Background

Patients with a diagnosis of Type 1 diabetes are at risk for severe hypoglycemia episodes due to insulin-induced hypoglycemia. Despite advances in diabetes treatments, severe hypoglycemia continues to be a frequent complication of insulin treatment for someone with the diagnosis of diabetes. These hypoglycemia episodes are considered an emergency and require immediate attention and treatment to prevent further loss of consciousness, seizures, and death.

A patient experiencing severe hypoglycemia presents with symptoms of confusion, decreased state of consciousness or unconsciousness. These patients are not able to manage hypoglycemia themselves and are not able to safely intake food or drink orally to increase blood sugar levels. As a result, a patient in this state will need assistance and administration of glucagon by a caregiver or a bystander to increase blood sugar levels to a safe level. The American Diabetes Association recommends prescribing glucagon for all individuals at an increased risk of severe hypoglycemia which is considered as a blood glucose $<54\text{mg/dL}$.¹

Glucagon was first prescribed in the 1960's as an emergency drug to treat severe hypoglycemia and intended to be administered intramuscular. This can be challenging for caregivers or bystanders that are not healthcare providers. Before 2018, due to the lack of drug stability once reconstituted, all glucagon rescue treatments required reconstitution at the time of administration. Therefore, the complexity of the reconstitution process often becomes a barrier to successful administration, increasing errors when performed in a stressful environment by non-healthcare providers.²

Recently, pharmaceutical companies have started to develop alternative, more stable forms of glucagon that do not require re-constitution. The purpose of this review is to discuss Dasiglucagon Hypo Pal, a newly approved ready to use glucagon, in its ease of use and patient safety.

Dasiglucagon

Dasiglucagon (Zegalogue) is a human glucagon analog that consists of twenty-nine amino acids with seven of these amino acids substituted to improve stability and reduce the formation of fibrils when dissolved in aqueous solution, thus providing physical and chemical stability. This next-generation glucagon analogue is the first-ready-to-use glucagon product that is provided in an aqueous formula.³

Like other forms of glucagon, dasiglucagon is a glucagon receptor agonist; therefore, it activates glucagon receptors in the liver, increasing blood glucose concentrations, and in turn, stimulates glycogen breakdown and the subsequent release of glucose.³ If the patient has sufficient hepatic glycogen stores the blood sugar will rise, implementing the anti-hypoglycemic activity of dasiglucagon. Dasiglucagon resembles endogenous glucagon, holding similar potency of native glucagon.⁴

The Food and Drug Administration (FDA) approved dasiglucagon for treatment of severe hypoglycemia in pediatric patients aged 6 years through adults in March 2021. Dasiglucagon is supplied in a single dose, ready-to-use pre-filled autoinjector and developed by Zealand Pharma A/S, Copenhagen, Denmark. The dosing for Dasiglucagon is 0.6mg for 6 years and older. The injection is subcutaneous and can be administered in the buttocks, lower abdomen, upper arms, or outer thighs. If the blood glucose level is not acceptable or at a safe level, after 15 minutes, another dose may be administered.⁵

Methods of Review

A library search was conducted using the search terms of ((inject*) AND (hypoglycemia OR low blood sugar OR blood glucose)) AND (dasiglucagon OR glucagon). This search strategy resulted in 3027 articles from the PubMed database. Further limitations were placed on the search to the years of 2018–2023, in print or online, equaling 986 articles. Lastly, a limiter of glucagon, insulin, and English language yielded twenty-three results. The twenty-three articles were critically appraised for relevance to this topic and for quality. For this review, eleven of the twenty-three articles/references were utilized.

Dasiglucagon Effectiveness for Hypoglycemia

Results from a randomized, double-blind study published in 2018 with fifty-eight patients with type 1 diabetes compared Dasiglucagon and GlucaGen response. (GlucaGen is a type of glucagon that requires reconstitution prior to use). The patients were in an induced hypoglycemic state. The hypoglycemic target for these patients was 55 mg/dL, achieved by IV insulin administration. Results showed that dasiglucagon provided a rapid increase in plasma blood glucose levels, reaching the maximum at around 35 minutes. The increase in blood glucose plasma increased greater than or equal to 20mg/dL to greater than or equal to 70 mg/dL within 6–10 minutes. This was a similar reaction time to GlucaGen, indicating that both preparations have similar plasma glucose response times. However, for this study, dasiglucagon was found to have a longer lasting effect on plasma blood glucose levels, indicating the longer lasting effect of dasiglucagon may reduce the risk of recurrent hypoglycemia after administration.⁶ One dose of 0.6mg of dasiglucagon provided rapid and sustained reversal of hypoglycemia with a half-life of 30 minutes. Peak glucose concentration is seen 35 minutes after administration, later than the peak of GlucaGen which occurs at 20 min².

An integrated analysis of safety and efficacy published in 2023 aimed to assess current available data from clinical trials on the safety and efficacy of dasiglucagon in adults with type 1 diabetes. The analysis included data from participants in two placebo-controlled and four non-placebo-controlled trials. Results from this analysis showed that dasiglucagon has a safety and tolerability like GlucaGen and a comparable plasma glucose recovery time, indicating its efficacy. These results indicate that dasiglucagon has the potential to become effective and reliable rescue treatment for severe hypoglycemia.⁵

Few treatment options have been successful in mitigating post bariatric hypoglycemia (PBH) in patients with Roux-en-Y gastric bypass surgery, a common complication. A conclusion from a study published in 2022 concludes that dasiglucagon can mitigate the PBH in this population of patients and may be a potential new therapy.⁷

Dasiglucagon's Ease of Use

Patient and caregiver preferences have not been studied to assess the preferences between the auto-injector glucagon (ready to inject) and the glucagon kit (requiring reconstitution before injection). However, some studies do suggest that patients and caregivers prefer the pre-filled autoinjector over the glucagon kit. A recent study showed that dasiglucagon had a higher rate of correct delivery than the emergency kit in 94% of participants. All participants of the study reported it was easier and less stressful than the emergency kit glucagon.⁸ The pre-filled auto-injector is the newest developed method of administering glucagon and is supplied in a ready to use, room temperature stable, liquid form of glucagon. Simulation studies have shown that the auto-injector is perceived by caregivers and people with T1 Diabetes as easier to use, safer, and faster, due to less preparation, than the standard glucagon kit that requires re-constitution.⁸

An open label, randomized, crossover, comparative device handling study compared the standard glucagon kit versus a dasiglucagon autoinjector kit and their ease of use. This was a simulated emergency hypoglycemia situation, and the purpose of the study was to compare, in a simulated scenario, the difference in device handling of dasiglucagon and a traditional glucagon emergency kit. The study was comprised of fifty-four participants with a mix of participants including people with diabetes, caregivers, and general bystanders. Findings from the study indicated that the dasiglucagon can be easier, administered more rapidly and reliable than a traditional glucagon kit that requires reconstitution.¹ An individual device questionnaire was implemented with a total of 35 participants completing the questionnaire. The thirty-five participants included seventeen caregivers and eighteen bystanders. Participants of the survey rated the dasiglucagon autoinjector easier than the glucagon emergency kit, receiving a score of greater than or equal to 4.5 out of five on a Likert scale for the tasks of preparation of the device, holding the device stable while injecting, administering the injection, recalling the steps, and following instructions.¹

The advantages of the dasiglucagon autoinjector will likely have clinical implications on quickness of administration, caregiver confidence and reduction of anxiety. The use of ready-to-use devices shows promise and have the ability of rescuing individuals quickly and efficiently to improve the patient's time to recovery from a hypoglycemic event.

Patient Safety

Dasiglucagon was shown to have a similar safety and tolerability as reconstituted glucagon. An analysis of placebo and non-placebo-controlled trials comparing dasiglucagon and glucagon revealed no serious adverse events occurred in the trials. The most common adverse effects were nausea and vomiting, and headache which are consistent side effects of novel glucagon, concluding that dasiglucagon was well tolerated in the studies.⁹ Any injection site reactions were mild, identified as redness, edema and pain on palpation of the site. Common adverse reactions of dasiglucagon are nausea, vomiting, headache, injection site pain, and diarrhea, again, the same as side effects of other forms of glucagon treatments.¹⁰

A double-blind parallel-group trial design was conducted in 2021 to evaluate immunogenicity in the use of dasiglucagon for severe hypoglycemia. A total of 112 participants were randomized 1:1 to receive three subcutaneous weekly doses of either 0.6 dasiglucagon or 1.0 mg recombinant glucagon (GlucaGen). Participants were followed for 15 weeks with testing for anti-drug antibodies to dasiglucagon. The findings were that no participants developed any treatment induced anti-drug antibodies, concluding data supports a low immunogenicity risk for dasiglucagon treatment of severe hypoglycemia.⁹

A few other items to note about dasiglucagon: administration with beta blockers may increase a patient's heart rate and blood pressure. If a patient is taking indomethacin, this can reduce dasiglucagon's ability to reverse hypoglycemia. If a patient is taking warfarin, the anticoagulant effect may be increased with the administration of dasiglucagon. However, these side effects are the same with other forms of glucagon.³ There are some contraindications to dasiglucagon. If a patient has pheochromocytoma or insulinoma, patients should not take this drug. The interaction with pheochromocytoma and dasiglucagon will cause substantial increase in blood pressure. If a patient has insulinoma, administration may cause hypoglycemia. These patients should receive oral glucose, if safe, or intravenous glucose.¹¹

Conclusion

Dasiglucagon provided rapid and effective reversal of hypoglycemia. The ready-to-use, aqueous formulation of dasiglucagon offers the potential to provide rapid and reliable treatment of severe hypoglycemia. This form of glucagon is safe and has potential to provide patients and caregivers with peace of mind and less anxiety with administration.

Disclosure

The author reports no conflicts of interest in this work.

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