

Intranasal Glucagon

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Abstract

Glucagon is an essential drug, used for the management of hypoglycaemia. Currently available injectable preparations are cumbersome, difficult to use and not easily acceptable by many patients. Injection glucagon is also not available in all parts of the world. Intranasal glucagon offers a novel, effective and convenient mode of delivery of this emergency drug. This review covers the basic and clinical pharmacology of nasal glucagon, and describes its potential use in practice.

Keywords: Hypoglycaemia, Insulin, Paediatric diabetes, Type 1 diabetes, Type 2 diabetes.

Introduction

Hormone replacement and supplementation is the essence of endocrine therapeutics. Various challenges and obstacles, however, make it difficult to mimic physiologic actions of endogenously secreted hormones with exogenous preparations. This is especially true in the case of peptide hormones, which are difficult to administer orally. Though the injectable method of delivery is available for most peptides, this is cumbersome and unappealing for the vast majority of patients. These limitations have led to a search for alternative routes of drug delivery.

The Nasal Route

One such method of administering drugs is the nasal route. Due to its anatomic and physiologic structure, the nasal route offers the advantages of easy absorption and efficacy, as well as convenience and acceptance.¹ Having been used since antiquity for drug delivery (tobacco in the form of "snuff"), this method is acceptable to the general public. Good blood supply, created by a dense capillary network, and a thin mucosal membrane, allows fast absorption of drugs, and results in rapid onset of action. This characteristic encourages the use of this route in emergency clinical situations, especially where injection therapy may be impractical or not feasible. The anatomic location is such that the intranasal route can be

used for self-administration, as well as drug delivery by a care giver.

Nasal powders are known to assist formulation of poorly water soluble active moieties. The intra nasal route allows delivery of larger drug doses, especially when powders are compared against intranasal liquids. Sumatriptan (for migraine), budesonide, beclomethasone and dexamethasone (corticosteroids) are the few nasal powders that are currently approved.

Nasal Hormone Delivery

Researchers have attempted to use this physiological means to deliver hormones such as insulin, glucagon, oxytocin, desmopressin, testosterone, and insulin-like growth factor 1 (IGF-1) as well.²⁻⁶

However, till recently, no sustained efforts have been made to develop a nasally administered pharmaceutical preparation of glucagon. The first application for intranasal glucagon has been received by the United States Food and Drug Administration in 2018. In this review, we discuss the physiology of glucagon, and the pharmacology of intranasal glucagon, focusing on its use in the management of hyperglycaemia. We also suggest other indications where intranasal glucagon may be used for diagnostic or therapeutic purposes.

Pharmacokinetics and Dynamics

Glucagon is well absorbed through the nasal membranes. In a single centre, open label study, intranasal glucagon was administered to participants during, and after recovery from, an episode of nasal congestion of the 56 participants, half received, and half did not get, a dose of the decongestant oxymetazoline. The pharmacokinetic properties of glucagon were similar in both groups. Glucagon levels touched their peak at 18 minutes, with glucose levels being highest at 30-42 minutes, post dose.⁷

In a clamp study conducted on 18 healthy men, using a single blind, randomized, cross over study design, the pharmacodynamics effects of a 1 mg dose of nasal glucagon were explored as compared to intravenous glucagon, infused over 30 minutes. Both routes of

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administration of glucagon were found to raise plasma glucose, but nasal glucagon reduced endogenous glucose output.⁸ This limited the rise in plasma glucose. Intra nasal glucagon is speculated to have a potential effect on the central nervous system, which may limit its ability to regulate glycaemic levels.

Clinical Trials

A phase 3 multicentre open label study evaluated effectiveness and ease of use of nasal glucagon in managing moderate/severe hypoglycaemic events in children/adolescents with type 1 diabetes, in the real world setting. Caregivers were trained in the use of 3 mg nasal glucagon in the event of moderate/severe hypoglycaemia, in the home or school setting. Treatment response was defined as awakening or returning to normal status within 30 minutes, and was backed by blood glucose levels checked at 15 minute intervals. Thirty three moderate/severe hypoglycaemic events occurred in 14 participants, and all responded to nasal glucagon within 30 minutes. Administration was reported to be easy or very easy by 93.9% caregivers. The majority (60.6%) of events were managed by nasal glucagon administration within 30 seconds. No serious adverse events were reported.⁹

A similar real world study was conducted in adults with type 1 diabetes. In total, 145 moderate and 12 severe hypoglycaemic episodes were reported by 69 participants. Hypoglycaemia resolved within 30 minutes in 95.7% of all cases, and treatment response was noted within 15 minutes in all the severe cases. Nasal glucagon, in a 3 mg dose, was found to be well tolerated and effective in increasing blood glucose levels and countering the hypoglycaemic effects of insulin.¹⁰

In an interventional study conducted on 77 adult participants, an open label randomized crossover design was used to assess the efficacy and safety of nasal glucagon in the treatment of insulin induced hyperglycaemia. After an overnight fast, hypoglycaemia was induced by an intravenous infusion of insulin, and then treated with either 3 mg nasal glucagon or 1 mg intramuscular glucagon in a crossover method,¹¹ success criteria (an increase in plasma glucose to ≥ 70 mg%, within 30 minutes of glucagon administration) was achieved in all but one intranasally treated participant. Mean time to success was 16 minutes for intranasal and 13 minutes for intramuscular glucagon. The common side effects were nausea in 35% and 38% and head/ facial discomfort in 25% and 9% of intranasal and intramuscular treated episodes respectively.

Patient Centricity and Health Economics

Health economic models suggest that nasal glucagon use can reduce health care costs for severe hyperglycaemia. This is achieved by reducing the use of emergency services, limiting the need for ambulance services, and increasing the proportion of patients discharged from emergency rooms without needing indoor admission.¹²

Scope For Use

Nasal glucagon, in a dose of 3 mg, is currently under American and European regulatory review. The advantage of ease of administration helps its score over injectable glucagon preparations currently in the market.

Intranasal glucagon, once approved, should find extensive scope for use in diabetes care. With minimal training, it can be used by children, adolescents and adults with diabetes who are prone to hypoglycaemia, and their care givers. The nasal preparation is a potential alternative method of delivery which should soon replace the current injectable preparation, which is difficult to use. In a situation of severe hypoglycaemia, where time is of essence, the few minutes that are saved by prompt administration of glucagon may make the difference between life and death. Intranasal glucagon should ideally be part of all hypoglycaemia, emergency room and disaster kits. It should also be available in schools and public places that are frequented by persons with diabetes.

With appropriate research, nasal glucagon may also find a place in dynamic endocrine testing.

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