INTRODUCTION

The traditional role of glucagon was to reverse life-threatening hypoglycemia in patients with diabetes unable to receive dextrose in the outpatient setting. However, in medical toxicology, glucagon is used “off label” early in the management of β-adrenergic antagonist and calcium channel blocker toxicity to increase heart rate, contractility, and blood pressure by increasing myocardial cyclic adenosine monophosphate (cAMP) via a non–β-adrenergic receptor mechanism of action. The use of glucagon is based primarily on animal studies and as well as human case series and case reports. The effects of glucagon are often transient.

HISTORY

Glucagon was discovered in 1923, just 2 years after the discovery of insulin.10 The positive inotropic and chronotropic effects have been known since the 1960s.12,15

PHARMACOLOGY

Chemistry/Preparation
Glucagon is a polypeptide counterregulatory hormone with a molecular weight of 3500 Da, secreted by the α cells of the pancreas. Previously animal derived, and possibly contaminated with insulin, the form approved by the US Food and Drug Administration (FDA) has been synthesized by recombinant DNA technology since 1998; therefore, it no longer contains any insulin.25

Mechanism of Action
In both animals and humans, glucagon receptors can be found in the heart, brain, and pancreas.22,33,64 Binding of glucagon to cardiac receptors is closely correlated with activation of cardiac adenylate cyclase (AC).52 A large number of glucagon binding sites are demonstrated, and as little as 10% occupancy produces near maximal stimulation of adenylate cyclase. Binding of glucagon to its receptor results in coupling with two isoforms of the G protein and catalyzes the exchange of guanosine triphosphate (GTP) for guanosine diphosphate on the α subunit of the G protein.21,51,69 One isoform is coupled to β agonists, while both isoforms are coupled to glucagon.69 The GTP-G,units stimulate adenylate cyclase to convert adenosine triphosphate (ATP) to cAMP.32,42 In animal hearts, glucagon inhibits the phosphodiesterase PDE-3.141 Selective inhibition of PDE-4 potentiated the cAMP response to glucagon in adult rat ventricular myocytes.64 Glucagon, along with β, agonists, histamine, and serotonin (but not β,agonists), also activates G, which inhibits cAMP formation in human atrial heart tissue.27
Evidence now suggests an additional mechanism of action for glucagon, independent of cAMP, and dependent on arachidonic acid. Cardiac tissue metabolizes glucagon, liberating mini-glucagon, an apparently active smaller terminal fragment. Mini-glucagon stimulates phospholipase A<sub>2</sub>, releasing arachidonic acid. Arachidonic acid acts to increase cardiac contractility through an effect on calcium. The effect of arachidonic acid—and therefore of mini-glucagon—is synergistic with the effect of glucagon and cAMP.

Stimulation of glucagon receptors in the liver and adipose tissue increases cAMP synthesis, resulting in glycogenolysis, gluconeogenesis, and ketogenesis. Other properties of glucagon include relaxation of smooth muscle in the lower esophageal sphincter, stomach, small and large intestines, common bile duct, and ureters.

Cardiovascular Effects
Investigations of the mechanism of action of glucagon on the heart have been performed on cardiac tissue obtained from patients during surgical procedures and in a variety of in vivo and ex vivo animal studies. The results are often species specific and are affected by the presence or absence of congestive heart failure. The inotropic action of glucagon is likely related to an increase in cardiac cAMP concentrations. Both the positive inotropic and chronotropic actions of glucagon are very similar to those of the β-adrenergic agonists, except that they are not blocked by β-adrenergic antagonists. Although in some canine experiments glucagon caused ventricular tachycardia, glucagon is not dysrhythmogenic in patients with severe chronic congestive heart failure, myocardial infarction–related acute congestive heart failure, or in postoperative patients with myocardial depression. The effects of glucagon diminish markedly as the severity and chronicity of congestive heart failure increases.

Volunteer Studies
Cardiovascular effects were extensively studied in 21 patients with heart failure who were given varied doses and durations of glucagon therapy. Eleven patients who received 3 to 5 mg via intravenous (IV) bolus had increases in the force of contraction, as measured by maximum dP/dT (upstroke pattern on apex cardiogram), heart rate, cardiac index, blood pressure, and stroke work. There was no change in systemic vascular resistance, left ventricular end-diastolic pressure, or stroke index. Additionally, glucose concentrations increased by 50% and the potassium concentrations fell. A study of nine patients demonstrated a 30% increase in coronary blood flow following a 50 µg/kg IV dose. Patients who received 1 mg via IV bolus also had an increase in cardiac index, but systemic vascular resistance fell, probably secondary to splanchnic and hepatic vascular smooth muscle relaxation. Patients who received an infusion of 2 to 3 mg/min for 10 to 15 minutes responded similarly to those who received the 3 to 5 mg IV boluses, but patients receiving boluses experienced significant dose limiting nausea and vomiting.

Pharmacokinetics and Pharmacodynamics
The volume of distribution of glucagon is 0.25 L/kg. The plasma, liver, and kidney extensively metabolize glucagon with an elimination half-life of 8 to 18 minutes. In human volunteers following a single IV bolus, the cardiac effects of glucagon begin within 1 to 3 minutes are maximal within 5 to 7
minutes, and persist for 10 to 15 minutes.\textsuperscript{45} The time to maximal glucose concentration is 5 to 20 minutes, with a duration of action of 60 to 90 minutes.\textsuperscript{14} Smooth muscle relaxation begins within 1 minute and lasts 10 to 20 minutes.\textsuperscript{14} The onset of action following intramuscular and subcutaneous administration occurs in about 10 minutes, with a peak at about 30 minutes.\textsuperscript{13}

Activation of AC in adipose, myocardial, and hepatic tissue and myocardial contractility requires pharmacologic levels of glucagon, exceeding 0.1 nM.\textsuperscript{52} At physiologic concentrations of glucagon below 0.1 nM, it appears to duplicate the cardiac metabolic effects of insulin by activating a phosphatidylinositol-3 kinase (PI3K)-dependent signal without stimulating AC.\textsuperscript{52} Tachyphylaxis or desensitization of receptors may occur with repetitive dosing. Experimental heart preparations exposed to glucagon for varying lengths of time demonstrated a decrease in the amount of generated cAMP.\textsuperscript{24,25} Possible explanations for tachyphylaxis include uncoupling from the glucagon receptor, increased PDE hydrolysis of cAMP, or both.\textsuperscript{24,26,27} Other experiments demonstrated a transient effect of glucagon on contractility and hyperglycemia, also suggesting tachyphylaxis.\textsuperscript{20,26}

**ROLE IN THE MANAGEMENT OF OVERDOSES WITH β-ADRENERGIC ANTAGONISTS**

Overdoses with β-adrenergic antagonists are particularly dangerous and are manifested by hypotension, bradycardia, prolonged atrioventricular conduction times, depressed cardiac output, and cardiac failure. Other noncardiovascular effects include alterations in consciousness, seizures, and, rarely, hypoglycemia.\textsuperscript{1,14,65} Management is often complicated, and many therapies, including atropine, isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, and various combinations, are used with variable success.\textsuperscript{13,14} Recently high dose insulin with dextrose (Antidotes in Depth: A17), and in the event of a cardiac arrest, IV fat emulsion (Antidotes in Depth: A20), have been added to the armamentarium. Animal studies document the ability of glucagon to increase contractility, restore the sinus node function after sinus node arrest, increase atrioventricular conduction, and rarely improve survival.\textsuperscript{24,45,46} In canine studies, high-dose insulin euglycemia (HIE) therapy has a more sustained effect on hemodynamic parameters and an improved survival rate compared with glucagon.\textsuperscript{24} Glucagon has successfully reversed bradydysrhythmias and hypotension in patients unresponsive to the aforementioned traditional xenobiotics, and should be administered early in the management of patients with severe overdoses.\textsuperscript{14,64} By increasing myocardial cAMP concentrations independent of the β receptor,\textsuperscript{26,44} glucagon is able to increase inotropy,\textsuperscript{15,26,45} and chronotropy.\textsuperscript{15,48,49,67}

Glucagon successfully reversed the bradycardia, low-output heart failure, and hypotension that developed in a premature newborn, presumably as a result of an inappropriately large prenatal dose of labetalol given to the mother. This neonate, delivered at 32 weeks’ gestation and weighing 1.8 kg, received 0.3 mg/kg glucagon IV initially and five additional doses of 0.3 to 0.6 mg/kg over the next 5 hours, with improvement in heart rate, blood pressure, and perfusion. Epinephrine and diuretics were also used.\textsuperscript{59}
Combined Effects with Phosphodiesterase Inhibitors and Calcium

Strategies for enhancing the effects of glucagon have involved combining it with the PDE-3 inhibitor amrinone (inamrinone), its derivative milrinone, and most recently rolipram, a selective PDE-4 inhibitor. In a canine model of propranolol toxicity, both amrinone (inamrinone) and milrinone, alone were comparable with glucagon, but the combination of amrinone and glucagon resulted in a decrease in mean arterial pressure. Tachycardia occurred when milrinone was used with glucagon. In an ex vivo model using strips of rat ventricular heart, rolipram enhanced the inotropic effect of glucagon and limited glucagon tachyphylaxis. However, because the evidence for the effectiveness of HIE was demonstrated in animal models and human case reports, combining glucagon with a phosphodiesterase inhibitor is no longer recommended.

The relationship between calcium and the chronotropic effects of glucagon was demonstrated in rats. Maximal chronotropic effects of glucagon are dependent on a normal circulating ionized calcium. Both hypocalcemia and hypercalcemia blunt the maximal chronotropic response.

ROLE IN CALCIUM CHANNEL BLOCKER OVERDOSE

Calcium channel blocker overdoses produce a constellation of clinical findings similar to those recognized with β-adrenergic antagonist overdoses, including hypotension, bradycardia, conduction block, and myocardial depression. Animal studies demonstrate the ability of glucagon to improve heart rate, atrioventricular conduction, and reverse the myocardial depression produced by nifedipine, diltiazem, and verapamil. However, there was no survival benefit attributed to glucagon in these studies, while a canine model of verapamil overdose comparing glucagon to HIE only revealed a survival benefit for HIE. Human case reports demonstrate improved hemodynamics.

ROLE IN REVERSAL OF HYPOGLYCEMIA

Glucagon was once proposed as part of the initial treatment for all comatose patients because it stimulates glycogenolysis in the liver. The theoretical rationale for this approach is only partially sound in that glucagon requires time to act and may be ineffective in a patient with already depleted glycogen stores. Patients with type 2 diabetes are more likely to respond than are patients with type 1 diabetes. The IV administration of 0.5 to 1.0 g/kg of 50% dextrose in adults rapidly reverses hypoglycemia and does not rely on glycogen stores for its effect. Therefore, IV dextrose is preferred over glucagon as the initial substrate to be given to all patients with an altered mental status presumed to be related to hypoglycemia (Antidotes in Depth: A12). Glucagon may retain some role as a temporizing measure, until medical help can be obtained, in settings such as in the home where IV access is not rapidly available.

In patients with insulinoma, after an initial hyperglycemic response glucagon may actually worsen hypoglycemia, as the result of a feedback increase in insulin.
ADVERSE EFFECTS AND SAFETY ISSUES

Side effects associated with glucagon include dose-dependent nausea, vomiting, hyperglycemia, hypoglycemia, and hypokalemia; relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon; and, rarely, urticaria, respiratory distress, and hypotension. Hypotension is reported up to 2 hours after administration in patients receiving glucagon as premedication for upper gastrointestinal endoscopy procedures. The hyperglycemia is followed by an immediate rise in insulin, which causes an intracellular shift in potassium, resulting in hypokalemia. It is unclear whether stimulation of the Na⁺-K⁺-ATPase in skeletal muscle also contributes to the hypokalemia as occurs with β-adrenergic agonists. Glucagon may increase the anticoagulant effect of warfarin.

Glucagon can also increase the release of catecholamines in a patient with a pheochromocytoma, resulting in a hypertensive crisis, which can be treated with phentolamine. Continuous prolonged treatment with glucagon might lead to a dilated cardiomyopathy, as was reported in a patient with a glucagonoma.

PREGNANCY AND LACTATION

Glucagon is FDA pregnancy category B. It is presumed that benefit exceeds risk. There are no reports of glucagon use during lactation. However, the size and peptide nature of glucagon suggest that the exposure to a lactating infant would be limited.

DOSAGE AND ADMINISTRATION

An initial IV bolus of 50 µg/kg, infused over 1 to 2 minutes, is recommended (3–5 mg in a 70-kg person). If clinically acceptable, then a longer duration of infusion may be used to minimize vomiting. Higher doses may be necessary if the initial bolus is ineffective, and up to 10 mg can be used in an adult. Using too small a dose can potentially decrease systemic vascular resistance. In some cases, the bolus dose should be followed by a continuous infusion of 2 to 5 mg/h (≤ 10 mg/h) in 5% dextrose in water, which can be tapered as the patient improves. This dosing regimen has never been studied and is based on case reports. Experimental heart preparations clearly demonstrate tachyphylaxis with continuous administration. Whether this occurs in humans is unclear, but might argue for repeated bolus infusions over 1 to 5 minutes rather than continuous infusion. In addition, the smooth muscle relaxation associated with a continuous infusion would be assumed to impede attempts at gastrointestinal decontamination with multiple-dose activated charcoal or whole-bowel irrigation.

FORMULATION AND ACQUISITION

Glucagon [rDNA origin] for injection is available as a sterile, lyophilized white powder in a vial, alone, or accompanied by Sterile Water for Reconstitution, also in a vial. It is also supplied in the form of a
kit for treatment of hypoglycemia with one vial containing 1 mg (1 unit) of glucagon [rDNA origin] for injection with a disposable prefilled syringe containing Sterile Water for Reconstitution, as well as a “10-pack” with 10 vials, each containing 1 mg (1 unit) GlucaGen (glucagon [rDNA origin] for injection). The glucagon powder should be reconstituted with 1 mL of sterile water for injection, after which the vial should be shaken gently until the powder completely dissolves. The final solution should be clear, without visible particles. The reconstituted glucagon should be used immediately after reconstitution, and any unused part discarded. Concentrations greater than 1 mg/mL should not be used. An adequate supply of glucagon in the emergency department is at least 20 1-mg vials, with assurance of another 30 mg in the pharmacy.

SUMMARY

- Glucagon can produce positive inotropic and chronotropic effects despite β-adrenergic antagonism and calcium channel blockade.
- Glucagon is often beneficial in the treatment of patients with severe overdoses of β-adrenergic antagonists and calcium channel blockers.
- The effects of glucagon may not persist and other therapies, such as insulin and dextrose, should also be considered (Chaps. 61 and 62).
- The relatively benign character of an IV bolus of glucagon in the patient with a serious overdose of a β-adrenergic antagonist or calcium channel blocker should lead the clinician to use glucagon early in patient management.
- Nausea and vomiting should be anticipated and managed.

References

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CrossRef [PubMed: 7864479]

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62.


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