

USE OF GLUCAGON AS AN ANTIDOTE FOR THE MANAGEMENT OF SEVERE β -BLOCKER OR CALCIUM CHANNEL BLOCKER OVERDOSE

TOXICOLOGY

There are 3 types of β -adrenergic receptors found in the human body. β_1 -receptors primarily reside in heart muscle, β_2 -receptors are primarily found in bronchial and peripheral vascular smooth muscle, and β_3 -receptors, which are found in adipose tissue and the heart. Activation of each of these receptors results in a variety of physiological responses. Stimulation of β_1 -receptors results in an increase in intracellular cyclic AMP leading to increased heart rate, contractility, and AV node conduction. Stimulation of β_2 -receptors results in relaxation (dilation) of the bronchial and peripheral smooth muscles. Stimulation of β_3 -receptors results in catecholamine-induced thermogenesis and may reduce cardiac contractility.

β -blockers are competitive antagonists of these β -adrenergic receptors. The most commonly used β -blockers are specific to the β_1 -receptor, resulting in an indirect decrease of intracellular levels of cyclic AMP with a resultant decrease in heart rate and contractility. Additional mechanisms explaining their physiological effects have been hypothesized, but antagonism of the β -adrenergic receptor is their primary mechanism of action.

As expected, the manifestations of β -blocker intoxication are merely an extension of their pharmacology. The most common effects of toxicity include bradycardia and hypotension, with myocardial depression and cardiogenic shock being noted in the most severe cases. Other symptoms can include heart block, mental status changes including coma and seizures, respiratory depression and bronchospasm and hypoglycemia.¹ These effects are

dependent upon the pharmacodynamic and kinetic characteristics of the specific agent ingested. Pharmacologic properties such as lipophilicity, membrane-stabilizing activity, and intrinsic sympathomimetic activity contribute to the degree of toxicity and are dependent upon which β -blocker is ingested. Symptoms of β -blocker intoxication can present as early as one to two hours following ingestion, and are usually present by the sixth hour following ingestion.²

GLUCAGON MECHANISM OF ACTION

Glucagon is a polypeptide hormone that is most often used therapeutically to treat severe hypoglycemia. It interacts with the Guanine Nucleotide-Binding Protein-Coupled Receptor (GPCR) on the plasma membrane of target cells. The primary effects of glucagon are mediated by cyclic AMP stimulated phosphorylation. Usually, the effects of glucagon are primarily reserved to the liver. At higher concentrations, however, glucagon exerts effects on other tissues, including the myocardium, resulting in an increase in cyclic AMP and thus, increased inotropic and chronotropic effects.^{1, 3}

RECONSTITUTION AND STABILITY

1mg Glucagon vials are stocked with an accompanying diluent (Sterile Water for Injection). When compounding the initial bolus, the reconstituted product should be placed in the appropriate size syringe for the volume being administered.

When compounding a bag for infusion, the product should be reconstituted with the provided

diluent and added to 5% dextrose (D5W). . It is important to note that **the hospital supply of glucagon can be consumed quickly when managing β -blocker intoxication, necessitating the acquisition of glucagon from nearby hospitals.** The LHS standard infusion on the "Med Drips" button is 10mg/100mL D5W.

Unfortunately, data concerning the stability of the product are not available. A compounded bag of glucagon would therefore be given a **24-hour expiration date** by the central pharmacy sterile products area in compliance with departmental policy.

DOSAGE AND ADMINISTRATION

Glucagon should be given as a **bolus dose of 5-10 mg (50-150 mcg/kg) over 1-2 minutes.** Repeat boluses may be given every 5-10 minutes. Glucagon has a relatively short duration of action (approximately 10-15 minutes). Therefore, a continuous **infusion of glucagon at a rate of 2-5 mg/hour (50-100 mcg/kg/hour)** with a max of 10mg/hr should follow bolus administration in order to decrease repeated boluses as well as the rate of adverse reactions associated with high concentrations, such as nausea and vomiting.^{1, 4}

Consider also using a calcium gluconate bolus and infusion (1-2gram bolus followed by a 0.5 – 1gram per hour infusion) if the patient has peripheral access, or calcium chloride for central line access to augment or take place of glucagon. Intravenous

calcium provides inotropic and hemodynamic support in this setting⁶.

MONITORING

Administration of glucagon can cause hypokalemia and hyperglycemia. When administering large doses for the treatment of B-Blocker intoxication, adequate monitoring of serum glucose and potassium should be performed to maintain these concentrations at normal levels (BG between 80-120 mg/dL and serum potassium at 3.5-5 mMol/L.) Monitoring of heart rate should be performed in order to assess response to therapy, with normal heart rates being desired (60-80 beats per minute).

CONTRAINDICATIONS

The use of glucagon is contraindicated in patients with a history of insulinoma or pheochromocytoma, as well as in patients with known hypersensitivity to the product.⁵

ADVERSE REACTIONS

The most commonly encountered adverse reactions that occur with glucagon administration are nausea and vomiting, with a high incidence being associated with more rapid infusions (1mg/min as an IV push or infusion rates of ~10mg/hr). Because of this, airway control should be considered before administration of glucagon. More rare adverse reactions include hypersensitivity reactions including hypotension, respiratory distress, and urticaria.

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