

## Safety of Glucagon Use During Endoscopic Retrograde Cholangiopancreatography in Patients With Diabetes and Renal Insufficiency: Case Discussion and Review of the Literature

Lisa Erlinger, PhD, CRNA<sup>1</sup>

Terri Monk, MD, MS<sup>2</sup>

Steven McAfee, MD<sup>3</sup>

### Affiliation:

1 Assistant Professor MidWestern University–St. Louis University, Director of Surgical and Anesthesia Services Wickenburg Community Hospital

2. Professor of Clinical Anesthesiology University of Missouri–Columbia

3. Anesthesiologist University of Missouri–Columbia

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### Abstract

We describe the use of glucagon during endoscopic retrograde cholangiopancreatography (ERCP) resulting in significant hyperkalemia. A 45-year-old man with physical classification 3 and type 1 diabetes mellitus, hypertension, and chronic kidney disease underwent ERCP with general anesthesia for evaluation of a bile duct stricture. After intravenous administration of 0.75 mg glucagon (0.25-mg doses over 1 hour), tall, peaked T waves were noted on the electrocardiogram in lead II. Blood was collected and sent to the laboratory for evaluation. The patient's potassium level was 6.6 mEq/L and his glucose concentration was 568 mg/dL (31.5 mmol/L). Calcium chloride 1000 mg was administered intravenously. His repeat potassium level was 6.1 mEq/L and his repeat glucose concentration 393 mg/dL (21.8 mmol/L). The remainder of the procedure was uneventful and his postoperative potassium level was 5.2 mEq/L.

### INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable diagnostic tool in the evaluation of pancreatic-related diseases such as choledocholithiasis, benign and malignant strictures, and biliary tract disease. ERCP was first introduced in the 1960s,<sup>1</sup> and its use has steadily grown to approximately 500,000 cases per year in the United States, according to the last reported data from 2009.<sup>2,3</sup> In the endoscopic portion of the examination, a side-viewing duodenoscope is passed through the esophagus and stomach into the second portion of the duodenum. The scope in this position can identify the major duodenal papilla and can be used to search for abnormalities. This structure is a projection of the hepatopancreatic ampulla (also known as the ampulla of Vater) into the duodenal lumen. The ampulla of Vater is the conjunction point of the ventral pancreatic duct and the common bile duct and thus acts as a conduit for drainage of bile and pancreatic excretions into the duodenum.<sup>4</sup> The ampulla of Vater contains the sphincter of Oddi.<sup>5</sup> Cannulation can occur in either the common bile duct or the ventral pancreatic duct. Once the duct is cannulated, either a cholangiogram (common bile duct) or a pancreatogram (pancreatic duct) is obtained fluoroscopically after injection of radiopaque contrast material into the duct.

Insulin and glucagon are hormones secreted by islet cells within the pancreas. Each counterbalances blood glucose levels to keep the body within the normal therapeutic range. One of the many functions of insulin is to decrease blood glucose by moving glucose into cells. Glucagon is released into the circulation when blood glucose is too low, increasing plasma glucose levels. This maintains homeostasis in the body and keeps blood glucose stable.<sup>6</sup>

Glucagon (rDNA origin) for injection (GlucaGen; Novo Nordisk A/S) is produced by expression of recombinant DNA in a *Saccharomyces cerevisiae* vector with subsequent purification. Glucagon for injection is an anti-hypoglycemic agent and inhibits gastrointestinal motility. Hepatic stores of glycogen are necessary for glucagon to produce an anti-hypoglycemic effect.<sup>7</sup> Glucagon induces liver glycogen breakdown, releasing glucose from the liver. Blood glucose concentrations rise within 10 minutes of injection, and peak concentration is attained approximately 30 minutes after injection.

Glucagon also inhibits gastrointestinal motility by relaxation of the smooth muscles. The administration of sphincter-relaxing agents, like glucagon, enables the endoscopist to extract small, common bile duct stones without performing a papillotomy.<sup>8</sup> A papillotomy is performed by cutting the ampulla of Vater to widen its outlet to improve bile drainage and allow the passage of stones from the common bile duct. Glucagon decreases the frequency and amplitude of phasic activity of the sphincter of Oddi.<sup>8-10</sup> Intravenous glucagon is often used during ERCP to inhibit duodenal motility and enhance cannulation. However, glucagon can cause significant side effects, including nausea and vomiting, hyperglycemia, and hyperkalemia in patients with diabetes.<sup>11</sup>

## CASE SUMMARY

A 45-year-old man weighing 61 kg with a body mass index of 22 presented for an ERCP with cholangiogram. Three months before the procedure, he had undergone a laparoscopic cholecystectomy with intraoperative cholangiogram. During this initial procedure, it was noted that he had a common bile duct stricture. The pathology results at that time revealed a high-grade dysplasia of the cystic duct stump. He was recommended to undergo further evaluation with an ERCP with common bile duct brushings and biopsies.

The patient's medical history included a 30-year history of type 1 diabetes mellitus, chronic kidney disease, hypertension, hyperlipidemia, and a 20-pack-year smoking history. Preoperative laboratory results revealed a creatinine level of 2.6 mg/dL (230  $\mu$ mol/L) and a glycosylated hemoglobin (HbA1c) value of 10.4%. He was taking insulin glargine (Lantus), 20 units subcutaneously at bedtime, and using an insulin lispro (Humalog) sliding scale regimen during the day with an average use of 40 units daily. His diabetes was poorly controlled with daily blood glucose values ranging from 200 to 300 mg/dL (11.1-16.6 mmol/L). His preoperative vital signs were blood pressure of 130/88 mm Hg and heart rate of 90 beats per minute. He had not taken any medications on the day of surgery. His preoperative fasting blood glucose concentration was 160 mg/dL (8.9 mmol/L) and his potassium level was 4.9 mEq/L.

General anesthesia was induced intravenously with 100  $\mu$ g fentanyl, 100 mg lidocaine, and 100 mg propofol. After administration of 100 mg succinylcholine, the patient was orally intubated and anesthesia was maintained with sevoflurane to maintain approximately 1 minimum alveolar concentration. The video gastroduodenoscope was advanced to the second part of the duodenum and an attempt was made to cannulate the common bile duct. Intravenous (IV) glucagon 0.25 mg was requested by the gastroenterologist to relax the common bile duct. This dose was repeated twice over the next 30 minutes. After the third dose, tall, peaked T waves were noted on the electrocardiogram (ECG), an acute change from the normal ECG at the start of the procedure. The patient's blood was drawn and sent to the laboratory and the findings revealed a potassium level of 6.6 mEq/L and a glucose concentration of 568 mg/dL (31.5 mmol/L). Calcium chloride 1000 mg IV was administered over 10 minutes with improvement in the ECG shown as a decrease in amplitude of the peaked T waves. Four puffs of nebulized albuterol were also administered via the endotracheal tube. Repeat measurements of electrolytes conducted 30 minutes later showed a potassium level of 6.1 mEq/L and a glucose concentration of 393 mg/dL (21.8 mmol/L). Calcium chloride 1000 mg IV was administered over 10 minutes with improvement in the ECG shown as a decrease in amplitude of the peaked T waves. Four puffs of nebulized albuterol were also administered via the endotracheal tube. Repeat measurements of electrolytes conducted 30 minutes later showed a potassium level of 6.1 mEq/L and a glucose concentration of 568 mg/dL (11.1 mmol/L). The procedure was completed, the patient was extubated without incident, and he was monitored in the post-anesthesia care unit for 2 hours. Repeat measurements of electrolytes showed a potassium level of 5.2 mEq/L and a glucose concentration of 505 mg/dL (28.0 mmol/L). The patient was transferred to the intensive care department for glucose management.

## DISCUSSION

Normally, hyperkalemia elicits its own "self-treatment." This is done automatically by the body with endogenous glucose and insulin release, insulin-increasing potassium tolerance, and endogenous glucagon, which provides enough glucose to prevent hypoglycemia.<sup>11</sup> This self-regulation allows for administration of glucagon in a nondiabetic patient to result in inconsequential increases in glucose or potassium. However, as far back as 1973, a study by Santeusano et al<sup>12</sup> raised the possibility of hyperglucagonemia in diabetic ketoacidosis. Santeusano et al had an incidental finding of clinical relevance. They warned that patients with diabetic ketoacidosis are at increased risk of developing hyperkalemia. This risk is increased if patients are administered potassium or encounter a stressful condition because endogenous insulin responsiveness is impaired by hypercatecholaminemia. They suggested that the risk may be excessive unless affected insulin action has been established, particularly in patients with kidney disease. Similarly, Massara et al<sup>13</sup> investigated the role played by glucagon in the regulation of plasma potassium. They found low blood insulin and increased glucagon could be one of the mechanisms that trigger or magnify the hyperkalemia observed in cases of severe stress for patients with decompensated diabetes.

Christensen et al<sup>14</sup> explored factors that affect the variability in heart rate during ERCP. The researchers divided the volunteers into 3 groups. Each group received an administration of butylscopolamine, glucagon, or saline, and the researchers looked for myocardial ischemia and changes in the variability of heart rate. Two patients in the butylscopolamine-free group developed ischemia, resulting in unexplained pathophysiologic changes.<sup>14</sup> The ST segment depressions in the Christensen et al study lasted 226 s and 550 s, respectively. Could this be the result of transient hyperkalemia from glucagon? No further information was given concerning patient histories to make any conclusions for practice.

Tall, peaked T waves are findings of concern in the perioperative setting, particularly, as in this case, when they represent a change from the patient's baseline. The differential diagnosis of prominent T waves can include hyperkalemia, myocardial ischemia, left ventricular hypertrophy, benign early repolarization, bundle branch block, pericarditis, and normal variant, especially in the young.<sup>15</sup>

Hyperkalemia or myocardial ischemia was most likely the cause in this case, because the T wave elevation developed as an acute change from the start of the procedure. The laboratory evaluation confirmed that hyperkalemia was the diagnosis. The treatment of acute hyperkalemia included administration of calcium chloride IV to stabilize the cardiac membrane from potentially fatal arrhythmias. The recommended dose is 10 to 20 mL of a 10% calcium chloride solution and a  $\beta$ -adrenergic agonist such as nebulized albuterol to redistribute extracellular potassium into the cells. A sodium bicarbonate–glucose–insulin mixture could also have been used. Sodium bicarbonate 0.5–1.0 mEq/kg IV shifted potassium intracellularly while the glucose–insulin infusion (50 mL of 50% glucose plus 10 units regular insulin) produced a sustained transfer of extracellular potassium into

the cells. Therapeutic agents could also have been administered to lower the total body potassium. Polystyrene compounds (Kayexalate) or loop-diuretics both increase potassium excretion via gastrointestinal and renal systems, respectively.

This case demonstrates the importance of considering alternative means of duodenal antiperistalsis and sphincter of Oddi relaxation to allow for ampullar cannulation in patients with diabetes and/or chronic kidney disease undergoing ERCP. One such agent is L-hyoscyamine, an anti-cholinergic, anti-muscarinic alkaloid that is frequently administered via the sublingual route. A review of the literature did not support widespread use of L-hyoscyamine. L-Hyoscyamine is associated with peri-procedural adverse effects including nausea and vomiting and has not been shown to decrease the amount of glucagon patients receive.<sup>11,16</sup> Perhaps a better strategy would be to minimize the use of glucagon in patients with diabetes at elevated risk for hyperkalemia.

## CONCLUSION

This is the first report of acute hyperkalemia during ERCP. Although rare, this complication can be life-threatening if not recognized and immediately treated. In nondiabetic patients, glucagon administration causes a modest increase in plasma potassium levels, but these effects are magnified in patients with diabetes, especially in individuals who are insulin deficient or have a history of uncontrolled diabetes. The anesthesia provider should be aware of the possibility of hyperkalemia during ERCP and its effects on the myocardium. It is important to formulate a suitable approach to the management of hyperkalemia during ERCP. It may be prudent to check serum potassium and blood glucose in all patients with diabetes, especially those with chronic kidney disease.

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