Possible dulaglutide-associated cholecystitis with safe continuation post cholecystectomy

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Purpose. Possible dulaglutide-induced cholecystitis, with successful resumption of dulaglutide after cholecystectomy, is discussed.

Summary. A 72-year-old White man was started on dulaglutide for outpatient management of type 2 diabetes, in addition to his existing antihyperglycemic regimen of metformin, glipizide, pioglitazone, and insulin glargine. His glycated hemoglobin (HbA_{1c}) concentration improved from 8.2% to 7.2% with the addition of dulaglutide. Furthermore, the use of dulaglutide did not lead to weight loss. After 16 months of treatment with dulaglutide, he presented to the emergency room with nausea, loss of appetite, and progressive sharp, nonradiating right upper quadrant pain. Based on symptom presentation, laboratory workup, and computed tomography scan results, acute cholecystitis was diagnosed. He underwent a cholecystectomy to remove what was found to be a gangrenous gallbladder. Per documented surgical dictation from the cholecystectomy, the gallbladder was removed, but portions of the biliary tree were left intact. The patient was continued on dulaglutide postoperatively without recurrence of bile stones, biliary tree disease, or abdominal symptoms at 8 months after initial cholecystitis incident.

Conclusion. A male patient with possible dulaglutide-induced cholecystitis was successfully continued on dulaglutide therapy post cholecystectomy without recurrent complications within the biliary tract.

Keywords: acute cholecystitis, dulaglutide, gallbladder diseases, GLP-1 agonists

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The use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) has increased over the past decade, a shift that aligns with updated American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" guidelines, which identify GLP-1RAs as second-line antihyperglycemic pharmacotherapy in certain patient populations.[1] In patients with significant atherosclerotic cardiovascular disease, chronic kidney disease, or chronic heart failure, a GLP-1RA can be considered an ideal agent if adequate glycemic control is not achieved with metformin monotherapy (per ADA guidelines). In type 2 diabetes there is a decrease in production of incretin hormones, one of which is glucagon-like peptide-1 (GLP-1). The diminished stimulation of GLP-1 receptors can lead to decreased insulin release, decreased insulin sensitivity, and hyperglycemia. The use of GLP-1RAs stimulates these receptors, which leads to decreased glucagon production, increased insulin sensitivity, delayed gastric emptying, increased satiety, and weight loss.[2] These positive metabolic adverse effects are in contrast to those that may occur with use of other antihyperglycemic agents such as sulfonylureas and thiazolidinediones, which are associated with weight gain.[1]

Recent literature shows that use of GLP-1RAs can result in a glycated hemoglobin (HbA_{1c}) reduction from 0.8 to 2 percentage points, which is similar to or greater than the reductions seen with the use of other traditional agents used in the treatment of diabetes, such

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as metformin (1 to 1.3), sulfonylureas (0.4 to 1.2), and thiazolidinediones (0.5 to 1.4).[3] In addition to advantageous HbA_{1c} reduction, GLP-1RAs are associated with a very low risk of hypoglycemia, which make them a desirable alternative to other antihyperglycemic agents in the geriatric population. Current data have also shown that use of several drugs in the GLP-1RA class can lead to favorable decreases in microvascular complications and may reduce the prevalence of cardiovascular events.[4]

Although GLP-1RAs have several advantages in the treatment of diabetes, they also confer other, less desirable, effects; nausea, diarrhea, constipation, flatulence, and vomiting are among the most common adverse effects. More concerning potential adverse effects include pancreatitis, gastroparesis, and cholelithiasis. At the time of publication, the package insert for dulaglutide, a drug in the GLP-1RA class, does not cite gallbladder complications as a potential adverse effect, nor to our knowledge is there any guidance as to whether GLP-1RAs are appropriate to use in patients with a history of gallbladder complications.[5]

A literature search was conducted in March 2020 via MEDLINE using the following search terms: "dulaglutide and gallbladder," "dulaglutide and cholecystitis," and "GLP-1 receptor agonists and gallbladder." Limited results on GLP-1RAs and gallbladder-based adverse events were found, and no information specifically on dulaglutide was found. The following patient case report describes a patient currently on dulaglutide who developed severe cholecystitis but continued dulaglutide after cholecystectomy.

Case presentation. A 72-year-old White man presented to the emergency room (ER) with right upper quadrant pain of 3 days' duration. His medical history was significant for type 2 diabetes (diagnosed at age 54 years), hyperlipidemia, coronary heart disease with stenting, and obesity. He reported alcohol use of 6 to 9 drinks per week but no history of smoking or illicit drug use.

KEY POINTS

- Dulaglutide use may increase a patient's risk of developing cholecystitis.
- Patients should be evaluated for increased risk of gallbladder complications before initiation of a glucagon-like peptide-1 receptor agonist (GLP-1RA).
- There is a potential for delayed gallbladder complications with use of GLP-1RAs.

The patient retired from transportation planning at the age of 70 years. He reported an active lifestyle, including aerobic exercise 5 times per week on average.

Before admission the patient's diabetes treatment was managed by an ambulatory care clinical pharmacy specialist and primary care provider on an outpatient basis. See Table 1 for the history of treatment. Due to previous weight gain (8.3 kg) with insulin, the patient and his care team determined that a trial of dulaglutide (0.75 mg weekly via subcutaneous administration) was preferred to further titration of insulin glargine. One month after starting dulaglutide, the patient reported some minor indigestion but attributed this to his erratic dietary choices. Two months after starting dulaglutide his self-monitored blood glucose levels were improved, with approximately half of his fasting glucose readings at goal of less than 130 mg/dL. His presentation to the ER occurred approximately 16 months after starting dulaglutide therapy.

The patient's antihyperglycemic regimen on presentation to the ER included metformin 1,000 mg twice daily, glipizide 20 mg twice daily, pioglitazone 45 mg daily, insulin glargine 20 units daily, and dulaglutide 1.5 mg weekly. Other medications included rosuvastatin 20 mg daily and nonprescription CoQ10, vitamin E, and marine collagen. Records from the patient's ambulatory care appointments indicated that he was adherent to his medication regimens.

Upon presentation to the ER, the patient had nausea, loss of appetite, and progressive sharp, nonradiating right upper quadrant pain that began shortly after eating nachos and tacos 3 days prior. He reported no vomiting, hematochezia, and melena. Ultrasound and CT scan results showed signs of gallbladder dilation, gallbladder wall thickening, multiple calculi, and pericholecystic fat stranding. He was found to have a positive Murphy's sign, and gangrenous cholecystitis was later diagnosed. See Table 2 for specific laboratory monitoring data. The patient's weight at the time of admission was 111.3 kg. Intravenous (IV) piperacillin/tazobactam 3.375 g and fluid resuscitation with lactated Ringer solution were started in the ER. The patient underwent a cholecystectomy on day 1 of admission. Per surgical notes, the liver was grossly normal, and the gallbladder was extremely inflamed and edematous with signs of gangrene. Due to adhesions, the planned laparoscopic procedure was canceled in favor of an open surgical approach. After successful removal of the gallbladder, the cystic duct was dissected and ligated; upon inspection, there was no drainage of bile following ligation. No dissection of the common hepatic duct occurred. A cholangiogram was not performed due to risk of injury to the biliary system. A Blake drain was placed in the gallbladder fossa before closure. IV piperacillin/tazobactam 3.375 g every 6 hours was continued postoperatively. Anaerobic cultures obtained from the bile within the gallbladder resulted in no microbial growth. Upon discharge at day 7 of hospitalization, the patient had his Blake drain removed, and prescriptions for amoxicillin/clavulanate (875 mg/125 mg) by mouth twice daily for 3 days and hydrocodone/acetaminophen (5 mg/325 mg) by mouth every 4 hours as needed for pain were

Table 1. Patient's Diabetes Treatment Regimen and Glycated Hemoglobin Levels

Timeframe	Medications	HbA_{1c} Level	Weight/BMI
Before initiation of dulaglutide therapy[a]	Metformin 1,000 mg orally twice daily Glipizide 20 mg orally twice daily Pioglitazone 30 mg orally daily Insulin glargine 25 units SC daily	8.2%	111.8 kg/33.43 kg/m^2
3 months after initiation of dulaglutide 0.75 mg SC weekly	Metformin 1,000 mg orally twice daily Glipizide 20 mg orally twice daily Pioglitazone 30 mg orally daily Insulin glargine 25 units SC daily Dulaglutide 0.75 mg SC weekly	7.5%	Not reported
2 months after dulaglutide dosing increased to 1.5 mg SC weekly	Metformin 1,000 mg orally twice daily Glipizide 20 mg orally twice daily Pioglitazone 30 mg orally daily Insulin glargine 25 units SC daily Dulaglutide 1.5 mg SC weekly	7.1%	113.8 kg/34.03 kg/m^2
3 months after pioglitazone dosing increased to 45 mg daily and insulin glargine dosing decreased to 20 units SC daily	Metformin 1,000 mg orally twice daily Glipizide 20 mg orally twice daily Pioglitazone 45 mg orally daily Insulin glargine 20 units SC daily Dulaglutide 1.5 mg SC weekly	7.2%	Not reported

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin, SC, subcutaneously.
[a]Previously trialed agents: sitagliptin (stopped due to dizziness) and rosiglitazone (self-discontinued by patient without reason noted).

Table 2. Laboratory Data Review[a]

Time	AST (U/L)	ALT (U/L)	Alk Phos (U/L)	Direct Bilirubin (mg/dL)	Total Bilirubin (mg/dL)	WBC (cells/μL)
Day 1 (admission)	35	40	81	0.6 H	3.2 H	24,800
Day 2 (preop)	137 H	104 H	156 H	1.3 H	3.2 H	18,400
Day 7 (discharge)	61 H	104 H	558 H	0.4 H	0.9	8,600
Day 18 (follow-up)	15	25	234 H	NA	0.7	7,300

Abbreviations: Alk Phos, alkaline phosphatase; ALT, alanine transferase; AST, aspartate transferase; H, high; NA, not available; WBC, white blood count.
[a]No baseline data prior to admission available for comparison.

dispensed. All other aforementioned home medications were continued at the time of discharge.

At his primary care follow-up appointment post discharge, the patient was recovering well and reported satisfactory glycemic control. His activity level was improving and was nearly at baseline. The patient was continued on dulaglutide with no gap in therapy; the endocrinology department was consulted and was agreed with this plan as the patient had no contraindications to dulaglutide use. At the time of this writing, the patient was 8 months post discharge and had reported no further complications related to dulaglutide therapy.

Discussion. This case details the occurrence of gangrenous cholecystitis in a patient 16 months after being prescribed dulaglutide. The GLP-1RA class is associated with a risk of possible gallbladder complications; however, the package insert for dulaglutide does not list this as a concern.[5] The clinical question as to whether future bile duct system complications post cholecystectomy are possible if a patient continues on GLP-1RA therapy remains unanswered. As noted in this case report, the patient was continued on dulaglutide after being discharged from the hospital after open cholecystectomy and 8 months later had no recurrent gastrointestinal or hepatobiliary complications.

Other agents within the GLP-1RA class include albiglutide, exenatide, liraglutide, lixisenatide, and semaglutide. In addition to the positive

aspects of GLP-1RAs, the mechanism of action confers a risk of gallbladder complications through slowed gastrointestinal tract motility and expanded time of gallbladder contraction.[6] This gastrointestinal tract slowing leads to the traditional adverse drug reactions (ADRs) for this medication class, such as abdominal pain, decreased appetite, diarrhea, nausea, and vomiting. In reviewing the package inserts of GLP-1RAs, those for albiglutide and liraglutide only list gallbladder complications as a warning or precaution. Furthermore, the ADR section of the package insert for liraglutide lists cholelithiasis (2%) and cholecystitis (1%) and for semaglutide lists cholelithiasis (<2%) as reported reactions in clinical trials, whereas the other GLP-1RAs have no gallbladder ADRs listed.[5,7-11] In 2019, Gether et al[6] published a review for gallbladder motility mechanisms. GLP-1RAs affected further down the feedback loop in the gastrointestinal tract, attempting to negate the negative effects on gallbladder motility. Specific studies on gallbladder emptying with liraglutide showed no effect on maximal gallbladder contraction but may have slowed the time needed for full contraction and refilling. It seems that GLP-2 may play a larger role in regulating gallbladder function; however, more data to ascertain if there is a connection to giving GLP-1RAs and therefore increasing GLP-2 are needed.[6] It has yet to be determined if gallbladder complications are a class effect or if particular medications in the GLP-1RA class are more likely to cause gallbladder complications.

A 2016 report by Pizzimenti et al[12] reviewed case reports and EudraVigilance data on GLP-1RAs. The researchers proposed that the cause of GLP-1RA–associated gallbladder complications may derive from rapid weight loss, slowed gallbladder contraction or emptying, reduced bile acid production, and loculation of inflammation. In addition to weight loss, diabetes, obesity, dyslipidemia, increasing age, and alcoholic liver cirrhosis are considered risk factors for stone formation.[13] The gallbladder complications were associated with use of exenatide (n = 60), liraglutide (n = 37), and lixisenatide (n = 3).[12] Our patient in this case report may be considered to have been predisposed to gallbladder complications due to his history of diabetes, obesity, and dyslipidemia. However, the patient did not have rapid weight loss because he maintained a consistent weight throughout treatment. A study by Faillie et al[14] looked at bile duct and gallbladder complications with the use of incretin-based drugs, including dipeptidyl peptidase IV inhibitors and GLP-1RAs. They noted that use of a GLP-1RA caused increased gallbladder complication risk in the first 180 days after therapy initiation and treatment for more than 180 days did not result in a statistically significant increase in this risk. Our patient had been treated with dulaglutide for 16 months before presenting with gangrenous cholecystitis and was continued on therapy for 8 months after his cholecystectomy.

Although a mechanistically contrived extrapolation may be made, to our knowledge, no reports looking at increased risk of complications within the biliary tree post cholecystectomy if a patient is continued on GLP-1RA therapy have been published. Our patient had preserved common bile, hepatic, and cystic ducts after his procedure. Because a risk of gallstone formation in the bile ducts pending bile concentration and oversaturation of cholesterol continues to exist, patients may still be at risk of complications even though the gallbladder has been removed.[15,16]

Assessment using the drug reaction probability scale of Naranjo et al[17] should typically be conducted to ascertain if there is a risk that an adverse reaction was more or less likely to have been caused by a suspected offending agent. The specific Naranjo score in this patient case is difficult to fully identify. No other reports of dulaglutide-induced gallbladder issues currently exist. The reaction occurred after dulaglutide was initiated but happened many months later, the reaction was improved by removing the gallbladder and not specifically by stopping the medication, and the patient had potential alternative causes (eg, diet and obesity); however, these variables have been consistently in place, and the adverse reaction was confirmed objectively through the removal of the gallbladder. All of these variables leave us with a score as high as 6 or as low as 0. The most likely score is 2 or 3, leaning toward dulaglutide as a possible cause for the cholecystitis. However, patient-specific risk factors, such as age, obesity, diabetes, and alcohol use, cannot be fully ruled out for playing a part in this patient's historical risk factors for cholecystitis.

Although the patient in this case report potentially developed cholecystitis in part due to dulaglutide use, he was successfully treated with dulaglutide for 8 months after cholecystitis, lending credence to the conclusion that it may be safe to continue or start GLP-1RA therapy in patients with a history of cholecystectomy, although there may remain a limited increased risk of choledocholithiasis. More research is needed before any clear conclusion can be formed.

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Disclosures

The authors have declared no potential conflicts of interest.

Additional information

The views expressed in this article are those of the authors and do not reflect the position or policy of the Department of Veterans Affairs or the United States Government.

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