MAYO CLINIC

Management of Hypertriglyceridemia-Induced Acute Pancreatitis in a Nondiabetic Patient

Jamie M. Reed, PharmD, BCPS; Breann M. Hogan, PharmD, BCPS; Navine Nasser-Ghodsi, MD; and Conor G. Loftus, MD

Abstract

Treatment strategies for hypertriglyceridemia-induced acute pancreatitis are not well defined in the current literature or guidelines. One therapeutic option is an insulin infusion accompanied by a dextrose infusion to avoid hypoglycemia. The purpose of this case report is to highlight dosing considerations for dextrose infusions in nondiabetic patients. We describe a case of hypertriglyceridemia-induced acute pancreatitis in a 34-year-old nondiabetic woman treated with a reduced-dose insulin infusion that was complicated by hypoglycemic episodes requiring dextrose infusion titrations. Empirical initiation of a higher dextrose concentration infusion with glucose level titrations should be considered to avoid hypoglycemia for nondiabetic patients treated with an insulin infusion to lower triglyceride levels. In this case, clinical pharmacy assistance was imperative for successful treatment with a reduced-dose insulin infusion and titrated dextrose infusion in the management of hypertriglyceridemia-induced acute pancreatitis.

© 2021 Mayo Foundation for Medical Education and Research. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/) ■ Mayo Clin Proc Inn Qual Out 2021;5(2):520-524

From the Department of Pharmacy (J.M.R., B.M.H.) and Division of Gastroenterology and Hepatology (N.N.-G., C.G.L.), Mayo Clinic, Rochester, MN; and Department of Pharmacy, Indiana University Health, Indianapolis (J.M.R.).

Acute pancreatitis is an inflammatory condition of the pancreas with classic symptoms including acute-onset epigastric abdominal pain, often accompanied by nausea and vomiting. The most common etiologies of acute pancreatitis are gallstones, alcohol consumption, genetic risk factors, medications, endoscopic retrograde cholangiopancreatography, and, less commonly, hypertriglyceridemia, which occurs in approximately 2% to 4% of cases.[1,2] It has been proposed that hypertriglyceridemia induces acute pancreatitis by the hydrolysis of triglycerides in the pancreas into free fatty acids, resulting in lipotoxicity.[3] Triglyceride levels greater than 500 mg/dL (to convert value to mmol/L, multiply by 0.0113) increase the risk of acute pancreatitis.[2,4,5] Optimal management strategies are not well defined given limited studies and case reports. Some therapeutic options that have been studied include insulin, heparin, or plasmapheresis.[6-10] Insulin therapy is commonly used and is an effective treatment strategy; however, the literature does not define dosing recommendations for concomitant dextrose infusions to prevent hypoglycemia. We describe a case of hypertriglyceridemia-induced acute pancreatitis in a nondiabetic female patient treated with insulin and dextrose infusions that was complicated by hypoglycemic episodes requiring dextrose titration.

REPORT OF CASE

The patient was a 34-year-old White woman weighing 77.5 kg who had a medical history notable for familial hypertriglyceridemia with previous episodes of acute pancreatitis related to hypertriglyceridemia in 2016 and 2017. She presented to the emergency department with severe radiating abdominal pain and was admitted to the gastroenterology service given the similarity of this presentation to her previous episodes of pancreatitis. Associated symptoms included nausea, chest tightness, and bloating. She had not consumed alcohol in the previous 12 months and had no history of tobacco use, illicit drug use, or use of estrogen products. Her family history was notable for paternal hypertriglyceridemia without any acute pancreatitis episodes. Her medications prior to admission included gemfibrozil (600 mg orally twice daily) and pravastatin (10 mg orally daily), with reported adherence.

Physical examination findings were unremarkable except for epigastric and left upper

Mayo Clin Proc Inn Qual Out ■ April 2021;5(2):520-524 ■ https://doi.org/10.1016/j.mayocpiqo.2020.08.015
www.mcpiqojournal.org ■ © 2021 Mayo Foundation for Medical Education and Research. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

quadrant tenderness without rebounding or guarding. Her abdomen was soft and nondistended with no evidence of masses or hepatosplenomegaly. No imaging was performed. Pertinent admission laboratory values were as follows: serum triglycerides, 3496 mg/dL; total cholesterol, 709 mg/dL (to convert value to mmol/L, multiply by 0.0259); plasma glucose, 98 mg/dL (to convert value to mmol/L, multiply by 0.0555); hemoglobin A_{1c}, 4.7% (to convert value to proportion of total hemoglobin, multiply by 0.01); lipase, 197 U/L (to convert value to μkat//L, multiply by 0.01667); lactate, 1.3 mmol/L; and white blood cell count, 13.9×10^9/L. Hypertriglyceridemia-induced acute pancreatitis was diagnosed based on the patient's presentation and pertinent laboratory results and was treated with insulin and dextrose infusions.

On day 1 of hospitalization, the patient was directed to eat nothing and received initial fluids as follows: 1000-mL bolus of 0.9% sodium chloride followed by lactated Ringer solution at 350 mL/h for 6 hours and subsequent lactated Ringer solution at 125 mL/h for 3.5 hours. After initial fluid resuscitation, a pharmacist-directed insulin infusion and concomitant dextrose infusion were initiated (Table 1). The endocrinology service was consulted to assist with hypertriglyceridemia management and recommended that the insulin infusion be empirically reduced from the standard starting dose of 0.1 U/kg per hour to 0.07 U/kg per hour in view of her lower baseline serum glucose concentrations. Insulin therapy was to be continued at the lower dose until triglyceride levels were less than 500 mg/dL. Triglyceride concentrations were measured twice daily (Figure 1). Blood glucose concentrations were measured hourly during the insulin infusion, and a hypoglycemic protocol was ordered (Figure 2). Hypoglycemia was defined as a glucose level of 70 mg/dL or less or the presence of hypoglycemic symptoms. Gemfibrozil (600 mg orally twice daily) and pravastatin (10 mg orally daily) were continued. Omega-3 fatty acids (fish oil, 2 g orally twice daily) were administered. Pain was managed with hydromorphone, which exacerbated her nausea and was subsequently discontinued. No additional pain management was required.

The intravenous insulin infusion was started at 0.07 U/kg per hour with concomitant infusion of dextrose 5% in water at 125 mL/h to prevent hypoglycemia. The initial glucose level was 95 mg/dL at approximately 11:00 AM on day 1. Glucose levels were measured hourly with the following results: 100 mg/dL, 116 mg/dL, 86 mg/dL, and 77 mg/dL, respectively. A glucose level of 77 mg/dL was measured at 4:08 PM, approximately 5 hours after starting the insulin infusion. The dextrose infusion was increased to dextrose 10% in water at 200 mL/h based on that level. Titration instructions for the nursing staff to adjust the dextrose infusion based on blood glucose levels were added per pharmacy recommendation: if the blood glucose level was less than 200 mg/dL, adjust rate to 200 mL/h; if the blood glucose level was greater than 200 mg/dL, adjust rate to 125 mL/h; if the blood glucose level was greater than 300 mg/dL, hold dextrose infusion until the blood glucose level was below 300 mg/dL. Subsequent hourly glucose levels remained low with the following results: 96 mg/dL, 100 mg/dL, 97 mg/dL, 99 mg/dL, and 96 mg/dL, respectively, despite dextrose 10% fluid administration. A glucose level of 55 mg/dL was noted at 8:59 PM on day 1. The patient was asymptomatic and was promptly treated with dextrose 50% in water, 12.5 g intravenously, which improved her glucose level to 93 mg/dL. No adjustments to the dextrose infusion were made at that time because clinical pharmacy personnel were unavailable. The next glucose measurements were 87 mg/dL and 65 mg/dL at 11:00 PM on day 1, which required additional dextrose 50% in water—a 12.5-g intravenous bolus for this second asymptomatic hypoglycemic episode. The dextrose infusion was not adjusted until 9:19 AM on day 2 of the infusion, shortly following measurement of an asymptomatic glucose level of 70 mg/dL and when clinical pharmacy staff was present. The dextrose infusion was increased to dextrose 20% in water at 200 mL/h. Titration instructions for the nursing staff to adjust the dextrose infusion based on blood glucose levels were added per pharmacy recommendation: if the blood glucose level was less than 200 mg/dL, adjust rate to 200 mL/h; if the blood glucose level was greater than 200 mg/dL, adjust rate to 100 mL/h; if the blood glucose level was greater than 300 mg/dL, hold the dextrose infusion until the blood glucose level was below

TABLE 1. Dextrose Infusion Titrations With Glucose Concentrations[a]

Time (h)	Dextrose concentration	Dextrose infusion rate (mL/h)	Serum glucose (mg/dL)[b]
0	D5W	125	95
5.5	D10W	200	77
22.5	D20W	200	70
48.25	D20W	125	103
50.25	Off		79
70	D20W	200	89
85	Off		135

[a]D5W, dextrose 5% in water; D10W, dextrose 10% in water; D20W, dextrose 20% in water.
[b]SI conversion factor: To convert glucose values to mmol/L, multiply by 0.0555.

300 mg/dL. The patient's glucose levels ranged from 81 mg/dL to 175 mg/dL while undergoing this dextrose infusion. At 11:30 AM on day 3, the dextrose infusion was decreased to dextrose 20% in water at 125 mL/h, and the patient was started on a clear liquid diet. Triglycerides were measured at 427 mg/dL at 12:00 PM on day 3, and the insulin and dextrose infusions were stopped.

The patient was transitioned to an oral diet and remained hospitalized to ensure that triglycerides were maintained at less than 500 mg/dL with this diet. On day 4 of the hospitalization, approximately 20 hours after maintaining an oral diet, her triglyceride level was 916 mg/dL. An insulin infusion of 0.07 U/kg per hour and dextrose 20% in water at 200 mL/h was resumed with titration instructions based on the previous infusion of dextrose 20% in water. These infusions were maintained for 15 hours without any episodes of hypoglycemia until the triglyceride level was 372 mg/dL, at approximately 10:00 PM on day 4. She was discharged on day 4 of hospitalization with a regimen of fenofibrate (600 mg orally twice daily), pravastatin (10 mg orally daily), omega-3 fatty acids (fish oil, 2 g orally twice daily), and a recommendation to start orlistat (120 mg orally 3 times daily with meals) as an outpatient.

Follow-up with the endocrinology service occurred at 2 weeks and 6 weeks postdischarge, with triglyceride levels noted at 280 mg/dL and 167 mg/dL, respectively. She reported adherence to her diet and medications: fenofibrate, pravastatin, omega-3 fatty acids (fish oil), and orlistat. At her 6-week follow-up postdischarge, the omega-3 fatty acids (fish oil) were discontinued.

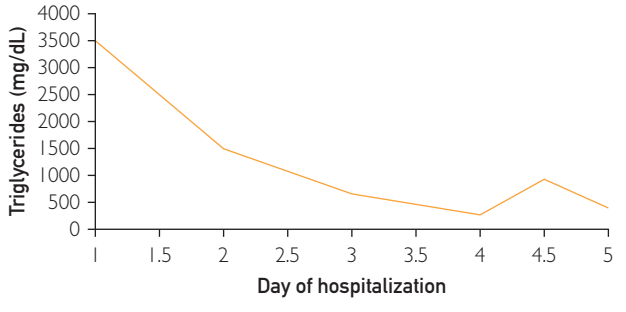

FIGURE 1. Triglyceride trend throughout hospitalization.

DISCUSSION

No consensus recommendations or guidelines currently exist for the management of hypertriglyceridemia-induced acute pancreatitis. Limited evidence and case reports have revealed efficacy with insulin, heparin, and plasmapheresis.[6-10] Insulin and heparin therapy have been studied as concomitant and monotherapy options to induce lipoprotein lipase to degrade triglycerides. Controversy regarding heparin therapy exists as it may ultimately deplete lipoprotein lipase and inhibit degradation of triglycerides, increasing the risk of recurrent hypertriglyceridemia-induced acute pancreatitis. This risk, as well as coagulopathy risks, was the reason that heparin was not selected for this patient. Plasmapheresis was not empirically considered because of its cost and logistics compared with insulin therapy.

Various dosing for insulin has been suggested based on case reports and case series, including intermittent and continuous infusions. The most consistent efficacy is reported with an insulin infusion at 0.1 U/kg per hour with a concomitant dextrose 5% infusion to prevent hypoglycemia.[6-10] There is currently no published evidence regarding nondiabetic patients experiencing hypoglycemia during the treatment of hypertriglyceridemia-induced acute pancreatitis.

Unlike our patient, type 2 diabetes mellitus is a common comorbidity in patients with hypertriglyceridemia. These patients are less likely to experience hypoglycemia even while receiving a set-rate insulin infusion. Alternative

Mayo Clin Proc Inn Qual Out ■ April 2021;5(2):520-524 ■ https://doi.org/10.1016/j.mayocpiqo.2020.08.015
www.mcpiqojournal.org

considerations should be made for nondiabetic patients to avoid hypoglycemia during treatment for hypertriglyceridemia-induced acute pancreatitis. Both evaluation of the insulin infusion rate and the dextrose infusion concentrations and rates are imperative to provide effective therapy and minimize the risk of hypoglycemia.

In our patient, a reduced insulin infusion rate of 0.07 U/kg per hour was effective in rapidly lowering triglyceride levels. It is unclear if the reduction in the insulin infusion rate prolonged the time to achieve triglyceride levels of less than 500 mg/dL. Even with a reduction in the insulin infusion rate, hypoglycemia was problematic for our patient. We empirically started with a dextrose 5% infusion per literature recommendations, but the patient quickly required additional adjustments to avoid hypoglycemia. We elected to increase the dextrose infusion, rather than further reducing the insulin infusion, to allow for continued treatment of the patient's acute hypertriglyceridemia. A central line was not placed for administration of dextrose 20% in our patient. Placement of a central line could be considered because dextrose 20% exceeds the upper-limit osmolality for a peripheral line.

On day 1 of the dextrose and insulin infusion, clinical pharmacy staff was unavailable overnight, and given the complexity of the situation, the overnight physician and nursing staff were uncomfortable with adjusting the dextrose drip. The nurses elected to use the standard hypoglycemia protocol with dextrose pushes for hypoglycemic symptoms and low blood glucose levels. This scenario highlights the importance of effective communication and education among physicians, nursing staff, and pharmacy personnel for a successful application of a titratable dextrose infusion, especially when clinical pharmacy staff is unavailable.

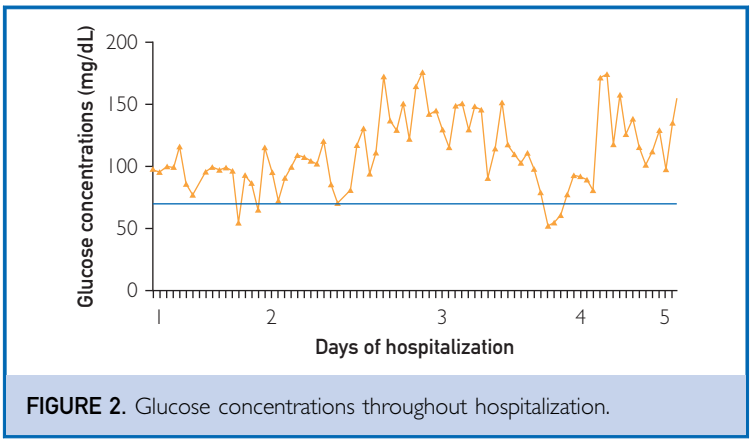

FIGURE 2. Glucose concentrations throughout hospitalization.

From this clinical experience, consideration of alternative dextrose infusion dosing in nondiabetic patients is recommended to maintain the insulin infusion dose close to the therapeutic goal. Empirical dextrose therapy could be initiated with infusion of dextrose 10% in water at a calculated maintenance intravenous fluid rate based on patient weight. The dextrose infusion should be titrated on the basis of glucose levels (Table 2). For glucose levels of 70 mg/dL or lower or symptomatic hypoglycemic episodes, we recommend increasing the glucose infusion concentration by doubling the dextrose 10% in water infusion rate or switching to dextrose 20% in water at the same initial infusion rate. If the glucose level is between 71 and 180 mg/dL, we recommend continuing the current dextrose infusion rate. If the glucose level is greater than 180 mg/dL, we recommend decreasing the glucose infusion

TABLE 2. Recommendation for Dextrose Infusion Titration Dosing in Nondiabetic Patients[a]

	Glucose range (mg/dL)[b]		
	≤70 or symptomatic hypoglycemic episode	71-180	>180
Dextrose infusion recommendation[c]	Increase glucose concentration by either double D10W rate or switch to D20W with same rate	Continue D10W at current infusion rate	Decrease glucose concentration by either reducing rate of D10W by half or switching to D5W with same rate

[a]D5W, dextrose 5% in water; D10W, dextrose 10% in water; D20W, dextrose 20% in water.
[b]SI conversion factor: To convert glucose values to mmol/L, multiply by 0.0555.
[c]Based on initial infusion with D10W at patient-specific maintenance intravenous fluid rate.

concentration by reducing the dextrose 10% in water by 50% or switching to dextrose 5% in water at the same initial infusion rate. Development of a protocol could be considered, with recognition that it may require patient-specific adjustments to prevent glycemic complications.

Clinical pharmacy consultation is recommended, if possible, to ensure appropriate euglycemic control and obtain recommendations for dextrose infusion titration. In this case, the pharmacists implemented the initial dextrose infusion titration instructions and provided multivariable adjustments (ie, concentrations and rates) based on patient progress, laboratory results, and volume status. The clinical pharmacists were proactive with the gastroenterology service through interdisciplinary rounds and frequent medical record monitoring. In addition, education on the dextrose titration instructions was provided for physicians and nursing staff. At our institution, clinical pharmacy personnel are available from 7 in the morning to 10 in the evening. During pharmacy off hours, it was recommended to utilize the titration instructions and the hypoglycemia protocol if needed. The clinical pharmacists' assistance in the management of dextrose titrations in our case was imperative for successful treatment and prevention of adverse events.

Our recommendations in this single case should be applied cautiously given other patient factors that may affect the blood glucose levels. We recommend close blood glucose monitoring throughout the time the patient is receiving the insulin and dextrose infusions. These titration recommendations should not be applied to patients with a history of diabetes mellitus, and adjustments are recommended when blood glucose and/or triglyceride goals are not met.

CONCLUSION

We present a case of hypertriglyceridemia-induced acute pancreatitis in a 34-year-old nondiabetic woman that was successfully treated with a reduced-dose insulin infusion and titrated dextrose infusion directed by clinical pharmacy.

Grant Support: This study was supported in part by a research grant from the Mayo Clinic Midwest Pharmacy Research Committee.

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Jamie M. Reed, PharmD, BCPS, Department of Pharmacy, Indiana University Health, 550 N University Blvd, Indianapolis, IN 46202 (jamiereed193@gmail.com).

ORCID

Jamie M. Reed: https://orcid.org/0000-0002-6941-1313; Breann M. Hogan: https://orcid.org/0000-0003-3547-4954

REFERENCES

1. Charlesworth A, Steger A, Crook MA. Acute pancreatitis associated with severe hypertriglyceridaemia; a retrospective cohort study. *Int J Surg*. 2015;23(pt A):23-27.
2. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. *JAMA Intern Med*. 2016;176(12):1834-1842.
3. de Pretis N, Amodio A, Frulloni L. Hypertriglyceridemic pancreatitis: epidemiology, pathophysiology and clinical management. *United European Gastroenterol J*. 2018;6(5):649-655.
4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary; a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Circulation*. 2019;139(25):e1178-e1181]. *Circulation*. 2019;139(25):e1046-e1081.
5. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline [published correction appears in *J Clin Endocrinol Metab*. 2015;100(12):4685]. *J Clin Endocrinol Metab*. 2012;97(9):2969-2989.
6. Kuchay MS, Farooqui KJ, Bano T, Khandelwal M, Gill H, Mithal A. Heparin and insulin in the management of hypertriglyceridemia-associated pancreatitis: case series and literature review. *Arch Endocrinol Metab*. 2017;61(2):198-201.
7. Samarasinghe S, Avari P, Meeran K, Cegla J. Management of hypertriglyceridaemic pancreatitis in the acute setting and review of literature. *BMJ Case Rep*. 2018;11(1):e227594.
8. Twilla JD, Mancell J. Hypertriglyceridemia-induced acute pancreatitis treated with insulin and heparin. *Am J Health Syst Pharm*. 2012;69(3):213-216.
9. Jin M, Peng JM, Zhu HD, et al. Continuous intravenous infusion of insulin and heparin vs plasma exchange in hypertriglyceridemia-induced acute pancreatitis. *J Dig Dis*. 2018;19(12):766-772.
10. Xie C, Stevens DC, Sturm T. Safe and effective triglyceride-lowering therapy for hypertriglyceridemia associated pancreatitis: insulin mono-therapy in a non-diabetic patient. *S D Med*. 2018;71(1):26-28.