CLINICAL VIGNETTE

Two Cases of Hypertriglyceridemia-Induced Pancreatitis

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Introduction

There are no current guidelines for intravenous insulin in acute management of Hypertriglyceride Pancreatitis (HTGP). HTGP is associated with increased severity of disease and number of complications. We present two patients with metabolic syndrome who had very severe hypertriglyceridemic pancreatitis (HTGP). We discuss the pathophysiology and acute management of HTGP.

Case 1

A 50-year-old man presented with one week of left lower quadrant pain radiating to his right side. His past medical history includes type 2 diabetes mellitus, morbid obesity, hypertension, hyperlipidemia, hypertriglyceridemia, chronic pancreatitis, coronary artery disease, atrial fibrillation, and sleep apnea. In the emergency room, he was diagnosed with acute pancreatitis, with a serum lipase of 3,879 (<160 U/L), and consistent computed tomography (CT) imaging. Serum triglyceride level was 6,895 (40-160 mg/dL), and serum glucose was 215 (70-110 mg/dL). He was made NPO, admitted to the ICU and treated with antiemetics, fluid, and started on insulin and dextrose infusions. The insulin infusion rate was started at 12 units/hr (0.1 units per kilogram (kg) per hr). This rate was increased by about 4 units each day, to a maximum infusion rate of 20 units/hr.

His triglycerides decreased from 6,895 to 2,750 mg/dL in the first 24 hours, and over the next 48 hours triglycerides further decreased to 894 mg/dL. He was then transitioned to subcutaneous insulin. His home medication: atorvastatin 80 milligrams (mg), Icosapent ethyl 2 grams twice a day, and fenofibrate 145 mg daily were restarted and continued as after discharge.

His apolipoprotein B/A ratio was elevated, with low apolipoprotein A-1, and elevated apolipoprotein B-100, indicating elevated cardiac risk.

Case 2

A 49-year-old man presented with one day of abdominal pain. He had poorly controlled type 2 diabetes mellitus, morbid obesity, hypertension, hyperlipidemia, hypertriglyceridemia, and previous episodes of acute pancreatitis.

In the emergency room, he was diagnosed acute pancreatitis, with a serum lipase of 271 (<160 units/L) and consistent CT imaging. Serum triglyceride level was 4,002 (40-160 mg/dL), and serum glucose was 265 (70-110 mg/dL). Patient was made NPO, admitted to the ICU and treated with antiemetics, fluid, and started on an insulin infusion.

Insulin infusion rate started at 18 units/hr (0.1 units/kg/hr). Triglycerides increased to 6,626 mg/dL and the insulin infusion rate was increased to 16 units/hr, with triglyceride decrease to 1,779. Insulin drip was then transitioned to subcutaneous insulin. He was started on fenofibrate, fish oil. Home atorvastatin was initially held given elevated transaminases. His course was complicated by severe hypocalcemia treated with intravenous calcium gluconate. His liver tests normalized and atorvastatin was restarted on discharge. His hypocalcemia resolved without further treatment. Apolipoprotein levels and genetic tests were not obtained.

Discussion

These two patients presented severe HTGP and metabolic syndrome (type 2 diabetes mellitus, obesity, hypertension, and hyperlipidemia). HTGP typically occurs in patients with underlying primary dyslipidemia who have a secondary condition such as metabolic syndrome, poorly controlled diabetes, alcohol consumption, or the use of certain medications.[1] However, these patients did not have known genetic primary dyslipidemias or physical exam findings consistent with familial hypertriglyceridemia.

Hypertriglyceridemia is defined as a fasting triglyceride level of $\geq$ 150 mmol/L by the Endocrine Society 2010 guidelines. The severity of hypertriglyceridemia is further categorized into mild (150-199 mg/dL), moderate (200-999 mg/dL), severe (1,000-1,999 mg/dL), and very severe ($\geq$2,000 mg/dL). Mild

and moderate hypertriglyceridemia are predictive for cardiovascular disease, with severe and very severe hypertriglyceridemia additionally predictive for pancreatitis.[2]

HTGP is also associated with increased severity of disease and complications compared to other types of acute pancreatitis. One study of 176 patients with severe acute pancreatitis with HTG $\geq$ 500 mg/dL reported more severe disease reflected by hypoalbuminemia, hypocalcemia, APACHE-II scores, renal failure, shock, infection, and overall mortality.[3,4]

Lipoprotein lipase (LpL) is expressed in adipose, skeletal, and cardiac muscle tissue where it hydrolyzes triglycerides in chylomicrons and VLDL to release free fatty acids (FFAs). At triglyceride levels of greater than 1,000 mg/dL, it is thought that LpL becomes saturated and cannot further break down and excrete triglycerides. Triglyceride levels can rapidly increase.[5] The diagnosis of HTGP is definitive when acute pancreatitis occurs with serum triglyceride level above 1,000 mg/dL.[6]

Hypertriglyceridemia is thought to cause pancreatitis by a number of mechanisms including the release of toxic free fatty acids from triglyceride-rich chylomicrons and increased viscosity of pancreatic blood flow leading to ischemia.[1,7] Release of free fatty acids from chylomicrons are directly cytotoxic to acinar and endothelial cells leading to ischemia and acidosis, both of which activate trypsinogen, triggering acute pancreatitis.[1] Additionally, it is thought that the high concentration of triglyceride-rich chylomicrons increases the plasma viscosity, further contributing to ischemia and acidosis, activating trypsinogen and triggering pancreatitis.[1]

There are five well-described familial primary etiologies of hypertriglyceridemia. Type I hyperlipidemia (familial chylomicronemia) is a rare, autosomal recessive disease caused by mutations in the LPL or apoC gene, typically presenting in childhood, leading to severe hypertriglyceridemia (HTG), cutaneous xanthomas, hepatosplenomegaly, and recurrent episodes of acute pancreatitis.[1] Type II (familial combined hyperlipidemia, FCHL) is autosomal dominant and associated with HTG, elevated VLDL, LDL, and apoB, underlying metabolic syndrome, and premature cardiovascular disease (CVD). Type III (familial dysbetalipoproteinemia) is due to a mutation in APOE leading to elevated VLDL, chylomicrons, HTG, xanthomas, orange palmar creases, and premature CVD. Type IV (familial hypertriglyceridemia, FHTG) is autosomal dominant and associated with HTG, elevated VLDL, and is not associated with increased CVD or any physical findings. Lastly, familial hypoalphalipoproteinemia (FHA, Tangier's Disease) is associated with HTG, low HDL associated with CVD.[1,4]

In addition to primary dyslipidemias, secondary etiologies such as insulin resistance and metabolic syndrome can lead to HTG. Insulin typically activates LpL, and in cases of poorly controlled type 2 diabetes mellitus and insulin resistance, inability to activate LpL leads to an accumulation of triglycerides through decreased hydrolysis and clearance.[1] Insulin has the added benefit of reducing serum glucose levels in patients with poorly controlled diabetes.[4]

Insulin's action on LpL is thought to explain its efficacy in treating HTGP. Unfortunately, validated guidelines for the treatment of HTGP do not currently exist. Management of HTGP currently focuses on conservative measures including dietary changes, introduction of medications such as fibrates, omega-3 fatty acids (eicosapentaenoic acid, EPA), and statins if indicated by CVD risk. In acute pancreatitis with HTG > 1,000 mg/dL, intravenous insulin is added. Guidelines on the dosing of insulin for optimal clearance of triglycerides have not been established.

Plasmapheresis is no longer recommended by the Endocrine Society due to elevated cost and risk with inadequate evidence that it decreases morbidity and mortality.[2] Additionally, the American Society for Apheresis (ASFA) grades apheresis to treat HTGP as 2C (weak recommendation).[8] A retrospective study on clinical outcomes in HTGP found no significant difference in mortality or complications between those who did and did not receive plasmapheresis.[9] Unfractionated heparin was previously thought to be useful due to its mechanism of stimulating LpL release from endothelial cells, however, subsequent reports show only a temporary increase in LpL activity and depleted LpL stores. Heparin is no longer recommended treatment for acute HTGP.[10]

In our two cases of very severe HTGP, insulin therapy was initiated at 0.1 units/kg/hr and increased based on rate of change of triglyceride level. Insulin was paired with dextrose solutions to maximize insulin infusion rates. In one comparative review of 34 patients with HTGP, the average insulin infusion rate was between 0.1-0.3 units/kg/hr, and it was co-administered with 5% dextrose infusions when the blood glucose was below 200 mg/dL.[11] The vast majority of these patients had significant reductions in serum triglycerides to at least less than 500 mg/dL after three to five days of intravenous insulin therapy. However, one patient in this series died from HTGP due to cardiac arrest from metabolic acidosis and electrolyte disturbances. Patients with HTGP are more likely to develop organ failure compared to other causes of pancreatitis.[11]

Much of the existing literature on acute management of HTGP centers on combined therapy with either apheresis or heparin infusions with intravenous insulin therapy. Future studies need to examine the efficacy of intravenous insulin therapy either in isolation or in combination with other conservative measures: diet, fibrates, statins, and omega-3 fatty acids. The Endocrine Society recommends against heparin infusions and plasmapheresis, and needs to assess optimal insulin infusion rates.[11] HTGP is clearly associated with increased morbidity, mortality, and severity of disease. There is need for a standardized protocol for treating patients with severe HTGP.

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