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ORIGINAL PAPER

Heparin and Insulin in the Treatment of Hypertriglyceridemia-Induced Severe Acute Pancreatitis

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Abstract Heparin and insulin stimulate lipoprotein lipase activity. Therefore, they reduce serum triglyceride levels. However, heparin and insulin's efficacy in treatment of hypertriglyceridemia-induced acute pancreatitis is not well established. We report a patient in whom heparin and insulin were used successfully.

Keywords Hypertriglyceridemia · Acute pancreatitis · Heparin · Insulin

Acute pancreatitis (AP) has been defined as the presence of a consistent clinical history and physical examination supported by serum amylase elevated to at least three times the upper limit of normal and positive pancreatic imaging. Severe pancreatitis has been defined as an APACHE II score ≥ 8 or a Ranson score ≥ 2 [1].

More than 75% of patients with hypertriglyceridemia-induced pancreatitis are either chronic alcoholics or uncontrolled diabetics. Hypertriglyceridemia may be primary (as seen in types I, IV, and V hyperlipoproteinemia) or secondary to diabetes mellitus, alcoholism, pregnancy, obesity, or use of certain drugs. Hypertriglyceridemia is thought to be the cause in 1% to 4% of patients with pancreatitis [2, 3].

Heparin and insulin stimulate lipoprotein lipase activity [4, 5]. Therefore, they reduce serum triglyceride levels. However, heparin and insulin's efficacy in treatment of hypertriglyceridemia-induced acute pancreatitis is not well established. We report a patient in whom heparin and insulin were used successfully.

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Case report

The patient is a 44-year-old man with a history of non-insulin-dependent diabetes mellitus (NIDDM) who presented to the emergency department for evaluation of the acute onset of abdominal pain. He presented with progressively increasing pain in the upper abdomen and vomiting for 2 days. His pain was severe, constant in character, radiating to the back and flanks, and decreased in intensity on sitting upright. He had no history of fever, constipation, or jaundice. His medical history was significant for NIDDM. He was uncertain of the names of the oral hypoglycemic and antilipidemic drugs that had been prescribed to him. He did not use tobacco or alcohol.

The physical examination revealed a temperature of 37°C, a blood pressure of 120/70, a pulse of 94/min, a respiratory rate of 16/min, a regular heart rate, clear lungs on auscultation, and a diffusely tender abdomen without rebound or guarding. The liver was palpable 2 cm below the costal margin in the midclavicular line. The spleen was not palpable and there was no mass or free fluid in the abdomen. Examination of the cardiovascular, respiratory, and nervous systems revealed no abnormal findings.

The patient's Ranson score at admission was positive for one criterion (white blood cell level, 18,800/mm^3). The glucose level was 345 mg/dL at admission. The glucose level does not represent the Ranson score because the patient already had NIDDM. His Ranson score 48 hr later was positive for four criteria (drop in hematocrit, calcium, oxygen saturation, and an increased base deficit). His APACHE-II (Acute

Table 1 Laboratory investigations

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 10
White blood cell count/mm^3	18,800	12,000	13,400	16,500	8,830	8,270	7,550
Plasma glucose (mg/dL)	345	167	220	190	279	198	162
Serum amylase (U/L)	976	258	33	32	33	—	—
Serum lypase (U/L)	382	121	61	40	28	—	—
ALT (IU/L)	40	21	19	16	24	26	19
AST (IU/L)	27	18	20	17	15	20	24
LDH (IU/L)	338	349	261	232	231	188	127
Serum calcium	6.8	6.5	6.8	7.2	7.7	8.9	10
Serum triglycerides (mg/dL)	1,707	713	589	474	345	195	180
Serum cholesterol (mg/dL)	499	296	261	218	168	131	126
CRP (mg/L)	142	—	—	96	—	24	—

Physiology and Chronic Health) score was 8. Relevant investigations on admission and hospital stay are listed in Table 1. The serum was lipemic (lactescent serum), with an elevated triglyceride level of 1707 mg/dl (normal, 40–200 mg/dl); serum amylase was 976 U/L (normal, 25–125 U/L); urine amylase was 8390 U/L; and serum lypase was 382 U/L (normal, 8–80 U/L) on day 1. A chest roentgenogram revealed bilateral pleural effusion. Ultrasonography revealed edematous pancreas with a small amount of peripancreatic fluid. CT scan suggested mild pancreatitis with no evidence of necrosis or involvement of peripancreatic fat planes. A repeat abdominal CT scan did not reveal worsening changes of the pancreas. Fundus examination revealed normal blood vessels with no evidence of lipemia retinalis.

Conservative management was started (nil per mouth, intravenous fluids, analgesics, proton pump inhibitors and antiemetics). Also, we started the patient on infusion of 5% dextrose with 3 U/hr regular human insulin (blood sugar controlled to <200 mg/dL) and injection of 5000 U heparin intravenously twice daily with the aim of reducing serum triglyceride levels. His pain decreased and vomiting subsided by day 2. Serum triglycerides decreased to 713 mg/dL. He was allowed clear fluids perorally on day 7 and a semisolid diet on day 10. Serum triglycerides decreased to 589 mg/dL on day 3. We could not assay blood samples from his siblings and children. During the remainder of his hospitalization, the patient's abdominal pain and laboratory values gradually improved. He recovered with heparin–insulin and conservative medical management and did not require surgical intervention. On hospital day 14, the patient was discharged in very good condition.

Discussion

The pancreas contains a high concentration of the digestive enzyme lipase, which hydrolyzes triglycerides to glycerol and free fatty acids. Normally, serum free fatty acids are bound to albumin and are nontoxic. High local concentrations of free fatty acids may develop locally in the pancreas if elevated serum triglycerides are hydrolyzed in the pancreas or if elevated serum triglycerides are hydrolyzed in the gland by the endogenous lipase. Saturation of albumin binding can then occur, with the release of large amounts of cytotoxic free fatty acids in the pancreatic circulation. Vascular endothelial damage may cause slugging of red blood cells, stasis, and pancreatic ischemic injury and inflammation. Lipoprotein lipase deficiency associated with chylomicronemia is an uncommon autosomal recessive disorder caused by many different lipoprotein lipase gene mutations and is characterized by high fasting plasma triglyceride levels, which can be complicated with acute pancreatitis. Patients with hypertriglyceridemia of >1000 mg/dL are at high risk for acute pancreatitis [6, 7]. Severe hypertriglyceridemia may play an important role in the aggravation of acute pancreatitis because circulating triglycerides continuously damage pancreatic tissue [8]. Recognizing that a plasma triglyceride level >500 mg/dL can cause a falsely normal amylase level is critical. The mechanism is thought to be interference with in vitro determination of the actual amylase level by prevention of the calorimetric reading of the assay end point. Serial dilutions of the patient's sample with the assay buffer to reduce interference of light transmission by hyperlipidemic serum can reveal an abnormal amylase value that was previously masked by the lactescent plasma [6, 9].

Hypertriglyceridemia-associated pancreatitis usually occurs when triglyceride levels are >1000 mg/dL, but it is uncertain how long these levels must be sustained before pancreatitis results. Hyperlipoproteinemia types I, IV, and V are associated with acute pancreatitis. Triglyceride levels >1000 mg/dL predispose to the development of pancreatic inflammation. More than 75% of patients with hypertriglyceridemia-induced pancreatitis are either chronic alcoholics or diabetics. Hypertriglyceridemia may be

primary (as seen in types I, IV, and V hyperlipoproteinemia) or secondary to uncontrolled diabetes mellitus, alcoholism, pregnancy, obesity, or use of certain drugs. Acute pancreatitis develops in 35%, 15%, and 30%–40% in types I, II, and V hyperlipidemia, respectively. The main treatment for hyperlipidemic severe acute pancreatitis is to decrease the serum triglyceride level and to prevent a systemic inflammatory response. Lowering serum triglyceride levels to <200 mg/dL can prevent pancreatitis [2, 3, 10].

Lipoprotein lipase is an enzyme produced by the capillary endothelial cells of muscles and fat; it mediates the hydrolysis of triglycerides into free fatty acids and glycerol. Its activity is thus crucial in decreasing serum triglyceride level. Hypertriglyceridemia >1000 mg/dL can provoke acute pancreatitis and its persistence can worsen the clinical outcome. On the contrary, a rapid decrease in triglyceride level is beneficial. Heparin and insulin stimulate lipoprotein lipase release and its activity and accelerate chylomicron degradation and, hence, are effective in rapidly reducing triglyceride levels [4, 5]. In a series of five patients with hypertriglyceridemia-induced pancreatitis, serum triglyceride decreased from a mean of 3822.2 to 888.8 mg/dL within a mean 2.8 days [4]. Also, Berger et al. have reported that serum triglyceride levels decreased to <500 mg/dL within 3 days in all cases [11]. All patients had rapid clinical resolution of pancreatitis. Our patient's serum triglyceride levels decreased to <500 mg/dL within 4 days and normalized within 7 days, with resolution of symptoms (with treatment of heparin and insulin infusion). Our patient received insulin, heparin, and antilipidemic agents to prevent deterioration of the disease by maintaining the serum triglyceride level within the normal range 7 days after onset of the disease. Intravenous insulin administration is the key therapy for diabetic patients with hypertriglyceridemia-induced AP. Intravenous insulin is safe and effective in the treatment of hypertriglyceridemia-induced AP, even in patients without diabetes mellitus [4]. Lipoprotein lipase activity, improved by chronic insulin administration, is further enhanced by the fibrate. This results in the most effective control of tryglyceride levels. Consequently, heparin–insulin treatment was very effect in reducing hypertriglyceridemia in a short period [4, 5].

Plasmapheresis has been performed in some patients to remove chylomicrons from the circulation, while heparin and/or insulin have been administered in other cases to rapidly reduce blood triglycerides. Plasmapheresis has also been used for the treatment of hypertriglyceridemia-induced pancreatitis. Although serum triglyceride could be decreased by plasmapheresis, there has been no formal therapeutic strategy to treat hyperlipidemic acute pancreatitis at present. This treatment modality is far more expensive and is not available except at tertiary care centers [12, 13].

We suggest that lipid lowering treatment in addition to heparin and insulin be further evaluated as first-line management of patients with hypertriglyceridemia-induced pancreatitis. Our results were in accordance with the report in the literature. Heparin/insulin is safe and effective in the treatment of hypertriglyceridaemia-induced pancreatitis. A low-fat diet and supplements of (n-3)fatty acids (fish oil), and fibrates are recommended for long-term maintenance therapy. In summary, hyperlipidemic acute pancreatitis has not only the general characteristics of severe acute pancreatitis, but also some specific characteristics. So, in addition to the conventional therapy for acute pancreatitis, a specific strategy should be taken into consideration.

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