Treatment of hypertriglyceridemia-induced acute pancreatitis with insulin

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Abstract

Introduction: Hypertriglyceridaemia (HT)-induced pancreatitis rarely occurs unless triglyceride levels exceed 1000 mg/dl. Hypertriglyceridaemia over 1,000 mg/dl can provoke acute pancreatitis (AP) and its persistence can worsen the clinical outcome. In contrast, a rapid decrease in triglyceride level is beneficial. Insulin-stimulated lipoprotein lipase is known to decrease serum triglyceride levels. However, their efficacy in HT-induced AP is not well documented.

Aim: To present 12 cases of AP successfully treated by insulin administration.

Material and methods: Three hundred and forty-three cases of AP were diagnosed at our clinic between 2005 and 2012. Twelve (3.5%) of these cases were HT-induced AP. Twelve patients who suffered HT-induced AP are reported. Initial blood triglyceride levels were above 1000 mg/dl. Besides the usual treatment of AP, insulin was administered intravenously in continuous infusion. The patients' medical records were retrospectively evaluated in this study.

Results: Serum triglyceride levels decreased to < 500 mg/dl within 2–3 days. No complications of treatment were seen and good clinical outcome was observed.

Conclusions: Our results are compatible with the literature. Insulin may be used safely and effectively in HT-induced AP therapy. Administration of insulin is efficient when used to reduce triglyceride levels in patients with HT-induced AP.

Introduction

Acute pancreatitis (AP) is a common condition with several aetiologies. Hypertriglyceridaemia (HT) is a rare but well known cause of AP, which can be a life-threatening complication if the degree of HT is severe enough. Hypertriglyceridaemia as a cause of AP reaches frequencies of 1–7%, according to the literature, when triglyceride levels reach more than 1,000 mg/dl [1–8]. More than 75% of HT-induced AP cases are either chronic alcoholics or uncontrolled diabetics [6]. Hypertriglyceridaemia may be primary (e.g. type I, IV, or V) or secondary (diabetes mellitus, alcoholism, pregnancy, obesity, utilisation of some drugs). In most cases that exceed 1500 mg/dl some form of primary HT or a genetic defeat in lipid metabolism may be seen. Genetic factors are effective in more than 60% of changes in serum lipids [1, 7, 8]. Apart from conventional methods of treatment, several less frequently used methods have been described in the literature to decrease the triglyceride levels rapidly, e.g. plasmapheresis, apoliprotein CII infusion, and use of insulin and heparin [4, 9, 10]. Heparin and insulin are known to stimulate lipoprotein lipase activity [11–13]. The objective of medical treatment is to increase lipoprotein-lipase activity, and to increase chylomicron breakdown, thus diminishing serum triglycerides to levels below 500 or even 200 mg/dl (when possible) using a variety of strategies, including insulin administration. There have been reports in which heparin and insulin have been used for acute reduction of triglycerides, although there are no established guidelines for the efficacy of these modalities. Insulin decreases triglycerides by stimulating lipoprotein lipase activity, which degrades triglycerides into fatty acids and glycerol [4, 10, 11, 13–15].

Aim

We report 12 cases of HT-induced AP that were successfully treated by insulin.

Material and methods

Three hundred and forty-three cases of AP were diagnosed at our clinic between 2005 and 2012. Twelve (3.5%) of these cases were HT-induced AP. Twelve patients who suffered HT-induced AP are reported. We used "Ranson criteria for non-biliary acute pancreatitis" for assessment of the severity of pancreatitis. Initial blood triglyceride levels were above 1000 mg/dl. Besides the usual treatment of AP, insulin was administered intravenously in continuous infusion. The patients' medical records were retrospectively evaluated in this study.

Results

Three hundred and forty-three cases of AP were diagnosed and treated at our clinic between 2005 and 2012, and 12 (3.5%) of these cases were HT-induced AP. Clinical and laboratory parameters of the patients are summarized in Table I. Eight patients were male and four patients were female. The mean age was 48 (35–65) years. The most significant complaint was increase abdominal pain. Nausea and vomiting were observed in most patients. The patients did not have diabetes or alcohol consumption habit. Chest and abdominal X-rays were normal. Cholelithiasis was not detected in abdominal USG. The mean plasma triglyceride level was 1146 (1004–1235) mg/dl, the mean amylase level was 414 (84–780) U/l, and the mean lipase level was 552 (198–1966) U/l. Abdominal computed tomography (CT) was performed for all patients. Patients were diagnosed with AP. According to Ranson criteria, 6 of 12 patients had severe pancreatitis that had a Ranson Severity score more than 3. Eight of the 12 patients were diabetic and others were primary HT. For all patients, oral nutrition was discontinued and conservative treatment was started with intravenous fluid with analgesic and antiemetic administration. Subsequently, patients were started on intravenous regular insulin infusion in 5% dextrose, making sure that their blood glucose levels were lower than 200 mg/dl. There was an improvement in abdominal pain and nausea-vomiting complaints. Following intravenous insulin treatment, triglyceride (TG) levels decreased to < 500 mg/dl in 3 days on average, amylase and lipase levels returned to normal levels after 3–4 days, and patients' abdominal pains were resolved. The mean hospitalisation period was 6 days on average [5–9]. Insulin infusions were discontinued after 3 days on average, patients showed clinical improvement, and their plasma TG levels were lower than 300 mg/dl. Patients' treatments were continued using lipid lowering agents following their discharge.

Discussion

Hypertriglyceridaemia may be responsible for 1–7% of all cases of AP [1, 3, 4, 6, 11, 13]. Chylomicronaemia may be responsible for 20% of AP in non-drinkers free of biliary tract disease. It was previously reported that HT was the cause of 56% of cases of gestational pancreatitis [16–19]. In many cases, determining the exact aetiology of pancreatitis may be complicated because of the role of ethanol in precipitating severe HT. The proportion of alcoholic pancreatitis caused by direct as opposed to secondary hyperlipidaemic effects is unknown.

Hypertriglyceridaemia-induced AP rarely occurs unless triglyceride levels exceed 1000 mg/dl [1, 4, 10, 15, 20]. On the contrary, mild to moderate elevations in triglyceride levels are quite common in the early phase of AP of any aetiology. Hypertriglyceridaemia-induced pancreatitis generally occurs when the triglyceride levels exceed 1000 mg/dl, but the exact period that is essential for HT-induced pancreatitis progression is unclear.

More than 75% of HT-induced patients are either alcoholics or diabetics. Hyperglyceridaemia may be primary (like type I, IV, V hyperlipoproteinaemia) or secondary (like uncontrolled diabetes mellitus), alcoholism, pregnancy, obesity, utilisation of some drugs) [11]. Type I, IV, and V hyperlipoproteinaemia may be seen with AP. The occurrence rate of AP in type I, II and V hyperlipidaemia may be 35%, 15% and 30–40%, respectively [11].

The exact mechanisms of HT-induced pancreatitis are not clear [1, 4]. Chylomicrons are triglyceride-rich lipoprotein particulars that are known to be responsible for inflammation. This condition generally occurs when serum triglyceride levels exceed 1000 mg/dl. Pancreas contains high amounts of lipase. Lipase hydrolyses triglycerides to glycerol and free fatty acids. In normal serum, free fatty acids are bound to albumin and nontoxic. Overloading of lipoproteins may lead to damage in circulatory flow in capillary beds. If this occurs in the pancreas, the resulting ischaemia might damage the acinar structures and expose pancreatic lipase. The generated proinflammatory non-esterified free fatty acids further damage pancreatic acinar cells and microvasculature [16]. Post amplification of the release of inflammatory mediators and free radicals may eventually lead to necrosis, inflammation, oedema, pancreatic ischaemic injury, stasis, slugging of red blood cells, and vascular endothelial damage. This hypothesised sequence of events was proven by studies showing that both triglycerides and free fatty acids caused oedema, haemorrhage, and elevated amylase levels. Hypertriglyceridaemia has also been shown to cause exacerbations in other experimental models of pancreatitis.

Studies using oral lipid-loading tolerance tests have documented elevated past-load plasma triglyceride lev-

Table I. Clinical and laboratory parameters of the patients with hypertriglyceridaemia-induced acute pancreatitis

Patients	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD
Age [years]/gender	41/Male	48/Female	54/Male	35/Male	43/Female	30/Female	59/Male	46/Male	40/Female	45/Male	65/Male	46/Male	46	9.75
Time to diagnosis [days]	3	3	2	3	2	1	3	2	1	3	2	2	2.25	0.75
Plasma glucose (70–110 mg/dl)	104	162	123	158	98	96	118	115	108	125	110	98	117.92	21.87
Total leucocyte count (4–11 × 10^3 cells/mm^3)	13 500	14 700	9 500	6 600	9 100	15 300	9 800	10 800	8 400	9 600	10 300	11 400	10 750	2589.31
AST [U/l] (5–37 U/l)	37	23	28	18	35	30	48	38	39	45	56	40	36.42	10.64
ALT [U/l] (0–41 U/l)	24	18	11	20	15	17	39	34	32	40	39	74	30.25	17.19
ALP [U/l] (< 130 U/l)	115	86	87	98	79	96	66	128	122	148	145	58	102.33	29.32
Serum amylase (25–125 U/l)	155	128	84	635	497	259	780	368	424	490	530	330	390.00	211.72
Serum lipase (10–60 U/l)	350	286	196	376	138	86	420	115	146	198	245	166	226.83	109.05
Serum calcium (9–11 mg/dl)	8.5	8.4	9.6	8.3	6.8	7.4	7.8	9.2	8.4	7.6	8.5	8.8	8.27	0.77
Serum albumin (3.5–4.8 mg/dl)	3	3.4	3.2	3.6	3.3	4	3.4	3.6	3.9	3.5	3.2	3.2	3.44	0.29
Serum triglycerides (50–250 mg/dl):														
d1	1118	1176	1228	1027	1004	1086	1130	1156	1124	1235	1190	1215	1140.75	74.74
d2	540	635	712	760	684	756	710	654	785	796	810	774	718.00	79.37
d3	355	464	489	496	476	481	528	498	494	524	590	520	492.92	54.51
d4	272	248	385	415	346	390	425	432	384	434	445	370	378.83	62.93
d5	243	232	358	366	252	324	373	290	296	276	356	298	305.33	49.81

els in patients with previous pancreatitis as compared with control subject. Interestingly, mutations in the lipoprotein lipase (LPL) gene have been identified in patients with HT-induced pancreatitis. Lipoprotein lipase deficiency with chylomicronaemia is a rare recessive disorder characterised by high serum fasting triglyceride levels that may be complicated with AP caused by different LPL gene mutations. normal amylase levels may be incorrectly determined when plasma triglyceride levels exceed 500 mg/dl.

In acute phase HT-induced pancreatitis should be treated in the same manner as other causes of pancreatitis. Currently, there is no clear evidence that HT-induced pancreatitis differs from other types of pancreatitis in terms of frequency of necrosis, complications, or outcomes. A similar approach to medical and diagnostic management is thus indicated.

There are various modalities in the treatment of HT, such as insulin and heparin, plasmapheresis, purified apo C II, and fibric acid derivatives [9, 10, 12, 20, 21].

In an acute setting, direct removal of chylomicrons can be easily done by plasmapheresis. Although plasmapheresis reduces the serum triglyceride levels, it is not a formal therapeutic strategy today.

Lipoprotein lipase is an enzyme that is produced by capillary endothelial cells of muscles and adipose tissues, which hydrolyses the triglycerides to glycerol and fatty acids [11]. Activity of LPL is very important in reducing serum triglyceride levels. Recognising that decreased LPL activity is a prominent cause of HT has fuelled attempts to enhance LPL activity. Heparin and insulin stimulate lipoprotein-lipase activity and accelerate chylomicron degradation [1]. Intravenous insulin and heparin were used in many patients in order to enhance LPL activity and accelerate the chylomicron destruction, and thus are effective in reducing the triglyceride levels rapidly. In several studies it was shown that with insulin and heparin therapy, serum triglyceride levels reduced significantly and pancreatitis improved. In our patients, serum triglyceride levels decreased and pancreatitis symptoms improved in seven days with insulin infusion. Intravenous insulin is an effective and safe method in the therapy of HT-induced AP cases. Diabetic patients should be treated with intravenous insulin infusion in order to obtain and maintain euglycaemia rapidly. Purified apoC-II infusion achieved temporary improvement in triglyceride levels and clinical condition in apoC-II-deficient patients.

Therapeutic effects following recovery from pancreatitis need to be directed at preventing recurrence by controlling triglyceride levels. Secondary HT causes should be treated simultaneously when they exist. Diabetes should be treated with oral hypoglycaemics or insulin in order to maintain strict glycaemic control. If hyperlipidaemia persists despite the fat reduced diet, lipid-lowering agents should be started. The fibric acid derivatives (fibrates) such as gemfibrozil are the drugs of first choice. These agents are generally well tolerated and highly effective if taken regularly and diet restrictions are continued. Also, omega-3 fatty acids, medium-chain triglyceride, and antioxidants may be supplemented.

The limitations of this study are the fact that it was a retrospective study, as well as the small number of cases.

Conclusions

Our results are compatible with the literature. Insulin may be used safely and effectively in HT-induced AP therapy. Hypertriglyceridaemia is a common clinical problem that can be seen in many medication and medical conditions. A remarkable rise in triglyceride levels may lead to pancreatitis, which is a serious and fatal complication. General and specific therapies are directed at reducing triglyceride levels in the acute phase of pancreatitis. Diet, pharmacological therapy, and avoiding triglyceride-elevating agents are the essential elements of preventing the future attacks. Hypertriglyceridaemia-induced AP covers not only the general characteristics of severe AP but also some specific characteristics. Thus specific strategies should be taken into consideration with the conventional therapy of AP.

Conflict of interest

The authors declare no conflict of interest.

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