Novel treatment (new drug/intervention; established drug/procedure in new situation)

Plasma exchange in the management of a case of hypertriglyceridaemic pancreatitis triggered by venlafaxine

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Summary

The authors present a case of a young, non-diabetic Caucasian male patient with long-standing depression who had recently been started on venlafaxine. He presented to the emergency department with central abdominal pain, drowsiness and vomiting with a raised serum amylase. He was diagnosed with acute pancreatitis (AP) that was confirmed following an abdominal ultrasound and CT. His initial biochemistry was immeasurable in the first 12 h of admission due to macroscopically visible hyperlipidaemia. In the absence of any other causes of AP, hyperlipidaemia was the most likely aetiology. He was transferred to the intensive care unit where he was managed by lipidic restriction, fluid resuscitation and 3 consecutive days of plasma exchange. Plasma triglyceride levels were reduced from 42.9 to 2.4 mmol/l following plasma exchange. He made a full recovery and at discharge was investigated for familial hypertriglyceridaemia and referred to a multi-disciplinary team for follow-up. His venlafaxine was stopped on admission.

BACKGROUND

Pancreatitis associated with hypertriglyceridaemia accounts for 1–4% of all cases.¹ Clinical presentation and evolution can be dramatic and early recognition of the association is important because rapid intervention to lower lipid levels is required to prevent further attacks. Most commonly, clinicians use diet and lipid-lowering medication; experiences with plasma exchange are limited both in the literature and in practice. This report presents a possible approach to the management of this disease by using plasma exchange therapy which rapidly corrects plasma lipids to normal values.

Furthermore, this case highlights the likely connection between venlafaxine therapy and hypertriglyceridaemic pancreatitis in this patient. The manufacturer acknowledges hypercholesterolaemia and hyperlipidaemia as infrequent but possible side effects.² It is most likely that on the background of familial hyperlipidaemia the antidepressant triggered elevated levels of plasma lipids responsible for the pancreatitis. These findings warrant further consideration and research about the safety of venlafaxine in patients with lipid metabolism derangement.

CASE PRESENTATION

We present the case of a 30-year-old patient who presented to the emergency department with a 1-week history of central abdominal pain and vomiting. The medical history included long-standing depression for which he had been started on venlafaxine 150 mg PO once a day, 3 months previously.

Despite acknowledging recreational alcohol consumption he denied recent excess consumption. He was otherwise fit and well. Enquiry about family medical history revealed that his mother and grandmother were treated with statins for dyslipidaemia and that his grandfather suffered a myocardial infarction. There was no family history of diabetes or autoimmune disease.

On the initial assessment he exhibited signs of the systemic inflammatory response syndrome (SIRS) with

tachypnoea and tachycardia and no obvious organ dysfunction. The abdomen was distended, tender on palpation in the epigastric and periumbilical area, with no guarding. Bowel sounds were high pitched and scarce. There was no clinical evidence of ascites. There were no signs of jaundice, goitre or xanthomas.

When venous blood was collected it developed lactescent deposits at the surface. Initially, two blood samples were not analysable due to increased viscosity.

INVESTIGATIONS

His initial blood results were: haemoglobin=161 g/l, white cell count=12.6, neutrophils=10.9, C reactive protein=411 mg/l, urea=5.5, creatinine=103, lactate dehydrogenase=376 U/l, bilirubin=22 µmol/l, alkaline phosphatase=106 IU/l, alanine transaminase=28 IU/l, amylase=2191 IU/l, triglycerides (TG)=42.9 mmol/l, cholesterol=15.4 mmol/l, high-density lipoprotein cholesterol=0.24 mmol/l.

An initial arterial blood gas showed a pH of 7.3, a base excess of -4.9 and a lactate of 4.7. The blood glucose level was 12.4 mmol/l. The serum calcium was 1.1 mmol/l. The calculated APACHE II score was 10 and the admission Ramsay score was 2.

A CT of his abdomen revealed large amount of fluid in the abdominal cavity surrounding the pancreas. The pancreas appeared oedematous with no evidence of necrosis. The appearances of the liver, gallbladder, spleen, kidneys and adrenals were normal. There was no evidence of pancreatic calcification or gallstones. The common bile duct was normal in size. There were bilateral moderate-sized pleural effusions.

DIFFERENTIAL DIAGNOSIS

- ▶ Hyperlipidaemic pancreatitis
- ▶ Alcohol related pancreatitis
- ▶ Gall stone pancreatitis
- ▶ Viral pancreatitis.

Figure 1 Triglyceride trend.

TREATMENT

Based on the clinical presentation, laboratory findings and imaging investigations a diagnosis of hyperlipidaemic acute pancreatitis were made. The patient was transferred to the intensive care unit. We instituted supportive therapy including fluid resuscitation and adequate analgesia; the patient was put nil by mouth and a proton pump inhibitor infusion was started. Central to active lipid-lowering therapy, we commenced plasma exchange via a dual-lumen central venous catheter. We used three sessions of therapeutic plasma exchange (TPE) in 3 consecutive days using 2 litres of human albumin solution 4.5%, 1 litre of colloid and 1 litre of fresh frozen plasma. The patient was started on a titrated heparin infusion both to prevent the extra-corporeal circuit from clotting and to treat the hyperlipidaemia. Despite adequate anticoagulation several filters were changed due to lipid accumulation on the membranes. An insulin infusion was also commenced to help lower the lipids.

OUTCOME AND FOLLOW-UP

The plasma exchange therapy was rapidly effective in reducing the plasma levels of TG and cholesterol. Following the initial TPE, which occurred in the first 24 h from presentation to emergency department, the TG level dropped from 42.9 to 14.7 mmol/L. The subsequent plasma exchanges performed on the following 2 days reduced the level to 2.4 mmol/L. Clinically the abdominal pain reduced in intensity, and the nausea ceased.

Figures 1 and 2, display changes in TG and amylase during the three episodes of TPE. The patient tolerated the plasma exchange well and required no cardiovascular support with inotropes or vasopressors.

Neutral fluid balance was maintained during the first two TPE sessions. As a consequence of overall positive fluid balance in the setting of systemic inflammation, the patient developed pulmonary oedema and one litre

of fluid was removed during the third TPE. Despite this, the combination of bilateral pleural effusions, atelectasis and acute respiratory distress syndrome (possible transfusion related acute lung injury), his respiratory function deteriorated and tracheal intubation and mechanical ventilatory support were required. Following 7 days of ventilation with low tidal volumes (6 ml/kg) and positive end-expiratory pressure (7 to 12 cm H₂O) along with active diuresis (overall negative balance of 5800 mls) his respiratory function improved sufficiently to allow successful extubation.

He continued to demonstrate signs of SIRS but despite several full septic screens no bacteria or fungi were identified. Further imaging of his abdomen did not demonstrate any evidence of abdominal sepsis.

Special consideration was given to his nutrition. After 3 days of gastrointestinal (GI) rest he was started on low volume low fat nasogastric feeding (10 mls/h) but unfortunately he did not absorb his feeding and we had to consider alternatives. A fat free total parenteral nutrition was commenced on the 5th day, for 20 h per day with a 4-h break. This provided 4.5 grams nitrogen and 800 kcal per day. Electrolytes, inorganic phosphate, calcium and microelements were supplemented. The patient remained haemodynamically stable and his respiratory function normalised over 10 days. He was discharged from out unit under the care of the surgical team and was referred for further investigations of his background lipidic disease. Venlafaxine has been replaced with duloxetine and his lipid levels will be monitored periodically.

DISCUSSION

Hypertriglyceridaemia is a recognised as a cause of pancreatitis but the mechanisms by which high levels of TG induce pancreatitis are not fully understood. It is believed that the level of circulating chylomicrons (CCs) is pivotal to the pancreatic insult. These TG lipoprotein particles

Figure 2 Amylase trend.

appear in the circulation when the level of TG rises to approximately 20 mmol/l.³ CCs are large in size and it is believed that they impede the microcirculation in the small capillaries of the pancreas causing inflammation and ischaemia thus triggering a cascade of events that lead to the known consequences of pancreatitis.⁴ Hypertriglyceridaemic pancreatitis has been cited in literature and the reported incidence varies between 1% and 10%.^{5 6} Given that elevated levels of TG trigger and sustain the pancreatic insult, the use of TPE to lower the circulating levels of these substances is a rational clinical approach and may prevent further attacks.

The classical approach to the management of pancreatitis is supportive: to rest the GI tract, suppress gastric acid production using a proton pump inhibitor, provide adequate analgesia, and fluid resuscitation and consider antibiotics if there is a high clinical index of suspicion of acute sepsis. Insulin is administered as an infusion and heparin as an infusion or as a bolus. The use of heparin and insulin is supported by experimental findings, which suggest that hypertriglyceridaemia is caused by lipoprotein lipase deficiency and its decreased activity. This enzyme plays an important role in the catabolism of lipoproteins. Insulin stimulates lipoprotein lipase synthesis and activity and enhances the degradation of chylomicrons to glycerol and fatty acids. Heparin is believed to mobilise the enzyme from the endothelium of the target organs into the plasma.^{3 7} Experiences with plasma exchange are not very common and few clinicians adopt this approach to lowering the circulating level of TG. No randomised controlled trial has compared the efficacy of insulin and heparin versus plasma exchange.⁸ The American Society for Apheresis Guidelines published in 2007 recommends plasma exchange for the management of hypertriglyceridaemic pancreatitis. Their recommendation is based on one non-randomised controlled trial with 29 patients, a few case series and 23 case reports.

The UK blood transfusion and tissue transplantation services recommend that plasma exchange should be considered in hypercholesterolaemia but there is no mention about its use in the management of hypertriglyceridaemic pancreatitis.⁹

In this case report, we demonstrate that plasma exchange provided a fast and reliable way to lower the TG from 40.3 mmol/l to 14.7 mmol within a few hours in the first episode of plasma exchange. A further plasma exchange on day 2 lowered the TG from 9.2 to 3.9 mmol/l. Following the first episode of plasma exchange the abdominal pain decreased considerably thus lowering the amount of his analgesic requirements.

An additional striking feature of this case report is the association between the usage of venlafaxine and the elevated levels of TG that most likely triggered the pancreatic insult. Based on the history taken from the patient and the family, there is clearly an element of familial lipid metabolism derangement. The patient denies alcohol abuse in the peri-event period and the CT scans excluded gallstones as a cause for the pancreatitis. In this context we have strong reason to believe that the venlafaxine was the exacerbating factor leading to the exceptionally high levels of TG and cholesterol. Venlafaxine is an antidepressant that acts by potentiating the neurotransmitter activity in the brain. It is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak dopamine reuptake inhibitor.² In the manufacturers leaflet that accompanies the medication, hypertriglyceridaemia and hypercholesterolaemia are listed as infrequent adverse effects of this therapy.² These data were obtained by studying the general population.² There is no reference to the possibility of excess risk posed by venlafaxine therapy in patients with lipid metabolism disturbances. A central aim of writing this case report was to outline the need for further investigation in this area and to increase awareness of this issue to medical professionals.

There are a limited number of examples in literature reporting the association between venlafaxine and pancreatitis. Venlafaxine is an antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) class. There is a significant amount of evidence related to the relationship between the selective serotonin reuptake inhibitors and SNRI, and the risk of lipid metabolism upset and pancreatitis.

A case control study performed by Norgaard *et al* during 1991 and 2003 in Norway showed a possible association between the usage of SSRIs and pancreatitis.¹⁰

A review of the WHO adverse drug reaction database found a total of 160 cases of pancreatitis related to SSRIs usage, and supported the theory that this class of agents may trigger pancreatitis in some occasions; also noting that these cases displayed a more severe course of the disease.¹¹

After reviewing the articles on Medline from 1966 to 2006, McIntyre *et al*¹² concluded that antidepressants negatively influence the lipid milieu to variable degrees and that more studies are necessary to establish a clearer picture of these interactions and their significance for clinical practice. The authors recommend routine evaluation of the lipid profile of patients during the initiation and maintenance stages of antidepressants.

Teitelbaum¹³ reports on a case of severe hypertriglyceridaemia in a patient initially taking fluoxetine and subsequently venlafaxine for depressive disorder, in the absence of any other triggering cause. Sequential lipid profiles of the patient, at the beginning and during the therapy with these agents, demonstrated progressing hypertriglyceridaemia and hypercholesterolaemia. Within 2 weeks from discontinuation of the venlafaxine, the lipid profile reverted to normal serum levels.¹³

Based on several clinical trials, The European Medicines Agency acknowledges that 5.3% of the patients treated with venlafaxine displayed clinically relevant increases in serum cholesterol as opposed to a 0% increase in the placebo groups.¹⁴

A review of the management of depression published in the American Journal of Medicine also recognises the potential for lipid metabolism disruption that venlafaxine may have.¹⁵

Again, two randomised, double-blind, placebo-controlled trials in children and adolescents published in the American Journal of Psychiatry report statistically significant changes in lipid levels associated with modified release venlafaxine therapy.¹⁶

It is important to remember the fact that these studies, which demonstrate relevant statistical associations, were performed on a general population and were not targeted to patients with a lipid metabolism disruption. We are unaware of the existence of class I evidence regarding the safety of venlafaxine and other SSRIs in this specific group.

The familial history of our patient is suggestive of a lipid metabolism derangement. The venlafaxine therapy was the triggering factor that caused the hypertriglyceridaemia and hypercholesterolaemia, which, in their turn, lead to the pancreatic insult.

We believe that our findings emphasise again the need for further investigations regarding the interactions of SSRIs and SNRIs with the lipid milieu. Clinicians should consider monitoring lipid profiles of patients at the start

of and during the therapy with this class of agents. Furthermore, unexplained abdominal pain in patients taking antidepressive medication should prompt the clinician to investigate for pancreatitis even in the absence of other risk factors.

Learning points

- ▶ Hypertriglyceridaemia accounts for up to 10% of all cases of pancreatitis and it is the most common cause after gallstones and alcohol.
- ▶ Lowering the TG level to less than 10 mmol/l had been reported to prevent further pancreatic insult. It is believed that cholesterol levels play a little role in the pathogenesis of pancreatitis.
- ▶ Plasma exchange is a non-standard but highly effective approach to lowering TG levels towards normal values in one to three episodes. It is generally well tolerated by the patient.
- ▶ Venlafaxine has a recognised possible effect on raising the TG and cholesterol levels. Consideration should be given when it is prescribed to a patient with a lipid metabolism dysfunction, especially if other precipitating factors are present.

Competing interests None.

Patient consent Obtained.

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