Hyperamylasemia and Hyperlipasemia after Cerebral Perfusion Pressure Guided Management in Severe Head Injury: A Case Report

Jinn-Rung Kuo, Che-Chuan Wang, and Chung-Ching Chio

Abstract- Augmented cerebral perfusion pressure (CPP) of at least 70 mmHg has become a popular treatment for patients with severe head injury. We report a case of a 33-year-old man who suffered from traumatic intracranial hematomas which were successfully evacuated by surgical procedures. Postoperatively the patient received CPP-guided treatment and was sedated with propofoland medicated with vascular volume expanders (hydroxyethyl starch, albumin), systemic vasopressors (norepinephrine, dopamine) as well as mannitol. However, hyperamylasemia and hyperlipasemia happened three days later. Because of the possibility of acute pancreatitis, the patient was prohibited from any oral intake and only intravenous fluids were supplied for 2 days. The amylase and lipase levels decreased gradually after discontinuation of the aforementioned medications. In this article, we review the literature and discuss the possible mechanisms underlying the elevated pancreatic enzymes. We conclude that pancreatitis related to propofol infusion probably plays a role in the pathogenesis of hyperamylasemia and hyperlipasemia in this patient.

Key Words: Cerebral Perfusion Pressure, Hyperamylasemia, Hyperlipasemia

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INTRODUCTION

Induced hypertension has become a popular treatment for severe head injury. In 2000, the American Association of Neurological Surgeons and the Brain Trauma Foundation advocated an elevation of cerebral perfusion pressure by at least 70 mmHg in such conditions. Heavy sedation with propofol, vascular volume expansion with hydroxyethyl starch (HES) and/or albumin, systemic vasopressors (norepinephrine and/or dopamine) and osmotic diuresis with mannitol are widely used in these patients[1-3].

In this report, we describe a patient who developed hyperamylasemia and hyperlipasemia after receiving CPP-guided treatment for 3 days. The etiologies of hyperamylasemia and/or hyperlipasemia include acute pancreatitis, side effects of the medications, and intracranial events[4-13]. The literature were reviewed to find a possible cause for the elevated pancreatic enzymes.

From the Department of Neurosurgery, Chi-Mei Medical Center, Tainan, Taiwan.
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Reprint requests and correspondence to: Chung-Ching Chio, MD. Department of Neurosurgery, Chi-Mei Medical Center, No. 901 Chung Hwa Road, Yung Kang, Tainan, Taiwan.
E-mail: Chiocc@ms28.hinet.net

CASE REPORT

A 33-year-old, 70-kg man was brought to the emergency room in deep coma (Glasgow Coma Scale E1VTM1) with a dilated right pupil after a traffic accident. Hematogram and serum biochemistry showed normal findings. The patient's serum alcohol level was 249 mg/dL (hospital normal value < 10 mg/dL). An abdominal ultrasound showed no hollow organ injury or internal bleeding. Brain computed tomography (CT) showed a left, acute subdural hemorrhage about 50 cc in volume, and there is also severe brain swelling. No facial injury was found. A decompressive craniectomy and evacuation of the subdural hematoma was performed immediately.

The patient's consciousness returned to normal and the endotracheal tube was removed the day after surgery. Unfortunately, his consciousness deteriorated to coma and the right pupil was dilated again 1 day later. Emergency brain CT showed delayed acute epidural hemorrhage (EDH) on the left side with a severe mass effect. He underwent another craniectomy to remove the EDH. An intracranial pressure (ICP) monitor was placed in the ipsilateral frontal parenchyma for postoperative CPP-guided management with CPP support set at 70 mmHg.

On return to the intensive care unit (ICU), propofol infusion was started to induce heavy sedation. During CPP-guided management, the dose of propofol was titrated to the patient's response and ranged from 2.8 to 9.3 mg/kg/hr (mean 5.96±0.42 mg/kg/hr) for 3 days. The average doses of norepinephrine and dopamine administered were 5.4±3.7 and 155.8±86.4 mg/day for

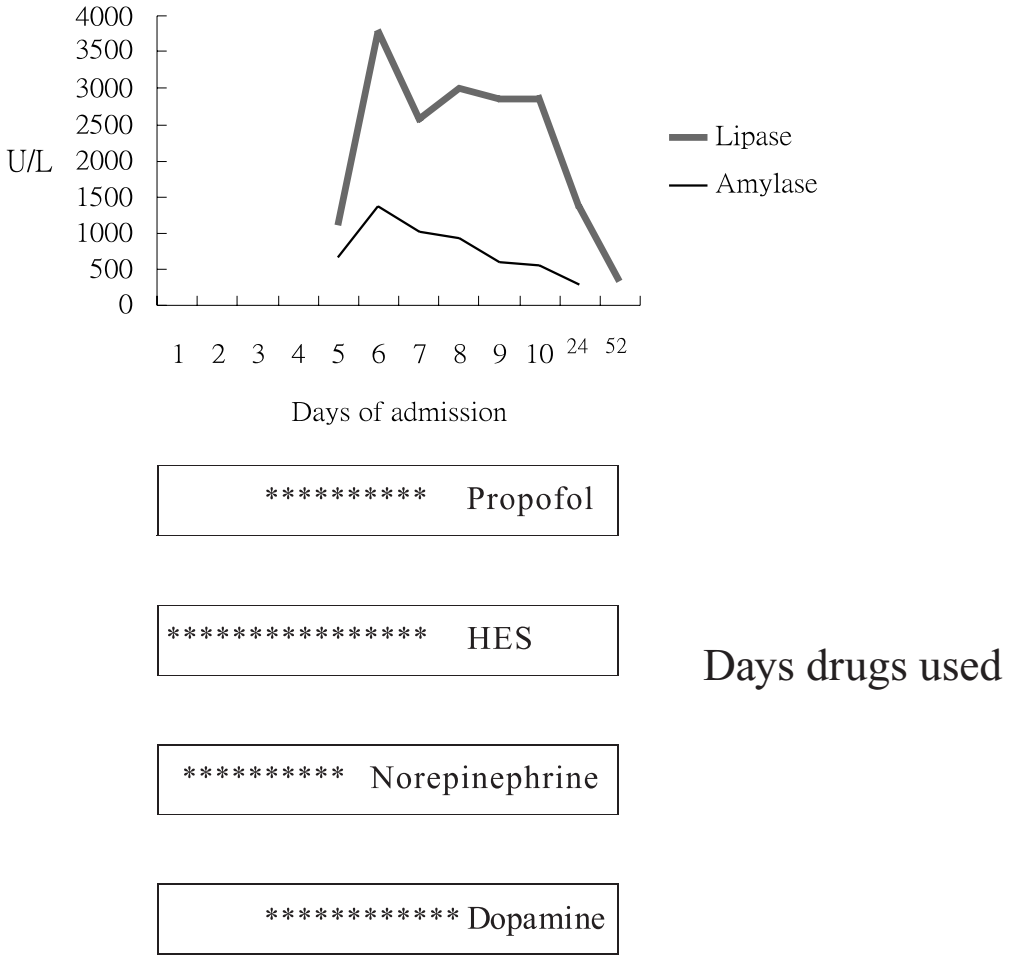

Figure. Changes in pancreatic enzyme concentrations after hospitalization with the history of drug administration.

3 and 4 days, respectively. The total dose of 10% HES was 5,000 mL. Mannitol (an osmotic diuretic) was given at an average dose of 115±19.1 g/day. Additional drugs given concurrently included albumin, phenytoin, metoclopramide, cefazoline, potassium chloride, morphine, ranitidine and acetaminophen.

On day 3 of the CPP-guided therapy, abnormal amylase and lipase levels up to 669 and 1,108 IU/L were noted and subsequently rose to 1,366 and 3,782 IU/L, respectively, on day 4. Although the patient's abdomen was soft and not distended, it was difficult to assess the presence and severity of abdominal pain due to heavy sedation. He was treated as acute pancreatitis and received no oral intake but only intravenous fluids for 2 days.

The patient was weaned off of propofol on day 6 after the ICP was stabilized. The total dose of propofol administered was approximately 2,680 mL. HES, norepinephrine and dopamine were then also discontinued, and the amylase and lipase levels gradually declined (Fig.). An abdominal ultrasound on day 6 showed a normal-appearing gallbladder without stones and no edematous changes in the pancreas. The patient was weaned off the mechanical ventilator on day 7. After 9 days of ICU care, he was transferred to the general ward without consciousness disturbance or any other apparent neurological deficits.

DISCUSSION

Lipases are secreted almost exclusively by the pancreas, except for the tiny amounts secreted by the salivary gland, the stomach and the liver. Although measurement of serum lipase has increased the diagnostic rate of acute pancreatitis[4], hyperlipasemia may appear in the absence of clinical or radiographic evidence of acute pancreatitis[7,8,14]. Amylase is secreted by the pancreas, salivary glands, thyroid gland, tonsils, lungs and fallopian tubes. However, the pancreas and the salivary glands play a decisive role in the serum amylase level. The reported causes of hyperamylasemia include primary pathologic processes involving amylase-releasing tissues, reduced amylase clearance, and central activation mechanisms[5].

Any injury to the pancrease and the salivary glands, the major sources of the amylase in serum, may cause hyperamylasemia. In this reported case there were no evidence of salivary gland injury nor abdominal trauma. Hyperamylasemia due to a traumatic mechanism was thus unlikely.

Amylase is catabolized by the kidneys and liver. Reduced amylase clearance may lead to elevation of serum amylase level, especially in cases of renal insufficiency and liver disease[5,15]. During CPP-guided management of our patient, the mean systemic arterial pressure was 112.6±5.6 mmHg, the intake of intravenous fluids was 7,113.3±2,589.9 mL/day and output of urine was 7,483.8±2,598.5 mL/day. The mean dosage of the osmotic diuretic mannitol, a nephrotoxic agent, was 115 ±19.1 g/day. According to these data, no hypotension or over-dehydration had occurred. The serum urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, bilirubin and alkaline phosphastase were all within normal limits. Because there was no evidence of renal or hepatic impairment, hyperamylasemia due to reduced serum amylase clearance seems unlikely.

HES has been widely used in hemodilution therapy for the treatment of cerebral perfusion problems. Usually infusion of HES would cause no changes in serum lipase level or in the amylase or lipase activity in duodenal secretions. However, hyperamylasemia has been shown to result from the formation of high molecular weight HES-amylase complexes, which cannot be filtered and eliminated easily by the renal glomerulus[11,16,17]. In this case, fluid resuscitation with 500 mL of middle-molecular weight 10% HES was given twice daily from days 1 to 5. The total amount of HES was 5000 mL. Although the formation of HES-amylase complex was not confirmed by gel filtration in this patient, it remains to be a possible explanation for the cause of hyperamylasemia.

Norepineprine and dopamine were reported to stimulate amylase secretion by the parotid gland and pancreatic acini in several experimental and clinical studies[18,19]. Elevated plasma catecholamines might play a role in the pathogenesis of pancreatic inflammatory disease[20]. The mechanism may involve decreased blood flow to the splanchnic system, leading to pancreatic ischemia. In this patient, vasopressors such as norepinephrine and

dopamine were infused continuously to support a CPP of 70 mmHg. The average doses of norepinephrine and dopamine administered were approximately 5.4 ± 3.7 and 155.8 ± 86.4 mg/day for 3 and 4 days, respectively. Because these vasopressors decrease blood flow to the splanchnic system, they may lead to pancreatic ischemia and may also stimulate amylase secretion by the parotid gland and pancreatic acini. Thus, vasopressors could elevate the serum level of pancreatic enzymes.

In a study of 60 patients with severe head injury, Vitale et al. (1987) showed that severe head injury activated the pathways that increase amylase levels in the blood. They suggested that the central nervous system may regulate the serum amylase levels[21]. It is possible that the central neural influences, activated by the stresses of severe trauma, alter pancreatic amylase transfer and release. In 1994, Justice et al reported that 25 (66%) of the 38 patients of intracranial bleeding had elevation of lipase levels and 17 of these 25 patients (45% of the total) had concomitant elevation of amylase levels[7]. The peak levels of serum amylase and lipase were 140 ± 109 U/L and 712 ± 614 U/L, respectively. Both amylase and lipase levels were elevated on days 8 and 12 of hospitalization. The proposed causes of pancreatic enzyme elevation in intracranial bleeding include vagal stimulation, altered modulation of central control of pancreatic enzyme release, and release of cholecystokinin from the brain. In 2001, Liu et al demonstrated that serum amylase and lipase elevation is associated with isolated intracranial events[8]. They assumed that intracranial events, whether caused by trauma or not, could initiate central activation of pancreatic enzyme release. The mechanism might be neural or hormonal, or is related to the stimulation of cytokine-producing pancreatic enzymes secreted from pancreatic and/or nonpancreatic tissues. In their report, the peak level of serum amylase was 402 ± 444 U/L and the peak lipase level was 474 ± 313 U/L. Both levels peaked simultaneously on days 14.5 ± 7.7 of hospitalization and day 8.8 ± 3.5 day post-craniotomy. In our patient, the peak levels of amylase, 1,366 U/L and lipase 3,780 U/L, were higher than those of previous reports. Both levels peaked simultaneously on day 6 of hospitalization, which was earlier than the previous reports. These findings suggest that serum amylase and lipase elevation is probably not associated only with intracranial bleeding in this case. Nonetheless, intracranial bleeding may play an important role in the pathogenesis of the elevation of pancreatic enzymes.

Acute pancreatitis is a common inflammatory disorder. Gallstones and ethanol abuse account for approximately 80% of cases. Other factors such as trauma, toxins, drugs, infection and idiopathic causes are also reported to cause acute pancreatitis[4]. The diagnosis of acute pancreatitis is made on the basis of the characteristic abdominal pain associated with hyperamylasemia and hyperlipasemia, and can be further confirmed by ultrasonography and/or CT findings[4]. However, the lack of radiographic evidence does not exclude the presence of mild pancreatitis. A definite diagnosis of acute pancreatitis can be difficult in patients with severe head injuries. These patients often suffer from altered mental status or are deliberately paralyzed to reduce the intracranial pressure. Clinical information obtained from physical examination thus may not be accurate. In our patient, the elevated amylase and lipase concentrations supported the diagnosis of pancreatitis. Although the patient's abdomen was soft and not distended, it was difficult to assess the abdominal pain with sedation by propofol. Oral intake was prohibited under a tentative diagnosis of pancreatitis. He received only intravenous fluids for 2 days until his consciousness became clear and he could take enteral feeding.

Long term alcohol abuse is usually required for the development of acute alcoholic pancreatitis. It is believed that most patients with acute alcoholic pancreatitis have acute inflammation superimposed on chronic pancreatitis. Nonetheless, in a minority of patients, alcohol may cause acute pancreatitis in the absence of chronic disease[22]. Our patient did not have a history of alcoholism or chronic pancreatitis. On arrival at the emergency room, his serum alcohol level was 249 mg/dL (hospital normal value <10 mg/dL). However, because the levels of amylase and lipase were peaked on day 6 of hospitalization, alcohol use as a possible cause of pancreatic enzyme elevation was unlikely in this case.

More than 85 drugs are reported to cause acute pancreatitis[4,23]. The patient was medicated with acetaminophen and ranitidine, both of which have been

reported to be associated with acute pancreatitis. However, he received only 1.5 g of acetaminophen as needed for fever. Such a small dose of acetaminophen is unlikely to cause acute pancreatitis, which is typically caused in situations of overdose (9.75-25 g)[24,25]. Ranitidine is a safe, widely used drug for the treatment of peptic ulcer and is rarely associated with serious adverse reactions. Pancreatitis associated with ranitidine has only been reported rarely[26]. Our patient received ranitidine 50 mg/day or prophylaxis of stress-induced ulcer on only days 1 and 2 of hospitalization. Since the peak levels of amylase and lipase happened on day 6 of hospitalization, pancreatitis due to ranitidine is unlikely.

Propofol, 2, 6-diisopropylphenol, available in an oil-water emulsion (1% aqueous propofol solution in 10% soybean oil, 2.25% glycerol and 1.2% purified lecithin), has become increasingly popular in the ICU for its sedative-hypnotic effect[27-29]. Propofol induced pancreatitis has been demonstrated with both short-term and prolonged therapy[30-32]. During CPP-guided therapy, our patient received a total dose of approximately 2,680 mL of propofol solution, equivalent to 26,800 mg of propofol in an intravenous 10% fat emulsion. Because fat is hydrolyzed by lipases which are secreted by the pancreas (and to a much lesser extent by the intestinal glands), propofol with bulk fat infusion is a possible cause of hyperlipasemia. In 1996, Gullo et al. reported two unusual cases of macroamylasemia associated with hyperlipasemia[14]. The possible mechanism for hyperlipasemia is that lipases may be bound to serum proteins, forming a macrocomplex that cannot be filtered and eliminated by the renal glomeruli. Although the formation of a lipase-protein complex was not confirmed by gel filtration in our patient, it remains a possible cause of hyperlipasemia.

Because hypertriglyceridemia is a known cause of pancreatitis, the possibility that pancreatitis is related to to the hypertriglyceridemia induced by propofol must be addressed[4]. In 1989, Gottardis et al. studied the changes of serum lipid concentrations in 10 patients receiving continuous propofol infusion for 3 days. They found that the serum lipid concentrations were not significantly influenced by propofol[33]. In 1990, Boyle et al. studied the lipid levels in 22 patients receiving propofol sedation for periods as long as 14 days. They demonstrated that the triglyceride levels were not significantly altered by propofol emulsion at infusion rates below 6 mg/kg/hr, but might be increased dramatically when the infusion rate of propofol exceeded this level[34]. Our patient received 3 days of high-dose propofol therapy. The infusion rate was ranged from 2.8 to 9.3 mg/kg/hr and the mean continuous infusion rate was 5.96 ± 0.42 mg/kg/hr. The patient's serum triglyceride level was within normal limits (170-175 mg/dL) in the ICU. Because we did not continuously monitor his triglyceride concentration, the possibility of transient hypertriglyceridemia could not be completely excluded as propofol was sometimes infused at a rate greater than 6 mg/kg/hr. Thus, pancreatitis due to hypertriglyceridemia induced by propofol probably play a role in the pathogenesis of the transiently elevated pancreatic enzymes in our patient.

CONCLUSION

The causes of elevated pancreatic enzymes in our patient might have been multifactorial. The definitive cause and effect relationship remained unclear. Because of the lack of published reports on the concurrent administration of propofol, vasopressors and HES for severe head injury, we were not able to establish a definite association between the elevated pancreatic enzymes and the medications. However, we would emphasize the possible association between propofol and pancreatitis. It must be kept in mind the potentially devastating consequences of acute pancreatitis when large doses of propofol were prescribed to the patients.

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