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■ Case Report ■

Hyperamylasemia following the trans-sphenoidal resection of pituitary tumor: can propofol-remifentanil TIVA cause postoperative hyperamylasemia?
-A case report-

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The trans-sphenoidal resection of a recurred pituitary tumor was performed in a 42 years old man under general anesthesia with propofol and remifentanil. Neither massive bleeding nor hypotension was observed intraoperatively, but bradycardia was sustained over five hours. The patient did not suffer from hypertriglyceridemia and there was no evidence of drug toxicity or vigorous intervention during the surgery, however hyperamylasemia was observed one day after the surgery. It is presumed that vagal stimulation by propofol and remifentanil infusion might induce bradycardia and abnormal pancreatic enzyme secretion consequently. **(Anesth Pain Med 2011; 6: 160～163)**

Key Words: Bradycardia, Hyperamylasemia, Propofol.

Hyperamylasemia may occur without abdominal pain due to a familial history, hypertriglyceridemia, drug toxicity, renal failure, cerebral injury, etc [1,2]. In those cases, diagnoses are often difficult and are made by excluding the causes. We report a case of hyperamylasemia thought to be caused by intense vagal stimulation from propofol-remifentanil anesthesia which was occurred following a minimally invasive trans-sphenoidal resection of a pituitary tumor.

CASE REPORT

A 42-year-old, 170 cm, 85 kg man presented for the resection of recurred macroadenoma that had been excised 5 years ago. His past medical history and physical examination were not remarkable for systemic diseases including hypertriglyceridemia or alcohol abuse. No abnormalities were found in preoperative laboratory tests.

Thirty minutes before surgery, valproate sodium 400 mg was injected for prophylaxis of seizure and glycopyrrolate 0.2 mg for premedication at ward. General anesthesia was induced with thiopental sodium 350 mg and rocuronium 70 mg under the monitoring of ECG (lead II), blood pressure (BP), heart rate (HR), peripheral oxygen saturation (SpO_2), and end-tidal CO_2 ($EtCO_2$). Anesthesia was maintained with oxygen 3 L/min, nitrous oxide 3 L/min, and sevoflurane 0.8－2.0 vol%, then ventilator was set by a tidal volume 650 ml and respiratory rate 11 breaths/min. Right subclavian vein and right dorsalis pedis artery were cannulated for continuous CVP and BP monitoring. BP was maintained at 120－150/60－80 mmHg and HR at 60－70 beats/min during the sevoflurane anesthesia. Surgery was started by a trans-sphenoidal approach and mannitol (15%, 85 g) was infused. Immediately after the surgery started, surgeon requested propofol and remifentanil TIVA because it could provide more advantageous anesthesia by the reduction of cerebral blood flow. Propofol was infused at the effective target concentration of 3.0－3.5 μg/ml and remifentanil at the infusion rate of 0.05 μg/kg/min. BP was maintained at 120－150/60－80 mmHg and HR at 50－60 beats/min during the first two hours of propofol-remifentanil anesthesia. Two hours after the propofol-remifentanil infusion, HR decreased to 40－50 beats/min while BP did not change significantly, so atropine sulfate 0.5 mg was injected. Immediately HR increased to 75 beats/min, but it decreased gradually to 40－50 beats/min over one hour period and maintained for about two and half hours. Atropine sulfate 0.5 mg was injected again. Then HR increased to 75 beats/min and the

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surgery was finished 30 minutes after the last injection of atropine sulfate. It took 5 hours and 50 minutes for surgery and 7 hours and 5 minutes for anesthesia. SpO_2 was maintained at 98－100%, $EtCO_2$ at 27－31 mmHg, and CVP at 5－7 mmHg during the surgery. Crystalloids were infused 3,100 ml, and total urine output was 1,250 ml (180 ml/hr on average). After reversal of muscle relaxation, the patient was extubated and transferred to a neurosurgery intensive care unit.

The patient was stable after the surgery. Valproate sodium 400 mg was infused twice daily for prophylaxis of seizure until the forth day after the surgery. Serum amylase level taken one day after the surgery showed 918 IU/L, which was four times higher than preoperative value (240 IU/L). The patient did not complain of any symptoms such as abdominal pain, nausea or vomiting, however, conservative treatments were conducted corresponding to pancreatitis. Serum amylase level decreased to 514 IU/L at the third day and to 422 IU/L at the forth day after surgery. Amylase level decreased to 294 IU/L at the fifth day after the surgery, however, serum lipase level had remained within normal limits since preoperative period (21－66.9 IU/L, normal 1－190 IU/L). Oral feeding was started and gabexate mesylate 60 mg was infused for pancreatitis up to the forth day after the surgery. The patient was discharged nine days after the surgery.

DISCUSSION

Hyperamylasemia mainly occur due to the pancreatic pathology such as pancreatitis, pancreatic tumor, or pancreatic intervention. About 35－45% of all hyperamylasemia were induced by pancreatitis and it is commonly caused by alcohol ingestion and gallstones [1]. When direct injury of pancreas exists, most patients complain of severe continuous and gradual upper abdominal pain, nausea, or vomiting. Low grade fever, tachycardia and hypotension are common due to the exudation of blood into retroperitoneal space. However, radiological findings and laboratory tests are needed for differential diagnoses as these symptoms are not limited to pancreatitis. Although no a single diagnostic test exists, positive findings on ultrasound or CT, abdominal pain, and the measurement of serum amylase and lipase levels are commonly used to diagnose pancreatitis. Serum amylase level is the most commonly used biochemical marker for the diagnosis of acute pancreatitis when it rises at least three times higher than the upper limit of normal value (30－135 IU/L) [2]. Since there were no history of pancreatic trauma and related symptoms, non-pancreatic cause of hyperamylasemia was suspected in this case. However, as painless pancreatitis could be exist, all possible causes were ruled out in a stepwise pattern.

One of the common causes of hyperamylasemia is hypertriglyceridemia. The proposed mechanism is that hydrolysis of triglycerides in pancreas leads to the accumulation of unbound fatty acids and it causes acinal cell injury. Moreover, chylomicrons plug the injured pancreatic capillaries and lead to ischemia [3]. Propofol has been reported to cause hypertriglyceridemia. It contains soybean oil 100 mg/ml, glycerol 22.5 mg/ml, egg yolk phospholipid 12 mg/dl, which is very similar to many proprietary lipid emulsion used for parenteral nutrition [4]. Although acute pancreatitis induced by a single dose exposure to propofol was reported, it is widely accepted that long term triglyceride levels between 1,000－2,000 mg/dl (from a prolonged [＞72 hours] infusion of propofol) are necessary to cause hyperlipidemic pancreatitis [3]. Serum triglyceride level was not measured in this case, however, propofol was used in a relatively low dose (effective target concentration 3.0－3.5 μg/ml) for the shorter period of time and he had no history of hypertriglyceridemia and alcohol abuse, either. Moreover, serum lipase level was within a normal range and pancreatic symptoms were totally absent. Therefore, hypertriglyceridemic pancreatitis was less concerned for the reason of hyperamylasemia.

Besides propofol, other drugs can cause hyperamylasemia. In this case valproate sodium was infused for five days. However, valproate sodium usually causes pancreatitis in children, not in adults and it is caused by accumulation of toxic metabolites when used at the concentrations higher than 20－80 mg/kg or used for long period of time [5]. In our case, about 47 mg/kg of valproate sodium was used up to the forth day after the surgery, however, the amylase level decreased from the first day after the surgery. If the hyperamylasemia was derived from valproate sodium, the amylase level should be increased during the course of valproate sodium administration. Thus, valproate sodium excluded from the causes of hyperamylasemia.

Hyperamylasemia also can occur in a patient with severe head injury. Liu et al. reported that old age and the severity of the head injury were the risk factors [6], while Justice et al. took hypotension for the reason [7]. Normal pancreatic exocrine function is under the both neural and hormonal control and the central control of both parasympathetic and sympathetic nervous systems is located in the midbrain. Modulation of normal neural balance is disrupted when intracranial pres-

sure rises in the cases of massive intracranial bleeding, cerebral contusion, or cerebral edema. Elevated intracranial pressure acts as a vagal stimulus and results in a marked increase in circulating pancreatic enzyme [7]. However, the surgery in this case was minimally invasive, so not likely causing hyperamylasemia.

Whatever the cause is, pancreatic enzyme seems to be secreted by vagal stimulation. Anagnostides et al. found that the cephalic phase of pancreatic secretion induced by sham feeding, which was not real eat something, but only see, smell, chow and spit food, stimulated central vagal nerve and induced pancreatic enzyme secretion consequently [8]. Rösch et al. found that lipase and chymotrypsin were in normal range, while amylase and trypsin levels were elevated in the electrically stimulated vagus nerve of rats. Serum amylase level was elevated by 3 to 5.5 folds according to the frequency of electrical stimulation [9]. Bourde et al. reported that vagal stimulation always produced a parallel increase in amylase, lipase levels, and trypsin activities which averaged out to 87%, 77%, and 81%, respectively [10]. These findings suggest that intense vagal stimulation may cause hyperamylasemia. What's unique in this case was vagal stimulation as evidenced by bradycardia for five hours which was resulted from the propofol-remifentanil infusion. Propofol did not depress baroreflex sensitivity directly, but it increase vagal tone and decrease in sympathetic tone by central mechanisms [11]. Remifentanil, like other opioid, can cause vagally mediated bradycardia [12]. Since minimum dose of remifentanil (less than 0.05 μg/kg/min) was used during the surgery, propofol was regarded as the major cause of bradycardia and remifentanil seemed to play a role additively.

Propofol might decrease systolic and diastolic arterial pressures and a systemic vascular resistance. Because propofol has no reflex tachycardia, it decreases cardiac output by 12% and it may be associated with the resetting of the reflex set point to allow slower heart rates despite decreased arterial pressures [13]. When cardiac output significantly decreases by propofol and/or remifentanil, pancreatic hypoperfusion may occur because pancreas, like the kidney, is highly vulnerable to ischemic necrosis. Warshaw and O'Hara. reported that hyperamylasemia had strong positive correlation with the presence of renal ischemic injury [14]. However, in the present case, perfusion pressure maintained well during all over the surgery. Moreover, there was no evidence of ischemic renal injury. Thus, we assume that pancreatic ischemia did not happen.

Atropine sulfate is known to inhibit pancreatic enzyme secretion partially or completely [8,15]. Nelson et al. reported that electrical stimulation of vagus nerve of rats increased serum amylase activity fivefold over baseline values and it was inhibited with atropine sulfate by 85% [15]. In contrast, Hashiba et al. reported that vagus nerve stimulation by propofol decreased HR significantly, whereas there was no difference in HR after propofol irrespective of atropine [11]. In this case, the HR was increased after atropine injection, but the effects of atropine did not last long.

In the absence of any clinical findings, imaging studies may not be warranted and enteral feeding may be continued safely. The elevation of enzyme may return to normal when causing factors are disappeared, therefore, no further treatment seemed to be needed. Understanding this phenomenon, unnecessary diagnostic process and treatment would be decreased. Furthermore, anesthetist should consider to maintaining cardiac output against low HR to protect kidney and pancreas from ischemic injury.

In conclusion, the infusion of propofol and remifentanil was implied to cause hyperamylasemia via vagal stimulation. It is noticeable because vagally induced hyperamylasemia was reported many times previously in both animal and human models, but we could not find anything due to propofol-remifentanil infusion. In this case, the central activation of pancreatic exocrine secretion seems to elevate serum amylase, which does not imply acute pancreatitis.

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