VIPoma Syndrome: Effect of A Synthetic Somatostatın Analogue, SMS 201-995

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Özet VIPoma sendromu oldukça nadir gözlenen, pankreasın nöro-endokrin bir tümörüdür. Bu çalışmamızda bir VIPoma olgusu ve tedavisinde somatostatin analoğunun (SMS 201-995) etkisi rapor edilmiştir. 32 yaşındaki erkek hasta şiddetli diare nedeniyle sıvı ve elektrolit replasmanı için çeşitli defa hastaneye yatırılmış. On ve 6 yıl önce mekanik ileus ve apandisit ameliyatları yapılmış. İki yıl önce bilgisayarlı tomografi, pankreas korpusunda bir kitle olduğunu göstermiş. Operasyonda tariflenen kitle gözlenememiş. Ancak buridere bağlı intestinal iskemi nedeniyle ileumdan 80cm.'lik segment çıkartılmış. Müteakiben günde 3-7 lt'yı bulan ishalleri oluşmuş. Gaita analizleri sekretuvar diareyi destekliyordu. İshal açlık dönemlerinde de devam ediyordu.

Vasoaktif intestinal polipeptid (VIP) laboratuvar güçlükleri nedeniyle incelenemedi. Serum gastrin, 5-hidroksi-indolasetik asit, gaitada yağ tayinleri, ince barsak biopsisi, baryumlu gastrointestinal tetkikler normaldi. Laksatif alışkanlığı yoktu. İshal, antibiyotik, spazmolitik, salazoprin, metranidazol tedavilerine cevap vermiyordu. İntravenöz (iv). hiperalimentasyon ve subkutan somatostatin analoğu (SMS 201-995) 300μ g/gün olarak başlandı. İshal dramatik şekilde kesildi. İki aylık tedavi süresince iv. sıvı ihtiyacı olmadı. Kilo aldı, SMS 201-995 kesildiğinde 17 gün ishal gözlenmedi. İshal başladığında tekrar somatostatin verildi ve hasta iyi durumda taburcu edildi.

Sonuç olarak bir VIPoma sendromu olgusu ve bunun tedavisinde somatostatın analoğunun etkili olduğu gösterilmiştir.

Anahtar kelimeler : VIPoma sendromu, Somatostatin

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VIPoma syndromes are extremely rare neuroendocrine tumors usually found in the islet cells of the pancreas[1]. VIPomas secrete vasoactive intestinal polipeptide(VIP), which acts as an neuromodulator of intestinal secretion[2,3].

In1958, Verner and Morrison called attention to the syndrome of watery diarrhea, hypokalemia and death from renal failure in association with islet cell tumor[4]. Synonyms for pancreatic cholera syndrome include: Verner-Morrison syndrome; VIPomas, watery diarrhea, hypokalemia, hypochlorhydria(WDHH) syndrome.

The biological actions of VIP have been reviewed by Said[5]. It has now become apparent that the major function of VIP is that of a neurotransmitter or neuromodulator[2,3,6]. Even though the effects of VIP on intestinal water and ion movement have been characterized in experimental animals[7], a controversy existed for many years over whether VIP is a mediator of intestinal secretion and diarrhea in pancreatic cholera syndrome, or was just a marker of the disease[8,9]. This controversy was based on the fact that not all patients with islet cell tumors and diarrhea have high plasma levels of VIP, and on the observation that high levels can be found in some healthy controls and persons abusing laxatives[10].

It is now established that VIP is the major mediator of the WDHH syndrome and that

may of the symptoms can be explained by the biological actions of VIP. Diarrhea disappears in patients with tumor removal when plasma VIP levels return to normal. Prolonged intravenous (iv.) VIP infusion (10 hours) in healthy subjects produces secretory diarrhea and causes metabolic acidosis, thus mimiching the clinical syndrome[7,11,12,13].

Intravenous infusion of native somatostatin (SMS) and subcutaneous administration of a synthetic somatostatin analogue, SMS 201-995 have been shown to reduce or abolish severe diarrhea in pancreatic cholera[11,13-17].

We report the patient has pancreatic cholera and effect of SMS 201-995 on diarrhea in such a patient.

CASE REPORT

A 32 years old man was referred to Ondokuz Mayıs University School of Medicine section of Gastroenterology because of progressively worsening watery diarrhea of two years' duration that had required frequent hospital admissions for fluid and electrolyte repletion. Ten years prior to admission, a operation was performed for mechanic ileus. Four years later, a operation was performed for apandisitis. The patient's condition was stable until two years prior to admission when he was admitted to the hospital for diarrhea. Abdominal computed tomographic scanning have showed a mass in corpus of the pancreas. Resulting of computed tomography a operation was performed for corpus of pancreatic mass, and because laparatomy revealed ischemic segment of ileus a 80cm and brid seperation was performed. Following surgery, he underwent computed tomography to evaluate the possible pancreatic mass, but the tomography did not reveal any lesion.

Subsequent to that surgery, large-volume diarrhea developed ranging from 3 to 7 liters per day. Stool analysis confirmed secretory diarrhea(stool water, 285 mosm/kg; sodium, 107 mEq/Liter; potassium, 18 mEq/Liter), and the large stool volume perssited during fasting. The stools were free of blood, pus and mucus, and tests for occult blood, leucocytes, culture, ova, parasites and laxatives were negative, No abnormalities were detected by upper endoscopy and rectosigmoidoscopy. Laboratory tests indicated the presence of hypokalemic acidosis(serum potassium 2.2 mEq/litre; bicarbonate, 16 mEq/liter). Plasma levels of vasoactive intestinal polipeptide(VIP), calcitonin were not detected for laboratory problems. Plasma levels of gastrin and urinary 5-hydroxyindoleacetic acid excretion were normal. Intragastric pH was 1.2. A quantitative stool collection for fat revealed 3 g per day. Examination of a small-bowel biopsy specimen showed normal mucosa. The plasma immunoglobulins value were normal.

Findings on radiologic examination of colon and small-bowel were normal except for the presence of some dilated loop of small bowel. Radionucliod shown no patologic value. Endoscopic retrograte pancreaticocholangiography was normal.

He reported a 12 kg weight loss during the last year, but no history of laxative abuse. Treatment with antibiotics, spasmolitics, metranidazol, salazopyrine failed to control the diarrhea.

When admitted to the hospital he was cachectic and dehydrated. The bowel sound was hyperactive. Liver and renal function were normal with heavy hypokalemia.

Stool weights at baseline while the patient was ingesting a regular diet averaged (3.200± 420 g per 24 hours) and remained unchanged with fasting (3.320 g fore one 24 hour specimen).

Intravenous hyperalimentation and subcutaneous administration of SMS 201-995, 300 µg daily. The drug dose was gradually decreased to 100µ g two time per day. The response to SMS 201-995 was impressive; bowel movements were reduced to one to formed stools per day. Stool volume decreased to less than 500 ml per day, weight increased steadily, and potassium bicarbonate concentration returned to normal. During maintenance therapy with the analogue, bowel movements decreased to one or two per day, stool were usually semiformed. The drug was well tolerated, and neither gastroperesis, nor postural hypotension was aggravated.

During somatostatin analogue administration for a period of two months, the patient did not require intravenous fluids and electrolytes. After the analogue was discontinued, diarrhea did not recur for seventeen days. When diarrhea returned, it reached pretreatment severity within three day(3.500 g/day) and responded within 6 hours when treatment with the analogue was renstated. The patient was discharged at good condition.

COMMENT

In 1957, Priest and Alexander described a patient with islet-cell tumor and severe watery diarrhea and hypokalemia[18]. In 1958, Verner and Morrison called attention to the syndrome of watery diarrhea, hypokalemia and death from renal failure in association with islet-cell tumor[4].

The major clinical manifestation of the syndrome is large-volume secretory diarrhea, with only about a fifth of cases having less than 3 liters of stool per day. Since the diarrhea is secretory, stool water is isotonic to plasma, and stool electrolytes account for all the osmolality. Diarrhea persists on fasting[19]. For practical purposes, a stool volume of less than 700 ml per day excludes the syndrome.

Table 1: VIPoma syndrome: Clinical presentation.

Constant features
Diarrhea
Hypovolemia
Acidosis
Hypokalemia
Variable features
Achlorhydria or hyhpochlorhydria
Hypercalcemia
Hypomagnesemia
Enlarged gallbladder
Myopathy or nephropathy (hypokalemic)
Rash
Flushing
Hyperglycemia
Lacrimal gland hypersecretion and excessive tearing

Large amounts of potassium and bicarbonate are lost in the diarrhea stool resulting in hypokalemia, acidosis and volume depletion.

In the few patients that have been studied appropriately, intestinal water and ion secretion has been demonstrated by perfusion studies[12,16,21-23]. Other clinical features of the VIPoma syndrome are listed in table 1 [24].

Achlorhydria and hypochlorhydria are often but not always present. Out of 43 patients reviewed by Warner and Morrison, only 14 had histamine-fast achlorhydria while another 16 had hypochlorhydria [25]. Achlorhydria was not present in our patient.

Hypercalcemia has been reported in 50 percent of cases[25], but the mechanism is not clear. There appears to be a negative calcium balance with increased bone resorption[26]. Tetany in patients with pancreatic cholera syndrome is thought to be due to hypomagnesemia and may occur in the presence of hypercalcemia.

Contrast to this observation we didn't observed hypercalcemia in our patient. Flushing is occassionally observed in these patients[27]. Some patients have circulatory disturbances with hypotension due to peripheral vasodilation, and severe hypertension may develop after tumor removal [28].

In patients with the VIPoma syndrome, a family history of the disease is usually absent However, the report of a father with multiple islet-cell adenomas and Zollinger Ellison syndrome and his son with VIPoma syndrome and a parathyroid adenoma suggest that VIP-producing tumor may occur as part of the multiple endocrine neoplasia type I syndrome[29].

Some clinical variants of VIPoma syndrome were described. These are variant VIPoma (islet-cell hyperplasia) and pseudo-VIPoma syndrome.

Several patients without pancreatic tumor were included[25,30]. It was stated that 14-20 percent of cases have islet-cell hyperplasia. Several experts in the field refuse to accept pancreatic islet-cell hyperplasia as part of the spectrum of the VIPoma syndrome. Some investigators did not find elevated plasma VIP levels in any patient with islet-cell hyperplasia and other doubts that this combination exists[31,32].

Many of the reports about such cases are difficult to interpret since the diagnosis of islet-cell hyperplasia in always poorly documented.

In fact VIP is not contained in normal pancreatic islet-cells, and hyperplasia of these cells should not lead to VIP production unless a tumor (adenoma or carcinoma) is already present. Hight plasma VIP levels and life-threatening diarrhea can be present in infants with nesidioblastosis, but this disease represents microadenoma and not just islet-cell hyperplasia. Likewise, in adults, the disease has to be reclassified as islet microadenomatosis or carcinomatosis, when watery diarrhea disappears after resection of a pancreas that contains enlarged islets with invasive features and VIP-positive cells on immunohistochemistry[32,33].

Co-secretion of peptide histidine, methionine (PHM), the human counterpart of peptide histidine isoleucine (PHI), has been found in patients with VIPomas. PHM concentration is hight in plasma, and both VIP and PHM are present in the same cells as indicated by immunohistochemistry[34]. PHM has similar effects on intestinal mucosa as VIP, but as a secretagogue it is 32 times less potent than VIP[35].

Pseudopancreatic cholera or chronic idiopathic secretory diarrhea is life-threatening condition because of the enormous water and electrolyte losses in diarrhea stool. Since, by definition, the cause of this disease is unknown, specific treatment is unavailable[36]. The clinical presentation resemless that of pancreatic cholera but no endocrine tumor or elevated plasma level of a secretalogue can be found[37]. Several empiric treatment trials have been recommended, but success is highly variable[38].

Decisions about angiography and laparotomy in these patients are difficult. On the basis of some investigators experience with pancreatic cholera syndrome and chronic secretory diarrhea of unknown origin[39], they would suggest the following scheme of management in patients with large-volume and chronic secretory diarrhea, but with no evidence of laxative ingestion or of an endocrine tumor by radiologic or sonagraphic techniques. If the plasma concentrations of endocrin tumor markers (VIP, calcitonin, pancreatic polipeptide) are normal or only midly and inconsistently elevated, they would recommend treatment with nonspesific remedies such as opiates for a period of up to six months. Only if there is no adequate response to these remedies or if severe diarrhea recurs when symptomatic therapy is withdrawn at six months should exploratory laparotomy be performed. On the other hand, if the plasma concentration of endocrine tumor markers is consistently and definitely elevated, it seems reasonable to carry out explora-

tory laparotomy regardless of the response to nonspecific medical therapy. If a tumor is not found at surgery then theirs tentative recommendation would be to do a "blind" distal pancreatectomy only in those patients in whom preoperative plasma concentrations of endocrine tumor markers were markedly and repeatedly elevated.

In our patients had a laparotomy but no pancreatic tumor had been observed. The clinical presentation of this case resembles that of pancreatic cholera but no endocrine tumor or elevated plasma level of a secretagogue can be found and stool electrolytes accounted for all the osmolality in stool water, the cause of the ileoectomy diarrhea was found to be abnormal small-bowel secretion.

Since some investigators have previously observed that somatostatin abolish abnormal small-bowel secretion in humans even when secretion is not due to a circulating secretagogue as in total villous atrophy[39,40], and since somatostatin delays small-bowel transit[41], it was reasonable to attempt treatment of our patient with this synthetic peptide.

When the long-acting somatostatin analogue SMS 201-995 was given, the patient's diarrhea decreased to the range that would be expected given his altered anatomy, and the patient was able to maintain a positive fluid and salt balance with oral intake alone.

It should be possible that the marked reduction of diarrhea during treatment with the analogue was due to two effects. First, somatostatin prolongs intestinal transit time. This has been shown for native somatostatin[41] and for the analogue[42]. A delay in transit was not the only mechanism involved and the somatostatin analogue probably had a direct effect on mucosal secretion. Although it is well established that somatostatin can affect mucosal secretion caused by circulating agents by reducing secretagogue release from endocrine tumors[12,15-17,43,44]. The investigator has also observed abolished secretion in a patient with total villous atrophy[39] and large volume diarrhea (5 liters per 24 hours). They postulate that in such patients, somatostatin affects secretion at the level of the mucosa by either hormonal, neural, or paracrine effects on the mucosal cell or by interference with intracellular events mediating intestinal secretion[40]. It is unclear why the discontinuation of the analogue after two months of therapy was not immediately accompanied by the recurrence of diarrhea. We do not think that the beneficial effect of the analogue simply represented a spontaneous remission, because when the diarrhea did recur, one month later, it responded promptly to the reinstitution of therapy with the analogue.

The observations described in this case report suggest that a trial of the somatostatin analogue should be undertaken in patients with intractable diarrhea caused by pseudopancreatic cholera syndrome or variant VIPoma.

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