

The watery diarrhea syndrome

Guidelines for treatment

Avram M. Cooperman, M.D.

Department of General Surgery

John J. Eversman, M.D.

Department of Endocrinology

Eugene I. Winkelman, M.D.

Department of Gastroenterology

The watery diarrhea syndrome (WDS) has generated much discussion, many isolated case reports, and considerable confusion in the pathogenesis, evaluation, and treatment of these patients.

It is likely that reported cases have emphasized the infrequency of WDS, the spectacular if not massive diarrhea (often from 6 to 8 liters/24 hr), and relief of symptoms after surgical treatment.

We, too, were impressed after successful treatment of two patients with WDS.¹ Our recent experience indicates WDS may be more common than has been thought; that one or more peptides alone or in combination may be responsible for WDS; that elevated levels of peptides may coexist with functional and nonfunctional tumors; and that operations should be limited when tumors or hyperplasia are not found.

Case reports

Case 1. A 51-year-old woman had a 6-month history of 10 to 12 tea-colored stools daily, muscle weakness, and an 11.25-kg (25 pounds) weight loss. The medical history was negative for similar illnesses. Physical examination revealed a thin, weak woman. Vital signs were normal. Laboratory and roentgenographic findings included hypokalemia (potassium level, 2.4 mEq/dl); an abnormal glucose tolerance test; and *Giardia lamblia* in the stool specimen. Complete barium studies of the gastrointestinal tract were normal. Despite 3 months of metronidazole

treatment, the diarrhea did not improve and the serum potassium level ranged between 2.1 and 2.4 mEq/dl. A 24-hour stool specimen revealed 72 mEq/liter of potassium and no pathogenic bacteria. A pancreatic tumor was suspected and a celiac and superior mesenteric arteriogram was done and was normal. An exploratory celiotomy was performed and a right adrenal medullary tumor 4 cm in diameter was excised. The remainder of the abdominal examination including palpation of the pancreas was normal. Microscopy showed a pheochromocytoma. Tissue and serum assays revealed elevated levels of vasoactive intestinal polypeptide (VIP) 7.2 ng/ml (Fisher's assay), 650 ng/ml (Said's assay), and 20,000 ng/g of tumor. She has remained well for 3 years.

Case 2. A 65-year-old man with a long-standing history of chronic loose stools was hospitalized for the acute onset of watery, nonbloody diarrhea (30 to 40 movements a day) unassociated with meals, cramps, or vomiting. Physical examination revealed mild dehydration. Hypokalemia (potassium level, 3.1 mEq/dl) was present. Stool losses of 4 liters each day led to acidosis and coma, despite the administration of intravenous fluids. Steroids given empirically (prednisone, 30 mg/day) slowed the diarrhea. He was ambulatory when dismissed from the hospital on a regimen of prednisone, 30 mg/day. The patient was asymptomatic when he transferred to the Cleveland Clinic. Steroid therapy was stopped when crescendo angina pectoris developed. Shortly after this, 18 stools were passed in 24 hours. Again stool losses became so great that weakness, dehydration, and acidosis developed. Stool analyses revealed a bicarbonate concentration of 79 mEq/liter; potassium, 99 mEq/liter; and sodium, 5 mEq/liter. Serum was obtained for peptide analyses (VIP, 310 ng/ml) as steroid therapy was resumed. Within 24 hours the diarrhea ceased. Abdominal angiograms were normal. He was treated with low doses of prednisone, 10 mg/day, for 14 months. He underwent an abdominal operation for a suspected malignant lesion, at which time an islet-cell tumor was found and distal pancreatic resection was done.

Tissue levels of VIP were elevated at 72 ng/g (Fisher).

Case 3. A 57-year-old man was examined for back pain, deep epigastric pain, and 15.75-kg (35 pounds) weight loss. Cancer of the pancreas was suspected. Results of routine laboratory tests were normal and an ultrasound examination revealed a solid pancreatic mass.

An exploratory laparotomy was done and an islet-cell carcinoma of the pancreas and diffuse hepatic metastases were found. Biopsies were taken and a splanchnic resection was done for relief of pain. During the next 3 months mild diarrhea (4 to 5 loose, watery bowel movements a day) developed. Serum levels of VIP were elevated at 1500 pg/ml. Diphenoxylate (Lomotil) controlled the diarrhea. The patient died of carcinomatosis a few months later.

Case 4. A 61-year-old woman was examined at the Cleveland Clinic in February 1976 because of 10 to 12 loose, watery stools a day. The diarrhea was episodic and had begun 3 months prior to hospitalization. She had a 22-year history of diabetes mellitus treated by 22 units NPH insulin. Results of physical examination and laboratory tests including complete blood count, SMA-12, and serum electrolytes were normal. She was dismissed on a regimen of diphenoxylate, 5.0 mg/day.

In April 1976, she was again hospitalized because of dehydration and diarrhea (20 to 30 loose, watery stools a day). Hyperchloremic acidosis and hypokalemia (potassium level, 3.0 mg/dl) were noted on admission. She was hospitalized for 10 weeks, during which time episodic bouts of diarrhea (up to 5 liters measured) were noted. They were not controlled by diphenoxylate or prednisone and unrelated to diet. Serum VIP levels from two assays with different normal values were 135 pg/ml (normal, < 100 pg/ml), 140 pg/ml (normal, < 50 pg/ml). Serum gastrin was 454 pg/ml, and with calcium infusion it was 621 pg/ml (20 min), 538 pg/ml (1 hr), 522 pg/ml (2 hr), and 740 pg/ml (3 hr). A myocardial infarction developed from which she recovered. A celiac and superior mesenteric arteriogram was normal.

In July 1976 she was hospitalized again because of dehydration, acidosis, and diarrhea (up to 25 stools a day). Between admission and laparotomy (August 18, 1976) she had several sieges of profound watery diarrhea, dehydration, and prerenal azotemia. Repeat angiograms showed encasement of the transverse pancreatic artery. On August 18, 1976, a laparotomy was done. The gallbladder was dilated; no retroperitoneal or pancreatic masses were found. A distal (40%) pancreatic resection was done and except for minimal pancreatitis no pathologic abnormalities were found. Assays of the pancreatic tissue revealed no peptide elevations. The diarrhea resumed postoperatively and she died suddenly 11 days after operation. An autopsy was not done.

Discussion

WDS has many names including Verner-Morrison syndrome,² pancreatic cholera,³ watery diarrhea, hypokalemia, and achlorhydria (WDHA),⁴ and Vipoma⁵ after the secretagogue VIP. All of these terms are descriptive, since they characterize features or agents associated with the syndrome in most patients.

In 54 cases reviewed by Verner and Morrison,⁶ the clinical features included stool volumes usually from 6 to 8 liters/24 hr, hypokalemia, and excessive loss of potassium (300 mEq/24 hr) in the stool. Also, more than half the patients had gastric achlorhydria or hypochlorhydria and diabetes mellitus; hypercalcemia and skin flushing were present less frequently.

The most common pathologic lesions are benign (30%) or malignant tumors (40%) usually pancreatic, and islet-cell hyperplasia (more than 20%).⁶ In more than 10% of patients, no identifiable lesion is found. Extrapancreatic tumors, particularly retroperitoneal (adrenal medullary,² ganglioneuromas⁶) and pulmonary also cause WDS.

The nature and isolation of the secretory substance responsible for WDS has evoked much discussion and disagreement. A variety of hormones and peptides including secretin,⁷ glucagon,⁷ VIP,² gastric inhibitory polypeptide⁸ (GIP), gastrin-glucagon,⁹ and prostaglandins¹⁰ have been incriminated as humoral mediators of this syndrome. Early studies incriminated secretin or a secretin-like substance because of activity on bioassay of tumor extracts from patients with this syndrome.¹¹ The combination of gastrin and glucagon in large doses has reproduced the clinical syndrome in canines,¹⁰ but the gastrin level is usually not elevated in humans with WDS. At least one case of elevated GIP levels has been reported.⁸ Certainly the peptide that has created the most interest has been VIP. This is a 28-amino acid peptide residue isolated in 1970 from porcine duodenum and upper small intestine by Said and Mutt.¹² The physiologic and pharmacologic actions have been characterized by several investigators and fit well with the clinical features of the syndrome, profound watery diarrhea,² vasodilatation,¹² hyperglycemia,⁶ stimulation of exocrine pancreatic and intestinal secretion,¹³ and inhibition of basal and stimulated gastric acid secretion.¹³ Bloom et al,¹⁴ Ebeid et al,¹⁵ and Said and Faloona¹³ have assayed tumors and sera from patients with WDS and found elevated levels of VIP in many patients. Unfortunately, the reliability, reproducibility, and sensitivity of this assay are variable. In some patients liver disease and elevated VIP levels are present without symptoms of WDS.¹⁵ Although VIP is thought to act via cyclic adenosine monophosphate (cyclic AMP), the few humans studied with WDS have had elevated VIP, but normal intestinal levels of cyclic AMP.^{5, 16} Kahn et al¹⁶

showed remission of symptoms in two patients with metastatic malignant disease and WDS after chemotherapy when VIP was undetectable.

Other peptides alone or in combination have caused WDS. Schmitt et al⁷ isolated serotonin, enteroglucagon, secretin, calcitonin, and VIP in tumor and serum from one patient with WDS, and Rambaud et al¹⁰ noted increased plasma and tumor levels of calcitonin, prostaglandins E and F_a and VIP.¹⁰

The secretory abnormality in WDS has been studied in only a few patients.^{5,7} Increased pancreatic secretin has been documented in one patient.⁷ In three patients recently studied by Krejs et al,⁵ a major abnormality was in the jejunum, which secreted excessive sodium, water, and chloride ions.⁵ The mean excessive unabsorbed fluid was 89 to 103 ml/hr. In one of three an ileal absorptive defect was also present. Jejunal perfusion studies were more than academic, since symptoms similar to WDS were present with surreptitious use of laxatives and diuretics.

Since WDS may be caused by intraabdominal and extraabdominal tumors, it is important to diagnose and accurately localize the cause of WDS before surgery. These four cases illustrate the spectrum of WDS and extend over earlier observations. The first two cases, although previously summarized, indicate the intermittent nature and varying severity of the diarrhea, the cure by excision of an adrenal medullary and pancreatic tumor, and a dramatic abatement of symptoms and return to normal of elevated levels of VIP after prednisone therapy.

The third patient with metastatic islet-cell carcinoma thought to be nonfunctioning had very high VIP levels in serum, yet the diarrhea that appeared later was mild and was controlled by

diphenoxylate. It is possible that many "nonfunctioning" pancreatic tumors are secreting hormones and peptides that are not causing symptoms. To know the frequency of nonfunctioning tumors, it is necessary that assays be done on excised lesions or biopsy specimens of endocrine lesions of the gut and pancreas.

Our fourth case illustrates and emphasizes the need for accurate preoperative diagnosis and the limitations of surgery in uncontrollable symptomatic patients when no lesion is found. For all patients suspected of having WDS, common causes must first be excluded. Stool analyses for parasites, barium roentgenograms of the stomach, small intestine and colon, and proctoscopic examination will exclude most intrinsic bowel diseases. Stool analyses should show high potassium content. Serum should be collected, frozen, and assayed for all hormones and peptides associated with the syndrome. Since the results of assays are not available for weeks, angiography or therapeutic trials with steroids or aspirin (if prostaglandins are the cause) may be tried. The results may be less than anticipated. If one or more peptides are elevated, then localization or surgical exploration may be justified. False elevations of peptides are not uncommon. Clinical decisions must be based on all factors.

At the time of abdominal surgery, a careful and thorough search should be made for a tumor. If a solitary benign or malignant lesion is found, excision may be done. If none is found, a distal pancreatic resection may be done in the hope that islet-cell hyperplasia and elevated peptide levels will be found. Resection beyond the mesenteric vein is unnecessary, unless a clear-cut abnormality is present. Even if islet-cell hyperplasia is present, the amount of pancreas to be resected is not known. Sub-

total pancreatectomy may provide relief of symptoms even though subsequent total resection may be necessary.⁶ We cannot overemphasize the limitations of blind, total, or partial pancreatic resection in these patients. Perhaps transhepatic portal venous sampling will be of assistance in these patients, since occult secreting lesions may be detected and localized by this method.

If a malignant lesion with metastases is found, treatment is more difficult and steroids, chemotherapy, or radiation may be tried with isolated instances of success. The outlook is poor, but worth the attempts to control the disabling diarrhea.

Summary

WDS has many and varied presentations from elevated peptide levels without diarrhea to profound watery diarrhea with known lesions.

Many peptides, notably VIP, have been incriminated in the syndrome, although the reproducibility and difficulty of performing these assays have cast doubt on their accuracy. Added to this problem have been elevated levels of peptides in patients without symptoms of WDS or abatement of symptoms while peptide levels remained elevated.

Four cases have been reported; one patient with an adrenal medullary tumor causing WDS; a second with an islet-cell tumor secreting VIP whose symptoms and VIP levels were controlled with prednisone; a third patient had metastatic carcinoma of the pancreas with minimal diarrhea and greatly elevated VIP levels; the fourth patient had severe uncontrolled diarrhea, and no tumor was found at surgery. In these patients, blind major pancreatic resections offer nothing unless islet-cell hyperplasia or occult lesions are found.

References

1. Cooperman AM, DeSantis D, Winkelman E, et al: Watery diarrhea syndrome; two unusual cases and further incidence that VIP is a humoral mediator. *Ann Surg* **187**: 325-328, 1978.
2. Verner JV, Morrison AB: Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. *Am J Med* **25**: 374-380, 1958.
3. Matsumoto KK, Peter JB, Schultze RG, et al: Watery diarrhea and hypokalemia associated with pancreatic islet adenoma. *Gastroenterology* **50**: 231-242, 1966.
4. Marks IN, Bank S, Louw JH: Islet cell tumor of the pancreas with reversible watery diarrhea and achlorhydria. *Gastroenterology* **52**: 694-708, 1967.
5. Krejs GJ, Walsh JH, Morawski SG, et al: Intractable diarrhea; intestinal perfusion studies and plasma VIP concentrations in patients with pancreatic cholera syndrome and surreptitious ingestion of laxatives and diuretics. *Am J Dig Dis* **22**: 280-292, 1977.
6. Verner JV, Morrison AB: Endocrine pancreatic islet disease with diarrhea; report of a case due to diffuse hyperplasia of nonbeta islet tissue with a review of 54 additional cases. *Arch Intern Med* **133**: 492-500, 1974.
7. Schmitt MG Jr, Soergel KH, Hensley GT, et al: Watery diarrhea associated with pancreatic islet cell carcinoma. *Gastroenterology* **69**: 206-216, 1975.
8. Elias E, Polak JM, Bloom SR, et al: Pancreatic cholera due to production of gastric inhibitory polypeptide. *Lancet* **2**: 791-793, 1972.
9. Barbezat GO, Grossman MI: Cholera-like diarrhoea induced by glucagon plus gastrin. *Lancet* **1**: 1025-1026, 1971.
10. Rambaud JC, Modigliani R, Matuchansky C, et al: Pancreatic cholera; studies on tumoral secretions and pathophysiology of diarrhea. *Gastroenterology* **69**: 110-122, 1975.
11. Zollinger RM, Tompkins RK, Amerson JR, et al: Identification of the diarrheogenic hormone associated with non-beta islet cell tumors of the pancreas. *Ann Surg* **168**: 502-521, 1968.
12. Said SI, Mutt V: Polypeptide with broad biological activity; isolation from small intestine. *Science* **169**: 1217-1218, 1970.
13. Said SI, Faloon GR: Elevated plasma and tissue levels of vasoactive intestinal peptide in the watery diarrhea syndrome due to pan-

- creatic bronchogenic and other tumor. *N Engl J Med* **293**: 155-160, 1975.
14. Bloom SR, Polak JM, Pearse AGE: Vasoactive intestinal peptide and watery-diarrhoea syndrome. *Lancet* **2**: 14-16, 1973.
15. Ebeid AM, Murray P, Hirsch H, et al: Radioimmunoassay of vasoactive intestinal peptide. *J Surg Res* **20**: 355-360, 1976.
16. Kahn CR, Levy AG, Gardner JD, et al: Pancreatic cholera; beneficial effects of treatment with streptozotocin. *N Engl J Med* **292**: 941-945, 1975.