VIPomas and the Watery Diarrhoea Syndrome

I. M. MODLIN, S. R. BLOOM

SUMMARY
Vaso-active intestinal polypeptide (VIP) is a recently discovered polypeptide widely distributed throughout the gastro-intestinal tract and nervous system. Elevated plasma VIP levels are found in gut and neural endocrine tumours producing the watery diarrhoea syndrome. Fifty per cent of these tumours are intrinsically malignant and the mortality rate may be as high as 30% even from the benign growths owing to the serious metabolic sequelae of the syndrome. The plasma VIP level is not elevated in any other non-tumorous diarrhoeal condition. The biological action of VIP closely resembles the clinical features of the Verner-Morrison syndrome and experimental evidence strongly suggests that VIP is the causal agent. The measurement of plasma VIP is of exceptional diagnostic value, since detection of elevated levels enables early removal of the tumour and may be life-saving.


There has been much speculation regarding the hormonal causes of diarrhoea and in some instances the implicated agent is now known. In recent times, however, the isolation of certain enteric polypeptides has suggested a neoplastic origin for some cases of watery diarrhoea.

In 1958 Verner and Morrison described a syndrome of refractory watery diarrhoea and hypokalaemia associated with non-insulin-secreting tumours of the pancreatic islets. Subsequently many similar cases were reported and suggestions made as to the cause. Gastrin and glucagon, secretin, pancreatic polypeptide, prostaglandins E, and E₂, serotonin and gastric inhibitory peptide have all at one time or another been put forward as the cause of the watery diarrhoea syndrome. Vaso-active intestinal polypeptide (VIP) was first isolated by Said and Mutt from porcine gut mucosa. In 1973 it was reported that the involved tumour contained a large amount of the newly discovered VIP and that VIP levels were extremely elevated. The relationship of VIP to the syndrome seemed likely because the biological action of VIP closely fitted the described symptoms of the patients. Thus VIP is a potent stimulant of small-intestinal juice production and a powerful inhibitor of gastric acid secretion. It also increases the hepatic output of glucose, stimulates pancreatic bicarbonate secretion, relaxes the gallbladder and causes vasodilatation. These factors may explain the frequent clinical findings of hypochlorhydria, diabetes, flushing attacks, high resting pancreatic juice production and a flaccid distended gallbladder. It was proposed that VIP was the cause of the Verner-Morrison syndrome and therefore a raised plasma VIP level would be helpful in diagnosis. This proposal, however, has not been generally accepted, especially since until the present time no direct evidence has existed to prove that VIP produced the watery diarrhoea syndrome.

CASE REPORT
A 61-year-old man had suffered from severe, painless watery diarrhoea for 5 years. Bowel motions occurred 10-12 times a day and contained no blood or mucus. Despite the patient having had barium enemas, sigmoidoscopy and a rectal biopsy, no abnormality other than mildly inflamed mucosa could be demonstrated. On the presumption that the patient had ulcerative colitis he was treated with prednisone and sulphasalazine, but to little avail. In August 1975, after a particularly severe episode of diarrhoea, he developed a quadriaparesis and was found to have a serum potassium level of 1.7 mmol/l. Intravenous potassium was necessary to reverse this paresis and thereafter he required oral potassium supplements. At this stage the plasma VIP level was estimated and found to be 258 pmol/l (normal < 20 pmol/l). Physical examination revealed no abnormality; in particular there was no evidence of an abdominal mass. His blood pressure was 130/110 mmHg with a pulse rate of 70/min.

Basal gastric secretion was nil and pentagastrin-stimulated peak acid output was 7 mmol/l (normal 19 ± 3 mmol/l). Plasma noradrenaline was 4.41 µg/l (normal < 0.7 µg/l), and urinary catecholamine levels were correspondingly elevated at 351 µg/g creatine (normal < 40 µg/g). Intravenous urography demonstrated a left suprarenal mass which selective arteriography confirmed to be a vascular tumour closely related to the left adrenal gland. Catheterization with selective venous sampling showed the highest levels of VIP and noradrenaline to be in the left renal vein area, suggesting that the tumour was the site of hormone production.

At operation a large left adrenal tumour was removed and this was followed by a dramatic fall in blood pressure which required infusion of considerable blood and plasma to restore the haemodynamic status to normal. Because of the absence of hypertension and cardiac abnormalities, no adrenergic blockade had been instituted before the operation.

The tumour was 12 cm in diameter, well encapsulated and weighed 560 g. Analysis demonstrated markedly elevated levels of VIP, adrenaline, noradrenaline and dopamine (0.57, 560, 300 and 6.500 ng/mg of wet tissue respectively). Histological examination showed a benign...
ganglioneuroma and immunofluorescent studies demonstrated the presence of VIP and noradrenaline in the cells.

After the operation the patient's plasma VIP level fell dramatically and the diarrhoea ceased (Fig. 1). In the 1 year since operation the patient has gained 15 kg in weight and now has normal bowel actions twice a day. Plasma VIP and catecholamine levels have remained normal.

**Plasma VIP Measurement**

Considerable care is necessary during specimen collection and assay to avoid erroneous results. VIP is rapidly destroyed by proteolytic enzymes as it possesses two separate double basic amino acid sequences which are particularly liable to degradation by trypsin-like enzymes. In addition, it contains a methionine residue which renders it liable to oxidative damage and two asparagine residues which are easily deaminated. As VIP is a highly basic molecule it is rapidly absorbed onto active surfaces, particularly those which are negatively charged. Blood should therefore be taken into a proteolytic enzyme inhibitor (aprotinin 1 000 kallikrein inhibitor units/ml blood) and then rapidly centrifuged and the plasma frozen within 15 minutes of venepuncture. Steady loss of immunoreactive VIP occurs at -20°C storage while thawing and refreezing accentuate this process. Lyophilizing of plasma is now considered the best technique for storage and transport without significant degradation.

By using an assay system sensitive to 1.5 pmol/l of plasma, we have found the normal plasma VIP concentration to be less than 10 pmol/l and the absolute upper limit in healthy subjects to be 50 pmol/l. Other reports have suggested that completely healthy individuals may have grossly elevated plasma VIP levels, but we have not observed this.

**VIP-Producing Tumours**

We have assayed samples from nearly 1 000 patients suffering from unexplained severe diarrhoea. In 39 of these patients the plasma VIP level was grossly elevated and in each case a tumour was present. The majority of these lesions were located in the pancreas, but in 7 individuals (4 children) the tumour was a ganglioneuroma or ganglioneuroblastoma (Fig. 2). Analysis of the tumour in each case always demonstrated high values of VIP. In more than half of these 39 cases there was no evidence of metastases and removal of the primary tumour resulted in plasma VIP returning to normal levels, with abrupt cessation of diarrhoea.

**Causal Role of VIP**

In 70% of VIP-producing tumours, plasma pancreatic polypeptide levels are grossly elevated and it is conceivable that pancreatic polypeptides may play a part in the development of the diarrhoeal syndrome. However, it has never been demonstrated physiologically or pharmacologically that pancreatic polypeptide can produce diarrhoea and, in fact, massive single doses produce only defaecation, without diarrhoea. Furthermore, many patients with gastrinomas, glucagonomas and insulinomas have very
Pseudo-Verner-Morrison Syndrome

We have examined 11 patients with the classic clinical picture of the watery diarrhoea syndrome, complete with severe hypokalaemia and, in most cases, hypochlorhydria, but with no evidence of a pancreatic tumour at laparotomy. These patients all had normal plasma VIP levels (Fig. 2). Occasionally pancreatic islet cell hyperplasia has been found in such patients, who are usually treated by partial pancreatic resection, although in some cases only a subsequent total pancreatectomy cured the diarrhoea. The term pseudo-Verner-Morrison syndrome has been applied to this condition and it almost certainly represents a different aetiology.

Treatment of Metastatic VIPomas

Although the course of the diarrhoea is fluctuant, death may occur in weeks or months. The reason for this is often that the diagnosis is made only in extremis, by which time severe metabolic sequelae are already present. Since almost 50% of patients may have hepatic metastases by the time of operation, curative surgery is often not possible. Clinical remission, however, correlates closely with plasma VIP levels and ablation of as much tumour tissue as possible is advisable. The customary methods of tumour enucleation or hepatic resection may not be feasible because of the patient’s condition or the number of secondaries. In these cases hepatic arterial perfusion with streptozotocin has been used, although percutaneous administration may be as effective. Hepatic arterial ligation effectively necroses liver metastases but this requires laparotomy and the effect is often short-lived owing to the rapid development of collaterals to the liver. More recently liver endocrine tumour metastases have been successfully treated by percutaneous hepatic arterial embolization. Clinical awareness of the syndrome and thus early diagnosis by plasma VIP measurement is therefore of great importance. Streptozotocin, a nitroso-urea antibiotic that inhibits DNA synthesis has proved very effective in treating disseminated pancreatic VIPomas. Remission periods of several years have been reported. We have demonstrated that lowering of the plasma VIP level by streptozotocin therapy closely parallels the reduction in diarrhoea and clinical remission (Fig. 3).

Fig. 2. Plasma VIP values. All the healthy normal subjects have values of less than 20 pmol/l. The patients with the pseudo-Verner-Morrison syndrome do not have elevated VIP levels. Levels greater than 20 pmol/l are indicative of a VIP-producing tumour. The dark circles represent pancreatic VIPomas while the open circles are the 7 VIP-producing neural tumours.

Fig. 3. A VIPoma with hepatic metastases treated with streptozotocin. A dramatic fall in plasma VIP level is associated with a marked diminution of diarrhoea.
Monitoring the plasma VIP level can give a good early indication of the imminence of a relapse and recurrence of the diarrhoea and of the need for further preventive cytotoxic therapy. In some cases, high doses of steroids (50-100 mg of prednisolone daily) are effective in temporarily controlling the diarrhoea but will lead to only a slight fall in plasma VIP concentrations. In this situation the effect of the steroids is probably directly on the bowel mucosa.

**Other Diarrhoeal Conditions**

In infective diarrhoea and inflammatory bowel diseases (Crohn's disease and ulcerative colitis) plasma VIP levels are not raised." Analysis of samples from patients with severe diarrhoea suffering from medullary carcinoma of the thyroid, purgative addiction, carcinoma of the lung, carcinoid syndrome and villous adenoma of the rectum revealed no elevation of plasma VIP levels." A rise in plasma VIP levels is found in bowel ischaemia, both clinically and experimentally." This situation often produces diarrhoea but the mechanism may not be the same, for in patients with a VIPoma the levels are persistently raised. The role of high plasma VIP levels in the pathogenesis of bowel ischaemia requires further study. In 3 patients with slightly elevated VIP levels, diarrhoea fluctuated in parallel to the plasma VIP concentration but so far no pancreatic tumour has been demonstrated in these subjects in spite of extensive investigation. It is possible that these individuals may have another mechanism for abnormal VIP release.

**CONCLUSION**

In patients suffering from the watery diarrhoea syndrome who have pancreatic and neural tumours, the plasma VIP level is elevated. The VIP concentrations in the tumour are increased and selective venous sampling of the lesion also demonstrates an extremely high VIP production locally. The pharmacological actions of VIP include a potent stimulation of small-intestinal juice secretion. Removal of the tumour or ablation of the metastases with streptozotocin causes reduced plasma VIP levels and a cessation of the diarrhoea.

Since porcine VIP is apparently immunochemically and chromatographically identical to human VIP, the fact that pigs infused with pure porcine VIP develop diarrhoea would strongly suggest a causal role of VIP in the pathogenesis of the human watery diarrhoea syndrome. The fact that this is achieved at plasma levels closely comparable to those found in humans adds further weight to the suggestion.

Since elevated VIP levels have not been demonstrated in any other diarrhoeal condition, plasma measurement is of exceptional diagnostic value. The mortality rate in the watery diarrhoea syndrome is directly related to the length of delay in detection and diagnosis of the tumour. Early detection of a raised plasma VIP level may thus be life-saving.

Dr I. M. Modlin is being supported by a scholarship from the South African Medical Research Council.

**REFERENCES**