A review of the Zollinger-Ellison syndrome – with particular reference to a patient treated with cimetidine

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Summary

A case of the Zollinger-Ellison syndrome, presented with watery diarrhoea, malabsorption and multiple duodenal ulcers. Resection of a gastrinoma from the head of the pancreas was ineffective. Cimetidine, administered for more than 30 months produced an immediate and sustained relief of symptoms with a gain in weight of 19 kg and improvement of the biochemical features of malabsorption. Gastric acid secretion has been markedly inhibited and duodenal ulceration healed.

Introduction

Zollinger and Ellison (1955) described the syndrome of recurrent peptic ulceration and gastric hypersecretion in association with a pancreatic islet cell tumour. For many years physicians and surgeons were agreed that total gastrectomy offered the best form of treatment.

Cimetidine, a histamine H₂-receptor antagonist, inhibits basal and stimulated gastric-acid secretion and promotes the healing of gastric and duodenal ulcers (Burland *et al.*, 1975a; Pounder *et al.*, 1976; Frost *et al.*, 1977; Gray *et al.*, 1977). A case is described which was treated successfully for more than 30 months solely with cimetidine. The relevant literature is reviewed.

Case report

A 65-year-old man admitted to Leeds General Infirmary in April 1976, gave a history of 2 years' intermittent watery diarrhoea (4-6 times/day), 19 kg weight loss, and mild postprandial dyspepsia, relieved by food and antacids, worse for the past month. On examination, apart from obvious recent weight loss, he appeared normal.

Laboratory investigations showed the blood urea, electrolytes and full blood count to be normal. Serum folate, plasma magnesium, cholesterol,

albumin and 5-hr urinary excretion of an oral load of 5 g of D-xylose were all reduced (Fig. 1), and faecal fat excretion elevated at 90 mmol/day (upper limit of normal 18 mmol/day).

Small bowel meal showed widening of the duodenal loop with gross thickening and irregularity of the mucosal folds in the duodenum and jejunum, evidence of malabsorption but none of inflammation or ulceration. Endoscopy revealed multiple small ulcers in the first and second parts of the duodenum. Endoscopic retrograde pancreatography showed the main pancreatic duct to be normal in size, with good branch filling, but failed to fill right out to the tail. There were 2 constant filling defects in the head and neck, and the whole duct appeared slightly irregular (Fig. 2).

Gastric acid secretory studies showed a mean basal acid output of 95 mmol/hr and after an intramuscular injection of pentagastrin (6 u/kg) a mean peak acid output of 134 mmol/hr (Table 1). Fasting serum gastrin levels on 2 mornings were 390 and 315 pg/ml (normal <99 pg/ml).

Coeliac axis angiography showed a rounded lesion in the head of the pancreas 4 cm in diameter, supplied from the posterior pancreatico-duodenal artery and displacing the gastro-duodenal artery medially without encasement (Fig. 3). The portal vein was normal and there was no evidence of hepatic pathology.

Before proceeding to laparotomy a trial of cimetidine was started in a dose of 200 mg thrice daily and 400 mg at night orally. This produced a rapid cessation of diarrhoea and a general clinical improvement. After 10 days' therapy, gastric acid studies, performed one hr after the normal morning oral dose of 200 mg of cimetidine, showed the mean basal and mean peak acid output to be inhibited by 95 and 42% of the presenting levels (Table 1). The fasting serum, gastrin had fallen to 180 pg/ml.

FIG. 1. Biochemical investigation. Hatched areas denote normal range: x at time of presentation; ● after 3 months' treatment with cimetidine one g/day.

FIG. 2. X-ray of pre-operative endoscopic retrograde cannulation of the pancreatic duct. The whole duct is irregular and arrows refer to filling defects in the duct in the head and neck.

In May 1976, after 11 days of cimetidine therapy, laparotomy revealed the mucosal folds in both the first and second parts of the duodenum to be grossly thickened. On the posterior aspect of the head of the pancreas just to the right of the superior mesenteric vein was a discrete encapsulated tumour 3 cm in diameter. No other tumours were palpable either in the pancreas or duodenal wall. The tumour was removed by incising the pancreatic capsule. The

ductal system was left intact. The light and electron microscopic appearances of the tumour were consistent with a gastrinoma replacing the cortex of a lymph node. Extraction of the tissue yielded 37.5 μg of gastrin immunoactivity/g wet weight of tissue.

Cimetidine was discontinued at the time of operation. After a stable first postoperative week, gastric aspiration rose to 4 litres/day with a return of gastric hyperacidity (Table 1). An intravenous

TABLE 1. Gastric acid secretion studies

	Mean basal acid output mEq/hr	Mean peak acid output mEq/hr
On presentation	94.9	134.4
*10th day on cimetidine (one g/day)	5.2	78.9
Laparotomy		
8th day post-laparotomy	64.9	104.8
*After 3 months on cimetidine (one g/day)	10.2	73.6

*Test performed one hr after morning oral dose of 200 mg of cimetidine

injection of secretin 3 i.u./kg produced a rise of fasting serum gastrin from 205 to 280 pg/ml within 10 min. Such a response would indicate a residual gastrin-secreting tumour.

Cimetidine was restarted with an immediate clinical improvement and reduction of fasting serum gastrin to 120 pg/ml. The patient was discharged home 5 days later on cimetidine 200 mg thrice daily and 400 mg at night.

Clinical outcome of treatment

Since starting cimetidine 30 months ago the patient has suffered no diarrhoea or indigestion. The 19 kg

weight loss was regained in only 7 months and since then active calorie restriction has been necessary. After 3 months' therapy, out-patient gastric acid studies, performed one hr after the normal morning oral dose of 200 mg of cimetidine, showed inhibition of the mean basal and mean peak acid output by 85 and 30% of the 8th postoperative day levels (Table 1). The appearances of the small bowel meal have improved, with less widening of the duodenal loop and thickening of the mucosal folds in the duodenum and jejunum. Duodenoscopy showed the duodenum to be healed with only one tiny ulcer 2 mm in diameter at the junction of the second and third parts.

The biochemical features of malabsorption have improved without any dietary supplements (Fig. 1). Only faecal fat excretion is elevated at 80 mmol/day. No clinical or biochemical evidence of metastasis has been observed.

Discussion and review

This case illustrates the use of cimetidine for the long-term treatment of Zollinger–Ellison syndrome. Previous medical therapies resulted in an 85% mortality and were abandoned in favour of total gastrectomy (Ellison and Wilson, 1967). However, total gastrectomy carries an immediate mortality of

FIG. 3. A subtraction X-ray from a selective coeliac axis arteriographic study. Arrows refer to a rounded lesion in the head of the pancreas, supplied by the posterior pancreaticoduodenal artery.

20% and can be as high as 70% for patients debilitated from previous gastric or pancreatic surgery (Ellison and Wilson, 1964). Oesophago-jejunostomy strictures, bacterial colonization of the small bowel, and malabsorption contribute to the inevitable weight loss and morbidity of this procedure (Bradley *et al.*, 1975; Thompson *et al.*, 1975). The use of H_2 -receptor antagonists to inhibit gastric acid secretion is both logical and preferable to such radical surgery.

Cimetidine has been used to treat 71 published cases of the Zollinger–Ellison syndrome (Bonfils *et al.*, 1977; Larkworthy and Davies, 1977; McCarthy *et al.*, 1977; McCarthy, 1978; Orchard and Peternel, 1977; Stage *et al.*, 1977). The largest series of 61 cases is the collected experience from the U.S.A. reported by McCarthy (1978). More than 50% of these patients had been treated for one year and 9 of them for longer than 18 months. Forty patients were controlled on 1200 mg/day and only 2 required > 2 g/day. Combination therapy with anticholinergics was both less efficient and less acceptable than a larger dose of cimetidine. Continuous therapy is essential in all but the occasional patient, as omission of a single dose may lead to an immediate relapse of symptoms. McCarthy (1978) reported 4 cases requiring an increased dose during periods of stress; 3 were subsequently returned to the previous maintenance level. The optimum dose is best titrated as an out-patient, when the patient is exposed to the stresses of everyday life.

In the first month of therapy patients may gain as much as 10 kg in weight. Some, as in the present case, actually require active calorie restriction. In contrast, only one of 6 patients reviewed 3–68 months after gastrectomy, had regained his immediate pre-operative weight and none his pre-illness weight (Bradley *et al.*, 1975).

Diarrhoea and duodenal ulcerations are extremely effectively treated with cimetidine. Thirteen per cent. of cases actually present with diarrhoea but 30% will experience it at some time during the illness. McCarthy (1978) noted diarrhoea in 60% of cases before therapy. This is difficult to interpret as more than 40% of the whole series had undergone previous gastric surgery. The mechanism of diarrhoea in the Zollinger–Ellison syndrome is related to gastric hyperactivity and hypersecretion. Intestinal hyperacidity inactivates pancreatic lipase and alters small bowel morphology, with impairment of lipolysis, absorption and hence steatorrhoea (Shimoda and Rubin, 1968). Another cause is previous gastric and/or pancreatic surgery. Although most reports of the use of cimetidine describe a reduction in stool frequency, few quantitate the malabsorption. Three of 5 cases reported by Bonfils *et al.* (1977) had diarrhoea and steatorrhoea but

while diarrhoea was improved with cimetidine in 2 cases, faecal fat studies were not repeated. In the present case, tests of small bowel function returned to normal after only 3 months' treatment. This has been accompanied by a considerable improvement in the appearance of the small bowel meal. Diarrhoea was also immediately controlled but despite these improvements steatorrhoea has persisted. There are several possible explanations for this: gastric acid output although reduced is still elevated and may result in a low duodenal pH. Maintenance of duodenal pH above 6, by cimetidine, in patients with pancreatic insufficiency has been shown to improve steatorrhoea and the duodenal recovery of oral pancreatic supplements (Regan *et al.*, 1977; Porro *et al.*, 1977). Prolonged hypergastrinaemia *per se* can also cause pancreatic insufficiency. The filling defects noted in the pancreatic duct may be the sites of other gastrinoma deposits which could progress to obstruct the pancreatic duct and produce pancreatic insufficiency. In view of the excellent clinical response this observation has not been pursued further.

Although in this case levels of serum gastrin decreased, this may reflect transient changes of secretion. McCarthy (1978) failed to demonstrate a consistent or sustained change of serum gastrin in patients receiving cimetidine.

Initial reports of the use of H_2 -receptor antagonists considered their value to be in the preparation of patients for definitive surgery. However, recent reports of the long-term use of cimetidine instead of surgery are very encouraging (Larkworthy and Davies, 1977; McCarthy, 1978). In McCarthy's series of 61 patients, 6 died, 4 owing to tumour progression, one each from exsanguination and post-gastrectomy (both were unreliable patients). This survival of 90% is a vast improvement compared with surgical therapy especially as 50% of the patients had undergone previous operations and would be a bad operative risk.

Laparotomy is still indicated for fit patients with no evidence of tumour progression, in whom excision of a solitary duodenal wall tumour may be curative. Unfortunately, such tumours only occur in 6% of cases. As 84% of gastrinomas are multifocal, excision of an apparently solitary tumour from other sites is inadvisable, as recurrence occurs in more than 50% of cases (Hoffman, Fox and Wilson, 1973; Friesen, Schimke and Pearse, 1972). Coeliac axis arteriography demonstrates 50% of primary tumours and is of value in the assessment of cases (Alfidi, Skillern and Crile, 1969).

Cimetidine is a potent drug with high patient acceptability, able to control symptoms, correct electrolyte imbalance, malabsorption and weight loss as well as heal upper gastro-intestinal ulceration. Although cimetidine reduces morbidity and

mortality, it acts solely on the end-organ response and has no direct effect on tumour secretion or progression. Chemotherapeutic agents with direct action on the tumour offer the best hope; the most promising of which, to date, is streptozotocin, which in some cases has produced a beneficial clinical response with reduction of tumour mass, serum gastrin and gastric acid secretion (Sadoff and Franklin, 1975; Hayes *et al.*, 1976; Stadil *et al.*, 1976). Local perfusion via a selective arterial catheter may be superior to the intravenous route. However, until more evaluation of such agents is available, cimetidine provides the most acceptable and effective form of treatment.

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References

- ALFIDI, R.J., SKILLERN, P.G. & CRILE Jr, G. (1969) Arteriographic manifestations of the Zollinger–Ellison syndrome. *Cleveland Clinic Quarterly*, **36**, 41.
- BONFILS, S., MIGNON, M., JIAN, R. & KLOETI, G. (1977) Cimetidine. In: *Proceedings of the Second International Symposium on Histamine H₂-receptor Antagonists*, p. 311, Excerpta Medica, Amsterdam.
- BRADLEY Jr III, E.L., ISAACS, J., HERSH, T., DAVIDSON, E.D. & MILLIKAN, W. (1975) Nutritional consequences of total gastrectomy. *Annals of Surgery*, **182**, 415.
- BURLAND, W.L., DUNCAN, W.A.M., HESSELBO, T., MILLS, J.G., SHARPE, P.C., HAGGIE, S.J. & WYLLIE, J.H. (1975) Pharmacological evaluation of cimetidine, a new histamine H₂-receptor antagonist, in healthy man. *British Journal of Clinical Pharmacology*, **2**, 481.
- CREMER, M. (1977) Cimetidine. In: *Proceedings of the Second International Symposium on Histamine H₂-receptor Antagonists*, p. 322, Excerpta Medica, Amsterdam.
- ELLISON, E.H. & WILSON, S.D. (1964) The Zollinger–Ellison syndrome, reappraisal and evaluation of 260 registered cases. *Annals of Surgery*, **16**, 512.
- ELLISON, E.H. & WILSON, S.D. (1967) Ulcerogenic tumours of the pancreas. *Progress in Clinical Cancer*, **3**, 225.
- FRIESEN, S.R., SCHIMKE, R.N. & PEARSE, A.G.E. (1972) Genetic aspects of the Zollinger–Ellison syndrome: Prospective study in two kindred: antral gastrin cell hyperplasia. *Annals of Surgery*, **176**, 370.
- FROST, F., RAHBK, I., RUNE, S.J., BIRGER JENSEN, K., GUDMAND-HOYER, E., KRAG, F., RASK-MADSEN, J., WULFF, H.R., GARBOL, J., GOTLIETS JENSEN, K., HOJLUND, M. & NISSEN, V.R. (1977) Cimetidine in patients with gastric ulcer: a multicentre trial. *British Medical Journal*, **2**, 795.
- GRAY, G.R.J., MCKENZIE, I., SMITH, I.S., CREAN, G.P. & GILLESPIE, G. (1977) Oral cimetidine in severe duodenal ulceration. A double-blind controlled trial. *Lancet*, **i**, 4.
- HAYES, J.R., O'CONNELL, N., O'NEILL, T., FENNELLY, J.J. & WEIR, D.G. (1976) Successful treatment of a malignant gastrinoma with streptozotocin. *Gut*, **17**, 295.
- HOFFMAN, J.P., FOX, P.S. & WILSON, S.D. (1973) Duodenal wall tumours and the Zollinger–Ellison syndrome: surgical management. *Archives of Surgery*, **170**, 334.
- LARKWORTHY, W. & DAVIES, H.L. (1977) Cimetidine in the management of the Zollinger–Ellison syndrome. *Postgraduate Medical Journal*, **53**, 749.
- MCCARTHY, D.M., OLINGER, E.J., MAY, R.J., LONG, B.W. & GARDNER, J.D. (1977) H₂-histamine blocking agents in the Zollinger–Ellison syndrome. *Annals of Internal Medicine*, **87**, 668.
- MCCARTHY, D.M. (1978) Report on the United States experience with cimetidine in Zollinger–Ellison syndrome and other hypersecretory states. *Gastroenterology*, **74**, 453.
- ORCHARD, J.L. & PERNEL, W.W. (1977) Cimetidine therapy in Zollinger–Ellison syndrome. *Journal of the American Medical Association*, **237**, 2221.
- PORRO, G.B., DOLCINI, R., GROSSI, E., PETRILLO, M. & PRADA, A. (1977) Cimetidine in the treatment of pancreatic insufficiency. *Lancet*, **ii**, 878.
- POUNDER, R.E., WILLIAMS, J.G., MILTON-THOMPSON, G.J. & MISIEWICZ, J.J. (1976) Effect of cimetidine on 24-hour intragastric acidity in normal subjects. *Gut*, **17**, 133.
- REGAN, P.T., MALAGELADA, J.R., DIMAGNA, P., GLANZMAN, S.L. & GO, V.L.W. (1977) Comparative effects of antacids, cimetidine and enteric coating on the therapeutic response to oral enzymes in severe pancreatic insufficiency. *New England Journal of Medicine*, **297**, 854.
- SADOFF, L. & FRANKLIN, D. (1975) Streptozotocin in the Zollinger–Ellison syndrome. *Lancet*, **ii**, 504.
- SHIMODA, S.S. & RUBIN, C.E. (1968) The Zollinger–Ellison syndrome with steatorrhea. *Gastroenterology*, **55**, 695.
- STADIL, F., STAGE, G., REHFELD, J.F.G., EFSSEN, F. & FISCHERMAN, K. (1976) Treatment of the Zollinger–Ellison syndrome with streptozotocin. *New England Journal of Medicine*, **294**, 1140.
- STAGE, J.G., RUNE, S.J., STADIL, F. & WORNING, H. (1977) Cimetidine. In: *Proceedings of the Second International Symposium on Histamine H₂-receptor Antagonists*, p. 306, Excerpta Medica, Amsterdam.
- THOMPSON, J.C., REEDER, D.D., VILLAR, H.V. & FENDER, H.R. (1975) Natural history and experience with the diagnosis and treatment of the Zollinger–Ellison syndrome. *Surgery, Gynecology and Obstetrics*, **140**, 721.
- ZOLLINGER, R.M. & ELLISON, E.H. (1955) Primary peptic ulceration of the jejunum associated with islet cell tumours of the pancreas. *Annals of Surgery*, **142**, 709.