CASE REPORTS

Cimetidine in the management of the Zollinger-Ellison syndrome

W. LARKWORTHY
M.B., F.R.C.P.(Ed.), D.C.H., R.A.F.

H. L. DAVIES*
F.R.C.S., F.R.C.S.(Ed.)

RAF Hospital, Nocton Hall, Lincoln

Summary

The first case of the Zollinger-Ellison syndrome treated from the outset continuously for more than a year with the histamine H_2 -receptor antagonist cimetidine is reported. Symptomatic response has been dramatic and sustained, marked endoscopic improvement has been observed with healing of oesophageal, gastric and stomal ulcers.

Introduction

In 1955, Zollinger and Ellison described the syndrome of recurrent peptic ulceration, gastric hypersecretion and an associated pancreatic tumour arising from non- β cells of the islets of the pancreas. Gastric hypersecretion in this condition is due to the production of large quantities of gastrin or a gastrin-like hormone by the tumour. Histamine is a mediator in the parietal cell response to gastrin, the site of action being characterized as the H_2 -receptor. Histamine H_2 -receptor antagonists reduce gastric acid secretion by blocking the action of histamine at H_2 -receptor sites. The newest agent in this group, cimetidine, has been shown markedly to inhibit basal and stimulated gastric secretion in normal subjects (Burland *et al.*, 1975a; Pounder *et al.*, 1976) and in patients with duodenal ulceration (Pounder *et al.*, 1975; Barbezat and Bank, 1977). Cimetidine appears to cause no significant side effects and to be free from the potential risk of agranulocytosis associated with its predecessor, metiamide (Burland *et al.*, 1975b). Initial reports indicate that cimetidine promotes healing of duodenal ulcers (Blackwood *et al.*, 1976; Bodemar and Walan, 1976; Gray *et al.*, 1977).

Case report

A 70-year-old jeweller was admitted in December

* Present address: Wing Commander H. L. Davies, Caernarvonshire and Anglesey General Hospital, Bangor, Caernarvonshire.

Correspondence: Wing Commander W. Larkworthy, RAF Hospital, Nocton Hall, Nocton, Lincoln.

1975 complaining of dyspepsia, vomiting and diarrhoea which had occurred in increasingly severe episodes since he had undergone vagotomy and partial gastrectomy in 1971. The operation has been carried out because of persistent vomiting and radiological evidence of ulceration at the pyloro-duodenal region. At operation there was evidence of old ulceration of the first part of the duodenum and a tumour was found involving the pylorus and the first part of the duodenum along the anterior wall. It was thought that the tumour was a leiomyoma but histological appearances were considered to be those of a carcinoid tumour.

Endoscopy was undertaken soon after admission. The lower oesophagus was severely inflamed and multiple ulcers were present above the oesophago-gastric junction. The gastric remnant was large with coarse nodular folds. The mucosa was uniformly inflamed and friable and a giant gastric ulcer involved much of the anterior wall of the stomach. There was also a deep penetrating ulcer of the posterior wall. The gastrectomy stoma was ulcerated throughout its circumference and there was ulceration of both efferent and afferent loops.

Basal gastric secretion studies showed a volume of 320 ml/hr and acid secretion of 28.8 mmol/hr. In response to insulin-stimulated hypoglycaemia the volume was 330 ml/hr and acid secretion 39 mmol/hr. Plasma gastrin levels were reported as >120 pmol/l (normal range 0.1-23 pmol/l) and on dilution levels of 472 and 504 pmol/l were reported. An intravenous injection of secretin 2 units/kg resulted in a rise of plasma gastrin from 640 pmol/l to 920 pmol/l within 15 min.

In January 1976 the patient developed a melaena which required transfusion. Two weeks later, he suffered a partial thickness myocardial infarct. A supply of cimetidine was obtained in February 1976, by which time he was experiencing almost continuous symptoms of nausea, epigastric and lower chest pain, with intermittent vomiting and watery diarrhoea. Treatment was started with oral cimetidine

200 mg three times daily and 400 mg at night. Within 20 min of taking the first tablet his symptoms disappeared and have not returned. Endoscopic review after treatment for a month showed remarkable improvement. The oesophagus showed mild inflammation but no ulceration, the gastric mucosa was diffusely reddened but coarse nodular folds were less evident. The giant gastric ulcer had healed and a small ulcer slough was seen on the posterior wall of the stomach.

The stoma appeared healthy but could not be examined adequately because of food residue. At endoscopy after 2 months treatment, the whole gastric mucosa appeared uniformly inflamed with a diffuse coarse black reticular appearance thought to be due to submucosal haemorrhages. Two months later when endoscopy was repeated, the gastric mucosa appeared healthy, mild inflammation surrounded the stoma and there was mild diffuse inflammation of the efferent loop. The patient has now been treated continuously for more than one year and the initial dose of cimetidine has not been changed. Endoscopic examination carried out on the anniversary of starting treatment showed no mucosal inflammation or ulceration whatsoever. The tumour block prepared in 1971 was available and fresh sections were made. The histological appearances were of an endocrine cell tumour consistent with a gastrinoma but immunological preparations for gastrin were negative owing to inappropriate fixation of the original biopsy material. Liver and pancreas scans were carried out and were normal.

Invasive investigation, laparotomy and further gastric surgery have been considered but rejected because the risks of surgery are high, the patient is now 70 years old, is, as far as he is concerned, in good health, and has suffered a myocardial infarction.

Discussion

The history suggests a gastrin-producing tumour, possibly in the pancreas or more probably a secondary tumour in the liver. That the original tumour lay outside the pancreas is of interest but is recognized. In a series reported by Howe (1965), 10% of tumours occurred in the duodenal wall and 2% as discrete adenoma of the pyloric region of the stomach. Carcinoid tumours are microscopically similar to gastrinoma and distinction may be possible only by immunological preparations for gastrin (Stremple, 1975).

The place of long term treatment with histamine H_2 -receptor antagonists in the management of cases of the Zollinger-Ellison syndrome will become clear as experience accumulates. In patients who are young or relatively young, provided the diagnosis has been made before any gastric surgery, total

gastrectomy with tumour removal followed by monitoring of the serum gastrin levels would appear still to be the treatment of choice and a period of pre-operative treatment with a histamine H_2 -receptor antagonist would improve the patient's condition and render the surgeon's task less difficult. However, surgical treatment is unlikely to be straight-forward as most patients will already have had some form of gastric surgery and Wilson and Ellison (1966) reported an associated survival of only 53% in patients who underwent total gastrectomy subsequent to a lesser procedure. After 14 months' treatment there has been no indication to increase the dose of cimetidine. Treatment has been given continuously, repeated absorption curves have shown some variability but effective blood levels have been reported on each occasion.

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