Effect of long-term treatment with cimetidine and antacids in Barrett’s oesophagus

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SUMMARY The effect of a long-term treatment (one to two years) with cimetidine (1-6 g per day) and an antacid (Regla pH) was evaluated in nine patients with a Barrett’s oesophagus. The results showed that such long-term treatment had a beneficial effect on the symptoms and endoscopic signs of oesophagitis and on the healing of a Barrett’s ulcer, but did not result in a regression of the squamocolumnar junction back towards the cardia. No significant changes were observed in the histological epithelial types in the biopsies taken below the squamocolumnar junction. No clinical or biochemical side-effects or changes in biochemical parameters were noted during this study.

A columnar lined oesophagus, the so-called Barrett’s oesophagus, is usually considered to be an acquired condition, developing as a consequence of gastric epithelial replacement of oesophageal squamous epithelium, destroyed after gastro-oesophageal reflux.1  3

There is increasing evidence that a Barrett type epithelium may predispose to oesophageal adenocarcinoma.2  4

Regression of the columnar-lined epithelium towards the cardia has been recently reported in man after successful anti-reflux surgery.5 We have previously shown that prolonged cimetidine-antacid treatment was of benefit in improving the moderate to severe lesions of reflux-oesophagitis.7

The aim of this study was to find out whether long-term treatment with such a cimetidine-antacid regimen was also effective in patients with reflux oesophagitis combined with a Barrett-type oesophagus and whether this prolonged treatment could induce a regression of the columnar epithelial type.

Methods

PATIENTS

Nine adult patients with a columnar-lined oesophagus were selected for this prospective study.

In all, the diagnosis of Barrett’s oesophagus was based upon endoscopic, manometric, and histological examination. The following criteria were used: the presence of a highly located squamo-columnar junction, either several centimetres above the manometrically estimated lower oesophageal sphincter (LOS) zone when measurable, or well above the respiration reversal point and a tubular segment with peristaltic activity; the presence in the distal tubular oesophagus of columnar epithelium being either gastric fundic (G), junctional (J), or specialised columnar (S) in type.9

Pregnant and lactating patients and patients with a concomitant duodenal and/or gastric ulcer or with previous gastric surgery were excluded. Informed consent was obtained from all patients.

Medical history

All patients were carefully questioned for symptoms such as heartburn, acid regurgitation, dysphagia, previous treatment, and duration of disease.

Manometric analysis

An infusion system was used as described previously.7 The LOS pressure was measured at the mid-respiration excursion point and fundic pressure was used as zero reference. The infusion system was introduced into the stomach of the fasting patient and withdrawn with increments of 1 cm up to the upper oesophageal sphincter. An average value of at least five LOS measurements was obtained per patient.
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**Endoscopy and biopsy**

All endoscopies were performed with the same endoscope (Olympus GIF-K) and by two endoscopists in order to determine accurately the following parameters: distance of highest point of the squamocolumnar junction from the incisors, length of the columnar-lined oesophagus, signs of oesophagitis using the endoscopic criteria previously described. Each patient was endoscoped by the same endoscopist. With increments of 1 cm, two biopsies were taken diagonally below, at, and above the squamocolumnar junction, noting the distance from the incisors. All biopsies were examined by two experienced pathologists. The different types of columnar epithelium were recorded and the degree of oesophagitis was defined using histological criteria previously described.

Where there was a combination of squamous- and columnar epithelium in one biopsy, the biopsy was considered to be taken from the squamocolumnar junction. All patients received a total dose of oral cimetidine of 1.6 g as two 200 mg tablets three times a day, with meals and again upon retiring, together with one antacid tablet (aluminum hydroxide magnesium carbonate; Regla pH; neutralising capacity: 38 mmol/10 ml) every two hours while awake, for two years. No other drugs, commonly used for the treatment of reflux disease were allowed during the test period.

The number of antacid and cimetidine tablets taken was controlled and recorded and any trial medication not consumed was registered, as an estimate of patient compliance.

Manometry and fibre-endoscopy with biopsy were performed in all patients immediately before the trial and at four month intervals during the study. Every two months the medical history was recorded and physical examination and laboratory analysis was performed (haemoglobin, ESR, peripheral blood count, platelets, plasma urea, serum creatinine, bilirubin, alkaline phosphatase, transaminases, lactic dehydrogenase, and urinalysis). Within three days of ending the trial another endoscopy with biopsy and manometry was performed.

**Results**

**Characteristics of patients**

The group of nine patients who fulfilled the above-mentioned criteria consisted of four female and five male patients with an average age of 62.6 years (range 42–80 years) and with an average duration of disease (heartburn, regurgitation, etc.) of 10.3 years (range two–40 years).

All patients had been treated in the past with antacids; three of them had received cimetidine (1–1.6 g), which was stopped for one to three months before the trial. Three patients were symptom-free, and six patients complained of heartburn, regurgitation, or dysphagia in the pretrial week. Endoscopy revealed evidence of reflux oesophagitis (four mild; three moderate) in seven patients in the area of the squamocolumnar junction. Two patients also showed a so-called Barrett’s ulcer, located in the distal part of the columnar-lined oesophagus. In one patient there was a biopsy-proven benign concomitant stenosis at the level of a distal ulcer. The localisation of the squamocolumnar junction ranged from 19–32 cm of the incisors. Histological examinations of the biopsies taken over an area of at least 10 cm below the squamo-columnar junction showed all three types of Barrett’s epithelium in three patients; gastric-fundic type and junctional type in five; and only junctional in one patient.

Manometry at the start of the study revealed an LOS pressure of 10 mm Hg only in one patient (the normal range in our laboratory being 15 to 25 mm Hg); in the others no LOS pressure could be clearly and reproducibly demonstrated. Normal peristaltic activity was present in most patients up to 35 cm from the incisors. Repetitive contractions in the distal part of the oesophagus were present in four patients.

**Experimental results**

Eight patients were treated for two years; one patient who became symptom-free refused further cooperation after one year. All initially symptomatic patients became symptom-free within four months except one, who continued to experience mild dysphagia during the two year trial period necessitating one mercury bougie dilatation after 20 months of treatment.

The final endoscopy revealed evidence of a mild oesophagitis in only one patient; the diameter and aspect of the distally located benign stenosis in the patient with mild dysphagia was essentially unchanged. After four, respectively eight months of treatment, the Barrett’s ulcers were healed. The endoscopically located squamocolumnar junctional area corresponded completely with the histological localisation. This localisation of the squamocolumnar junction did not change in any of the patients, as can be seen from the table.

The histological types of columnar epithelium in the 3 cm segment underneath the junction did not change substantially except for a slight increase towards the specialised columnar type.
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Distance of the squamocolumnar junction from the incisures (cm), with subtypes of columnar epithelium (J: junctional; S: specialised columnar; G: gastric fundic) in the 1, 2, 3 cm segment underneath the junction.

Discussion

A columnar-lined oesophagus has been reported in up to 11% of patients with symptomatic reflux disease who come to endoscopy; it is generally considered to be a precancerous condition. The incidence of an adenocarcinoma in the oesophageal body of patients with a Barrett’s oesophagus has been reported in up to 9%. The treatment of patients with a Barrett’s oesophagus is, in principle, analogous to that used in patients with reflux disease. Some authors advocate medical treatment for symptomatic patients with a columnar-lined oesophagus, although results of such medical treatment are scanty. Others feel that anti-reflux surgery is always indicated in the case of young patients or those with intractability and severe bleeding. A regression of the metaplastic columnar epithelium towards the cardia after successful anti-reflux surgery has been reported in only two studies. Whether the apparent regression of the Barrett’s epithelial lining is real, and not, perhaps in part, secondary to anatomical changes after the surgical intervention, is unknown.

Cimetidine has been shown to be superior to placebo in gastro-oesophageal reflux disease, also in the endoscopically moderate to severe stages of the disease. In the case of a Barrett’s oesophagus, only a few reports are available reporting a beneficial effect of cimetidine in patients with a so-called Barrett’s ulcer. With these data in mind, it was logical to find out to what extent prolonged medical therapy, such as a combination of anti-reflux measures, antacids, and cimetidine, did improve the lesions and did induce a regression of the columnar epithelium in patients with a Barrett’s oesophagus. Such regression upon successful therapy without disturbance of the anatomy could greatly support the idea of potential reversibility of the metaplastic epithelium, perhaps thereby lessening the risk of malignancy.

The results of our study show that long-term treatment with cimetidine and antacids has indeed a beneficial effect with regard to symptomatology and endoscopic signs of oesophagitis and ulceration. One patient, with a stricture at the site of an ulcer, needed one dilatation during the study, probably because of scarring of the healed ulcer; this corresponds with the fact that cimetidine probably has no beneficial effect on strictures in patients with a Barrett’s oesophagus. Long-term treatment with cimetidine and antacids did not result in a regression of the squamocolumnar junction back towards the cardia. In addition, no significant changes were observed in the histological epithelial types in the biopsies taken immediately below the squamocolumnar junction.

This study does not, therefore, support the potential reversibility of the metaplastic epithelium as seen after surgery. Manometry showed that nearly all patients with a Barrett’s oesophagus in this study had no detectable LOS and that even prolonged treatment with cimetidine had no effect on the LOS pressure. Whether ongoing reflux because of marked LOS sphincter incompetence explains the lack of mucosal reversibility is unknown. The apparent discrepancy between the surgical and cimetidine treatment can perhaps be
explained by the fact that both treatment modalities are different. Successful anti-reflux surgery probably reduces gastro-oesophageal reflux and this may promote the regression of the columnar epithelium, whereas cimetidine merely reduces acid production in the stomach and does not affect gastro-oesophageal reflux. In view of the frequency of the development of carcinoma of the oesophagus in these patients, it may therefore be assumed that surgical treatment is the most suitable for patients with a Barrett’s oesophagus.

Cimetidine proved to be a safe and clinically well-tolerated drug. From this study we may conclude that cimetidine and antacids have a favourable effect upon the clinical and endoscopic findings in patients with a Barrett’s oesophagus.

When no regression of the metaplastic epithelium can be obtained, we feel that endoscopic surveillance should be considered in order to detect oesophageal cancer at an early stage.

References


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