ALIMENTARY TRACT

Natural history of gastro-oesophageal reflux disease without oesophagitis

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Abstract

This retrospective study was undertaken to characterise the clinical course and reflux pattern of patients with gastro-oesophageal reflux without evidence of oesophagitis. We investigated 33 patients (12 women, 21 men; mean age 36 years) with typical symptoms, a negative oesophagoscopy, and a 24 hour oesophageal pH-metry indicative of pathological gastro-oesophageal reflux. All patients received antacids or prokinetic drugs or both for three to six months. Nineteen of 33 patients still had symptoms at the end of treatment, of whom five had developed erosive changes of the oesophageal mucosa. The other 14 discontinued treatment and remained asymptomatic during a six month follow up period. Comparison of the pretreatment pH-metry data of the 19 symptomatic patients and the 14 asymptomatic patients showed no differences in the pattern of gastro-oesophageal reflux in the two groups. We conclude that in a substantial proportion of patients with pathological reflux without oesophagitis symptoms may persist and mucosal lesions may develop during conventional treatment without any apparent change in the reflux. Patients who developed endoscopic oesophagitis did not have a more severe pretreatment pattern of gastro-oesophageal reflux when compared with those who did not develop oesophageal mucosal damage.

Gastro-oesophageal reflux is a common complaint in the adult population. According to Richter and Castell the prevalence of daily heartburn in apparently healthy people is as high as 7%.¹ In a recent paper Heading reports a prevalence of 5% for heartburn in the Western adult population,² whereas a prevalence of 12% was found in a Danish survey.³ The prevalence of gastro-oesophageal reflux without oesophagitis has been estimated to be approximately 50% greater than that of oesophagitis,⁴ though it has recently been suggested that oesophagitis is the most frequent pathological finding in patients submitted to upper gastrointestinal endoscopy in general gastroenterological practice.²

Despite the high frequency of reflux without oesophagitis, knowledge of its epidemiology and natural history is limited, mainly because of inconsistency in terminology and diagnosis, as pointed out by others.^{2,5} As far as diagnosis is

concerned, however, the recent availability of methods for extended oesophageal pH monitoring has made it possible not only to define objectively the presence of reflux, relating it to the patient's symptoms, but also to evaluate the degree of acid exposure of the oesophageal mucosa.

The aims of our study were to ascertain (i) whether in patients with pathological reflux but no oesophagitis medical treatment with anti-secretory drugs is effective in achieving symptom control and in preventing the development of erosive changes, and (ii) whether severe pretreatment reflux may be associated with an unfavourable outcome.

Methods

The study consisted of the retrospective analysis of 33 outpatients referred to our unit from January 1987 to December 1988 for typical symptoms of gastro-oesophageal reflux – heartburn or regurgitation, or both – and who had a negative oesophagoscopy but had evidence of pathological reflux as assessed by pH-metry. Demographic, clinical, and endoscopic features of the patients are given in Table I.

Daytime and nocturnal symptoms were scored separately according to Lieberman⁶ as follows: mild 1, moderate 2, severe 3, or unbearable 4, with two additional scores assigned for nocturnal awakening (1) or spontaneous regurgitation (1), making a maximum possible score of 10. None of the patients had evidence of macroscopic oesophagitis according to the Savary and Miller endoscopic classification.

Erythema, friability, or granularity of the oesophageal mucosa was accepted as the equivalent of the absence of lesions. No biopsy samples were obtained during endoscopy. Oesophageal pH studies were performed as described elsewhere.⁷ Pathological reflux was defined as total time with oesophageal pH below 4 exceeding 7%. This threshold has previously been found to be

TABLE I Demographic, clinical, and diagnostic features of patients with gastro-oesophageal reflux without oesophagitis

Mean age (range) (years)	45.9 (21–76)
M/F ratio	21/12
Smokers (%)	27.2
Alcohol consumers (%)	27.2
Mean symptom duration (range) (years)	3.7 (0.4–20)
Hiatal hernia (%)	30.6
Mean % reflux time (range)	12.1 (7.5–30.0)

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Figure 1: Total % of gastro-oesophageal reflux before treatment according to symptom response.

an optimal discriminator between physiological and abnormal reflux.⁷

All patients received open conventional medical treatment consisting of a three month

Figure 2: Daytime and night time % of gastro-oesophageal reflux before treatment according to symptom response to treatment.

TABLE II Results of treatment with antacids or prokinetic drugs, or both, in patients with gastro-oesophageal reflux without oesophagitis (Figures are numbers (%) of patients)

Treatment:	
Antacids	11/33 (33)
Antacids + prokinetic drugs	22/33 (67)
Asymptomatic patients:	
After three months	11/33 (33)
After six months	14/33 (39)
Endoscopic oesophagitis	5/33 (10.5)

course of antacids (Maalox, 10 ml six times a day, with a total neutralising capacity of about 140 mmol/l HCl) or a prokinetic drug (domperidone, 10 mg tablets three times a day, to be taken 30 minutes before meals), or both. This was the ordinary treatment for pathological reflux without oesophagitis in our unit at the time of the study, and was chosen because of the good symptomatic effect and the absence of appreciable side effects. No advice was given on diet or antireflux measures to any of the patients.

At the end of the three month treatment a clinical and endoscopic reassessment of the patient's condition was performed. Patients who were still symptomatic but had a persistent negative oesophagoscopy were given a further three months of treatment, and in those on a single drug regimen the combination of both drugs was started. In patients who became asymptomatic – that is, a symptom score < 3 – and with confirmed absence of oesophagitis treatment was progressively tapered. The prokinetic agent was finally discontinued and patients were advised to take antacids only when necessary – for example, in case of heartburn or severe regurgitation. These patients were subsequently followed up for at least six months, with clinical evaluation at this time or if symptoms relapsed for more than a week. Finally, patients who were found to have mucosal defects at the control endoscopy entered a controlled trial on the effect of different dosages of ranitidine in healing oesophagitis, the results of which are reported elsewhere.⁸ In this group of patients control pH monitoring was performed before starting the new treatment and after three days of drug washout.

Results

The results of treatment are summarised in Table II. As far as subjective response is concerned, 11 of the 33 patients (33%) were completely symptom free after 12 weeks of treatment, and after a further 12 weeks 14 patients were symptom free (39%). Endoscopy showed the presence of new erosive changes in five patients (all of whom were symptomatic). When the pH monitoring data for reflux before treatment were divided into two groups of patients according to subsequent favourable (n=14) or unfavourable (n=19) response to treatment there were no clear cut differences in average per cent reflux time, either during the total 24 hour period (Fig 1) or during daytime and night time considered separately (Fig 2). Average total % reflux was 12.9% and 11.6% in the two groups respectively ($p > 0.05$). The same is true when the data are divided into two groups according to subsequent presence

Figure 1 is a scatter plot showing the percentage of total time with pH < 4 for patients with and without oesophagitis during Daytime and Night time. The y-axis represents the percentage of total time with pH < 4, ranging from 0 to 40, with a break between 25 and 40. The x-axis categories are: Patients with oesophagitis (n=5), Patients without oesophagitis (n=28), Patients with oesophagitis (n=5), and Patients without oesophagitis (n=28). Horizontal lines indicate the mean for each group.

Time Period	Group	n	Mean (%)	Range (%)
Daytime	Patients with oesophagitis	5	~16	8.5 - 38
	Patients without oesophagitis	28	~12	5 - 25
Night time	Patients with oesophagitis	5	~11	6 - 13.5
	Patients without oesophagitis	28	~9	0 - 39

Figure 4: Daytime and night time % of gastro-oesophageal reflux before treatment according to the development of oesophagitis.

Discussion

Data on the natural history of pathological reflux without oesophagitis are scanty and outdated. Reports in the 1960s and 1970s⁹⁻¹⁰ suggest overall a benign outcome in most patients, with symptoms disappearing rapidly after diagnosis, even in the absence of treatment: according to these studies, therefore, clinical improvement is common, even with modestly effective or no medical treatment, and also in severe cases of oesophagitis. In the patients investigated in these surveys, however, pathological gastro-oesophageal reflux was not diagnosed by means of pH monitoring, whereas this technique, which is at present considered standard, is now widely available. Furthermore, these follow up studies did not include endoscopic control in the evaluation of the patient. Finally, we have reported¹¹ that 15 patients with symptomatic and uncomplicated reflux, who were followed up for 12 months after symptoms disappeared after eight weeks of treatment with a prokinetic drug (domperidone 20 mg three times a day) or ranitidine (150 mg twice a day), showed a 20% symptomatic relapse rate during a one year follow up without treatment. In all cases newly developed endoscopic oesophagitis was found.

We therefore undertook this retrospective analysis to assess whether symptomatic gastro-oesophageal reflux patients without mucosal damage will favourably respond to three to six months of treatment with antacid or prokinetic drugs, or both. These drugs were expected to exert a positive effect on symptoms¹² without interfering with the course of the reflux, as documented by our previous observation, in patients with reflux disease but without oesophagitis, that after stopping treatment symptoms may disappear despite persisting acid reflux.¹¹ As it turned out, only 14 of the 33 patients became completely symptom free after completing treatment, whereas in the remaining 19 patients only the symptom score was reduced compared with the pretreatment score. It is of interest that the duration of acid exposure time before treatment was not predictive of outcome, as indicated by a similar mean 24 hour % reflux time in the groups with favourable and unfavourable outcomes (12.9% and 11.6%, respectively; $p>0.05$). This is at variance with our previous observation that the pretreatment percentage of reflux is a valid prognostic indicator of favourable outcome in patients with ulcerative/erosive oesophagitis.¹³ Also, in the five patients who were found to have oesophagitis the

Figure 5: Daytime and night time % of gastro-oesophageal reflux before and after treatment in five patients developing oesophagitis.

pretreatment reflux % was not significantly higher than that in the remaining 28 patients (14.4% v 11.7%).

Finally, we compared the pretreatment and post-treatment duration of reflux in the five patients who developed oesophagitis during treatment. Again, no significant differences were found between the two (16.3% v 8.8%), indicating that the initial severity of reflux is not directly related to the subsequent course of the disease. It is interesting that during the follow up period all 14 patients who became asymptomatic remained symptom free, even if active treatment was being discontinued.

We can affirm that conventional treatment with antacids or prokinetic agents, or both, failed completely to abolish symptoms in a substantial proportion of patients without oesophagitis but with gastro-oesophageal reflux disease as objec-

tively defined by pH-metry studies. In particular, progression to a more severe clinical form of reflux disease was observed in five of 33 patients. Lastly, the degree of acid exposure time before treatment is of no value in identifying patients who will have an unfavourable symptomatic response to medical treatment. A more aggressive initial policy of treating patients with reflux (H_2 receptor antagonists or diet and anti-reflux measures, or both) is therefore probably required.

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