The Medical Management of Gastro-Oesophageal Reflux Disease

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Key Words

Barrett's oesophagus · Gastro-oesophageal reflux disease · Lifestyle interventions · Medical therapy · Oesophageal adenocarcinoma

Abstract

Background: Gastro-oesophageal reflux disease (GORD) is a common global phenomenon. It is associated with the backflow of gastric contents proximally, typically due to transient relaxations of the lower oesophageal sphincter. Various factors contribute to GORD, including obesity, smoking, alcohol and pregnancy. The primary concern of GORD is its association with the development over time of Barrett's oesophagus and, ultimately, oesophageal adenocarcinoma. **Summary:** This review focuses on the various medical interventions that are useful in the treatment of GORD. **Key Messages:** Various lifestyle interventions such as weight loss and smoking cessation are useful in the treatment of GORD. Medical therapy relies on the use of acid suppressants such as proton pump inhibitors and histamine H₂ receptor antagonists.

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Introduction

Gastro-oesophageal reflux disease (GORD) is rising in prevalence. Evidence suggests that chronic GORD is associated with the development of worsening inflamma-

tion, Barrett's oesophagus, dysplasia and, ultimately, adenocarcinoma. Survival of oesophageal adenocarcinoma is bleak with an estimated 5-year survival rate of 15%. Hence, appropriate management of GORD is needed in order to hinder progression.

This review highlights the current evidence in reference to the medical management of GORD.

Lifestyle Measures

Initial management relies on lifestyle-based improvements including a focus on smoking and alcohol cessation, weight reduction, raising the head of the bed, reduction of eating meals late and reduction of foods that can primarily lead to enhanced reflux occurrence. These include coffee, chocolate, spiced, acidic and heavily fatty foods.

Kaltenbach et al. [1] screened 2,039 studies and identified trials that examined GORD in relation to lifestyle measures. Exposure to tobacco, alcohol, chocolate and high-fat meals decreased lower oesophageal sphincter pressure. However, neither tobacco nor alcohol cessation was associated with improvement in oesophageal pH or symptoms. Head of bed elevation and left lateral decubitus position improved the overall time that the oesophageal pH was <4.0. Weight loss improved oesophageal pH and symptoms.

Focusing on body mass index (BMI), Jacobson et al. [2] observed a relationship between increasing BMI and

reflux symptoms in women (multivariate p for trend <0.001). As compared to women who had a BMI of 20.0–22.4, the multivariate odds ratios for frequent symptoms were 0.67 for a BMI of <20.0 ; 2.20 for a BMI of 25.0–27.4, and 2.93 for a BMI of 35.0 or more.

A further study focused on 24-hour pH measurements in morbid obesity, where 5 out of 17 patients had pathological acid reflux prior to weight loss. This was reversed to normal in 3 subjects but remained abnormal in 2 [3].

A study on posture noted the percentage of time during which oesophageal pH was <5 , and the number of reflux episodes was decreased when patients were in a bed-up position as compared to sitting or lying. There was no significant difference when sitting and lying positions were compared. The results, however, suggested that in the bed-up position, patients will have an improvement in symptoms [4].

A further study compared the effect of three sleeping positions on gastro-oesophageal reflux: elevation of the head of the bed on 8-inch bed blocks; elevation by a foam wedge, or a flat position. No difference in reflux frequency between the positions was noted. The wedge caused a statistically significant decrease in the time that the distal oesophageal pH was <4 as compared to the flat position. Elevation on blocks caused an improvement in parameters, but this was not statistically significant [5].

Pharmaceutical Management

Cremonini et al. [6] undertook a meta-analysis which included more than 20 patients with GORD treated with either a proton pump inhibitor (PPI) or a histamine H_2 receptor antagonist (H2RA) for at least 2 weeks. The odds ratio for response to active treatment compared to placebo was 3.71 (95% CI 2.78–4.96).

Chiba et al. [7] reported that the overall healing proportion irrespective of drug dose or treatment duration (<12 vs. 12 weeks) was highest with PPIs ($83.6 \pm 11.4\%$) compared to H2RAs ($51.9 \pm 17.1\%$), sucralfate ($39.2 \pm 22.4\%$) or placebo ($28.2 \pm 15.6\%$). The mean heartburn-free proportion was highest with PPIs ($77.4 \pm 10.4\%$) compared to H2RAs ($47.6 \pm 15.5\%$). PPIs showed a significantly faster healing rate and provided faster heartburn relief.

A further study randomly assigned 247 patients with erosive oesophagitis to treatment with either 30 mg lansoprazole once daily or 150 mg ranitidine twice daily. Lansoprazole healed oesophagitis in 92.1% of patients after 8 weeks of treatment and was significantly superior to

ranitidine which healed oesophagitis in 69.9% of patients ($p < 0.001$) [8].

A double-blind controlled study randomly allocated patients to either omeprazole 40 mg once daily or ranitidine 150 mg twice daily. The healing rate after 4 weeks of treatment was 85% in those treated with omeprazole and 40% in those treated with ranitidine ($p < 0.001$). Patients treated with omeprazole showed a significantly faster and greater relief in heartburn than patients treated with ranitidine [9].

Van Pinxteren et al. [10] noted that the relative risk (RR) for heartburn remission in placebo-controlled trials was 0.35 for PPIs (95% CI 0.26–0.46), 0.77 for H2RAs (95% CI 0.60–0.99) and 0.86 for prokinetics (95% CI 0.73–1.01). PPIs were significantly ($p < 0.05$) more effective than H2RAs and prokinetics. In the treatment of endoscopic negative reflux disease, the RR for heartburn remission was 0.68 for PPI compared to placebo and 0.84 for H2RA compared to placebo.

Gralnek et al. [11] noted that at 8 weeks, there was a 5% (RR 1.05; 95% CI 1.02–1.08) relative increase in the probability of healing of erosive oesophagitis with esomeprazole, yielding an absolute risk reduction of 4%. Esomeprazole conferred an 8% (RR 1.08; 95% CI 1.05–1.11) relative increase in the probability of GORD symptom relief at 4 weeks.

Gerson et al. [12] analysed omeprazole sodium bicarbonate therapy twice daily and noted normalisation of supine pH in 100% of patients.

Additional research analysed patients receiving dextansoprazole MR 60 or 90 mg or lansoprazole 30 mg once daily. Dextansoprazole MR healed 92–95% of patients, while lansoprazole healed 86–92% of patients ($p > 0.025$). Week-4 healing was greater than 64% with all treatments. An analysis of 8-week healing of patients with moderate-to-severe oesophagitis demonstrated that dextansoprazole MR 90 mg was superior to lansoprazole. All treatments effectively relieved symptoms and were well tolerated [13].

Lee et al. [14] performed a randomised study of 48 healthy subjects who received dextansoprazole MR 60 mg once daily 30 min before meals. The results revealed no statistically significant differences in the mean 24-hour intragastric pH between dosing before dinner or an evening snack compared to breakfast; however, there was a small (0.2) but statistically significant difference between lunch and breakfast.

Gunaratnam et al. [15] assessed optimal PPI dosing and noted that optimal dosers took PPIs with or up to 60 min before meals. Their results highlighted that only 46%

of patients dosed optimally. Fifty-four percent dosed suboptimally with 21 of 54 (39%) dosing more than 60 min before meals.

A multicentre double-blind trial randomised patients to treatment for 8 weeks with either single-dose esomeprazole (40 mg once daily; $n = 138$) or lansoprazole 30 mg twice daily ($n = 144$). The findings highlighted that single-dose esomeprazole was at least as effective as twice-daily lansoprazole for the percentage of heartburn-free days (54.4 and 57.5%, respectively) [16].

In a trial focused on maintenance therapies for reflux oesophagitis, the study groups were treated with cisapride (10 mg 3 times a day), ranitidine (150 mg 3 times a day), omeprazole (20 mg per day), ranitidine plus cisapride or omeprazole plus cisapride. The study highlighted that omeprazole was significantly more effective than cisapride ($p = 0.02$) or ranitidine ($p = 0.003$), and combination therapy with omeprazole plus cisapride was significantly more effective than cisapride alone ($p = 0.003$), ranitidine alone ($p < 0.001$) or ranitidine plus cisapride ($p = 0.03$) [17].

The efficacy of on-demand treatment with omeprazole 20 or 10 mg or placebo has also been analysed. Results revealed that after 6 months, the remission rates were 83% (95% CI 77–89) with omeprazole 20 mg, 69% (95% CI 61–77) with omeprazole 10 mg and 56% (95% CI 46–64) with placebo ($p < 0.01$ for all intergroup differences). The use of antacids proved highest in the placebo group and lowest in the omeprazole 20 mg group. Treatment failure was associated with more than a doubling of antacid use [18].

Step-down management of GORD has been investigated. Forty-one of 71 patients (58%) were asymptomatic off PPI therapy after 1 year of follow-up. Twenty-four of 71 patients (34%) required H2RAs, 5 of 71 patients (7%) required prokinetic agents and 11 of 71 patients (15%) remained asymptomatic without medication [19].

Fackler et al. [20] analysed 23 healthy volunteers and 20 GORD patients. The administration of PPI and 1 day of H2RA was the only therapy that significantly decreased gastric pH < 4 compared to PPI twice daily alone ($p < 0.001$).

Richter et al. [21] randomised patients to omeprazole 20 mg once daily, ranitidine hydrochloride (HCl) 150 mg twice daily or ranitidine HCl 150 mg twice daily plus metoclopramide HCl 10 mg 4 times daily. After 1 week, 13% of patients receiving omeprazole had complete resolution of all GORD symptoms compared to 1 or 3% of patients receiving ranitidine or ranitidine/metoclopramide, respectively ($p < 0.001$). At week 8, 80% of pa-

tients with oesophagitis grade 2 or higher were healed with omeprazole [$p < 0.001$ vs. ranitidine (40%) and ranitidine/metoclopramide (46%)].

A double-blind study used metoclopramide 10 mg 4 times daily, domperidone 20 mg 4 times daily or placebo randomly. As a whole, the treatment showed a significant symptomatic response in all three treatment groups ($p < 0.0001$). Eleven patients complained of side effects with metoclopramide. Two patients described side effects with domperidone, including 1 woman with galactorrhoea [22].

Grossi et al. [23] investigated oesophageal motility in GORD patients 24 h before and after the administration of baclofen. Baclofen increased the basal tone of the lower oesophageal sphincter in comparison with baseline ($p = 0.02$), with a reduction in the number of transient lower oesophageal sphincter relaxations ($p = 0.01$). Furthermore, baclofen induced a decrease in the swallows ($p = 0.02$) and primary oesophageal body waves ($p = 0.04$).

A further study of patients with persistent heartburn or regurgitation in spite of PPI therapy concluded that after addition of baclofen 20 mg 3 times daily, duodenal reflux had significantly decreased [6.1% (interquartile range 0.8; 10.3) of the time; $p < 0.05$] [24].

More evidence comes from Cange et al. [25] who studied 20 patients with established reflux disease. Baclofen 40 mg or placebo was given with a washout period of 4 weeks. The results showed a significant reduction in the number of reflux episodes during the 0- to 4-hour (7.9 vs. 16.5, $p < 0.0001$; post-prandially: 6.0 vs. 11.2, $p < 0.0001$) and 0- to 12-hour (46.5 vs. 73, $p = 0.0001$; post-prandially: 18.8 vs. 29.3, $p < 0.0001$) periods.

Closing Remarks and Summary

- Lifestyle intervention is paramount with a focus on weight loss and avoidance of reflux-triggering foods.
- PPI therapy is the treatment of choice before meals, initially once daily and increased to twice daily as required.
- H2RAs are add-on treatments to the use of PPIs.
- Currently, baclofen is not approved for the treatment of GORD, and research continues in this regard.

Disclosure Statement

The authors report that they have no conflicts of interest.

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