Clinical review

Fortnightly review

Treatment of gastro-oesophageal reflux disease in adults

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Gastro-oesophageal reflux disease is caused by retrograde flow of gastric contents through an incompetent gastro-oesophageal junction. The disease encompasses a broad spectrum of clinical disorders from heartburn without oesophagitis to severe complications such as strictures, deep ulcers, and intestinal metaplasia (Barrett's oesophagus).[1] The prevalence of heartburn, the most typical symptom of gastro-oesophageal reflux disease, is extremely high,[2] but most people with reflux do not seek medical help for this condition and treat themselves with over the counter preparations. Oesophagitis (defined by mucosal breaks) is less frequent, occurring in less than half of patients undergoing endoscopy for reflux symptoms. Symptoms and severity of oesophagitis are poorly correlated. Although reflux may remain silent in patients with Barrett's oesophagus, heartburn can severely affect the quality of life of patients with negative endoscopy results. The natural course of the disease also varies considerably.[2] Patients with gastro-oesophageal reflux disease seen by gastroenterologists usually have a chronic condition with frequent relapses, whereas those who rely on general practitioners' help usually have less severe disease, consisting of intermittent attacks with prolonged periods of remission.

Relief of symptoms and prevention of relapses are the primary aims of treatment for most patients. However, healing is also an important objective for those with moderate to severe oesophagitis or complications, or both. These goals can now be achieved, at least in part, for nearly all patients thanks to the recent development of effective drugs, especially proton pump inhibitors. The last decade has also seen the rapid development of laparoscopic surgery.

Summary points

- Most patients with dominant heartburn have no signs of oesophagitis at endoscopy. However, chronic relapsing gastro-oesophageal reflux disease can severely affect quality of life
- In primary care many patients can be successfully treated by intermittent courses of drugs on demand
- Alginate-antacids and H_2 receptor antagonists are useful in patients with mild disease
- Cisapride is as effective as H_2 receptor antagonists in short term treatment and can prevent relapse in mild oesophagitis
- Proton pump inhibitors relieve symptoms and heal oesophagitis more completely and faster than other drugs. They are effective throughout the disease spectrum, and maintenance therapy prevents recurrences
- The principles of laparoscopic and open antireflux surgery are the same. In skilled hands, similarly good results have been reported up to two years after both approaches
- In young fit patients laparoscopic surgery may be a cost effective alternative to a lifetime of drug treatment

Methods

Several reviews on the treatment of gastro-oesophageal reflux disease have been published recently,[3–6] and this information has been supplemented by a Medline search covering 1995-7. We also used a database created during a recent workshop (Genval, Belgium, October 1997). From the 429 references available in this database we selected those reporting trials comparing proton pump inhibitors with other drugs, treatment of patients with negative endoscopy results, meta-analysis of trials, evaluation of laparoscopic surgery, and cost-utility analysis.

Medical treatment

Lifestyle and dietary recommendations

Lifestyle and dietary recommendations, together with antacids, have long been the mainstay of treatment. The recommendations were based on physiological studies showing reduced acid exposure, at least in some instances.[7] In fact, the effectiveness of these measures has not been established by well controlled trials. The role of obesity in the pathogenesis of the disease, as well as the benefit of weight loss, has not been proved. No benefit has been shown from giving up smoking or discontinuing the use of drugs such as bronchodilators in asthmatic subjects.[8] Although it is

wise to stop smoking or reduce the consumption of fatty foods for other reasons, not much benefit can be expected in gastro-oesophageal reflux disease. Raising the head of the bed[9] and avoiding lying down within three hours after dinner may be useful, especially for patients with severe regurgitation or nocturnal symptoms. When specific foods or drugs are poorly tolerated by a patient it is logical to avoid or withdraw them.

Antacids and alginate-antacids

Though several placebo controlled trials have failed to establish their efficacy,[10] epidemiological studies have shown that antacids and alginate-antacids are often used successfully as self treatment by people with reflux who do not seek medical help.[11] The combination of antacids with alginate is more effective than antacids alone. In a large open trial of alginate-antacid taken on demand, most patients with mild oesophagitis remained in good clinical remission during the six months of the study.[12]

Prokinetics

Since gastro-oesophageal reflux disease is primarily a motility disorder the use of prokinetics has an excellent rationale. Bethanechol and the anti-dopaminergics metoclopramide and domperidone have proved slightly effective. However, their marginal benefit is often offset by poor tolerance. They have now been superseded by cisapride, a 5-hydroxytryptamine ($5\text{-}HT_4$) receptor agonist which enhances oesophageal peristaltic waves, increases oesophageal sphincter tone, and accelerates gastric emptying.[13]

In short term treatment of gastro-oesophageal reflux disease cisapride (10 mg four times a day or 20 mg twice daily) has proved more effective than placebo and nearly as effective as H_2 blockers in relieving symptoms and healing oesophagitis.[13] Cisapride (10 mg twice daily or 20 mg at bedtime) also prevents relapses in patients with mild oesophagitis.[14]

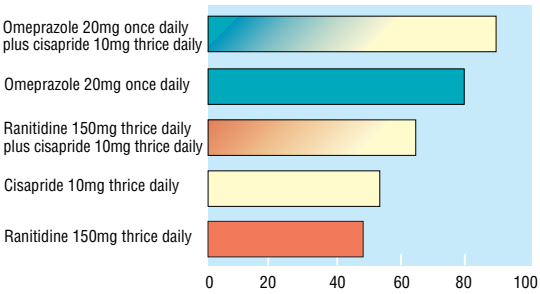
Sucralfate

Sucralfate is a polysulphate sucrose salt which is supposed to protect oesophageal mucosa. Conflicting results have been reported in trials in patients with gastro-oesophageal reflux disease. It has little, if any, role in modern antireflux therapy.

Acid suppression

H_2 receptor antagonists

H_2 receptor antagonists (cimetidine, ranitidine, famotidine, and nizatidine) were the first acid suppressors shown to be effective in short term treatment of gastro-oesophageal reflux disease.[15] However, the benefit was less than initially expected, especially in severe oesophagitis, for which the average gain in healing has not exceeded 10%. Moreover, maintenance therapy with standard doses of H_2 blockers (for example, 150 mg ranitidine twice daily) does not prevent relapses.[16] There are many reasons for the limited efficacy of these drugs, including tolerance (reduced efficacy over time[17]) and incomplete inhibition of postprandial gastric acid secretion.[15 16] Increasing the dose[18] and dosing frequency improves the efficacy, although it probably reduces compliance and increases cost.



Comparison of five maintenance strategies in prevention of relapse of reflux oesophagitis[19] (reproduced with permission)

Combined treatment with prokinetics is less effective and more expensive and inconvenient than monotherapy with proton pump inhibitors.[19]

Nevertheless, because of their excellent safety profile, H_2 blockers are useful in some patients with mild gastro-oesophageal reflux disease when they can be taken as needed. Their availability as over the counter drugs is currently being evaluated,[20] and they may eventually partly replace antacids. Special formulations (such as a wafer or effervescent tablets) may be more appropriate for this use.[21 22]

Proton pump inhibitors

Proton pump inhibitors act at the final step in acid secretion by blocking H^+/K^+ ATPase irreversibly in gastric parietal cells. Omeprazole (20 and 40 mg daily) was the first proton pump inhibitor extensively evaluated in reflux oesophagitis, and lansoprazole (30 mg daily) and pantoprazole (40 mg daily) have also been used. A recent meta-analysis of 43 therapeutic trials conducted in patients with moderate or severe oesophagitis confirmed the advantage of proton pump inhibitors over H_2 blockers.[23] The proportion of patients successfully treated was nearly doubled with proton pump inhibitors, and the rapidity of healing and symptom relief were about twice that with H_2 blockers. Their superiority is also clear in mild oesophagitis and patients with negative endoscopy results.[24] Omeprazole (20 mg or 10 mg daily) has also been shown to be better than cisapride.[25] Quality of life is restored to normal with omeprazole.[25]

The efficacy of proton pump inhibitors is maintained with time,[19] and a meta-analysis of long term trials[26] has confirmed that continuous maintenance therapy with omeprazole (20 mg or 10 mg daily) achieves significantly better results than maintenance with 150 mg ranitidine twice daily (figure). Interestingly, the relief of heartburn during omeprazole treatment is highly predictive of healing.[26] Therefore, no further endoscopic investigation is required in asymptomatic patients taking proton pump inhibitors (unless initial endoscopy shows severe oesophagitis or complications). Many patients with mild disease do not require continuous maintenance therapy. Recent studies have shown excellent results for symptom relief and quality of life with omeprazole on demand (20 or 10 mg daily).[27]

The main issue concerning prolonged use of proton pump inhibitors in gastro-oesophageal reflux disease is safety. Although proton pump inhibitors are well tolerated, some concern exists about the risk of malignancy after 10 or 20 years of potent acid suppression. Proliferation of endocrine cells has been reported in relation to hypergastrinaemia as a result of hypochlorhydria, which is non-specific for proton pump inhibitors. In fact, the risk of endocrine neoplasia seems extremely low and of no clinical relevance for most patients, whereas that of developing atrophic gastritis (a premalignant condition for adenocarcinoma) is more important and deserves more complete evaluation.[28] Since the risk of atrophic gastritis seems related to *Helicobacter pylori* infection some authors recommend eradication of this bacterium before embarking on long term acid suppression. However, the benefit of this strategy is not yet adequately demonstrated.

Antireflux surgery

The principle of every surgical procedure, whether open surgery or laparoscopic repair, is to restore an anti-reflux barrier by recreating a sufficient pressure gradient in the distal oesophagus and to close the hiatal hernia.

Open surgery

Excellent results can be obtained with different procedures such as total fundic wrap (Nissen operation) or partial fundoplications (such as Toupet's procedure). The preferred and probably most efficient anti-reflux procedure is the "floppy" Nissen fundoplication, which has been developed to avoid the side effects of the original fundic wrap (dysphagia, gas bloat syndrome, and inability to burp). Success rates of up to 90% can be achieved, with almost no mortality and morbidity. After 10 to 20 years some deterioration can occur, usually associated with wrap disruption.[29]

Laparoscopy

The technical aspects of laparoscopic fundoplication have been extensively described. Routine use of a postoperative nasogastric tube is unnecessary, and a soft diet is introduced on the first postoperative day. Patients are generally discharged by the first or second postoperative day and are usually able to return to work within two weeks after their operation. However, laparoscopic Nissen fundoplication is a demanding technique and requires different skills from other procedures such as cholecystectomy. The learning curve is a determining factor in the rate of the postoperative complications.[30] Severe complications are noted in 0.5-2% of cases.[31] Oesophageal perforation, a potentially lethal complication, occurs in 0.5-1.5% of all cases and is related to the surgeon's expertise.

Postoperative dysphagia, with or without reflux symptoms, can also complicate laparoscopic repair.[32] Final success rates range from 90% to 100%, and follow up in most (retrospective) series does not exceed one year. In a prospective randomised trial of laparoscopic versus open Nissen fundoplication Watson et al observed no difference in relief of symptoms at three months.[33]

No trials have compared modern medical and surgical treatments of gastro-oesophageal reflux disease, although some are in progress. In men with complicated gastro-oesophageal reflux disease open surgery is significantly more effective than traditional medical treatment (ranitidine, metoclopramide, antacids, and sucralfate) in improving symptoms and oesophagitis for up to two years.[34]

How to manage gastro-oesophageal reflux disease

Management of gastro-oesophageal reflux disease depends mainly on age (and concomitant illness), severity of symptoms and oesophagitis, and outcome of initial treatment.

Initial treatment

In patients with mild or moderate heartburn the first approach is usually to combine lifestyle modifications with alginate-antacids. This is adequate to relieve symptoms in a large proportion of patients presenting to general practice. However, in young adults presenting with no alarming symptoms (such as dysphagia, anaemia, or weight loss) there is now good consensus on use of acid suppressors without endoscopic assessment. Short courses of H_2 blockers or proton pump inhibitors can be given without risk of missing a life threatening condition. In patients over 45 years of age and those with alarming symptoms, endoscopy is mandatory to exclude malignancy and assess the severity of oesophagitis, which is an important predictor of therapeutic response. When endoscopy gives normal results in a patient with atypical symptoms the diagnosis of gastro-oesophageal reflux disease should be established before any treatment is recommended. Twenty four hour pH monitoring with symptom analysis may be useful, although a trial of proton pump inhibitors may be a more attractive and cheaper option. Rapid relief of symptoms seems to have good sensitivity for diagnosis of gastro-oesophageal reflux disease, but the results need to be confirmed in further prospective studies.[35]

In patients with negative endoscopy results and those with mild oesophagitis two options are now available. Firstly, the classic stepwise approach (with cisapride or H_2 blockers as the first treatment and proton pump inhibitors given only to non-responders) or, secondly, a top down strategy, starting with proton pump inhibitors and titrating down to lower doses or a less effective acid suppressor or prokinetic. There is no definite evidence from randomised clinical trials to recommend one or the other of these strategies, although the top down approach may ultimately be more cost effective.[36]

In patients with moderate or severe oesophagitis proton pump inhibitors are the mainstay of treatment. Insufficient response should be managed by gradually increasing the dose. Few patients are resistant to proton pump inhibitors, and such an eventuality should lead to reconsideration of the diagnosis and functional investigations, especially pH monitoring to control the efficacy of the proton pump inhibitor regimen. Non-responders to proton pump inhibitors do not seem to be good candidates for surgery, except those with persisting regurgitation.

Some cases require more specific management. Peptic strictures are usually successfully managed by endoscopic dilatation combined with proton pump inhibitors,[37] which are more cost effective than H_2 blockers.[38] Patients with Barrett's oesophagus are at risk of developing adenocarcinoma,[39] but the need for endoscopic and histological surveillance depends on the general state of the patient. Neither surgery nor specific drug treatment has been shown to reduce the risk of malignancy. Trials combining photoablation of Barrett's metaplasia and proton pump inhibitors are in progress.[40]

Long term management

In most cases relief of symptoms and healing of oesophagitis can be achieved after adequate initial treatment. The key issue is long term control of the disease. Intermittent, on demand drug treatment is suitable for patients with mild or moderate symptoms and infrequent relapses. However, if symptoms recur shortly after treatment has been stopped, maintenance treatment (usually with proton pump inhibitors) is highly effective and certainly the best option for older patients or those at risk from surgery. Surgery may be preferable to a lifetime of drug treatment for a young fit patient with frequent relapses.[41] Laparoscopic surgery is now the preferred approach for many patients and surgeons. However, even the economic benefit of this strategy over proton pump inhibitors remains to be established and will probably require more than 10 years of follow up evaluation.[42] Therefore, caution is required before the indications for laparoscopic surgery are extended. Ideally, this procedure should be performed only in specialist centres with expertise in managing gastro-oesophageal reflux disease.

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Endpiece
A Priori

Writers could probably get along quite well without *A Priori*, and I dislike the expression for I can never remember exactly what it means.

From *A Sense of Asher*, selected by Ruth Holland (BMA Publications, 1984)

Lesson of the week

Deaths from low dose paracetamol poisoning

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Patients with serum paracetamol concentrations below the standard treatment line may develop acute liver failure

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Paracetamol is the most commonly used substance in self poisoning (about 70 000 cases annually in Britain[1]) and is the most frequent subject of inquiries to the National Poisons Information Services.[2] Paracetamol overdose is the commonest cause of acute liver failure in the United Kingdom,[3] accounting for at least half of all cases sent to tertiary referral units. To decrease the chance of liver damage in cases of paracetamol overdose, protocols and guidelines for treating patients with an antidote before referral to specialist care have been drawn up. The antidote acetylcysteine should be given to all patients with a serum paracetamol concentration >200 mg/l four hours after ingestion of the drug. A nomogram in which this value is joined to an end point of 25 mg/l at 16 hours allows identification over this period of the patients who should receive the antidote.[4] If the antidote is not given, over 60% of patients with serum paracetamol concentrations above the treatment line may develop serious liver damage, and of these about 5% will die.[5] Recent studies also suggest that acetylcysteine given after 16 hours, even at the stage of encephalopathy, can reduce the frequency of multiorgan failure and improve survival.[6 7] Factors that have been reported to enhance hepatotoxicity include chronic alcohol misuse,[8] eating disorders,[9] and enzyme inducing drugs,[10] and in each of these contexts treatment is advisable below the treatment line.

No deaths have been reported in any of the major treatment trials of paracetamol overdose,[11–14] however high the initial serum paracetamol concentration, provided acetylcysteine was given within 10 hours of the drug's ingestion. Furthermore, there was only a 2% incidence of serious liver damage (defined by an aspartate transaminase concentration >1000 IU/l) in patients with an initial serum paracetamol concentration above the 300 mg/l (2 mmol/l) line, when treated with intravenous acetylcysteine within 10 hours, compared with an expected incidence of 90%.[15] These data suggest that serious hepatotoxicity should be uncommon and death extremely rare after a paracetamol overdose provided patients are treated within 10 hours; most cases present to an accident and emergency department in this time.[16] Yet there have been reports of patients presenting within this time with serum concentrations below the treatment line who nevertheless develop fatal acute liver failure despite having no additional risk factors.[17] Factors which may account for such cases include concealment of the real time of overdose and number of tablets taken or an enhanced susceptibility to liver damage.

Case reports

Case 1—A 16 year old girl presented to her accident and emergency department four hours after ingesting 20 paracetamol tablets (10 g). She had no additional risk factors for enhanced hepatotoxicity. Her serum paracetamol concentration was 156 mg/l, and she was discharged after receiving 50 g of a proprietary formulation of activated charcoal. Over the next two days her family noted that she was becoming progressively confused and drowsy. She represented 48 hours after the initial assessment. On examination she was encephalopathic (Glasgow coma score 9), icteric, dehydrated, and tachypnoeic, and had an international normalised ratio of 6.3 and an arterial pH of 7.16. Investigations showed serum concentrations as follows: alanine aminotransferase >7 500 IU/l, bilirubin 87 μmol/l, glucose 1.9 mmol/l, and creatinine 146 μmol/l. She was started on an acetylcysteine infusion and treatment for acute liver failure, and was electively ventilated before transfer. She continued to deteriorate with rising intracranial pressure, and underwent a total hepatectomy. A liver transplant was carried out 36 hours later but as there was no recovery of brain stem function by 10 days after the overdose ventilatory support was withdrawn.

Case 2—A 24 year old man presented to his accident and emergency department within four hours of ingesting 64 paracetamol tablets (32 g). He had a history of alcohol misuse (about 100 units per week). Four hours after the overdose he had a serum paracetamol concentration of 178 mg/l. He was given 50 g of activated charcoal and discharged. Over the next two days he had worsening abdominal pain and was vomiting. He represented 48 hours after the overdose. He was retching profusely, was icteric, and had bilateral subconjunctival haemorrhages. Investigations showed a serum glucose concentration of 2.1 mmol/l, a serum creatinine concentration of 218 μmol/l, an international normalised ratio of 8, and an arterial pH of 7.3. He was started on acetylcysteine before transfer and, despite developing grade 3 encephalopathy, his liver recovered to the extent that his international normalised ratio fell to 2.2. His progress was complicated by oliguric renal failure, lobar pneumonia, and ventricular arrhythmias. He died from septicaemia and persistent multifocal seizures on the sixth day after the overdose.

Case 3—A 38 year old man presented to his accident and emergency department after ingesting 50 paracetamol tablets (25 g). He had no apparent risk factors for enhanced hepatotoxicity. Four and a quarter hours after the overdose his serum paracetamol concentration was 178 mg/l. He was admitted to a psychiatric ward for further observation. Over the next two days he became increasingly confused and aggressive and was noted to be icteric and had periorbital bruising. Investigations showed a serum glucose concentration of <1 mmol/l, a serum creatinine concentration of 435 μmol/l, an international normalised ratio of 6, and an arterial pH of 7.45. He was electively ventilated and transferred. He continued to deteriorate as a result of pneumonia, fungal sepsis, and increasing intracranial pressure. He died on the 10th day after the overdose.

Case 4—A 34 year old woman presented to her accident and emergency department after ingesting 30 paracetamol tablets (15 g). She had no known risk factors for enhanced hepatotoxicity. Six hours after the overdose her serum paracetamol concentration was 122 mg/l. After psychiatric review she was discharged but represented two days later with a 24 hour history of malaise, vomiting, and abdominal pain. At that time she was fully alert and orientated but clinically dehydrated. Her pulse was 92 sinus rhythm and she had a blood pressure of 90/60 mm Hg, diffuse abdominal tenderness, an international normalised ratio of 10, and an arterial pH of 7.4. Investigations showed serum concentrations as follows: glucose 2 mmol/l, sodium 130 mmol/l, potassium 4.5 mmol/l, urea 11.9 mmol/l, and creatinine 229 μmol/l. She was transferred but despite full supportive treatment died on the 15th day after the overdose while awaiting liver transplant.

Discussion

The course and outcome of the four case histories raise questions about the initial management of these patients. Although the patients were medically reviewed within six hours of overdose, acetylcysteine was not given and three patients were discharged with no follow up.

The history of alcohol misuse in case 2 suggests that his serum paracetamol concentration of 178 mg/l four hours after the overdose should have been compared with the high risk line (100 mg/l at four hours) rather than the standard treatment nomogram. Cases 1, 3, and 4 had no known additional risk factors for enhanced hepatotoxicity, and the timing of the overdose in these cases was thought to be accurate, but despite this the patients developed acute liver failure within 48 hours of discharge. The most likely explanation is an error in the timing of the overdoses. If the overdoses in cases 1 and 4 had been taken two hours earlier an error in timing would have given non-toxic concentrations (156 mg/l at four hours and 122 mg/l at six hours) above the treatment line at presentation whereas a one hour error in case 3 would have had the same effect.

Alternatively the rapid onset of acute liver failure might have been the consequence of an overdose before the presenting overdose, or the patients may have been more susceptible to the hepatotoxic effects of paracetamol. Wide intersubject and ethnic differences in the metabolism of paracetamol have been reported: one report showed a 60-fold range in the metabolic activation of paracetamol between subjects, and a threefold variation in glucuronide and sulphate conjugation,[18] suggesting a subgroup of patients profoundly more susceptible to the hepatotoxic effects of paracetamol. This has never, however, been proved in the context of an overdose.

Clinical course

The four cases developed signs of progressive liver failure over a 24 hour period before representing with severe and established liver disease. Cases 1 and 3 had increasing confusion, and cases 2 and 4 had abdominal pain and vomiting. If these patients and those accompanying them had been offered clear and written instructions on when to return, treatment of the incipient hepatic failure might have been more effective.

There is no evidence that activated charcoal is an effective treatment four hours after paracetamol overdose,[15 19] and apart from one case of a patient developing a toxic paracetamol concentration after an initial non-toxic concentration[20] there is no evidence to recommend serial testing.

Of 42 treatment nomograms received from accident and emergency departments across the United Kingdom all used the 200 mg/l treatment line as recommended by the National Information Service. We are aware of one hospital in the south west which has adopted the 150 mg/l treatment line as a result of a fatality—this nomogram, widely used in the United States, joins 150 mg/l (1.0 mmol/l) at four hours with 30 mg/l (0.2 mmol/l) at 12 hours.[12] We recommend that all patients presenting with a serum paracetamol concentration >150 mg/l should be treated with acetylcysteine, with a treatment threshold of 100 mg/l for those patients with known risk factors. The costs of this modification are small compared with the morbidity, the treatment costs of delayed recognition of a patient with acute liver failure, and prevention of a death.

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