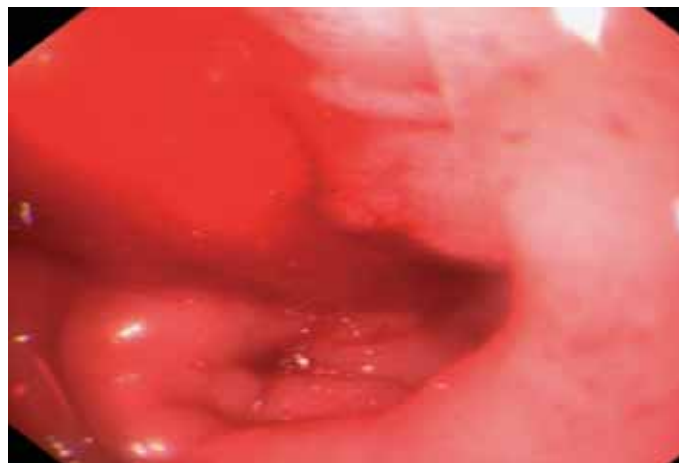


# Peptic ulcer disease

## — pharmacological treatment

By Daniel Greer, BPharm, Msc, MRPharmS

Treatment of peptic ulcer disease involves stopping bleeding by endoscopic therapy and removing the cause of the problem, which is most commonly non-steroidal anti-inflammatory drugs or *Helicobacter pylori*. This article describes the treatment options available



A bleeding duodenal ulcer, viewed during endoscopy

**A** definitive diagnosis of peptic ulcer disease (PUD) can only be made by performing an endoscopy. Most patients in the hospital setting will have been referred for endoscopy because they have one or more alarm symptoms (see p242). Patients who have not had PUD confirmed by endoscopy should be managed as for undiagnosed dyspepsia. The two treatment strategies for undiagnosed dyspepsia are either a month of empirical proton pump inhibitor (PPI) therapy or testing for and treating *Helicobacter pylori*. Treatment of undiagnosed dyspepsia is described in more detail in the National Institute for Health and Clinical Excellence clinical guideline on dyspepsia.

### Initial therapy for bleeding

Peptic ulcer is the most common cause of acute upper gastrointestinal haemorrhage. In patients with major bleeding, the immediate priority is to correct fluid loss and restore blood pressure. Fluids (crystalloids or colloids) should be administered and a blood transfusion should be performed if the haemoglobin level is less than 10g/dl.<sup>1</sup> Thereafter, prompt endoscopy is required to identify the cause of bleeding and provide local therapy to control it.

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Patients admitted to hospital with bleeding are often taking non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin, and these should be stopped as soon as possible. Patients may also be anticoagulated with warfarin, increasing the risk of bleeding. The decision to reverse anticoagulation, risking thromboembolic consequences, must be weighed up against the risk of continued bleeding by maintaining the patient in an anticoagulated state. The decision will depend on the indication for warfarin and the health status of the patient. Generally, after appropriate endoscopic management (see p244), warfarin can be restarted within a few days, although this decision should be made on an individual patient basis. If rapid resumption of anticoagulation is required, intravenous heparin or subcutaneous low molecular weight heparin may be used.

Should anticoagulation need to be reversed, guidelines recommend a combination of intravenous vitamin K (5mg) and prothrombin complex concentrate, of which the latter achieves a more rapid and complete reversal of anticoagulation than using fresh frozen plasma.<sup>2</sup> Treatment with vitamin K alone is insufficient in an acute bleeding situation since it can take up to 12 hours for full reversal of anticoagulation.

Antibiotic therapy is not routinely required before patients undergo endoscopy, but those with prosthetic heart valves or previous endocarditis may be at risk of endocarditis and should receive suitable prophylaxis as detailed in the British National Formulary (section 5.1).

### PPI therapy

Proton pump inhibitor therapy is widely used for patients presenting with gastrointestinal bleeding, although the clinical benefit of PPI therapy over and above the standard recommended endoscopic therapy of adrenaline, heat therapy and/or clips (see p244) remains unclear. A Cochrane review found that PPI treatment in patients with peptic ulcer bleeding reduces rebleeding and surgical intervention rates but has no effect on mortality.<sup>3</sup> This finding was independent of the route of PPI administration or whether there was application of initial endoscopic therapy.

British Society of Gastroenterology guidelines recommend the use of high dose PPI infusions (a stat dose of 80mg followed by 8mg/h for 72h) in patients with evidence of recent bleeding found at endoscopy.<sup>1</sup> This regimen (using omeprazole) was used in a study which, at 30 days, demonstrated a reduction in rebleeding, blood transfusion requirements and length of stay. At 30 days rebleeding occurred in 6.7 per cent of patients, compared with 22.5 per cent in the placebo group, equivalent to a number needed to treat (NNT) of six.<sup>4</sup>

PPIs are thought to prevent rebleeding in the acute stage by raising the intragastric pH and stabilising the clotting process. The high dose regimen has been shown to increase mean intragastric pH to above six, the pH required for such stabilisation. It should, however, be pointed out that other studies

included in the Cochrane review have shown a similar reduction in rebleeding rates using oral omeprazole 40mg twice daily.

Empirical acid suppression is often used in acute gastrointestinal bleeding before endoscopic confirmation of the underlying cause, although there is no strong evidence to support this practice. An ongoing Cochrane review on the use of PPIs before endoscopic diagnosis should help clarify this area.<sup>5</sup>

**Other drugs** Other drugs used for acute upper gastrointestinal bleeding include somatostatin and tranexamic acid. High dose somatostatin suppresses acid secretion and reduces splanchnic blood flow, while tranexamic acid is an antifibrinolytic. However, British Society of Gastroenterology guidelines say that more evidence is required before these therapies can be routinely recommended.<sup>1</sup>

### — Treatment after endoscopy

Drug treatment following endoscopy depends on whether a gastric or duodenal ulcer is found, and whether the ulcers are associated with NSAIDs, *H pylori* or both. NICE guidelines for dyspepsia set out recommended treatments according to the findings at endoscopy. Initial therapy is summarised in Panel 1.

### — *H pylori*-associated ulcers

*H pylori* is associated with 95 per cent of duodenal ulcers and 80 per cent of gastric ulcers. For patients in the acute hospital setting, *H pylori* is most commonly detected by biopsy-based urease tests such as the CLO test ("Campylobacter-like organisms" test, ie, the rapid urease test), performed during endoscopy. Obtaining the result of a CLO test may take up to 24 hours, and pharmacists can help ensure that the test is followed up and that any *H pylori* eradication therapy needed is correctly prescribed. Further acid suppression after eradication is unnecessary, although in practice PPI therapy is often continued for a month after significant bleeding episodes.

### — Benefits of eradication

Eradication of *H pylori* has been shown to increase the rate of healing of duodenal ulcers compared with acid suppression alone. After four to eight weeks, an average of 69 per cent of duodenal ulcer patients receiving acid suppression will be healed. Eradication of *H pylori* increases this by a further 5.4 per cent, an NNT of 18. Healing of gastric ulcers on the other hand, is not increased by *H pylori* eradication.

The principal benefit of eradication is the reduction in ulcer recurrence rates, thereby removing the need for long-term acid suppression therapy. Of patients with duodenal ulcers, 39 per cent of those receiving short-term acid suppression will be free from ulcers

## Panel 1: Summary of initial therapy for peptic ulcer disease (adapted from NICE guidelines)<sup>1</sup>

Diagnosis	Treatment	Follow up
DU or GU, <i>H pylori</i> +ve	Eradication of <i>H pylori</i>	GU — rescope at six to eight weeks post-treatment
DU or GU, NSAID use	Stop NSAID if possible Full dose PPI for one to two months	<i>H pylori</i> +ve — repeat carbon-13 urea breath test to check eradication (ensure acid suppression therapy is stopped for two weeks)
DU or GU, NSAID use and <i>H Pylori</i> +ve	Stop NSAID if possible Full dose PPI for eight weeks Eradicate <i>H pylori</i>	Continued NSAID use — gastroprotection required

DU = duodenal ulcer, GU = gastric ulcer

after three to 12 months. Eradication increases this by 52 per cent (NNT=2). For gastric ulcers, the equivalent figures are 45 per cent with acid suppression, increased by a further 32 per cent by eradication (NNT=3).

### — Choice of first line therapy

*H pylori* eradication is achieved by a combination of antibiotic therapy and acid suppression. Various combinations of dual, triple, one and two week therapies have been used, and the efficacy of these are reviewed in the full NICE guideline. One week triple therapy in a regimen containing clarithromycin is considered to be the gold standard. PPI-based dual therapy has been shown to be less effective than triple therapy, and regimens containing a PPI, amoxicillin and metronidazole are less effective than clarithromycin-based regimens.

NICE guidelines recommend either a PAC500 regimen (full dose PPI, amoxicillin and clarithromycin) or PMC250 regimen (full dose PPI, metronidazole and clarithromycin) for seven days, as first line therapy (see Panel 2, p248). These regimens are equally effective, and achieve eradication in 80–85 per cent of patients. For the PAC regimen, a dose of 500mg clarithromycin rather than 250mg has been shown to give higher eradication rates, while for the PMC regimen 250mg clarithromycin is as effective as 500mg. Although the PMC250 regimen is cheaper than the PAC regimen there are some concerns that use of this therapy first line may induce resistance to both metronidazole and clarithromycin. Resistance to amoxicillin does not seem to be common so this may be a potential reason for using PAC500 as a first line therapy.

Increasing the course length to 14 days increases eradication rates by about 10 per cent, although this was not found to be cost-effective when modelled by NICE. The increased course length is also likely to result in lower adherence.

Eradication of *H pylori* in duodenal ulcers should be checked by retesting using a carbon-13 urea breath test. There is a small risk that gastric ulcers may be malignant, therefore patients should receive repeat endoscopy and biopsy, retesting for *H pylori* six to eight weeks after starting treatment. Acid suppression therapy should be stopped two weeks before retesting as acid suppression therapy increases the possibility of false negative results. Should a patient remain positive for *H pylori* after initial treatment, a regimen that uses different antibiotics from those used previously should be chosen. A European consensus report in 2000 suggested a quadruple drug regimen of a twice daily PPI, bismuth subsalicylate/subcitrate 120mg four times daily, metronidazole 400mg three times daily, and tetracycline 500mg four times daily for a minimum of seven days.

Patients who receive *H pylori* eradication therapy should be counselled on the importance of completing the course of antibiotics, and it should be explained that successful eradication will greatly reduce the chance of ulcer recurrence. As with most antibiotics, the most common side effects are gastrointestinal (eg, nausea and diarrhoea). Patients should avoid alcohol when on regimens containing metronidazole, and patients taking the quadruple regimen should be warned that their tongue and stools may turn black temporarily, a side effect of the bismuth salt.

### — NSAID use plus *H Pylori*

The role of *H pylori* eradication in NSAID-associated ulcers is less clear.<sup>6</sup> Eradicating *H pylori* does not appear to make a difference to healing rates, whether or not the NSAID is discontinued. Should the NSAID need to be continued after ulcer healing, eradication of *H pylori* is a less effective secondary prevention strategy than continued acid suppression with PPIs. There is some evidence that

continued presence of *H pylori* may even be beneficial should NSAIDs need to be continued with gastroprotection. In both the OMNIUM and ASTRONAUT studies, patients receiving a NSAID and omeprazole after ulcer healing had a lower relapse rate if they were *H pylori*-positive.<sup>7,8</sup>

In practice, NSAIDs are stopped where possible in patients with PUD, and most clinicians will eradicate *H pylori* when it is found in the presence of ulcer disease. NICE guidelines recommend eradication after two months of full dose PPI therapy.

For NSAID naive patients with previous ulceration or dyspepsia, *H pylori* eradication before starting NSAID treatment reduces the risk of ulcer formation, although this is only likely to be practical in those who may need long term NSAIDs (eg, in rheumatoid arthritis) rather than those taking a short course, and the cost effectiveness of such a strategy is unclear.<sup>6</sup>

### — NSAID-associated ulcers

For NSAID-associated ulcers, NSAIDs should be stopped where possible, and simple analgesia should be prescribed in its place (paracetamol with or without a moderate opiate). This is possible in most patients, but those with inflammatory diseases such as rheumatoid arthritis may depend on NSAIDs for effective pain con-

trol. Studies have demonstrated that ulcer healing can be achieved with PPIs in the continued presence of NSAIDs. In the OMNIUM study<sup>7</sup> 75 per cent of patients were successfully treated after eight weeks of omeprazole 20mg. These rates were comparable to 400µg of misoprostil (71 per cent, a non-significant difference). In the ASTRONAUT study<sup>8</sup> 80 per cent of patients were successfully treated after eight weeks, superior to 150mg twice daily of ranitidine (63 per cent,  $P<0.001$ ). However, both studies included patients with endoscopic erosions as well as ulcers. NICE guidelines recommend four to eight weeks' treatment with a PPI, whether or not NSAIDs are discontinued.

Drug therapy for those continuing NSAIDs after ulcer healing is described in the section on prophylaxis (p249).

### — Other ulcers

The prevalence of *H pylori* is falling with successive birth cohorts, so ulcers unrelated to *H pylori* are becoming a proportionally greater problem. These ulcers should heal with a four- to eight-week course of PPI, but other issues should be considered. These include failure to detect *H pylori* due to recent acid suppression or antibiotic use, inadvertent NSAID use, other drugs (eg, bisphosphonates, sustained release potassium

## Panel 2: *Helicobacter pylori* eradication regimens

### ■ PAC500

PPI full dose *bd*  
Amoxicillin 1g *bd*  
Clarithromycin 500mg *bd*

### ■ PMC250

PPI full dose *bd*  
Metronidazole 400mg *bd*  
Clarithromycin 250mg *bd*

### ■ Alternative regimen for treatment failure

PPI full dose *bd*  
Tripotassium citratobismuthate (De-Nol) 120mg *qds*  
Metronidazole 400mg *tds*  
Tetracycline 500mg *qds*

All regimens should be for seven days

chloride), and alternative diagnoses such as Zollinger-Ellison syndrome or Crohn's disease. Pharmacists can play a role in ensuring a detailed drug history is taken, and in particular checking for NSAIDs or aspirin that may be contained in over-the-counter products such as cold and flu remedies.

## Prophylaxis

Prophylactic drug therapy for PUD is indicated for certain patient groups taking NSAIDs, either as primary prevention or secondary prevention for those with a history of PUD. Risk factors for PUD in patients taking NSAIDs, are shown in Panel 3.

The most effective strategy for minimising NSAID-induced ulceration is to limit use of NSAIDs, encouraging the use of paracetamol-based analgesia, and using NSAIDs for short courses to manage episodes of acute inflammation. The lowest dose of the safest NSAID (eg, ibuprofen 400mg three times daily) should be used.

Should a patient in a high risk group require an NSAID, the options are to use a traditional NSAID with a concurrent gastroprotectant, or to consider use of one of the cyclo-oxygenase (COX)-2 selective agents. An important consideration when interpreting results of trials of these agents is the outcome measure used. The most important outcome is whether serious gastrointestinal bleeds can be prevented, and failing that, whether symptomatic ulcers can be prevented. Unfortunately, many studies have carried out prospective endoscopies in all patients and reported outcomes such as gastric erosions and non-symptomatic ulcers, the clinical significance of which are unknown.

### Panel 3: Factors associated with a high risk of gastrointestinal complications with NSAID therapy<sup>9</sup>

- Age 65 years and over
- Previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation
- Concomitant use of medicines that are known to increase the likelihood of upper gastrointestinal adverse events (eg, steroids and anticoagulants)
- Presence of serious co-morbidity, such as cardiovascular disease, renal or hepatic impairment, diabetes or hypertension
- Requirement for the prolonged use of maximum recommended doses of standard NSAIDs

**H<sub>2</sub> antagonists** H<sub>2</sub> antagonists should not be used for gastroprotection. Standard doses have been shown endoscopically to prevent duodenal ulcers but not gastric ulcers, while double doses (eg, 300mg ranitidine twice daily) have been shown to reduce the incidence of endoscopically detected ulcers but not symptomatic ulcers or serious gastrointestinal complications.<sup>10</sup>

**Misoprostil** The production of protective prostaglandins is inhibited by NSAIDs. This is thought to be the mechanism of NSAID-induced ulceration. Misoprostil, a prostaglandin analogue, replaces gastroprotective prostaglandins. This agent was found to decrease the incidence of serious gas-

trointestinal events (relative risk 0.57, 95 per cent confidence interval 0.36–0.91).<sup>10</sup> The main drawback with misoprostil is the incidence of diarrhoea, particularly at the higher dose of 200µg four times daily which was used in the largest trial demonstrating reduction in serious gastrointestinal events.

**Proton pump inhibitors** A reduction in serious events has not been demonstrated with PPIs, but they do reduce the incidence of symptomatic ulcers.<sup>10</sup> The number of patients studied in these trials is relatively small compared with the large body of data for COX-2 inhibitors, so it is possible that significant effects have not been detected due to type 2 errors.

**COX-2 inhibitors** In theory, COX-2 inhibitors inhibit the production of inflammatory prostaglandins while preserving production of gastroprotective prostaglandins driven by COX-1. The actual clinical benefit of these drugs has generated much controversy. The three large clinical outcome trials: celecoxib (CLASS), rofecoxib (VIGOR) and lumiracoxib (TARGET) demonstrated a reduction in serious gastrointestinal events compared with traditional NSAIDs, although in the case of CLASS this was only in a subgroup not taking aspirin.<sup>11-13</sup> The presentation of the CLASS results has since been criticised, principally because the trial was originally planned as two studies over one year, and the results published were combined six-month data extrapolated to a predicted one-year incidence. Subsequently released actual 12-month data showed no significant difference in complications or symptomatic ulcer rates between COX-2 and NSAID groups.

Increases in cardiac events initially seen in the rofecoxib group in VIGOR were confirmed in later randomised controlled trials for rofecoxib (resulting in the voluntary withdrawal of the drug) and also for celecoxib and parecoxib/valdecoxib. Following a review by the European Agency for the Evaluation of Medicinal Products, COX-2 inhibitors are now contraindicated in cardiovascular, cerebrovascular and peripheral vascular disease, as well as in heart failure (New York Heart Association class II-IV). Etoricoxib is also contraindicated in uncontrolled hypertension. COX-2 inhibitors should not be used in patients receiving low dose aspirin, because any gastroprotective benefits are likely to be lost.

Theories for the increased incidence of cardiac events with COX-2 inhibitors include a thrombogenic effect, accelerated atherosclerosis or hypertension. There is a mechanism for this in that inhibition of COX-2 in the endothelium reduces the production of prostaglandin I<sub>2</sub>, which would normally inhibit platelet aggregation, inhibit smooth muscle proliferation, and produce vasodilation. This leaves the prothrombotic effects of COX-1 produced thromboxane (released from platelets) unopposed.

### Choice of agent

There is little in the way of head to head studies to guide choice of drug class. Omeprazole 20mg was found to be more effective and better tolerated than misoprostil in preventing endoscopic ulcers in the maintenance phase of the OMNIUM study although the dose of misoprostil used was only 200µg *bd*.<sup>7</sup>

A trial comparing diclofenac plus omeprazole versus celecoxib in patients with previous bleeding ulcers found similarly high rebleeding rates (6.4 per cent and 4.9 per cent) at six months, demonstrating that neither strategy is without substantial risk in this group.<sup>14</sup>

On a basis of cost, safety and tolerability, PPIs are most commonly used for gastroprotection. Misoprostil is an option but side effects seem to limit its widespread use, while COX-2 inhibitors are an option if patients are not on aspirin and do not have any contraindications.

### Patients taking aspirin

Whether to provide gastroprotection for high risk patients on low dose aspirin is less clear. The risk of gastrointestinal bleeding in patients taking aspirin (50-162.5mg) is nearly doubled (odds ratio 1.59). This compares with a four-fold increased risk for patients taking NSAIDs. Using low dose aspirin (75mg) helps to minimise risk, but using enteric-coated preparations does not reduce the risk of upper gastrointestinal bleeding.<sup>15</sup>

Since the most important risk factor is considered to be previous upper gastrointestinal bleeding, it would be sensible to use gastroprotection in this group of patients. Aspirin taken together with NSAIDs also increases the risk compared with taking NSAIDs alone, so this group should normally receive gastroprotection. Based on studies of NSAIDs, misoprostil and PPIs are likely to be effective as gastroprotective agents.

Clopidogrel is often used as an alternative to aspirin in patients with a history of PUD, on the basis that incidence of gastrointestinal bleeding was less than aspirin in the CAPRIE study.<sup>16</sup> However, in this study clopidogrel was compared with 300mg aspirin, and patients with history of PUD were excluded. A recent trial compared clopidogrel to aspirin 80mg plus a PPI (esomeprazole 20mg twice daily) in patients with a history of aspirin-associated gastrointestinal bleeding, and found a cumulative rebleeding rate of 8.6 per cent in the clopidogrel group compared to 0.7 per cent in the aspirin/PPI group over 12 months.<sup>17</sup> It would seem that aspirin plus a PPI would be the safer choice in this group.

### Summary

Treatment of PUD centres on initial stabilisation and cessation of any acute bleeding by endoscopic therapy followed by removal, where possible, of the main causes of ulceration (NSAIDs or *H pylori*). Acid suppression therapy (principally with PPIs) is required in some cases to complete ulcer healing. Options for primary and secondary prevention of NSAID-associated ulcers in high risk patients are misoprostil, PPIs or a COX-2 selective agent.

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