Clinical audit

Improving management of duodenal ulcer disease

Malcolm C Bateson, Brian L Diffey

Summary

Audit of treatment of duodenal ulcer disease has allowed management to improve and keep abreast of rapid advances in care. Eradication of *Helicobacter pylori* was assessed by ^{14}C urea breath test one to two months after anti-*Helicobacter* therapy. The old triple therapy regime of bismuth, tetracycline and metronidazole for two weeks was found to be toxic and of low effectiveness (82%). Regimes with lansoprazole for one month and antibiotics for one week gave 90–98% success rates. The best success has been with regimes containing both clarithromycin and a nitro-imidazole. There was complete success in 98% of 109 patients given quadruple therapy with lansoprazole 30 mg daily for one month plus tetracycline 500 mg twice daily, clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily for one week.

Keywords: clinical audit, duodenal ulcer disease, *Helicobacter pylori*

Clinical audit is critical appraisal of healthcare activity, designed to obtain the best results for patients. It is based on current procedures and recommendations. Research, by contrast, attempts to establish new ideas and treatments by rigorous assessment outside routine medical care, and generally requires ethical approval and specific patient consent.

Both clinical audit and original research are necessary to make progress through logical developments, and there are areas where the two concepts merge. Management of peptic ulcer disease has been completely revised in the last 20 years. Powerful antacid drugs became available with cimetidine in 1976 and ranitidine in 1981. Subsequently, omeprazole was introduced, followed by lansoprazole in May 1994 and pantoprazole in October 1996, which are currently half the price for an equivalent dosage. These H_2 receptor antagonists and proton pump inhibitors reliably heal peptic ulcers, but relapse is common. The identification of *Helicobacter pylori* infection as an essential but insufficient explanation for duodenal ulcer allowed an approach to prevention of relapse, which is a very frequent problem. Eradication of the organism will heal ulcers, but even more significantly it will stop them returning.^{1,2}

The World Congress of Gastroenterology meeting in Sydney August 1990 issued a consensus statement that all patients with chronic duodenal ulcers should be offered

anti-*Helicobacter* therapy. The US National Institutes of Health meeting at Bethesda in February 1994 further recommended that all duodenal ulcer and benign gastric ulcer patients should be considered for anti-*Helicobacter* therapy.

Treatment of *H. pylori* initially focused on the 'standard' triple therapy with bismuth, metronidazole, and either amoxycillin or tetracycline for two weeks.^{3,4} This was promoted by the National Health Service Centre for Reviews and Development in a news sheet in September 1995. Alternative regimes were based on proton pump inhibitor drugs plus either two or three antibiotics for one week, or quadruple therapy with bismuth and two antibiotics for one week.^{5–8} The best regimes should produce an *H. pylori* eradication rate of 90% or more.^{3,4}

A host of techniques for assessment of *H. pylori* infection is available. These include IgG ELISA serology (useful in patients not given formal anti-*Helicobacter* therapy and in epidemiological surveys), and gastric antral forceps biopsy at diagnostic endoscopy for histology and urease testing.^{9,10} After treatment, the best noninvasive indicator of success is a negative ^{13}C - or ^{14}C -urea breath test.^{1,11–14}

Methods

The ^{14}C -urea breath test was set up locally in January 1992, and offered to all duodenal ulcer patients whose anti-*Helicobacter* and proton pump inhibitor therapy had been completed at least one month previously. Initially, the published cut-off range of <1% dose administered per mmol $\text{CO}_2 \times$ body weight in Kg on a 30-minute breath sample was used. Two definite false-negatives were identified with this method (0.8% and 0.9%), with persistent infection and symptomatic proven duodenal ulcer disease. Analysis of the first 1200 patients confirmed that there was a bimodal distribution of positive and negative results, with a good separation at 0.75% dose per mmol $\text{CO}_2 \times$ body weight. Breath samples were taken at 20 and 30 minutes after oral ^{14}C urea in fasting patients, and the highest value of breath $^{14}\text{CO}_2$ excretion was taken as the result to avoid false negatives.

All duodenal ulcer patients were offered anti-*Helicobacter* therapy as well as specific standard primary ulcer-healing therapy from January 1992. Successful treatment was assessed by urea breath tests, at least four weeks after all antibiotic, bismuth and proton pump inhibitor therapy was complete.

Department of
Medicine, General
Hospital, Bishop
Auckland, County
Durham, UK
MC Bateson

Department of
Medical Physics,
Dryburn Hospital,
County Durham, UK
BL Diffey

Accepted 16 April 1997

Patients were identified from positive endoscopy records or definite radiology of active ulceration. When gastroscopy was performed immediately before therapy a gastric antral forceps biopsy was taken for urease solution or gel testing, read finally the following day to avoid false negatives as far as possible.

Local sensitivity patterns to the antibiotics used were measured by E-test with a preliminary 24-h anaerobic culture for metronidazole sensitivity.

Results

No patients gave a history of recent aspirin, nonsteroidal anti-inflammatory drug (NSAID), or steroid use.

BISMUTH TRIPLE THERAPY

A total of 101 consecutive chronic duodenal ulcer patients were given full H₂ receptor antagonist or proton pump inhibitor therapy and then 'standard' triple therapy. For two weeks they took bismuth chelate 120 mg qds, tetracycline 500 mg qds, and metronidazole 400 mg tds (BTM). Enrolment was conducted from January 1992 to April 1994. Negative urea breath tests four to eight weeks after therapy were seen in 83 (82%; 95% confidence interval (CI) 75–90%). Side-effects such as nausea, vomiting, diarrhoea and pseudomelana were very common. Patients required counselling with regard to expected side-effects and continuation of therapy. Two patients developed bloody diarrhoea. Disappointing success rates and an unacceptable level of side-effects led to the abandonment of this regime, despite its modest cost.

LANSOPRAZOLE-BASED THERAPY

From May 1994 all duodenal ulcer patients were offered lansoprazole 30 mg daily for one month as primary ulcer-healing and symptom-relieving therapy. For the first week different antibiotic combinations were used. A urea breath test was performed four to eight weeks after all therapy was complete. It was aimed to enrol 100 or more patients in each regime, but serial analysis of results show that conclusions could be safely made after the first 40–50 patients.

Lansoprazole, amoxycillin, metronidazole (LAM)

The first 104 patients received lansoprazole 30 mg daily for one month, and for the first week of this, amoxycillin 500 mg tds and metronidazole 400 mg tds. Six other patients alleged penicillin sensitivity so could not be offered this regime. There were 71% males. Age range was 32–76 years (median 55). Three patients had had previous failed anti-*Helicobacter pylori* treatment with different regimes (one twice).

Ninety two breath tests were negative (88% success; CI 82–94); 57/63 (90%) patients who had a positive urease test immediately before treatment had a negative breath test. Two patients had diarrhoea, and two had vomiting. Four additional patients did not attend for urea breath testing, though they had apparently taken the treatment without problems and

have not presented with recurrent symptoms. The strict intention-to-treat analysis gave a 92/108 (85%) success rate.

Lansoprazole, clarithromycin, tinidazole (LCT)

The next 112 patients received lansoprazole 30 mg daily for one month, and for the first week of this clarithromycin 250 mg bds and tinidazole 500 mg bds. No patients had to be excluded. There were 69% males. Age range was 23–82 years (median 58). One patient had had previous failed therapy with a different regime.

One hundred and four breath tests were negative (93% success; CI 87–98); 56/61 patients (92%) with a positive urease test immediately before treatment had a negative urea breath test. One patient had bloody diarrhoea and one had nausea. One additional patient did not attend for urea breath test. Strict intention-to-treat analysis success was 104/113 (92%).

Lansoprazole, tetracycline 250 mg bds, clarithromycin, metronidazole (LTCM)

The next 74 patients received lansoprazole 30 mg daily for one month, and for the first week tetracycline 250 mg bds, clarithromycin 250 mg bds and metronidazole 400 mg bds. No patients had to be excluded. There were 68% males. Age range was 26–80 years (median 57). Five of these patients had previously had failed treatment with other regimes (one twice).

Sixty-nine breath tests were negative (93% success; CI 87–99); 44/49 (90%) patients who had a positive urease test immediately before therapy had a negative urea breath test. One patient had diarrhoea and also rectal bleeding, probably in this instance from a local anal cause. Two patients did not attend for urea breath testing. Strict intention-to-treat analysis was 69/76 (91%) success.

Lansoprazole, tetracycline 500 mg bds, clarithromycin, metronidazole (LTCM2)

The next 109 patients received lansoprazole 30 mg daily for one month and for the first week tetracycline 500 mg bds, clarithromycin 250 mg bds, and metronidazole 400 mg bds. No patients had to be excluded. There were 69% males. Age range was 17–84 years (median 59). Two patients had previously failed on an alternative regime, one twice.

One hundred and seven breath tests were negative (98% success); 74/76 (97%) patients with a positive urease test had a negative breath test. Two patients had diarrhoea and two patients had vomiting. Four other patients did not attend for urea breath test. Strict intention-to-treat analysis was 107/113 (95%) success.

ANTIBIOTIC SENSITIVITY

In total, 94 separate sensitivity cultures showed that *H. pylori* was sensitive to amoxycillin. There was one culture resistant to tetracycline and two each to clarithromycin and to metronidazole. The organism therefore showed 98–100% sensitivity to the antibiotics used in this study.

Discussion

The field of *H pylori* research is advancing very rapidly with 1000 or more papers each year and several books. The approach outlined allowed patients to receive the best available treatment even in an atmosphere of constant change.

The original two-week triple BTM regime was an advance on previous ulcer eradication therapy, which often depended on long-term antacid drugs. It proved difficult to use despite initial hopes and cannot now be recommended.⁸ Though side-effects may be less and thus compliance better using BTM for one week, the efficacy remains below the audit standard at 82–83%.⁸

Lansoprazole was originally licensed to heal duodenal ulcers in a one-month course of 30 mg daily. It was used in this way throughout the current study. Two years later, it was licensed for short-term anti-*Helicobacter* regimens. It may be that treatment for longer than one week with lansoprazole is not necessary in duodenal ulcer, but this has not yet been rigorously proved. It would ideally need a proper randomised prospective control trial with check gastroscopy, not recommended in routine patient management. However, negative urea breath tests are a useful surrogate marker of duodenal ulcer healing.¹³ Using antibiotics for the first week of a four-week course of lansoprazole should ensure not only almost complete rapid primary ulcer healing but also long-term cure. Only two successfully treated patients in this study have had a relapse of duodenal ulcers and *H pylori* infection over the first five years.

All the antibiotics used had good activity against local *H pylori*. The regimes using low-dose clarithromycin and nitro-imidazole achieved best results with a success rate significantly better than BTM bismuth triple therapy (χ^2 , $p < 0.001$).

The regimes should not be used in women who may be pregnant, but can otherwise be generally recommended in adults. Quadruple therapy was statistically significantly superior

Summary points

- spontaneous duodenal ulcers are regularly caused by *H pylori* with normal or increased gastric acid production
- iatrogenic duodenal ulcers can be caused by aspirin, NSAIDs and corticosteroids
- uncommonly, duodenal ulcers are caused by hypercalcaemia or hypergastrinaemia
- eradication of *H pylori* is a prime objective of duodenal ulcer treatment
- the urea breath test is the best noninvasive method of assessing *H pylori* infection. A negative test after treatment is a useful surrogate marker of duodenal ulcer healing. The audit standard is 90% negative
- bismuth-tetracycline-metronidazole treatment is toxic and of low efficacy (82%)
- proton pump inhibitor therapy plus two or three antibiotics for one week achieves a 90–98% *H pylori* eradication rate. The best regimes include clarithromycin and a nitro-imidazole. Quadruple therapy with additional tetracycline may be best of all

with the higher dose of tetracycline (χ^2 , $p < 0.05$ vs LAM, LAM+LCT, and LAM+LCT+LTCM). Compliance was very good in these studies, and the few defaulters from urea breath testing appeared to have had mainly social rather than medical reasons for default. Side-effects were not a big problem, but 1–2% of patients on these vigorous regimes may expect to have bloody diarrhoea. This has been self-limiting to date and no cultures have been positive for *Clostridium difficile*, though this organism may be suspected in these patients.

In conclusion, these studies have allowed modern developments to be smoothly integrated into standard medical care and produce treatment schemes that can be generally recommended. Lansoprazole 30 mg daily plus one week's antibiotic therapy achieved 90–98% success in ensuring absence of *H pylori* infection. Almost all patients should have primary ulcer healing. This is an attractive option for radical cure of duodenal ulcer.

- Hopkins RJ, Girardi LS, Turney EA. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. *Gastroenterology* 1996; **110**: 1244–52.
- Penston JG. Clinical aspects of *Helicobacter pylori* eradication therapy in peptic ulcer disease (review article). *Aliment Pharmacol Ther* 1996; **10**: 469–86.
- Marshall BJ. *Helicobacter pylori*. *Am J Gastroenterol* 1994; **89**: S116–28.
- Tytgat GNJ. Treatments that impact favourably upon the eradication of *Helicobacter pylori* and ulcer recurrence (Review article). *Aliment Pharmacol Ther* 1994; **8**: 359–68.
- Bell GD, Powell KU, Burrig SM, et al. *Helicobacter pylori* eradication: efficacy and side effect profile of a combination of omeprazole, amoxycillin and metronidazole compared with four alternative regimens. *Q J Med* 1993; **86**: 743–50.
- Bazzoli F, Zagari RM, Fossi S, et al. Short-term low-dose triple therapy for the eradication of *Helicobacter pylori*. *Eur J Gastroenterol Hepatol* 1994; **6**: 773–7.
- Dalla Libera M, Pazzi P, Carli G, et al. High effectiveness and safety of one-week antibiotic regimen in *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 1996; **10**: 203–6.
- de Boer W, Driessen W, Jansz A, Tytgat G. Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. *Lancet* 1995; **345**: 817–20.
- Taha AS, Reid J, Boothmann P, et al. Serological diagnosis of *H pylori* – evaluation of 4 tests. *Gut* 1993; **34**: 461–5.
- Thillainayagam AV, Arvind AS, Coom RS, Harrison IG, Tabaqchali S, Farthing MJG. Diagnostic efficiency of an ultra-rapid endoscopy room test for *Helicobacter pylori*. *Gut* 1991; **32**: 467–9.
- Logan RPH, Dill S, Bauer FE, et al. The European 13C-urea breath test for the detection of *Helicobacter pylori*. *Eur J Gastroenterol Hepatol* 1991; **3**: 915–21.
- Marshall BJ, Plankey MW, Hoffman SR, et al. A 20-minute breath test for *Helicobacter pylori*. *Am J Gastroenterol* 1991; **86**: 438–44.
- Hopkins RJ, Girardi LS, Turney EA. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. *Gastroenterology* 1996; **110**: 1244–52.
- McColl KEL, El-Nujumi A, Murray L, et al. The *Helicobacter pylori* Breath Test: a surrogate marker for peptic ulcer disease in dyspeptic patients. *Gut* 1997; **40**: 302–6.