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One week's anti-*Helicobacter pylori* treatment for duodenal ulcer

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Abstract

This open study tested whether eradication of *Helicobacter pylori* (*H pylori*) heals duodenal ulcers as well as decreasing recurrence. *H pylori* was detected in patients with endoscopic duodenal ulcers by histology, CLO-test, culture, and ^{13}C-urea breath test (^{13}C-UBT). Tripotassium dicitrato bismuthate (120 mg) and amoxycillin (500 mg) each four times daily, were given for seven days, with 400 mg metronidazole five times a day on days 5–7. The ^{13}C-UBT was repeated immediately after treatment and endoscopy repeated within 21 days. After treatment unhealed ulcers were reinspected one month later and healed ulcers followed up by ^{13}C-UBT alone for 12 months. Of 45 patients, 44 were available for follow up. Mean pretreatment excess $\delta^{13}CO_2$ excretion was 25·6 per mil, which fell to 2·4 per mil immediately after finishing treatment, indicating clearance of *H pylori* in every patient. At the second endoscopy (median interval 20 days from start of treatment) 33 of 44 (75%) duodenal ulcers had healed. Ten of the remaining 11 duodenal ulcers were smaller and those 10 healed in the next two weeks with no further treatment. Two patients' ulcers that initially healed with clearance of *H pylori* recurred three weeks later (both had metronidazole resistant *H pylori*). *H pylori* was eradicated in 28 of 44 (64%) patients (^{13}C-UBT negative for median follow up 10·2 months). Overall 41 of 43 (93%, 95% confidence intervals 81%–99%) duodenal ulcers were healed at one month. This study suggests that one week of anti-*H pylori* triple treatment is effective in healing duodenal ulcers.

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Helicobacter pylori (*H pylori*) causes non-autoimmune gastritis[1] and is one important factor in the aetiology of recurrent duodenal ulcer.[2] Thus recurrence of *H pylori* precedes ulcer recurrence,[3] the density of antral *H pylori* increases the rate of ulcer recurrence[4] and successful eradication of *H pylori* after duodenal ulcer healing substantially prevents recurrence.[5–7] All of these studies, however, focused on the role of *H pylori* in recurrence of duodenal ulcers rather than on primary ulcer healing. We have previously developed a novel one week triple treatment that eradicated 93% of metronidazole sensitive *H pylori*.[8] We have now for the first time investigated healing of duodenal ulcers with this regimen as the sole primary treatment.

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Patients and methods

After routine diagnostic endoscopy of the upper gastrointestinal tract patients with a duodenal ulcer greater than 5 mm in diameter were invited to enter and give written consent to the study, which was approved by the Parkside ethics committee. Patients with previous gastric surgery, known bleeding diathesis, taking oral anticoagulants, or who had been treated in the previous two months with bismuth compounds or antibiotics known to be active against *H pylori* were excluded. Patients taking H_2 antagonists, proton pump inhibitors, or whose ulcers had recently bled were not excluded.

Endoscopes were disinfected with an automatic washing machine (Olympus EW20)[9] after each examination and the biopsy forceps were sterilised by autoclaving.

ASSESSMENT OF H PYLORI STATE

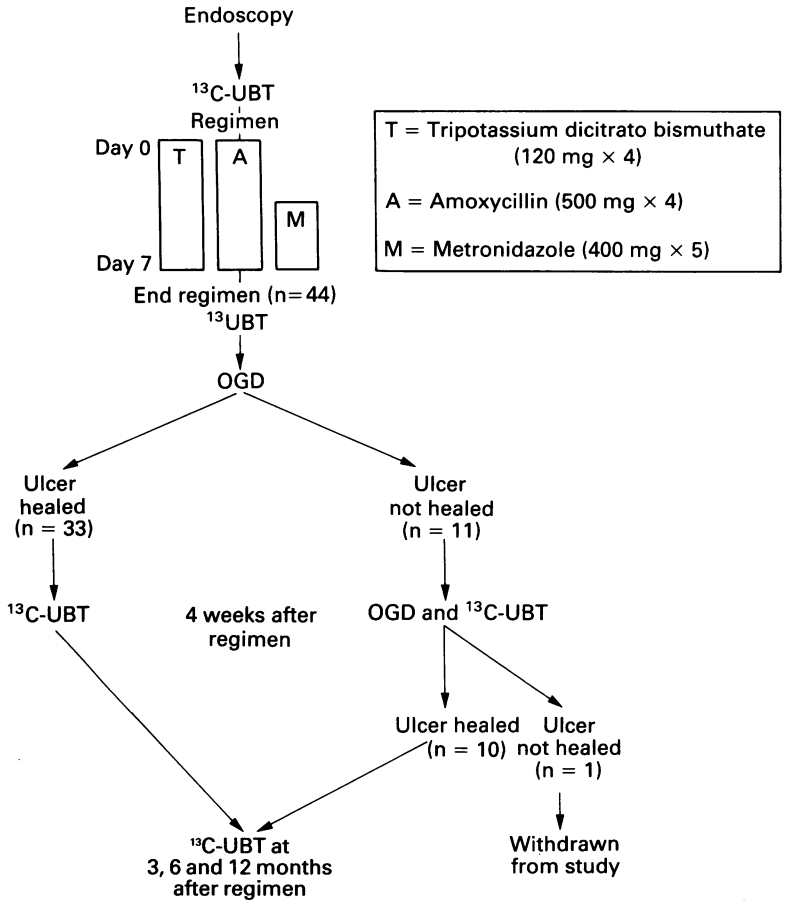
The presence of *H pylori* was assessed by the ^{13}C-urea breath test (^{13}C-UBT), histological examination of two antral biopsy specimens, CLO-test (Delta West Ltd, Western Australia), and culture (two antral biopsies, selective and non-selective media, microaerophobic conditions for up to 10 days). Tests for metronidazole sensitivity (5 μg) were completed by an in vitro disc method (mast sensitivity discs, Mast Laboratories, Liverpool). Metronidazole resistant or metronidazole sensitive *H pylori* are subsequently referred to as MR *H pylori* and MS *H pylori*, respectively.

Patients were classified as *H pylori* positive by a positive ^{13}C-UBT and CLO-test together with positive histology or culture. Clearance of *H pylori* was defined as a negative ^{13}C-UBT at the end of treatment. Eradication was defined as a negative ^{13}C-UBT one month after the end of treatment (negative ^{13}C-UBT=excess $\delta^{13}CO_2$ excretion <5 per mil).[10]

^{13}C-UREA BREATH TEST

The ^{13}C-UBT (European standard protocol)[10] was completed within 24 hours of the initial endoscopy in all patients. Briefly, a baseline sample of expired breath was obtained before ingesting a fatty liquid test meal to delay gastric emptying. After 10 minutes, 100 mg ^{13}C-urea (99% pure, Cambridge Isotopes, Boston, USA) in 50 ml of tap water was swallowed and distributed within the stomach by turning the patient to the left and right decubitus position. Two litre serial breath samples were collected every five minutes into a large reservoir collecting bag, from which a single 20 ml sample was taken at the end of the test and analysed by mass spectrometry (BSIA, Brentford, London). A positive result was defined as excess $\delta^{13}CO_2$ excretion >5 per mil, as determined from previous studies.[10]

Patients with a positive ^{13}C-UBT and positive



Outline of study design with the number of patients with healed ulcers at first or second follow up. OGD=endoscopy.

CLO-test were given 120 mg tripotassium dicitrato bismuthate and 500 mg amoxycillin, each four times a day, for seven days (days 1–7). Metronidazole (400 mg) was given five times a day for the last three days (days 5–7). This high dose was used to decrease the risk of promoting the development of MR *H pylori*.

FOLLOW UP

Immediately after the end of eradication treatment, a second ^{13}C-UBT was performed to assess clearance (to determine the effectiveness of treatment), followed as soon as possible by a second endoscopy to assess ulcer healing. In those patients with healed ulcers further ^{13}C-UBTs were done at one, three, six, and 12 months: they were re-endoscoped only if ulcer symptoms recurred. Patients whose ulcer had not healed were again endoscoped and had a ^{13}C-UBT one month after the end of eradication treatment. If the ulcer was healed, they had further ^{13}C-UBTs at three, six, and 12 months (Figure).

Ulcer healing and relapse, metronidazole sensitivity, and eradication

No of patients	H pylori *cleared*	*Ulcer healed at first follow up*	H pylori *eradicated*	*Ulcer healed only at one month*	*Ulcer recurred or unhealed*
MS *H pylori* (23)	23	15	20	8	0
MR *H pylori* (12)	12	12	2	0	2
M sensitivity not known (9)	9	6	6	2	2
Total (44)	44	33	28	10	4

Patients who failed to clear *H pylori* after treatment, or whose ulcers failed to heal, or who had recurrent *H pylori* at one month were not studied further.

Confidence intervals on proportions are based on the binomial distribution.

Results

The Figure shows the study design. The Table summarises ulcer healing and relapse, metronidazole sensitivity, and eradication data.

PATIENTS

Forty five patients (27 men, median age 37, range 17–76 years) with duodenal ulcers (>5 mm) and *H pylori* were entered into the study; 44 are available for follow up. The remaining patient declined further endoscopy and follow up because he had no symptoms. Twenty two patients were smokers, five presented with either haematemesis or melaena, of whom three had been started on H_2 antagonists within 24 hours of the initial endoscopy, and a further three patients had duodenal ulcers resistant to standard treatment: 300 mg ranitidine at night (n=1), 400 mg cimetidine twice a day (n=1), or 40 mg omeprazole in the morning (n=1), each for one month. Any treatment with H_2 antagonists or proton pump inhibitor was stopped within 24 hours of the initial endoscopy in all patients.

ENDOSCOPY

At the second endoscopy 33 of 44 (75%, 95% confidence intervals (95% CI) 60%–87%) ulcers were completely healed, 10 of the remaining 11 were smaller (median diameter 3 mm), and one was larger. The median interval between the end of treatment and the second endoscopy was 13 days (range 1–31 days, variation due to missed appointments and holidays).

One month after the end of treatment 10 of the initially unhealed 11 ulcers had healed completely without any further treatment in the intervening three weeks. The remaining ulcer had increased in size (MR *H pylori*). Two patients whose ulcers initially healed (both infected with MR *H pylori*) had an early symptomatic ulcer recurrence, which was confirmed at endoscopy three weeks after the end of treatment. Thus overall 43 of 44 (98%) duodenal ulcers healed after the one week *H pylori* eradication regimen, with 41 of 44 (93%, 95% CI 81%–99%) still healed at one month.

H PYLORI AND METRONIDAZOLE SENSITIVITY

All 44 patients were colonised by *H pylori* as detected by a positive ^{13}C-UBT and positive antral histology. The ^{13}C-UBT became negative in all 44 patients immediately after finishing treatment indicating that the treatment regimen had cleared *H pylori* in every patient. *H pylori* was grown from 38 of 44 patients and metronidazole sensitivity established in 35: 12 (34%) isolates were resistant and 23 (66%) were sensitive to metronidazole. In these 23 patients the

ulcers were healed at one month or earlier in 20 of 23 (87%, 95% CI 60%–95%) (Table), with neither recurrent symptoms nor recurrence of *H pylori* during subsequent follow up (median= 10, range 6–14 months). In the 12 patients with pretreatment MR *H pylori* duodenal ulcer healing was achieved in all 12, but *H pylori* was eradicated in only two of 12 (17%).

FOLLOW UP

Overall *H pylori* was eradicated in 28 of 44 patients (64%, 95% CI 48%–76%). In these patients there was no evidence by ^{13}C-UBT of recurrent *H pylori* at three and six months and no recurrence of ulcer symptoms during this period of follow up. In the other 16 patients the ^{13}C-UBT became positive indicating failed eradication: in these 16 with persistent *H pylori*, one duodenal ulcer had not healed at one month follow up, two had recurrent ulcers within three weeks of finishing treatment, and five had recurrent dyspepsia but no recurrent ulcers on repeat endoscopy.

Discussion

For many years the treatment of duodenal ulcer has been based on Schwartz's dictum 'no acid – no ulcer', and whereas this is remarkably successful with 90%–100% duodenal ulcer healing within two months of antisecretory treatment, there is a disappointingly high rate of ulcer recurrence on stopping treatment – 50% can recur within six months.[11] It is now clear that acid inhibitors do not change the natural history of the underlying ulcer diathesis. The natural history can be changed, however, by eradication of *H pylori*, which decreases the incidence of ulcer recurrence.[5–7]

Previous studies of duodenal ulcer and *H pylori* (with comparatively lengthy treatment regimens of antibiotics in conjunction with either bismuth salts, or antisecretory agents) have focused on recurrence of *H pylori* and relapse to duodenal ulcers,[5–7] whereas all the studies of duodenal ulcer healing with bismuth monotherapy were done before the discovery of *H pylori*.

ULCER HEALING

This study is the first to examine the alternative strategy of using an anti-*H pylori* regimen as the primary (and only) treatment for healing duodenal ulcers. On an intention to treat basis 75% of duodenal ulcers healed on the seven day *H pylori* eradication regimen. Ulcer healing was not complete in 11 patients at the first follow up endoscopy (median interval from the end of treatment nine days). Further treatment was not needed and 10 of 11 duodenal ulcers healed completely within 28 days, or earlier, after finishing eradication treatment, achieving a 93% healing rate at one month after the end of the regimen.

This open pilot study was uncontrolled, but the results are comparable with a recent two week trial of 20 mg omeprazole in the morning *v* 150 mg ranitidine twice daily with two week healing rates of 86% and 63% respectively.[12]

BISMUTH

There are no studies of the rate of duodenal ulcer healing with bismuth salts after less than four weeks of treatment[13–15] and it is possible that the 75% healing rate could have been due to the bismuth in our triple treatment regimen. In studies with bismuth salts as the sole agent, healing and prevention of recurrence may have been promoted by the anti-*H pylori*, mucosal protective, or other properties of accumulated bismuth. Bismuth monotherapy can heal duodenal ulcers without inhibition of acid secretion,[13 15] but it is not clear whether the benefit is due to suppression of *H pylori* or other mechanisms – for example, decreasing pepsin.[16] Eradication rates with bismuth salts alone, however, are very low.[17]

H PYLORI

Although many workers are at present attempting to identify pathogenic factors characterising strains of *H pylori* associated with duodenal ulcers,[18–21] our study suggests that regardless of pathogenicity, the overall load of the organism may be important in determining the clinical outcome. Thus in two patients duodenal ulcers healed after suppressing *H pylori* to a low level of infection (excess $\delta^{13}CO_2$ excretion 1·3 and 2·1 per mil for each patient at the end of treatment). Within days of finishing treatment the level of infection, as measured by the ^{13}C-UBT, had returned to pretreatment levels: this was followed by ulcer recurrence 10 days later.

METRONIDAZOLE SENSITIVITY

Duodenal ulcers healed in all the 23 patients infected with MS *H pylori*. In 20 of these 23 patients *H pylori* was eradicated and neither ulcer nor *H pylori* had recurred within the nine months of follow up. The ulcers also healed in the 12 patients with MR *H pylori*, but *H pylori* was eradicated in only two of 12. Although those patients with persistent *H pylori* are at risk of duodenal ulcers, symptomatic ulcer recurrence has so far not occurred in any patient. Recurrence without symptoms is possible but could be delayed, as seen after bismuth monotherapy,[14 15] which generally only suppresses *H pylori*.[17]

We and others have shown that the most important factor in preventing recurrent duodenal ulcer is the success of the treatment regimen in eradicating *H pylori*. Previous studies suggest that any regimen that includes metronidazole will not work if the stomach is infected with MR *H pylori*.[8 21 22] The design of this study prevented the exclusion of patients with MR *H pylori* and this is the most likely reason for the low overall eradication rate. For optimal management strategy, routine in vitro antibiotic sensitivity tests are desirable before attempting to eradicate *H pylori*, in order to treat patients with drugs that are likely to be successful against their bacteria and to prevent the emergence of resistant strains.

Although no formal symptom assessments were made in this study, no patient needed additional treatment after their initial one week eradication regimen, including the patients with unhealed ulcers at the first follow up endoscopy.

The main conclusion of this study is that one week's triple treatment (which had been shown to be highly effective in eradicating *H pylori*) is highly effective in healing duodenal ulcers. Ulcer healing is probably, but not certainly, due to clearance of *H pylori* rather than to other effects of the bismuth, amoxycillin, or metronidazole. The ulcers that healed after clearance of *H pylori* all remained healed during the period of follow up if the *H pylori* had been eradicated, but two of those whose *H pylori* had been cleared but not eradicated recurred during follow up.

This approach to duodenal ulcer healing poses new problems, particularly that of MR *H pylori*. Anti-*H pylori* regimens containing metronidazole will not be successful in areas where the incidence of MR *H pylori* is high.[22] Further studies, including symptom assessments and follow up endoscopy in all patients are needed, before the proper place of this strategy in the management of duodenal ulcer can be established.

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