Healing with basic fibroblast growth factor is associated with reduced indomethacin induced relapse in a human model of gastric ulceration

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Abstract

Background—Acid stable basic fibroblast growth factor (bFGF) promotes angiogenesis and healing of gastric ulcers in rats and reduces subsequent non-steroidal anti-inflammatory drug (NSAID) induced relapse.

Aims—To test in a double blind, placebo controlled, three way crossover study whether bFGF promotes healing and reduces subsequent relapse in a human model of gastric ulceration.

Subjects—Twelve healthy volunteers.

Methods—Subjects took aspirin 900 mg twice daily (days 1–3) with bFGF 0.1 mg twice daily or cimetidine 400 mg twice daily or placebo (days 1–14) and then indomethacin 50 mg thrice daily (days 15–21). Endoscopy was performed on days 1, 4, 8, 15, and 22 during each treatment period. Eight antral biopsy specimens were taken on day 1 and the number of unhealed biopsy induced mini-ulcers and NSAID induced erosions counted during subsequent endoscopies.

Results—Basic FGF and cimetidine were protective against aspirin and indomethacin induced duodenal (but not gastric) injury compared with placebo. There was significant relapse of biopsy induced mini-ulcers after indomethacin only in the placebo group (0 (0–0) before v 1 (0–4.5) after; p>0.05). TGP-580 was detected in serum of one volunteer.

Conclusions—Healing with bFGF (and cimetidine) was associated with reduced NSAID induced ulcer relapse in this model of gastric ulceration.

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Keywords: basic fibroblast growth factor, cimetidine, gastric ulcer, non-steroidal anti-inflammatory drugs, prostanoids.

Non-steroidal anti-inflammatory drugs (NSAIDs) promote peptic ulceration and delay ulcer healing. Currently available drug therapy for healing and secondary prevention of NSAID associated gastric ulcers is unsatisfactory. If NSAID therapy is continued, gastric ulcer healing is often followed by recurrence (>50% at six months). Misoprostol (a prostaglandin E₁ analogue) has been shown to reduce gastric ulcer recurrence but diarrhoea is common and often necessitates cessation of treatment. Early studies demonstrated no benefit of H₂ receptor antagonists for prevention of gastric ulceration. However maintenance high dose ranitidine has recently been reported to lower gastric ulcer recurrence after healing.

The mechanism by which NSAIDs impair ulcer healing and promote recurrence is not well understood although inhibitory actions on granulation tissue angiogenesis and ulcer rim epithelial cell proliferation have been reported in humans. There is evidence that mucosal abnormalities persist at the site of an ulcer for some time after ulcer healing and this may explain why gastric ulcers tend to recur at the same site. These findings have led to the idea of ‘quality of healing’ – that is, the thickness of the mucosal scar, the depth of new epithelium, and continuity of muscularis mucosa. It has been proposed that impairment of ulcer healing mechanisms may reduce ‘quality of healing’ and predispose healed gastric mucosa to future ulceration.

Basic fibroblast growth factor (bFGF) is an 18 kDa protein found in normal human gastric mucosa, which is upregulated in ulcer granulation tissue. Preliminary studies in humans have shown that gastric ulcers are associated with low bFGF levels in intact mucosa suggesting bFGF ‘deficiency’ may underline a predisposition to ulceration. Basic FGF has potent angiogenic properties in vitro and in vivo. A more acid stable form of bFGF (bFGF CS-23 or TGF-580; Takeda Chemical Industries, Osaka, Japan) promotes angiogenesis and healing of acetic acid induced gastric ulcers and cyanemine induced duodenal ulcers in rats. We have shown, in an open pilot study, that oral bFGF therapy in patients with NSAID associated gastric ulcers is associated with a healing rate of 44% at one month and a mean 90% reduction in area of unhealed ulcers. Recent evidence suggests that healing of acetic acid induced ulcers in rats with bFGF is associated with a reduction in indomethacin induced ulcer relapse after cessation of bFGF therapy (Sato H, personal communication). A reduction in NSAID induced ulcer relapse by ‘angiogenic’ therapy could be explained by improved ‘quality of healing’.

Acute aspirin induced mucosal injury in healthy volunteers is a well established model and has proved to be predictive of the effects of both prostanoids and H₂ receptor antagonists when given as prophylaxis against NSAID associated ulcers in patients.
Recently, we and others have extended this model to permit investigation of healing mechanisms using biopsy induced mini-ulcers as a model of ulcer healing. In this paper we investigate the effects of indomethacin on relapse of mini-ulcers in healthy volunteers and compare the effects of bFGF and cimetidine on this as well as on prevention and healing of aspirin and indomethacin induced mucosal injury.

Methods

Ethical approval and volunteer recruitment

The study was approved by the University of Nottingham Medical School Ethics Committee. Volunteers of either sex were studied if they were aged between 18 and 45 years and were within 10% of desirable weight (according to Metropolitan Life tables). Volunteers were excluded if they were smokers, had a history of dyspepsia, peptic ulceration or malignancy or were women of child bearing potential not using medically acceptable means of contraception. Other exclusion criteria were presence of anaemia, a bleeding diathesis or use of concomitant medication except oral contraceptives. Written informed consent was obtained from all volunteers.

Study design

The study was a double blind, three way, placebo controlled crossover trial with randomised treatment order determined by Latin square design. A washout period of at least 14 days was included between treatment periods.

Drug therapy

Figure 1 outlines drug therapy administered during each treatment period. Volunteers took aspirin 900 mg twice daily for the first three days, one hour after the first endoscopy and 30 minutes before meals to induce acute mucosal injury. Volunteers also started on day 1: TGP-580 (0·1 mg twice daily) and sodium bicarbonate (NaHCO3 1 g twice daily); cimetidine (400 mg twice daily) and NaHCO3 (1 g twice daily); placebo and NaHCO3 (1 g twice daily).

Placebo for both TGP-580 and cimetidine were given where appropriate. TGP-580 (acid stable bFGF) was given as 0·1 mg active drug in 0·5 g dextran powder, which was dissolved in a glass cup of tap water along with 1 g NaHCO3 powder. TGP-580 placebo was given in a similar fashion. Cimetidine 400 mg twice daily and placebo were given in capsule form and were taken at the same time as TGP-580/placebo and NaHCO3. These drugs were taken immediately after meals (at least 30 minutes after aspirin ingestion). On day 15, all drugs were stopped and volunteers were given indomethacin capsules (50 mg thrice daily) for seven days (Fig 1). Volunteers were asked to abstain from alcohol during treatment periods.

Endoscopy

Unsedated upper gastrointestinal endoscopy was performed on days 1, 4, 8, 15, and 22 of each treatment period (Fig 1). To ensure consistency of evaluation, 89% of endoscopies were performed by one author (MH). Other endoscopies were carried out by two experienced endoscopists.

At each endoscopy, the number of erosions (haemorrhagic and non-haemorrhagic) was recorded separately for the oesophagus, stomach, and duodenum.

At endoscopy on day 1 (baseline), eight antral floor biopsy specimens (A-H) were taken in a straight line, 1 cm from the pylorus (measured using a custom made endoscopic measuring device). Each biopsy specimen was at least 1 cm away from neighbouring samples. All specimens were taken using the same forceps (FB-25K, Olympus, Tokyo, Japan). Two biopsy specimens were placed in 10% formalin for histological examination. Two biopsy specimens were used for measurement of ex vivo prostaglandin E2 synthesis. Breached mucosa at each biopsy site was designated a mini-ulcer and its position carefully noted for assessment of subsequent healing and future relapse. A biopsy induced mini-ulcer was recorded as healed if no defect in mucosa was visible endoscopically.

At endoscopy on day 4 (post-aspirin), the number of biopsy induced mini-ulcers (A-H) remaining unhealed was counted. Two pairs of biopsy specimens were taken for measurement of ex vivo prostaglandin E2 synthesis; one pair from the first two pre-existing biopsy induced mini-ulcers (A-B) and one pair from intact antral mucosa distant from existing mini-ulcers (L-M).

Endoscopy was repeated on day 8 (healing phase) and 15 (pre-indomethacin) and the number of healed biopsy induced mini-ulcers (A-H) was recorded. On day 15 two further antral biopsy specimens were taken from intact mucosa for measurement of ex vivo prostaglandin E2 synthesis (N-P). After seven days of indomethacin treatment, volunteers underwent a final endoscopy (day 22). The number of biopsy induced mini-ulcers (A-H), which had occurred in pre-recorded positions, was counted and fresh samples were taken from intact mucosa and healed biopsy induced mini-ulcers produced just before indomethacin therapy (N-P).
Blood and urine sampling
Blood was obtained from each volunteer before the start of the study for routine haematological (full blood count, white cell count, and clotting screen) and biochemical (urea and electrolytes, plasma glucose, liver function tests, serum amylase) investigations. Urine was obtained for dipstick analysis of protein, blood, and glucose. A commercially available pregnancy test was also carried out on urine of female volunteers. At the end of the study the investigations carried out above were repeated.

At each endoscopy blood was taken and allowed to clot at 37°C for 60 minutes. Serum was then stored at -30°C before assay of serum thromboxane B₂ and serum TGP-580 concentrations.

Serum thromboxane B₂ measurement
Serum thromboxane B₂ (TXB₂) was measured by radioimmunoassay as previously described. Results are expressed as ng/ml of serum.

Serum TGP-580 measurement
Serum TGP-580 was measured by sandwich ELISA. Briefly, serum and standards were added to phosphate buffered saline (PBS) containing 100 μg/ml heparin (Sigma, Poole, UK) and 1 mg/ml mouse IgG (Sigma) and were placed in 96 well plates coated with (25 μg/ml) murine monoclonal antibody against TGP-580 (ATI-3, Takeda). ATI-3 shows no cross reactivity with wild type bFGF up to 1000 pg/ml (data not shown). After overnight incubation at 4°C and PBS washes, the Fab' fragment of a murine monoclonal anti-bFGF antibody (3H3) conjugated with horseradish peroxidase (Takeda) was added to each well (3 μg/ml) and incubated for four hours at room temperature. After further PBS washes, OPD/H₂O₂ was added and absorbance at 490 nm was measured at 60 minutes after stopping the reaction within 2 M H₂SO₄.

The intra-assay and inter-assay coefficients of variation for the TGP-580 ELISA were 8% and 17% respectively. Limit of detection was 3 pg/ml.

Ex vivo prostaglandin E₂ synthesis measurement
Ex vivo prostaglandin E₂ (PGE₂) synthesis was measured as follows. Two antral biopsy specimens were washed in 1 ml 10 mM TRIS-HCl pH 7.4+0.15 M NaCl (TRIS-saline) and then vortexed for 60 seconds in 500 μl TRIS-saline. The supernatant was collected and stored at -70°C before assay of PGE₂ using a radioimmunoassay as previously described. The net weight of the biopsy specimens was then measured. Results are expressed as pg/mg wet weight of specimen.

Histological assessment
Formalin fixed biopsy specimens were embedded in paraffin wax. Sections were stained with haematoxylin and eosin and toluidine blue. The presence or absence of *Helicobacter pylori* was recorded by a histopathologist blinded to the origin of the sections.

Histological assessment was carried out on biopsy specimens taken on day 1 (baseline) for each of three treatment periods per volunteer.

Adverse event reporting
Volunteers were questioned about new or continuing symptoms, or both, at each endoscopy and were told to contact the endoscopist if new symptoms developed between visits.

Statistical analysis
The number of erosions and unhealed biopsy induced mini-ulcers present are expressed as the median value with interquartile range (IQR). Differences in erosion and unhealed biopsy induced mini-ulcer counts at different time points were compared within treatment groups by the Wilcoxon signed rank test for paired data. Differences between treatment groups were analysed by the Wilcoxon rank sum test adjusting for period effects by Koch’s method for a two period cross over adapted for a three period cross over using SAS (version 6.08). Prostaglandin E₂ and thromboxane B₂ data were normally distributed and were analysed using Student’s t test.

A value of p less than 0.05 was taken as significant and p less than 0.1 as of borderline significance.

Results

Twelve volunteers underwent all three treatment periods. One volunteer declined to continue the study after completing one treatment period because of intolerance of endoscopic procedures. All data were included for statistical analysis. Mean (SEM) age of volunteers was 26 (1) years (eight male). All volunteers were *Helicobacter pylori* negative.

The mean (SEM) washout period between treatments was 37 (3) days (range 14–70 days).

Healing of biopsy induced mini-ulcers
Eight antral biopsy induced mini-ulcers were produced on day 1 in all cases. Biopsy site lesions were easily distinguishable from drug induced erosions by their 'punched out' appearance. The median number of unhealed biopsy induced mini-ulcers reported on days 4, 8, and 15 for all three treatment periods are shown in Fig 2. Neither bFGF nor cimetidine accelerated healing of biopsy induced mini-ulcers compared with placebo.

Indomethacin induced relapse of biopsy induced mini-ulcers
Indomethacin therapy was associated with a significant increase in biopsy induced mini-ulcers from 0 (median, IQR 0–0) pre-indomethacin to 1 (0–4.5) post-indomethacin; p<0.05, Fig 3). However, there was no significant increase in the number of mini-ulcers after prior treatment with bFGF (0 (0–3.25) to 0...
bFGF reduces indomethacin induced relapse in a model of gastric ulceration

Development and healing of aspirin induced gastric and duodenal erosions

The Table shows the median number of erosions in the stomach and duodenum during aspirin therapy and the subsequent healing phase (up to day 15). Aspirin caused a significant increase in gastric mucosal injury on day 4 in all three treatment groups (p<0.05). All erosions had healed by day 15 in all three groups. There was no effect of bFGF or cimetidine on prevention or resolution of aspirin induced gastric mucosal injury. Aspirin pro-

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**Figure 2:** Healing of biopsy induced mini-ulcers. Eight biopsy specimens (A-H) were taken from the antrum on day 1. The number of unhealed biopsy induced mini-ulcers on days 4, 8, and 15 are shown for three treatment periods. Results are expressed as the median value (bold line), interquartile range (box), and data points within 1.5 times the 25th percentile (bars).

**Figure 3:** Relapse of biopsy induced mini-ulcers by indomethacin after treatment with (A) placebo, (B) bFGF or (C) cimetidine. Lines join the number of unhealed mini-ulcers before and after indomethacin therapy for individual volunteers. Previous treatment with placebo was associated with a significant increase in mini-ulcers (p<0.05) but there was no relapse of mini-ulcers if indomethacin followed bFGF or cimetidine therapy.

(0–3)) or cimetidine (0 (0–5) to 1 (0–3); Fig 3). Pairwise comparisons suggested that the mini-ulcer relapse rate was higher in the placebo group compared with bFGF and cimetidine groups although only at borderline levels of significance (p=0.09 and 0.06 respectively).
duced a significant increase in duodenal erosions but only in the placebo group (p<0.05). There was no discernable acceleration of healing of erosions by bFGF or cimetidine.

**Indomethacin induced gastric and duodenal erosions**

As shown in the Table, the number of gastric erosions tended to increase after indomethacin therapy but this was less than with aspirin and did not reach statistical significance in any of the treatment groups. Indomethacin caused an increase in duodenal erosions in all treatment groups although this only reached statistical significance after prior placebo ingestion (p=0.04).

**Ex vivo prostaglandin E₂ synthesis**

**Effect of drugs** – Aspirin considerably impaired gastric mucosal PGE₂ synthesis (28.0 (5.4) pg/mg (mean (SEM)) before aspirin v 3.0 (1.1) pg/mg after aspirin; p<0.005). Basic FGF and cimetidine had no effect on aspirin induced depression of PGE₂ synthesis. By day 15, PGE₂ synthesis returned to values similar to those measured before aspirin therapy (47.4 (13.2) pg/mg). Basic FGF and cimetidine therapy did not affect recovery of PGE₂ synthesis. Indomethacin reduced PGE₂ production by gastric mucosa significantly (19.7 (7.0) pg/mg; p<0.01) but not to the same degree as aspirin. Previous bFGF or cimetidine therapy did not abrogate the effect of indomethacin.

**Changes at the edge of mini-ulcers** – PGE₂ synthesis was measured in paired biopsy specimens from biopsy induced mini-ulcers and neighbouring intact mucosa on day 4 (after aspirin) and day 22 (after indomethacin). In all three groups, PGE₂ synthesis was increased at the site of a mini-ulcer compared with intact mucosa on day 4 despite aspirin therapy. However this only reached statistical significance when cimetidine was used (7.4 (2.5) pg/mg (mean (SEM)) mini-ulcer v 1.9 (0.9) pg/mg intact mucosa; p=0.03). Similarly, PGE₂ synthesis was increased at mini-ulcers compared with intact mucosa on day 22. There was a significant increase in PGE₂ synthesis only when bFGF had been given before indomethacin therapy (26.1 (10.6) pg/mg mini-ulcer v 12.7 (5.7) pg/mg intact mucosa; p=0.03).

**Serum thromboxane B₂ concentrations**

Aspirin caused a profound decrease in serum TXB₂ in all volunteers within all of the treatment periods (mean (SEM) TXB₂ 424.7 (51.1) ng/ml before aspirin v 0.9 (0.1) ng/ml after aspirin; p<0.0001). By day 15, TXB₂ concentrations had risen to pre-treatment values in every instance (mean (SEM) TXB₂ 523.7 (29.4) ng/ml, day 15; before indomethacin). Indomethacin therapy was also associated with a significant reduction in TXB₂ (mean (SEM) TXB₂ 90.6 (21.6) ng/ml, after indomethacin; p<0.0001 compared with the value before indomethacin).

**Adverse events**

There were few symptomatic adverse drug events. All were mild and did not necessitate cessation of drugs. Epigastric discomfort or a hungry sensation was noted during aspirin therapy in three volunteers. Two volunteers complained of headache during indomethacin therapy. Other adverse events included nausea (1), mouth ulcers (1), and one episode of self limiting diarrhoea and vomiting during cimetidine therapy. A pruritic, dry, scaly rash on the flexor aspect of both arms was noted by one volunteer during treatment with TGP-580 in the period between aspirin and indomethacin ingestion. During this time, TGP-580 was detected in serum (0.41 ng/ml; day 8 and 0.18 ng/ml; day 15). The rash resolved spontaneously after two weeks. There was no past history of skin rash nor did this lesion return during two subsequent treatment periods.

TGP-580 was not detected in any other serum sample taken during the study. Abnormalities in post-study blood investigations were noted in three cases. One female volunteer had a haemoglobin value of 11.4 g/dl (MCV 90 fl, before study 13.0 g/dl), one male volunteer had mild leucopenia (3.7X10⁹/l, before study 4.4X10⁹/l) but normal neutrophil and lymphocyte counts and one male volunteer had a slight reduction in neutrophil count (2.38 to 1.62X10⁹/l) without any significant change in total white cell count.

**Discussion**

In this study, we developed a model of gastric ulcer relapse, building on an earlier study of mini-ulcer healing and data from others. We used biopsy sites as mini-ulcers, which are distinguishable endoscopically from NSAID associated erosions and have a different natural history. In contrast with erosions, biopsy sites have discernable depth. Although the depth of the mucosal defect is limited, it is comparable with many NSAID associated gastric ulcers, which are often very superficial. Also we have previously shown that misoprostol accelerates healing of mini-ulcers, which is in agreement with clinical data on gastric ulcer healing in patients.

We used aspirin at the time of mini-ulcer formation so that we could pursue a secondary aim of investigating prevention and healing of aspirin induced erosions. However, our pri-
mary objective was to investigate the influence of the initial healing agent (bFGF or cimetidine) on subsequent mini-ulcer relapse after exposure to another NSAID. In this instance, we used indomethacin (which causes comparatively few gastric erosions\textsuperscript{27}), which was started two weeks after mini-ulcer formation, at which time, we expected complete healing of mini-ulcers.\textsuperscript{29} During the relapse phase, a total of 19 mini-ulcers relapsed in volunteers who had originally received placebo and who had completely healed gastric mucosa at the start of indomethacin treatment.

Unfortunately, interpretation is complicated by the fact that some subjects had unhealed mini-ulcers at the start of the relapse phase and that there were more unhealed mini-ulcers in the two active treatment groups than the placebo group at this time. However, these differences did not reach statistical significance and the number of unhealed mini-ulcers fell during exposure to indomethacin in the bFGF and cimetidine groups in contrast with the increase in mini-ulcers observed in the placebo group. These findings show that subsequent mini-ulcer relapse in humans varies according to the initial healing regimen. In future studies we intend to avoid the potential confounding issue of healing rate by using a longer healing period to ensure complete healing of mini-ulcers before the relapse phase.

The finding that previous treatment with bFGF and cimetidine protects against indomethacin induced relapse of mini-ulcers confirms data obtained using a rat model of gastric ulcer relapse (Satoh H, personal communication).

We have shown that healing with bFGF is associated with increasing PGE\textsubscript{2} synthesis in mini-ulcers after indomethacin therapy. There is evidence that PGE\textsubscript{2} is angiogenic in vivo\textsuperscript{28} and controls gastric epithelial cell proliferation.\textsuperscript{29} Basic FGF promotes its own synthesis in cell culture experiments\textsuperscript{30} and there is evidence that bFGF promotes synthesis of the inducible form of cyclooxygenase.\textsuperscript{31} Therefore the effects of bFGF may continue after stopping ingestion. It can be proposed that bFGF improves quality of healing and renders healed mucosa less susceptible to recurrent breakdown by promoting angiogenesis or increasing prostaglandin mediated cytoprotection, or both. The mechanism of action of cimetidine in this instance is less clear. However there are data suggesting that cimetidine may have an immunomodulatory action distinct from other H\textsubscript{2} receptor antagonists\textsuperscript{32 33} and ‘cytoprotective’ properties\textsuperscript{34} and this could explain an alteration of healing mechanisms or increased mucosal resistance to further injury, or both. It should be noted that the cimetidine data are most confounded by the number of unhealed mini-ulcers present at the start of the relapse phase, in that statistical analysis rules out a carry over effect of either bFGF or cimetidine as the explanation for the observed drug effects.

Basic FGF (and cimetidine) did not accelerate healing of biopsy induced mini-ulcers in this study. A possible explanation is that the time course of healing of biopsy induced mini-ulcers is too short to show any drug effect.

Aspirin induced upper gastrointestinal injury is a well established model in studies with healthy volunteers. Gastric and duodenal injury produced by aspirin in this study was similar to that seen in previous studies using aspirin. Therefore it is unlikely that NaHCO\textsubscript{3} treatment in itself (used here to increase intra-gastric bFGF stability) reduced aspirin induced injury. Moreover, the neutralising activity of NaHCO\textsubscript{3}, used in this study was 20 mEq/day which is significantly lower than reported neutralising activity required for peptic ulcer healing (%120 mEq/day).\textsuperscript{17} Aspirin caused profound inhibition of platelet cyclooxygenase-1 in all cases but serum TxB\textsubscript{2} concentrations returned to pre-treatment values before indomethacin therapy and before each new treatment period ruling out any possible carry over effect of aspirin or indomethacin.

The lack of protection against aspirin induced gastric injury by bFGF in this model was in agreement with the lack of effect of subcutaneous bFGF in an acidified aspirin induced injury model in rats.\textsuperscript{35 36} In view of the known actions of bFGF (for example, angiogenesis), this is not surprising; exogenous bFGF would be expected to promote the healing phase of mucosal lesions.\textsuperscript{37} However bFGF (and cimetidine) afforded some protection against aspirin and indomethacin induced duodenal injury, which has not been reported in animal studies. Basic FGF promotes restitution of frog gastric mucosa in vitro\textsuperscript{38} and IEC-6 cell monolayers,\textsuperscript{38} which could explain a cytoprotective action of bFGF in humans.

In this study, adverse drug events were uncommon and not serious. Dyspepsia related to aspirin therapy is well recognised\textsuperscript{25} as is headache with indomethacin.\textsuperscript{39} Unlike previous studies,\textsuperscript{17 40} TGP-580 was detected in serum of one volunteer who developed a rash. Severe gastroduodenal mucosal injury (which could have increased mucosal permeability to TGP-580) was not seen in this instance. There was no evidence of systemic absorption of TGP-580 in any other volunteer.

In summary, we have used biopsy induced mini-ulcers as a model of gastric ulcer in healthy volunteers and showed that previous treatment with both bFGF and cimetidine reduces indomethacin induced relapse of such lesions. There was a small protective effect of bFGF and cimetidine on aspirin and indomethacin induced duodenal (but not gastric) injury. Treatment with bFGF for two weeks was safe but was detected in serum of one volunteer and may have caused a skin rash. Further studies of the effect of bFGF on quality of ulcer healing are required to confirm that bFGF therapy reduces future ulcer relapse. The use of indomethacin may find a role as an adjuvant to treatment with an acid suppressing agent. A combination of these two drugs could promote early ulcer healing and reduce future ulcer relapse rate after treatment is stopped.

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