

## Omeprazole versus placebo for acute upper gastrointestinal bleeding: randomised double blind controlled trial

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### Abstract

**Objective**—To investigate the possible therapeutic role of omeprazole, a powerful proton pump inhibitor, in unselected patients presenting with upper gastrointestinal bleeding.

**Design**—Double blind placebo controlled parallel group study. Active treatment was omeprazole 80 mg intravenously immediately, then three doses of 40 mg intravenously at eight hourly intervals, then 40 mg orally at 12 hourly intervals. Treatment was started within 12 hours of admission and given for four days or until surgery, discharge, or death.

**Setting**—The medical wards of University and City Hospitals, Nottingham.

**Subjects**—1147 consecutive patients aged 18 years or more admitted over 40 months with acute upper gastrointestinal bleeding.

**Main outcome measures**—Mortality from all causes; rate of rebleeding, transfusion requirements, and operation rate; effect of treatment on endoscopic appearances at initial endoscopy.

**Results**—Of 1147 patients included in the intention to treat analysis, 569 received placebo and 578 omeprazole. No significant differences were found between the placebo and omeprazole groups for rates of transfusion (302 (53%) placebo *v* 298 (52%) omeprazole), rebleeding (100 (18%) *v* 85 (15%)), operation (63 (11%) *v* 62 (11%)), and death (30 (5.3%) *v* 40 (6.9%)). However, there was an unexpected but significant reduction in endoscopic signs of upper gastrointestinal bleeding in patients treated with omeprazole compared with those treated with placebo (236 (45%) placebo *v* 176 (33%) omeprazole;  $p < 0.0001$ ).

**Conclusions**—Omeprazole failed to reduce mortality, rebleeding, or transfusion requirements, although the reduction in endoscopic signs of bleeding suggests that inhibition of acid may be capable of influencing intragastric bleeding. Our data do not justify the routine use of acid inhibiting drugs in the management of haematemesis and melaena.

### Introduction

Acute upper gastrointestinal bleeding continues to be an important reason for admission to hospital. Up to 20% of patients require surgery and 10% may die.<sup>1-3</sup> Trials of medical treatments aimed at reducing mortality and morbidity from upper gastrointestinal bleeding have been largely unrewarding. Large trials have shown no clear reduction in reducing all cause mortality with various ulcer healing drugs including histamine H<sub>2</sub> receptor antagonists,<sup>4,5</sup> fibrinolytic inhibitors such as tranexamic acid,<sup>6</sup> and drugs with known actions at multiple sites in the gastrointestinal tract such as somatostatin.<sup>12</sup> However, meta-analyses of data from published trials have suggested that histamine H<sub>2</sub> receptor antagonists<sup>8</sup> and fibrinolytic

inhibitors<sup>11</sup> may confer therapeutic benefit. Histamine H<sub>2</sub> receptor antagonists seem to reduce rates of rebleeding, operation, and death by about 10%, 20%, and 30% respectively.<sup>8</sup> These observations suggest that inhibition of gastric acid secretion may be capable of influencing outcome. We therefore examined the hypothesis that profound suppression of gastric acid secretion with the proton pump inhibitor omeprazole decreases morbidity and mortality from acute upper gastrointestinal bleeding.

Omeprazole is the first available benzimidazole proton pump inhibitor with the capacity effectively to abolish acid secretion.<sup>14</sup> We have shown that a regimen of high dose intravenous omeprazole causes a rapid and profound inhibition of acid secretion.<sup>15</sup> We report the results of a randomised double blind placebo controlled clinical trial of its effectiveness in patients presenting with haematemesis or melaena.

### Patients and methods

We examined the death, rebleeding, and operation rates and transfusion requirements in patients admitted to University and City Hospitals, Nottingham, with upper gastrointestinal bleeding between May 1986 and November 1989. Rebleeding was defined as overt haematemesis; passage of fresh blood from the rectum; a fall in haemoglobin concentration of more than 20 g/l within any 24 hour period after the first 24 hours; shock in the presence of continuing melaena; or the presence of fresh blood in the stomach or duodenum, or both, at repeat endoscopy when further bleeding was suspected.

All patients with overt upper gastrointestinal bleeding or a history of haematemesis or melaena, or both, within 24 hours preceding admission were eligible for entry into the study provided they did not meet any of the exclusion criteria. These criteria were age below 18 years; pregnant; the presence of severe physical illness making active treatment according to the protocol inappropriate (for example, terminal disease or advanced malignancy); bleeding of such severity that immediate surgery was indicated; trivial bleeding such that active management was unnecessary; bleeding developing in patients who had been admitted to hospital for other reasons; previous participation in the study; inability to start treatment within 12 hours of admission; and potential for drug interactions—for example patients taking phenytoin and warfarin. Ethical approval was obtained from the Nottingham hospitals ethics committees. Wherever possible eligible patients gave verbal consent to inclusion in this study and patients who were unwilling to participate were not enrolled. Consent was not sought from patients who were too unwell to understand the study's aims.

### TREATMENT

Each treatment pack contained four intravenous

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doses and six oral doses of omeprazole or matching placebo. The treatments were randomised in blocks of 10. The intravenous formulation was supplied as a freeze dried compound and solvent in a twin pack vial and ampoule combination. Immediately before use 10 ml of the solvent (40% polyethylene glycol 400 and phosphate buffer in water) was added to the freeze-dried compound and thoroughly mixed. The intravenous placebo was mannitol, which appears identical to freeze-dried omeprazole and was given in an identical fashion. Injections were given over five minutes. Oral omeprazole 40 mg was given as two hard gelatin capsules each containing 20 mg as enteric coated granules. The oral placebo was identical in appearance.

The trial was double blind. Patients were considered for entry immediately after admission to hospital and were given trial treatment without endoscopic confirmation of bleeding or its site. Each patient was given omeprazole 80 mg or placebo intravenously as soon as possible after admission. A second intravenous dose of omeprazole 40 mg or placebo was given between four and 11 hours later. The interval was varied in order to synchronise subsequent dosing schedules. Two further intravenous doses of omeprazole 40 mg or placebo were given at eight hourly intervals, followed by six oral doses of omeprazole 40 mg or placebo given at 12 hourly intervals over three days. Treatment was continued (whether or not rebleeding occurred) for up to 101 hours or until operation, death, or discharge. Thereafter subsequent treatment was at the discretion of the managing physician.

#### ENDOSCOPY AND CLINICAL MANAGEMENT

Endoscopy was generally performed within 24 hours of admission, but gastroenterologists at both hospitals were available on a 24 hour basis for earlier endoscopy in patients whose clinical condition required it. Endoscopists were asked to record the presence or absence of signs predictive of rebleeding: blood in the stomach, red clot on lesion, active bleeding, black spots on lesion, visible vessel. Endoscopic treatment of bleeding such as injection of varices was allowed at the discretion of the endoscopist.

Patients were cared for by the admitting medical team, who made decisions about clinical management, blood transfusion, and surgery. Patients were managed in general medical wards or in a high dependency unit, depending on the severity of bleeding. Gastroenterologists in both hospitals were available for advice but did not enter into the primary management of patients other than those initially admitted under their care. Concurrent treatment with histamine H<sub>2</sub> receptor antagonists, bismuth chelate, carbenoxolone, or sucralfate was not allowed but on completion of the study treatment further drugs could be given at the discretion of the supervising physician. Non-steroidal anti-inflammatory drugs and aspirin were stopped on admission to hospital.

#### CRITERIA FOR STOPPING TREATMENT

Trial treatment was stopped and the patient withdrawn if the patient was considered not to have had upper gastrointestinal bleeding; severe medical problems developed that necessitated breaking the treatment code; the patient was unwilling to continue in the study; or there was non-compliance with the study protocol. Interim analyses of overall mortality, based on the O'Brien and Fleming procedure for group sequential tests,<sup>16</sup> were performed by an independent statistician after 200 and 500 patients had completed the trial in order to screen for unsuspected hazards associated with omeprazole.

#### REVIEW OF DEATHS

A final diagnosis was assigned to each patient at

death or discharge on the basis of details available in the clinical record form. In addition, the hospital records and necropsy reports of all patients who had died during the trial were reviewed by RFAL and CJH to confirm the cause of upper gastrointestinal bleeding and assess the contribution bleeding had made to death. This review was carried out before the randomisation code was broken. Deaths were categorised as follows. (1) Upper gastrointestinal bleeding was the direct cause of death, as shown by continued melaena, haematemesis, fall in haemoglobin concentration, etc, and including cardiac arrest when haemoglobin <80 g/l. (2) Upper gastrointestinal bleeding caused hospital admission but subsequently had stopped or become trivial. Death from medical complications (for example, pneumonia). (3) Death after surgery had controlled bleeding. (4) Death during or after surgery which had not controlled bleeding. (5) Upper gastrointestinal bleeding was incidental to the condition leading to death (for example, death from stroke secondary to pre-existing thrombocytopenia). (6) Significant upper gastrointestinal bleeding never shown—normal appearance on endoscopy and no fall in haemoglobin concentration. This included deaths where bleeding was shown to arise from beyond the duodenum. Some of these patients were classified as "other" or "cause unclear" in the primary endoscopic diagnosis and whose final diagnosis was based on review of case records. (7) Death where gastroduodenal perforation followed bleeding. (8) Others—causes of death not classified above (for example, carcinoma of pancreas).

Deaths were categorised according to whether the cause of bleeding was from duodenal ulceration, gastric ulceration, gastric erosions, oesophageal ulceration or oesophagitis, gastric cancer, oesophageal varices, abnormalities distal to the descending duodenum, and other or unknown causes.

#### STATISTICAL ANALYSIS

All study variables were analysed according to intention to treat. Main variables were also analysed by the per protocol approach, in which patients violating the protocol regulations were excluded. All decisions on exclusion of patients from analysis were taken before breaking the treatment code.

Mortality in all patients and in the subgroup of patients with confirmed upper gastrointestinal bleeding and in those with gastric and duodenal ulcers was analysed. The associations between trial treatment, treatment centre, age ( $\leq 54$ , 55-64,  $> 64$  years), initial systolic blood pressure ( $\leq 100$ ,  $> 100$  mm Hg), and bleeding site (gastric ulcer, duodenal ulcer, other) and rebleeding, operation, and death were examined.

The proportion of patients with each outcome (death, operation, etc) was analysed with the Mantel-Haenszel test stratified by centre.<sup>17</sup> Continuous variables were tested by Wilcoxon tests stratified by centre. Confidence intervals for proportions were calculated by using the standard normal approximation. The effect of possible prognostic factors on binary variables (mortality, operation, and rebleeding) was analysed by logistic regression models.<sup>17</sup> The sample size (1100 patients) was based on an assumption of a reduction of mortality from all causes by omeprazole from 10% to 5% ( $\alpha=0.05$ ,  $1-\beta=0.8$ , two tailed significance).<sup>18</sup>

#### Results

We randomised 1154 patients into the study. Four of these patients were not given the study treatment (one omeprazole group, three placebo group) and in three the treatment given could not subsequently be clearly identified. The remaining 1147 patients were successfully randomised to receive omeprazole ( $n=578$ )

or placebo (n=569). Of these, 698 patients were admitted to University Hospital and 449 to City Hospital. Table I shows that the treatment groups were well matched for possible prognostic features. Most (1063) patients were examined by endoscopy; 937 were examined within the first 24 hours. The commonest reason for endoscopy not being performed was the need for urgent surgery. The groups were well matched for time of endoscopy and for amount of treatment received. There were 98 protocol violations (62 patients were prescribed concomitant H<sub>2</sub> antagonists, 18

entered the trial for a second time, 15 started treatment more than 12 hours after admission, and three were under age or possibly pregnant) leaving 529 on placebo and 520 on omeprazole available for per protocol analysis. Table II shows the primary endoscopic and final diagnoses: the distribution of disease randomised to each treatment was similar.

#### CLINICAL OUTCOME

Table III shows the outcome in patients analysed by intention to treat. Patients receiving omeprazole had slightly lower transfusion requirements and rebleeding rates than control patients, but these differences were not significant. Moreover, the death rate was slightly higher in patients who received omeprazole (6.9%) compared with those treated with placebo (5.3%), though the difference was not significant.

Table III also shows the outcome in 1049 patients included in the per protocol analysis. Results in these patients were similar to those obtained in the intention to treat analysis. Results in the 945 patients with confirmed upper gastrointestinal bleeding (477 omeprazole, 468 placebo) also showed a similar pattern of results. In this group 29 (6.1%; 95% confidence interval 4.0% to 8.2%) of those who received omeprazole and 23 (4.9%; 2.9% to 6.9%) of those who received placebo died (NS). Table IV shows that the pattern of results in patients with peptic ulcers was also generally similar to that seen in the group as a whole. There was an excess of deaths in patients with duodenal ulcer treated with omeprazole rather than placebo (16 v eight), but this difference was not significant. A total of 155 patients (73 omeprazole group, 82 placebo group) was taking aspirin or non-aspirin non-steroidal anti-inflammatory drugs. Of these, 91 had ulcers (41 omeprazole group, 50 placebo group). Sixteen (10%) of the 155 patients died (nine in omeprazole group, seven in placebo group). All but two of the patients taking non-steroidal anti-inflammatory drugs who died had peptic ulcers. Of patients with oesophageal varices, three who received omeprazole and three who received placebo died. Thirty nine patients received endoscopic treatment (15 in omeprazole group, 17 in placebo group); treatment was of variceal sclerotherapy (20 patients) or treatment of ulcer bleeding by diathermy, heater probe, or sclerotherapy (11 with duodenal ulcer, four with gastric ulcer). Five of the patients who received endoscopic treatment died (three in omeprazole group, two in placebo group).

#### ADJUSTMENT FOR AGE AND OTHER PROGNOSTIC FACTORS

The group treated with omeprazole were slightly older than the placebo treated group (table I). Standardising the mortality according to the bands in table I resulted in a small reduction in mortality in the omeprazole group to 6.7% (95% confidence interval 4.6% to 8.8%) with no change in the placebo group at 5.3% (3.4% to 7.3%).

Logistic regression was used to analyse the combined effects of age, initial systolic blood pressure, bleeding site, centre, and treatment group on rates of rebleeding, operation, and death. For all three outcomes increasing age ( $p < 0.0001$ ) and a low initial systolic blood pressure ( $p < 0.001$ ) were the strongest prognostic factors. The presence of a gastric or duodenal ulcer was a significant factor for rebleeding ( $p < 0.01$ ) and operation ( $p < 0.005$ ) but not for death ( $p = 0.12$ ). The treatment centre was unrelated to all three outcomes. Relations between treatment groups and rebleeding ( $p = 0.10$ ), operation ( $p = 0.64$ ), or mortality ( $p = 0.33$ ) were not significant.

#### RESULT OF ENDOSCOPY

In contrast with the results concerning rates of rebleeding, operation, and death, treatment with

TABLE I—Demographic details of patients randomised to receive placebo or omeprazole for upper gastrointestinal bleeding

	Placebo group	Omeprazole group
No of patients	569	578
M/F	354/215	375/203
Mean (SD) age	59 (19)	60 (19)
Mean (SD) systolic blood pressure	129 (26)	127 (25)
Mean (SD) pulse	90 (16)	91 (16)
Mean (SD) haemoglobin	11 (3)	11 (3)
No (%) with haemoglobin <100 g/l	188 (33)	192 (33)
No (%) with:		
Haematemesis	395 (69)	402 (70)
Melaena	324 (57)	309 (53)
Previous peptic ulcer	146 (26)	152 (26)
Previous upper gastrointestinal bleeding	117 (21)	135 (23)
Previous gastric surgery	37 (7)	35 (6)
No (%) given endoscopic treatment	16 (3)	21 (4)
No (%) aged (years):		
<60	243 (43)	233 (40)
60-74	197 (35)	191 (33)
≥75	129 (23)	154 (27)

TABLE II—Primary endoscopic and final diagnoses by treatment group. Figures are numbers (percentages) of patients

	Initial diagnosis		Final diagnosis	
	Placebo group (n=569)	Omeprazole group (n=578)	Placebo group (n=569)	Omeprazole group (n=578)
Ulcers	262 (46)	250 (43)	280 (49)	274 (47)
Oesophageal	23 (4)	31 (5)	23 (4)	28 (5)
Gastric	85 (15)	87 (15)	93 (16)	97 (17)
Duodenal	154 (27)	132 (23)	164 (29)	149 (26)
Erosive disease	102 (18)	123 (21)	99 (17)	120 (21)
Oesophagitis or hiatus hernia	51 (9)	66 (11)	49 (9)	62 (11)
Gastritis	43 (8)	40 (7)	42 (7)	40 (7)
Duodenitis	8 (1)	17 (3)	8 (7)	18 (3)
Mallory-Weiss tears	17 (3)	18 (1)	20 (4)	19 (3)
Oesophageal varices	16 (3)	12 (2)	16 (3)	13 (2)
Carcinoma of stomach	1 (<1)	6 (1)	7 (1)	11 (2)
Leiomyoma	1 (<1)	2 (<1)	1 (<1)	2 (<1)
Vascular lesion		1 (<1)		1 (<1)
Normal/no bleed/cause unclear	104 (18)	99 (17)	108 (19)	99 (17)
Other	22 (4)	23 (4)	38 (7)	39 (7)
Endoscopy not done*	44 (8)	44 (8)		

\*For most patients in whom endoscopy was not done the final diagnosis was based on clinical and operative information available at the time of discharge or death.

TABLE III—Clinical outcomes in patients with upper gastrointestinal bleeding. Figures are numbers (percentages) of patients unless stated otherwise

	Intention to treat analysis		Per protocol analysis	
	Placebo group (n=569)	Omeprazole group (n=578)	Placebo group (n=529)	Omeprazole group (n=520)
Rebleeding	100 (18)	85 (15)	91 (17)	77 (15)
Transfusion	302 (53)	298 (52)	279 (53)	263 (51)
Transfusion of ≥3 units of blood	237 (42)	226 (39)	217 (41)	202 (39)
Operation	63 (11)	62 (11)	57 (11)	56 (11)
Median time to discharge (days)	6	5	6	5
Death	30 (5.3)	40 (6.9)	29 (5.5)	35 (6.7)
Difference (95% confidence interval) in death rate (omeprazole-placebo)	1.6% (-1.2% to 4.4%)		1.2% (-1.7% to 4.1%)	

TABLE IV—Number (percentage) of patients with peptic ulcers with various clinical outcomes

	Gastric ulcer		Duodenal ulcer	
	Placebo group (n=93)	Omeprazole group (n=97)	Placebo group (n=164)	Omeprazole group (n=149)
Rebleeding	23 (25)	26 (27)	47 (29)	32 (21)
Operation	16 (17)	18 (19)	34 (21)	27 (18)
Death	5 (5)	7 (7)	8 (5)	16 (11)

omeprazole was associated with a highly significant reduction in the incidence of endoscopic signs of bleeding (table V). Patients who received omeprazole had lower rates of blood in the stomach, active bleeding, red clot on the lesion, and black spots on the lesion than patients receiving placebo.

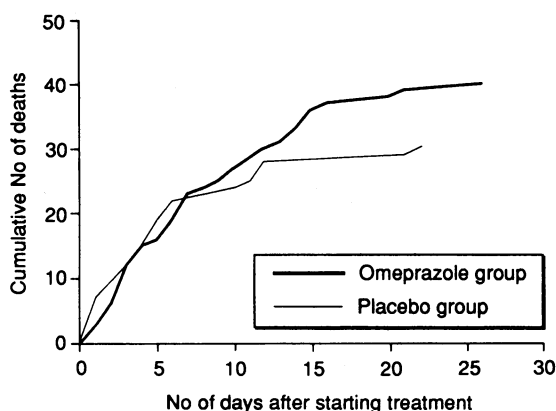
TABLE V—Number (percentage) of patients with signs of bleeding on endoscopy

	Placebo group (n=525)	Omeprazole group (n=534)	p Value
Any sign	236 (45)	176 (33)	<0.0001
Blood in stomach	131 (25)	107 (20)	
Red clot on lesion	115 (22)	85 (16)	
Active bleeding	73 (14)	53 (10)	
Black spots on lesion	58 (11)	39 (7)	
Visible vessel	16 (3)	22 (4)	

Some patients had more than one sign.

#### POSTOPERATIVE AND LATE DEATHS

On an intention to treat basis 20 of the 40 patients treated with omeprazole who died did so after surgery compared with six of 30 patients given placebo (table VI). The difference in postoperative death rates (20 out of 62 patients given omeprazole who had operations versus six out of 63 patients given placebo) was significant ( $p=0.004$ ). Twelve patients treated with omeprazole died after surgical control of bleeding compared with four who received placebo. This included nine who received omeprazole and four who received placebo with bleeding from ulcers, erosions, or oesophagitis. Nine of the patients in the omeprazole group who died had cancer (four gastric, four colonic, one cervix) compared with only two in the placebo group (one gastric, one colonic). Lower gastrointestinal bleeding accounted for five deaths in the omeprazole group versus none in the placebo group. Recipients of omeprazole also seemed to have had somewhat more complex operations; 14 patients had gastrectomies (versus eight in placebo group) and five had colectomies (versus none in placebo group). These differences probably explain the larger number of patients in the omeprazole group (24 versus 11 in placebo group) who died on or after day 6 of admission (figure).



Cumulative mortality for patients with upper gastrointestinal bleeding treated with placebo and omeprazole

TABLE VI—Cause of upper gastrointestinal bleeding and role in patients' death after review

Role of bleeding in death (review categories)	Duodenal ulcer, gastric ulcer, erosions, and oesophagitis		Gastric cancer		Varices		Cause not known/bleeding not confirmed		All patients		Postoperative deaths	
	Placebo	Omeprazole	Placebo	Omeprazole	Placebo	Omeprazole	Placebo	Omeprazole	Placebo	Omeprazole	Placebo	Omeprazole
Continued bleeding (1, 4)	8	7	1	1	3	3	0	0	12	11	1	2
Medical complications (2)	3	4	0	0	0	0	2	2	5	6	1	0*
Died after surgery had controlled bleeding (3)	4	9	0	2	0	0	0	1	4	12	4	12
Bleeding incidental or not demonstrated (5, 6, 7, 8)	4	3	0	1	0	0	5	7	9	11	0	6
Total	19	23	1	4	3	3	7	10	30	40	6	20

\*One patient died after laparotomy for mesenteric embolus after stopping warfarin because of a bleeding gastric ulcer.

There was no evidence of any toxic effect of omeprazole in the form of altered liver function, unexpected hepatic or renal failure, or sudden unexpected death, and careful review showed no particular pattern of events preceding death in the omeprazole group. No individual anaesthetic drug was associated with the excess mortality in the omeprazole group.

#### Discussion

We found no reduction in mortality in unselected patients presenting with upper gastrointestinal bleeding who were given omeprazole. There were no significant differences in the rates of rebleeding or operation or transfusion requirements between the two groups. However, the overall death rate of 6% was nearly half that expected. Confidence intervals were consistent with the possibility of a real but undetected benefit as well as possible harm caused by treatment. Moreover, patients treated with omeprazole were by chance more likely to die postoperatively, to have cancer, or to be bleeding from the lower gut than those treated with placebo.

Treatment with omeprazole was associated with a significant reduction in active bleeding and other signs evident at endoscopy. This was unexpected as changes in endoscopic signs had not been seen in patients given active treatment in previous studies in Nottingham.<sup>4,10</sup> For example, in a similarly designed study of cimetidine and tranexamic acid 25% of patients receiving placebo, 26% of those receiving cimetidine, and 29% of those receiving tranexamic acid had blood in the stomach at endoscopy.<sup>4</sup> In the present study the rate for active bleeding in the placebo group (25.1%) was very similar, suggesting that the patient cohort was similar to those we have previously studied. Changes in endoscopic signs were not selected as an end point before the trial and reduction in such signs could be a chance finding. Nevertheless, the probability that a reduction of this size would be observed by chance is less than one in 10 000, making it likely that the reduction was a consequence of drug treatment. In preliminary dose ranging studies before starting this study we showed that the regimen chosen for the study increased median pH to >4 within 1 hour in patients with duodenal ulcers,<sup>15</sup> so a reduction in endoscopic signs of bleeding is plausible.

As in previous studies,<sup>19,21</sup> patients with signs of recent haemorrhage were more likely to have rebleeding than those without, and this was seen in both treatment groups. Despite early reductions in signs of bleeding with omeprazole mortality was not reduced. This raises the possibility that the high doses of omeprazole that we were using might be toxic and obscure a beneficial effect of omeprazole on mortality. Since the excess of deaths in the omeprazole group occurred in postoperative patients, an interaction with anaesthetic drugs, leading to hepatic or renal failure might account for the deaths, but we found no evidence of this. In patients in intensive care units raised intragastric pH has been reported to be associ-

ated with the development of pneumonia.<sup>22,23</sup> Review of the notes of patients who died showed no evidence suggesting an excess of pneumonia in patients taking omeprazole, although this may have been missed as the study was not specifically designed to detect this.

#### DIFFERENCES BETWEEN OMEPRAZOLE AND PLACEBO GROUPS

In theory improved endoscopic appearances in patients receiving omeprazole might delay operation, and this could explain the apparent increase in post-operative deaths of patients with ulcers, erosions, or oesophagitis. However, there was no difference in the timing of operation in these patients. Much of the increased postoperative mortality in patients taking omeprazole was attributable to more patients dying of cancer or lower gastrointestinal bleeding—diagnoses not likely to be affected by treatments aimed at elevating intragastric pH. Some of these patients had “open and shut” laparotomies, whereas others had delayed operations for lower gastrointestinal lesions, which nevertheless caused death within the 40 days of our study protocol. It seems more likely that the excess postoperative deaths in these patients occurred by chance rather than as a result of a (theoretical and unspecified) harmful effect of omeprazole on patients with cancer or lower gastrointestinal lesions. Patients on omeprazole also tended to have more complex operations than those receiving placebo, which could have affected later outcome. It is equally difficult to decide whether the increased proportion of deaths in patients with duodenal ulcer who received omeprazole has implications. We have seen similar trends in previous studies using other drugs<sup>4,10</sup> so the possibility that acid suppression is harmful in one specific subgroup of patients may deserve further investigation.

Our study illustrates some of the problems of investigating treatments intended to reduce the mortality from haematemesis and melaena. As well as the differences between the two groups in the causes of death, the study lacked the statistical power that was intended. Despite an aging population with a pattern of underlying disease and severity of bleeding comparable with that seen in our previous studies,<sup>4,10</sup> the mortality from haematemesis and melaena was significantly lower than in our earlier studies. This means that, despite being the largest trial of treatment of upper gastrointestinal bleeding reported, it was still too small to detect changes in mortality of clinical relevance. The confidence intervals for the effect of omeprazole could still be compatible with a 30% reduction in death rate. Such a reduction would be of clinical interest, but to detect a reduction in mortality from 6% to 4% with 80% power a trial of over 4200 patients would be required. The fall in mortality seen in our patients is similar to changes attributed by others to the use of purpose built units with dedicated teams.<sup>2,6,24,25</sup> Our data suggest that background changes, such as possible improved fitness of elderly patients,<sup>26</sup> may be more important.

The administration of acid inhibiting drugs to patients with haematemesis and melaena remains widespread despite a lack of evidence for their value. Our failure to show a beneficial effect on clinically important end points with an inhibitor as potent as omeprazole is further evidence that this practice is unjustified. The interesting observation that omeprazole is associated with reductions in endoscopic signs of bleeding warrants further investigation but does not

support the use of acid inhibition since there is no evidence yet that a reduction in endoscopic stigmata is of clinical benefit.

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- 1 Allan R, Dykes P. A study of the factors influencing mortality rates from gastrointestinal haemorrhage. *Q J Med* 1976;45:533-50.
- 2 Hunt PS, Hansky J, Korman MG. Mortality in patients with haematemesis and melaena; a prospective study. *BMJ* 1979;i:1239-40.
- 3 Silverstein FE, Gilbert DA, Tedesco FJ, Buenger NK, Persing J. The national ASGE survey on upper gastrointestinal bleeding. II. Clinical prognostic features. *Gastrointest Endosc* 1981;27:80-93.
- 4 Barer D, Ogilvie A, Henry D, Dronfield M, Coggon D, French S, et al. Cimetidine and tranexamic acid in the treatment of acute upper gastrointestinal bleeding. *N Engl J Med* 1983;308:1571-5.
- 5 Walt RP, Cottrell J, Mann SG, Freemantle N, Langman MJS. Randomised, double blind, controlled trial of intravenous famotidine infusion in 1005 patients with peptic ulcer bleeding. *Gut* 1991;32:A571-2.
- 6 Fleischer D. Etiology and prevalence of severe persistent upper gastrointestinal bleeding. *Gastroenterology* 1983;84:539-43.
- 7 Morris DL, Hawker PC, Brearly S, Simms M, Dykes PW, Keighley MRB. Optimal timing of operation for bleeding peptic ulcer: prospective randomised trial. *BMJ* 1984;288:1277-80.
- 8 Collins R, Langman M. Treatment with histamine H<sub>2</sub> antagonists in acute upper gastrointestinal haemorrhage. Implications or randomised trials. *N Engl J Med* 1985;331:660-6.
- 9 Bordley DR, Mushlin AI, Dolan JG, Richardson WS, Barry M, Polio J. Early clinical signs identify low risk patients with acute upper gastrointestinal haemorrhage. *JAMA* 1985;253:3282-5.
- 10 Somerville KW, Henry DA, Davies JG, Hine KR, Hawkey CJ, Langman MJS. Somatostatin in treatment of haematemesis and melaena. *Lancet* 1985;i:130-2.
- 11 Henry DA, O'Connell DL. Effects of fibrinolytic inhibitors on mortality from upper gastrointestinal haemorrhage. *BMJ* 1989;298:1142-6.
- 12 Christiansen J, Ottenjann R, Arx FV. Placebo-controlled trial with the somatostatin analogue SMS 201-995 in peptic ulcer bleeding. *Gastroenterology* 1989;97:568-74.
- 13 Peterson WL. Pharmacotherapy of bleeding peptic ulcer—is it time to give up the search? *Gastroenterology* 1989;97:796-7.
- 14 Clissold SP, Campoli-Richards DM. Omeprazole. An updated review. *Drugs* 1988;34:1-41.
- 15 Walt RP, Reynolds JR, Langman MJS, Smart HL, Kitchingman G, Somerville KW, et al. Intravenous omeprazole rapidly raises intragastric pH. *Gut* 1985;26:902-6.
- 16 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
- 17 Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research*. Belmont, California: Lifetime Learning Publications, 1982:419-75.
- 18 Fleiss JL. *Statistical methods for rates and proportions*. 2nd ed. New York: John Wiley and Sons, 1981:173-5.
- 19 Foster DN, Miloszewski KJA, Losowsky MS. Stigmata of recent haemorrhage in diagnosis and prognosis of upper gastrointestinal bleeding. *BMJ* 1978;ii:1173-7.
- 20 Griffiths WJ, Neumann D, Welsh JD. The visible vessel as an indicator of uncontrolled or recurrent gastrointestinal haemorrhage. *N Engl J Med* 1979;300:1411-3.
- 21 Storey DW, Bown SG, Swain PC, Salmon PR, Kirkham JS, Northfield TC. Endoscopic prediction of recurrent bleeding in peptic ulcers. *N Engl J Med* 1981;305:915-6.
- 22 Driks MR, Craven DE, Celli RC, Manning M, Burke RA, Garvin GM, et al. Nosocomial pneumonia in intubated patients given sucralofate as compared with antacids or histamine type 2 blockers. The role of gastric colonisation. *N Engl J Med* 1987;317:1376-82.
- 23 Garvey BM, McCambley JA, Tuxen DV. Effects of gastric alkalinisation on bacterial colonisation in critically ill patients. *Crit Care Med* 1989;17:211-6.
- 24 Holman RAE, Davis M, Gough KR, Gartell P, Britton DC, Smith RB. Value of a centralised approach in the management of haematemesis and melaena: experience in a district general hospital. *Gut* 1990;31:504-8.
- 25 Sanderson JD, Foley N, Vicary FR. Optimising patient care in upper gastrointestinal haemorrhage: specialised units are the answer. *Gut* 1990;31:A1206.
- 26 Jagger C, Clarke M, Clarke SJ. Getting older—feeling younger: the changing health profile of the elderly. *Int J Epidemiol* 1991;20:234-8.

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## Correction

### Risk of epilepsy after febrile convulsions: a national cohort study

Several authors' errors occurred in table II of this paper by C M Verity and Jean Golding (30 November, p 1373). In the first column of table II the number of children who had tonic-clonic seizures who had not had febrile convulsions should have been 32; the number of tonic-clonic seizures expected in children who had febrile convulsions should have been 0.9; and the number observed/expected should have been 11.