Cimetidine therapy does not prevent rebleeding from peptic ulceration

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Summary

One-hundred and five patients admitted to hospital with symptoms of acute upper gastrointestinal haemorrhage shown at endoscopy to be due to peptic ulceration were entered into a prospective double-blind controlled trial of cimetidine versus placebo therapy. The trial therapy was commenced within 12 hr of admission and continued for 7 days. Cimetidine therapy made no difference to the transfusion requirements, rebleeding rate or number of operations performed in patients with either gastric or duodenal ulcers, nor was it of benefit in patients aged over 65 years of age.

KEY WORDS: gastric ulcer, duodenal ulcer, aspirin, vagotomy, pyloroplasty.

Introduction

The majority of patients with acute upper gastrointestinal haemorrhage will stop bleeding spontaneously after admission to hospital. There is, however, still an overall mortality of up to 10%, most marked in the elderly and those who rebleed after admission (Allen and Dykes, 1976). Following rebleeding, surgical mortality may be as high as 28.8% compared with 7.8% in those who do not rebleed (Jones *et al.*, 1973). Therapy that reduced the incidence of rebleeding would therefore be expected to lower mortality substantially.

Raising intragastric pH reduces local fibrinolysis and increases platelet aggregation (Green *et al.*, 1978) and provides a possible basis for the prevention of rebleeding. Oral antacid administration in doses sufficient to neutralize gastric acid is inconvenient and may have systemic side effects in elderly patients.

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The H_2 -antagonist, cimetidine, is a potent inhibitor of basal and stimulated gastric acid secretion (Burland *et al.*, 1975), reducing the blood loss from experimental gastric erosion (Odonkor, Mowat and Himel, 1981). It might therefore be expected to reduce the likelihood of recurrent bleeding within a few days of an initial haemorrhagic episode, and is frequently given in this clinical situation, usually intravenously. However published studies of cimetidine in bleeding ulcer disease have not convincingly shown that it is of benefit, and such therapy is expensive and potentially toxic. We therefore undertook a prospective double-blind controlled study to test the possible benefits of cimetidine therapy after hospital admission for bleeding peptic ulceration.

Patients and methods

One-hundred and thirty consecutive patients admitted to Leicester General Hospital during an 18-month period with symptoms of acute upper gastrointestinal bleeding were entered into the trial with the prior approval of the Area Ethical Committee, the physician in charge and the informed consent of the patient. Those requiring immediate surgery for continuing uncontrolled haemorrhage were excluded.

A careful history was taken particularly with regard to previous illness and ingestion within the previous 14 days of salicylates and other drugs capable of causing upper gastrointestinal symptoms. Fibreoptic oesophagoduodenoscopy was performed within 6 hr of admission by an experienced endoscopist. One-hundred and five patients with a gastric ulcer (GU) or duodenal ulcer (DU) identified as the likely source of blood loss (defined by the presence of fresh or old blood or clot in the ulcer base or a visible vessel) were given cimetidine or a placebo of identical appearance on a double-blind basis. Drug allocation followed endoscopic diagnosis and was stratified for diagnosis and age above and below

65 years. Cimetidine was given as an initial 200 mg intravenous bolus followed by a continuous infusion of 1200 mg daily for 2 days. After this cimetidine tablets (200 mg tds, 400 mg nocte) were administered for a total of 7 days. Placebo was given as an identical regimen of injection and tablets. Concomitant therapy consisted of antacids as required to relieve symptoms and a normal diet within 48 hr of admission. Blood and plasma substitutes were given as clinically indicated.

Following the initiation of therapy, fresh melaena, haematemesis, significant tachycardia or a hypotensive episode were considered to be due to recurrent or continued bleeding and the patient was withdrawn from the trial.

Statistical analysis used Student's *t*-test and the chi-squared test with Yates' correction, as appropriate; significance was determined at the level of $P < 0.05$.

Results

From a consecutive series of 130 patients who presented with acute upper gastrointestinal bleeding, 105 patients with peptic ulcers were entered into the trial. Fifty-one patients had a GU, 54 had a DU on endoscopy and their clinical details are summarized in Table 1. Severe haemorrhage was defined as the presence of at least one of the following; a history of syncope, a tachycardia of more than 100/min, or a systolic blood pressure less than 100 mmHg on admission.

Recurrent bleeding occurred in 32% of the GU and 28% of the DU group. Those patients with GU who had a history of irritant drug ingestion had a much lower rate of rebleeding (6/30; 20%) than those patients with no such history (10/21; 48%, $P < 0.05$). GU patients with a previously diagnosed GU were significantly more likely to rebleed after admission (9/17; 53%) than those without such a history (7/34; 21%, $P < 0.02$). These differences were not present in the DU group.

Cimetidine therapy had no effect on the rebleeding rate (Table 2). In patients with GU, 31% ($\pm 8\%$, s.e.m.) of the placebo-treated patients rebled compared to 32% ($\pm 9\%$) of the cimetidine-treated; the difference is non-significant. Patients with DU similarly showed no benefit from cimetidine. Placebo treatment was associated with a 24% ($\pm 7\%$) rebleeding rate, while cimetidine therapy carried a 31% ($\pm 8\%$) rate. Neither was any difference apparent when groups were analysed for age above 65 years, or in those who presented with severe haemorrhage. Antacids were consumed in insignificant amounts by all groups.

Surgical treatment for recurrent bleeding was required in seven (14%) of GU patients and six (11%) of those with DU; this was unaltered by cimetidine therapy. Details of surgery are presented in Table 3. No post-operative deaths or serious complications occurred. There were two deaths during rebleeding episodes, both in old women aged 78 and 87 years, with other medical illness (senile dementia, hepatic cirrhosis) who did not undergo surgery.

TABLE 1. Clinical details of patients

Group	Gastric ulcer	Duodenal ulcer
Number	51	54
Age (years $\pm$ s.d.)	68.4 $\pm$ 15.7	61.6 $\pm$ 14.5
Male/female	27/24	43/11
Presenting symptoms of haematemesis (%)	14	20
Presenting symptoms of melaena (%)	37	45
Presenting symptoms of haematemesis and melaena (%)	49	35
Severe haemorrhage (%)	80	65
History of peptic ulcer (%)	33	37
History of major medical illness (%)	31	33
Irritant drug ingestion (%)	59	46
Haemoglobin on admission (mean, range g/dl)	9.2 (4.7–16.9)	9.7 (2.8–14.9)
Transfusion requirement (median, range units)	4 (0–15)	3 (0–9)

TABLE 2. Lack of influence of cimetidine on rebleeding

	Treatment	(Number of patients)	No rebled	Rebled
Gastric ulcer	Cimetidine	(22)	15	7
	Placebo	(29)	20	9
Duodenal ulcer	Cimetidine	(29)	20	9
	Placebo	(25)	19	6

TABLE 3. Surgery required for rebleeding

Group	Patient Age/Sex	Treatment	Days after admission	Operation (number performed)
GU over 65 years old	68/m	Cimetidine	3,5	Underrun (1)
	84/f		4,2	Billroth I (3)
	73/f	Placebo	4,3	Underrun (1)
	78/f			V & P (1)
GU under 65 years old	57/m	Placebo	2	Roux-en-Y and vagotomy (previous Polya gastrectomy)
DU over 65 years old	83/f	Cimetidine	4	V & P
	67/m	Placebo	1,6	V & P
DU under 65 years old	45/m	Cimetidine	2,2	V & P (2)
	26/m	Placebo	2	V & P

V & P = vagotomy and pyloroplasty; GU = gastric ulcer; DU = duodenal ulcer.

Discussion

There have been several previous trials of cimetidine in acute upper gastrointestinal bleeding. Prophylactic therapy with cimetidine reduces the blood loss due to gastric erosions in selected high-risk patients (Speranza, Basso and Bagarani, 1981). Prospective double-blind placebo-controlled trials of the efficacy of cimetidine in haemorrhage due to peptic ulceration have shown conflicting results. La Brooy *et al.* (1979) studied 101 patients in a multicentre trial, giving cimetidine 800 mg orally at entry and 1.2 g daily or placebo. Of all patients in the trial, 11 of 51 on cimetidine rebled compared to 12 of 50 on placebo; cimetidine was of no benefit in the elderly, in severe bleeding, or in the 70 patients who had a peptic ulcer identified at endoscopy. Similarly Hoare, Bradby and Hawkins (1979) reported a trial of 66 patients admitted with bleeding peptic ulceration; results on the first 40 patients in this trial had been previously published (Dykes and Hoare, 1977). Of patients with DU, only 2 of 14 treated with cimetidine rebled compared to 10 of 19 on placebo, the majority of these patients were over 65 years old and cimetidine significantly reduced rebleeding in the elderly group ($P < 0.05$). No such benefit was seen in patients with DU. Carstenson *et al.* (1980) studied a group of 88 patients admitted with severe haemorrhage requiring immediate transfusion: 30% of all patients with peptic ulcers required surgery within an average of 19 hr after admission, and cimetidine made no difference to the transfusion requirements or the need for further surgery. In 96 patients with less severe haemorrhage (patients with arterial bleeding visible at endoscopy were excluded), Galmiche *et al.* (1980) gave cimetidine 1.6 g/day iv for 3 days followed by 4 days oral treatment. He found that patients with a GU were significantly less likely to

rebleed if given cimetidine, as were patients over 50 years old and those taking anti-inflammatory analgesics before admission. Two further trials of cimetidine versus placebo have shown no benefit of cimetidine but the numbers of patients were too small to reliably detect a possible difference (Pickard *et al.*, 1979; Macklon, Roberts and James, 1979).

In a study of this nature, the numbers of patients in each diagnostic category and the rate of rebleeding (i.e. the test of efficacy of cimetidine) determine the chance that the trial will fail to detect a genuine benefit of cimetidine treatment. Small groups and a low rate of rebleeding increase the likelihood of such a type II statistical error (Feinstein, 1977).

Even though our study contains the largest number of patients in each category (GU and DU), and has a similar rate of rebleeding to previous studies, we would expect to detect only a 16% change in the overall rate of rebleeding due to cimetidine with 95% confidence; none of the previous trials provide this power.

We could not confirm the suggestion that elderly patients with GU benefitted from cimetidine (Hoare *et al.*, 1979), neither did treatment delay the need for emergency surgery or the transfusion requirement. The overall mortality rate was low (two deaths) since the trial was designed to exclude patients with life-threatening and continued haemorrhage, who generally undergo emergency surgery after resuscitation. Patients with a GU who had either a past history of peptic ulceration or had not taken aspirin-like drugs prior to admission were particularly likely to rebleed. These patients are an identifiable high-risk subgroup in which further trials of therapy to prevent rebleeding are needed.

We conclude that cimetidine therapy does not significantly influence the rebleeding rate within 7

days of admission to hospital with a bleeding peptic ulcer. Cimetidine therefore has no rational place in the early management of bleeding peptic ulcer except to initiate healing; this can be achieved equally well be enteral therapy when oral intake has been resumed.

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