Refractory duodenal ulcer

K D BARDHAN

From the District General Hospital, Rotherham, Yorks

SUMMARY A refractory duodenal ulcer was arbitrarily defined as one that had failed to heal completely after treatment with cimetidine 1 g daily for three months. Of 66 patients with refractory duodenal ulcer, healing eventually occurred in 37 patients, after treatment for an average of 7.4 months. But 28 patients did not heal despite treatment for an average of 9.4 months; and one patient defaulted. In 41 patients the daily dose of cimetidine was increased to 2 g: the ulcers in 31 patients healed. In eight patients the daily dose was increased to 3 g and healing occurred in four patients. Eighteen patients required admission on 22 occasions because of severe symptoms despite treatment. Nine patients underwent surgery but in five the results were poor. Differences in clinical and endoscopic features between refractory and non-refractory ulcer patients were small. Acid and pepsin secretion were similar and gastrin concentrations normal. Blood levels of the drug and suppression of acid secretion were both satisfactory. Identification of refractory ulcer patients at the start of treatment was therefore not possible. Refractoriness could occur at any time during the course of the disease, previous treatment with cimetidine often having resulted in rapid healing, but subsequent relapses were also usually refractory. The cause of refractoriness remains unknown and the rather poor results of surgery in this series suggests that optimal management of these patients remains to be determined. Refractoriness probably indicates a changed natural history of the disease and in some patients a more poor prognosis.

Most duodenal ulcers heal within a month of treatment with cimetidine. Of the remainder the majority heal in another one to two months of continued treatment.¹ Some ulcers do not heal even after a longer period of cimetidine therapy and can be considered as being 'refractory' or resistant to standard treatment. This paper presents observations on the characteristics and the course of the first 66 such patients, encountered between 1977 and 1980.

A refractory duodenal ulcer is arbitrarily defined as one that has failed to heal fully within three months of treatment with cimetidine 1 g daily, taken as 200 mg tablets three times daily and 400 mg at bedtime. This definition derives from personal experience of 495 episodes of duodenal ulceration treated between 1978 and 1980 with cimetidine 1 g daily. The cumulative healing rate was as follows: at one month, 78%; at two months, 83%; and at three months, 93%. Healing was defined as complete disappearance of all ulcers and erosions and replacement either by a scar(s) or by mucosa, even if the

mucosa still appeared inflamed.

Methods

PATIENTS

Patients with duodenal ulcer(s) or with erosion(s) or with both, proven by endoscopy, were treated with cimetidine 1 g daily. Endoscopy was repeated after one to two months to check for healing. If ulcer(s) or erosion(s) were still present, the treatment was continued and healing was reassessed by endoscopy at three months. If healing was incomplete at about six to nine months, cimetidine was doubled to 2 g, even if the patient was asymptomatic, although in some patients the increase in dose was made earlier if symptoms continued or recurred. Cimetidine was increased to 3 g in the few patients in whom the combination of the 2 g dose, high dose antacid (up to 300 ml, equivalent to about 1000 mmol, daily) and rest, usually in hospital, failed to relieve severe symptoms.

In 45 patients with refractory ulcers, basal and maximal gastric secretion were each collected for one hour, the latter after stimulation with intramuscular pentagastrin 6 µg/kg (Peptavlon®;

Address for correspondence: District General Hospital, Moorgate Road, Oakwood, Rotherham S60 2UD.

Received for publication 22 July 1983.

Imperial Chemical Industries, Alderley Park, Macclesfield, UK). Acid was measured by electro-metric titration to pH 7, and pepsin assayed by a modified haemoglobin substrate colorimetric method.² In order to assess the effect of cimetidine on acid and pepsin secretion, 30 of these 45 patients had a further gastric secretion study after taking cimetidine. They took their tablets (200 mg, 400 mg, or 600 mg if their daily dose was 1 g, 2 g, or 3 g respectively) one hour before starting basal collection. For comparison, similar studies were also performed in seven patients with non-refractory ulcer.

Blood cimetidine concentrations were measured in 37 patients. A single sample was drawn one hour after taking the tablets and the serum was frozen at -20°C . Cimetidine concentrations were later measured by high pressure liquid chromatography on Lichosorb Si-60 support using an acetonitrile-methanol-water-ammonia solvent (Wickham Laboratories, Wickham, Hampshire, UK). Serum gastrin concentrations of refractory ulcer patients were measured by radioimmunoassay (Supra-regional Assay Service at the Hammersmith Hospital, London) in fasting blood samples; the patients were on cimetidine at the time the blood was taken. The antibody used measures both G17 and G34 gastrins.

STATISTICAL METHODS

Differences in characteristics between refractory and non-refractory ulcer patients was assessed by Student's t test and χ^2 test as appropriate. The degree of acid and pepsin inhibition produced by cimetidine was assessed by a one-tailed Student's t test, and analysis of variance was used when comparing the inhibition in the refractory ulcer patients as a whole with the non-refractory ulcer patients.

ETHICAL CONSIDERATIONS

This study is part of a wider programme on ulcer treatment and follow up, which was approved by the Rotherham Ethical Committee. Informed consent was obtained from all patients.

Results

HEALING

Thirty seven of 66 refractory duodenal ulcers eventually did heal, after a mean treatment period of 7.4 months (range four to 14 months) but 28 did not heal, despite an average treatment period of 9.4 months (range four to 20 months), one patient being lost to follow up.

Of the 37 patients whose ulcers were judged to

have healed, in the majority this was confirmed by endoscopy. In eight patients, the assessment was made at operation. The latter patients had active lesions (proven by endoscopy) a few weeks earlier, but as at laparotomy the duodenum was not opened in every instance, healing may have been over-estimated.

DOSE OF CIMETIDINE AND HEALING

The relation between the dose of cimetidine and healing is shown in Figure 1. Only eight patients healed on the standard (1 g) dose of cimetidine; but 29 of 41 patients given higher doses (2 g and 3 g) did eventually heal.

SURGERY

Despite being on cimetidine 18 of the refractory duodenal ulcer patients had to be admitted on 22 occasions to control severe pain which either persisted after starting treatment or developed after initial improvement or after a pain free interval. On the first admission, six patients came to surgery as their pain could not be controlled. The remaining 12 patients improved and were discharged; but four of these patients had to be readmitted as their symptoms worsened, often within a few weeks. On the second admission, three of the four patients had surgery. The indication for surgery in all nine patients (seven men, two women) was intractable pain despite treatment.

At laparotomy only one patient was found to have

Fig. 1 Dose of cimetidine and healing. *These nine patients had healed on cimetidine 1 g daily but their ulcers recurred despite continued treatment. Therefore no further treatment at this dose was given but instead it was increased to 2 g. **In two, three, and three patients on the 1 g, 2 g, and 3 g dose respectively, healing was judged by appearances at laparotomy. ***Includes the single patient found to have an active ulcer at operation. Among patients unhealed at the end of the study, 17 were on cimetidine 1 g, seven on 2 g, and four on 3 g.

an active ulcer. Seven patients had a vagotomy and drainage and the other two patients had highly selective (proximal gastric) vagotomy. Five of the nine patients operated, however, have had bad results after surgery (follow up one to three years). In three the ulcer has recurred, and two continue to have disabling pain, heartburn, vomiting, and diarrhoea, although their ulcers remain healed. Of the three patients with ulcer recurrence, two have responded to further treatment with cimetidine.

OUTCOME OF PREVIOUS TREATMENT WITH CIMETIDINE

Refractoriness developed unpredictably and seemed unconnected with the number of previous short courses of cimetidine treatment. Eighteen patients had a refractory ulcer on their first exposure to the drug. The others had had between one and six courses of cimetidine for healing earlier but only occasional episodes of ulceration were refractory. Thus 20 patients had one previous course of cimetidine and in five of these patients the ulcer took longer than three months to heal. In contrast five patients had three courses of cimetidine and another five patients had four courses of cimetidine and in each instance healing was rapid. Relapses

after a refractory episode occasionally healed quickly but in general once refractoriness developed, subsequent attacks were also refractory.

PROFILES OF REFRACTORY AND NON-REFRACTORY DUODENAL ULCER PATIENTS (Tables 1 and 2)

The patients with refractory ulcer were compared with 105 non-refractory patients seen consecutively in 1980. The refractory ulcer patients tended to be younger but with a longer history, and to have bled more frequently in the past. More members of their family had suffered from ulcer disease and more of them had medium sized or large ulcers and moderate or severe duodenitis. But there was no difference in the sex ratio, smoking pattern, the number of ulcers, or the proportion who also had erosions, and the degree of duodenal deformity.

The basal and maximal secretion of acid and pepsin in the refractory ulcer patients measured before treatment was similar to that of non-refractory ulcer patients. Furthermore, the proportion of patients with relatively high or low pepsin-to-acid ratio was similar in both groups. Gastrin was measured in 75 blood samples from 50 patients. The concentrations were slightly raised (above 50, which is the upper limit of the normal range but less than

Table 1 Differences between patients with refractory and non-refractory duodenal ulcer: history

	Refractory	Non-refractory	Significance
1 Age: mean (years) $\pm$ SE	40.4 $\pm$ 1.6	45.7 $\pm$ 1.2	p<0.05
$\leq$ 40 years	52%	30%	
2 Sex: men	73%	84%	NS
3 Smokers	84%	76%	NS
4 Duration symptoms			
(a) Mean (years) $\pm$ SE	12.0 $\pm$ 1.2	9.6 $\pm$ 0.8	p<0.01
(b) $\leq$ 5 years	25%	52%	
(c) 6-20 years	60%	34%	
5 Pattern of symptoms			NS
(a) Unchanged with time	21%	24%	
(b) Steady increase of symptoms	32%	24%	
(c) Initially unchanged and then an abrupt increase of symptoms	34%	39%	
(d) Steady increase followed by an abrupt increase of symptoms	13%	13%	
Mean time since sudden worsening of symptoms (years)	3.3	3.2	NS
6 Complications			
(a) Haemorrhage	15%	4%	p<0.01
(b) Perforation	3%	0%	NS
7 Family history of ulcer	60%	41%	p<0.01
8 Had used cimetidine earlier	79%	39%	p<0.001
9 Treatment immediately before the refractory episode			p<0.001*
(a) Nil	42%	61%	
(b) Placebo (part of trial)	6%	17%	
(c) Cimetidine 400 mg nightly (low dose maintenance treatment)	38%	22%	
(d) Cimetidine 1 g daily (full dose maintenance treatment)	14%	0%	

* Statistical analysis was done by comparing combined numbers of patients on cimetidine and combined numbers of patients not on active treatment. A significantly higher (p<0.001) proportion of patients already on cimetidine were in the refractory duodenal ulcer group.

Table 2 Differences between patients with refractory and non-refractory duodenal ulcer: investigations

	Refractory	Non-refractory	Significance
1 Endoscopy*			
(a) Ulcer medium or large	80%	63%	p<0.05
(b) ≥2 ulcers	17%	19%	NS
(c) Erosions present	36%	34%	NS
(d) Duodenitis moderate or severe	64%	41%	p<0.001
(e) Deformity moderate or severe	37%	41%	NS
2 Gastric secretion	(n=45)	(n=98)	
(a) Basal acid output: mean (mmol) ± SE	4.8±0.6	5.6±0.4	NS
>10 mmol/h	10%	13%	
(b) Maximal acid output: mean (mmol) ± SE	29.6±1.8	31.9±1.0	NS
>40 mmol/h	16%	18%	
(c) Basal pepsin output: mean (mg) ± SE	35±3	44±2	NS
>60 mg/h	13%	21%	
(d) Maximal pepsin output: mean (mg) ± SE	108±8	123±4	NS
>200 mg/h	10%	4%	
3 Fasting gastrin: mean (pmol/l) (normal up to 50)	22	not measured	

* Findings at endoscopy before starting cimetidine. Ulcer size was judged arbitrarily, and most ulcers were round or oval. Duodenitis was assessed by appearances, not by histology: it takes into account extent and severity of oedema and inflammation. Deformity of duodenal cap was assessed by number and depth of pseudo diverticulae, distortion, and by extent of shortening along its long axis.

90 pmol/l) in seven patients, all of whom were on high dose cimetidine at the time the blood samples were taken. Measurements could be repeated in only two patients and in both the concentrations had returned to normal. Gastrin concentrations were not measured in non-refractory ulcer patients as there was no clinical indication.

EFFECT OF CIMETIDINE ON PAIN

At the time of the latest ulcer recurrence two-thirds of the 66 patients with a refractory ulcer had moderate or severe symptoms. The remainder had little or no symptoms: these patients were either already on cimetidine or on placebo (in a separate study) and their ulcer recurrence was detected at periodic routine check endoscopy. Unlike the patients with non-refractory duodenal ulcer where pain reduction on cimetidine was swift and sustained, in the refractory ulcer patients the course was often variable and unpredictable, and the relationship between the symptomatic response and ulcer healing erratic.

EFFECT OF CIMETIDINE ON THE LESIONS

A total of 255 endoscopies was performed during 274 patient months. At the start of treatment, two-thirds of the patients had duodenal ulcers, a quarter both ulcers and erosions, and the remaining one-tenth had erosions only. During treatment the proportions were reversed: patients with only ulcers decreased to about a quarter whereas those with erosions, with or without ulcer(s), increased to three-quarters.

CIMETIDINE: BLOOD CONCENTRATIONS

Blood concentrations of cimetidine at one hour after taking the drug were measured in 31 patients with refractory ulcer. The therapeutic range is 0.5 to 1.5 µg/ml, at which levels acid secretion is inhibited to the degree required for ulcer healing. Only three patients, including one patient with a non-refractory ulcer, had blood concentrations below 0.5 µg/ml, although it is possible that the peak could have been missed. Eleven patients, including the remaining five with non-refractory ulcer, had blood concentrations within the therapeutic range. The other 23 patients with a refractory ulcer had blood cimetidine concentrations above this range.

EFFECT OF CIMETIDINE ON ACID AND PEPSIN SECRETION

The degree of acid reduction varied markedly between individuals (Fig. 2) but the mean reduction of acid secretion was as great in the resistant as in the responsive patients; and several patients who had failed to heal showed marked reduction in acid secretion. The degree of inhibition of acid secretion did not appear to be dose related, and the inhibition in the non-refractory ulcer group was not different from that in the refractory ulcer groups (Table 3). In contrast with the marked effect on acid output, cimetidine produced less consistent and relatively little change in pepsin secretion.

Discussion

Duodenal ulcers that fail to heal quickly on

Fig. 2 Maximal acid secretion before (circles) and during (triangles) cimetidine treatment.

cimetidine are increasingly recognised to be a problem but until recent years have been little studied.¹⁻⁹ There is no uniform definition of such 'cimetidine resistance' and the only common feature has been that the 'resistant' patients had delayed or absent healing on cimetidine.

The cause of refractoriness is unknown, except in the Zollinger-Ellison syndrome,^{10,11} which was excluded in the present study. Factors that might retard the rate of healing have been extensively studied.¹ These include the effects of: age, sex,¹²⁻¹⁴ smoking, drinking, manual occupation,⁶ army service,^{3,8} the size and shape of the ulcers,^{15,16} duodenal stenosis,¹⁷ and the pretreatment levels of acid secretion. The results, however, are conflicting or inapplicable to the patients in the current study.

Other possible causes for refractoriness are failure to take the drug, inadequate absorption, and failure to suppress acid secretion. Although non-

compliance was not studied in detail, failure of normal drug absorption was excluded and others have shown that the blood cimetidine concentrations observed are therapeutically effective.¹⁸⁻²⁴ The observations made by other investigators that suppression of acid secretion by cimetidine is similar in those with refractory and with non-refractory ulcers was confirmed,²⁵ although another group noted that the suppressibility of nocturnal acid secretion was decreased in patients with delayed healing and that doubling the dose of cimetidine had no further effect.²⁶

The correct method of management of patients with refractory duodenal ulcer is uncertain. There are three approaches: measures to increase acid inhibition, or to increase mucosal defence, and surgery. Increased acid inhibition can be effective as ranitidine, which is more potent than cimetidine, heals ulcers when the latter in standard doses has failed,^{5,8,9,27} but healing does not occur in all patients.²⁸ There is little information available on the effects of promoting mucosal defence with drugs such as carbenoxolone or prostaglandins but sucralfate, which forms an 'ulcer seal', has been claimed to heal duodenal ulcers resistant to cimetidine.²⁹

Surgery has been found effective when cimetidine has failed^{3,4,7} but not in the current study where half the patients have had unsatisfactory results, which is twice that expected.³⁰ One possible explanation for the poor results is that patients in the current study were 'more refractory' than those reported by others in that their ulcers had not healed on high dose cimetidine whereas other investigators had used only standard doses. A second possibility is that an 'inadequate' operation was chosen and that vagotomy with antrectomy would have been more logical. The latter operation was indeed planned but in the surprising absence of evidence at laparotomy

Table 3 Effect of cimetidine on acid secretion

Patient group	Basal			Maximal		
	Before treatment	During treatment	Significance	Before treatment	During treatment	Significance
Refractory DU						
On cimetidine						
1 g (n=6)	6.1±2.1	2.1±0.9	NS	32.7±3.3	15.1±3.3	p<0.05
2 g (n=15)	6.6±1.8	2.0±1.1	p<0.005	31.0±2.0	21.0±2.2	p<0.005
3 g (n=9)	6.6±1.6	5.2±2.4	NS	33.7±4.5	24.5±4.7	p<0.05
Non-refractory DU.						
On cimetidine						
1 g (n=7)	4.4±1.1	0.2±0.1	p<0.005	25.3±2.1	14.4±4.2	p<0.005

Patients who had secretion studies both before and during cimetidine treatment.
Acid secretion, mmol/h: mean ± SEM.

of aggressive ulceration, such as penetration and dense adhesions, this seemed a drastic step; but in retrospect it may have been a better choice.

The present study suggests that the development of refractoriness may mark a change in the natural history of duodenal ulcer disease, and in some patients indicates the onset of an increased virulence of the disorder and a worsening of the prognosis. But none of the findings in this study or in those by other investigators adequately explain why some duodenal ulcers are refractory, particularly those of patients who had previously had ulcers which responded to cimetidine in standard dosage. This emphasises our continuing lack of knowledge of factors other than acid secretion which initiate and maintain ulceration of the duodenal mucosa.

I am indebted to Dr C D Holdsworth and Dr K G Wormsley for their helpful advice; to my colleagues in Rotherham for their support, and to Mr John Beresford, Miss Caroline Franks, and Dr D Rowley-Jones (of Smith, Kline & French) for statistical analysis and blood cimetidine assays.

References

- Bardhan KD. Non-responders to cimetidine treatment. In: Baron JH, ed. *Cimetidine in the 80's*. Edinburgh: Churchill Livingstone, 1981.
- Ishaque M, Bardhan KD. An assessment of the radial diffusion method for the measurement of gastric pepsin and its comparison with the haemoglobin substrate colorimetric method. *Clin Chim Acta* 1978; **87**: 259-63.
- Hannigan BG. Duodenal ulcer in servicemen. *JR Army Med Corps* 1980; **126**: 133-4.
- Blackett RL, Johnston D. Cimetidine and duodenal ulcer: can surgery cure the failures? [Abstract] *Gut* 1981; **22**: A434.
- Mohammed R, Mitchell KG, MacKay C. The treatment of 'cimetidine resistant' peptic ulcers by ranitidine hydrochloride: a new histamine H₂ receptor antagonist. *Curr Med Res Opin* 1981; **7**: 523-5.
- Hasan N, Sircus W. The factors determining success or failure of cimetidine treatment of peptic ulcer. *J Clin Gastroenterol* 1981; **3**: 225-9.
- Gray GR, McWhinnie D, Smith IS, Gillespie G. Five-year study of cimetidine or surgery for severe duodenal ulcer dyspepsia. *Lancet* 1982; **1**: 787-8.
- Roberts DM, Wilson JA, Ratcliffe GE, Waring AJ, Reilly MJ, Lloyd JS. Clinical trial of ranitidine in the treatment of peptic ulcer. *Br J Clin Pract* 1982; **36**: 9-12.
- Witzel L, Wolbergs E. Peptic ulcer healing with ranitidine in cimetidine resistance. *Lancet* 1982; **2**: 1224.
- McCarthy DM. Report on the United States experience with cimetidine in Zollinger-Ellison syndrome and other hypersecretory states. *Gastroenterology* 1978; **74**: 453-5.
- Stage JG, Stadil F. Cimetidine and the Zollinger-Ellison syndrome. In: Baron JH, ed. *Cimetidine in the 80's*. Edinburgh: Churchill Livingstone, 1981.
- Peden NR, Boyd EJS, Wormsley KG. Women and duodenal ulcer. *Br Med J* 1981; **282**: 866.
- Sonnenberg A, Müller-Lissner SA, Vogel E *et al*. Predictors of duodenal ulcer healing and relapse. *Gastroenterology* 1981; **81**: 1061-7.
- Bianchi Porro G, Prada A, Petrillo M, Lazzaroni M. Women and duodenal ulcer. *Br Med J* 1981; **283**: 235.
- Kohli Y, Misaki F, Kawai K. Endoscopic follow up observation of duodenal ulcer. *Endoscopy* 1972; **4**: 202-8.
- Nava G, Pippa G, Ballanti R, Papi C. Role of ulcer morphology in evaluating prognosis and therapeutic outcome in duodenal ulcer. *Scand J Gastroenterol* 1979; **14**: suppl 54: 41-3.
- Massarrat S, Eisenmann A. Factors effecting the healing rate of duodenal and pyloric ulcers with low-dose antacid treatment. *Gut* 1981; **22**: 97-102.
- Pounder RE, Williams JG, Hunt RH, Vincent SH, Milton-Thompson GJ, Misiewicz JJ. The effects of oral cimetidine on food-stimulated gastric acid secretion and 24-hour intragastric acidity. In: Burland WL, Simkins MA, eds. *Cimetidine. Proceedings of the second international symposium on histamine H₂ receptor antagonists*. Amsterdam-Oxford: Excerpta Medica, 1977.
- Bodemar G, Norlander B, Walan A, Larson R. Short and long-term treatment with cimetidine in peptic ulcer disease and the pharmacokinetics of cimetidine. *Scand J Gastroenterol* 1979; **14**: suppl 55: 96-106.
- Rune SJ, Hesselheldt P, Larsen NE. Clinical and pharmacological effectiveness of cimetidine in duodenal ulcer patient. *Scand J Gastroenterol* 1979; **14**: 489-92.
- Brater DC, Peters MN, Eshelman FN, Richardson CT. Clinical comparison of cimetidine and ranitidine. *Clin Pharmacol Ther* 1982; **32**: 484-9.
- Festen HPM, Diemel J, Lamers CBH, Van Schaik A, Tangerman A, Van Tongeren JHM. Is the measurement of blood cimetidine levels useful? *Br J Clin Pharmacol* 1981; **12**: 417-21.
- Webster J, Barber HE, Hawksworth GM *et al*. Cimetidine - a clinical and pharmacokinetic study. *Br J Clin Pharmacol* 1981; **11**: 333-8.
- Gugler R, Fuchs G, Dieckmann M, Somogyi A. Cimetidine plasma concentration - response relationships. *Clin Pharmacol Ther* 1981; **29**: 744-8.
- Foschi D, Nosenzo MA, Rovati V. The effects of intravenous cimetidine on pentagastrin stimulated secretion in patients with duodenal ulcer refractory to cimetidine therapy. *Hepatogastroenterology* [Abstract] 1980; **27**: F16.
- Gledhill T, Buck M, McEwan J, Paul A, Hunt RH. Effect of cimetidine 1 g/day and cimetidine 2 g/day on

- nocturnal intragastric acidity and acid secretion in cimetidine non-responders. [Abstract] *Gut* 1982; **23**: A454.
- 27 Mazzacca G, D'Agostino L, D'Arienzo A, Piai G, Sabbatini F, Verre C. Cimetidine or ranitidine non-responder patients: treatment of duodenal ulcers resistant to one H₂ blocker with the other. [Abstract] *Scand J Gastroenterol* 1982; **17**: suppl 78: 408.
 - 28 Galmiche JP, Tranvouez JL, Denis Ph, Ndjitoyap C, Colin R. Treatment with ranitidine of duodenal ulcers resistant to cimetidine – clinical and pH metric results. *Gastroenterol Clin Biol* 1983; **7**: 50 A.
 - 29 Guslandi M, Ballarin E, Tittobello A. Sucralfate in refractory duodenal ulcers. [Abstract] *Gut* 1983; **24**: A498.
 - 30 Johnston D. Treatment of peptic ulcer and its complications. In: Taylor S, ed. *Recent advances in surgery*. Edinburgh: Churchill Livingstone, 1980.