Ranitidine compared with cimetidine in the short-term healing of duodenal ulcer

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Summary

The efficacy of ranitidine (150 mg twice daily) and cimetidine (200 mg three times daily and 400 mg at night) in the short-term healing of duodenal ulcer has been assessed in a randomized controlled trial involving 106 patients. There were 3 drop-outs. Forty-two out of 53 patients (79%) treated with ranitidine had healed ulcers at 4 weeks compared with 37 out of 50 treated with cimetidine (74%). This difference is not significant. At 8 weeks the healing rate for ranitidine (98%) was significantly greater than that for cimetidine (86%) ($P < 0.05$). There was no significant difference in healing rates between men and women and between smokers and non-smokers. Side effects were not a problem with either drug. There were no differences of clinical significance between laboratory values in the two treatment groups, although a minor increase in mean creatinine levels occurred in the cimetidine-treated group.

KEY WORDS: ranitidine, cimetidine, duodenal ulcer.

Introduction

Ranitidine, the second H_2 receptor antagonist to be introduced into clinical practice in the United Kingdom, has been shown to have a marked inhibitory effect on gastric acid secretion, greater than that of cimetidine. We report a trial comparing ranitidine and cimetidine in the short-term healing of duodenal ulceration.

Patients and methods

Patients with endoscopically proven duodenal ulcer have been admitted to a single-centre randomized single-blind (endoscopist) trial of treatment with ranitidine 150 mg b.d. or cimetidine 200 mg t.d.s. and 400 mg at night. The trial was approved by the Ethical Committee of Victoria Hospital, Blackpool, according to the Declaration of Helsinki. The pur-

pose of the study was explained to the patients. None of the patients had received ulcer healing agents in the previous month. Patients were excluded if they had gastric ulceration, previous gastric surgery, pyloric stenosis, recent treatment with 'ulcerogenic' drugs, recent perforation, concurrent serious disease and if they were pregnant, liable to conceive during the trial or if they were breast-feeding. After an initial clinical, haematological and biochemical assessment, endoscopy was carried out to confirm the presence of duodenal ulceration and informed consent obtained. Consecutive patients were admitted according to a previously determined schedule. Supplies of antacid (Rennies–Nicholas Laboratories) and the treatment drug were issued. At 2 and 4 weeks, the baseline assessments were repeated and a count of the treatment tablets made to assist in determining compliance. Healing, defined as complete epithelialization of the ulcer, was assessed by endoscopy at 4 weeks. Endoscopy was repeated at 8 weeks if the ulcer was unhealed at 4 weeks. Distribution and counting of treatment tablets were undertaken by staff in the Department of Gastroenterology, Victoria Hospital, Blackpool, who had no communication with the clinical assessor or the endoscopist.

Statistical methods

(1) Ulcer healing has been assessed using the two-sided Mantel–Haenszel chi-square test without continuity correction (Snedecor and Cochran, 1967).

In view of the difference in length of dyspeptic history between the two treatment groups, an analysis of the efficacy data was carried out after stratification into two groups with a relative short (under 5 years) or long (over 5 years) history.

(2) Data for selected laboratory investigations were analysed for differences between the mean or geometric mean values in the treatment groups at the pretreatment and 28-day visits. The calculation of

TABLE 1. Background data for patients completing the trial

	Ranitidine	Cimetidine
No. completed trial	53	50
Sex (M/F)	39/14	39/11
Age (yrs):		
mean (range)	48 (19–76)	48 (25–76)
Weight (kg):		
mean ± s.d.	71 ± 12	69 ± 12
Smokers/non-smokers	39/14	31/19
Duration of		
dyspepsia (yrs):		
mean (range)	5·7 (0–30)	13 (0–31)
Duration of current		
episode (weeks):		
mean (range)	6·5 (0–24)	8 (0–32)

Note: there is a difference in the duration of dyspepsia between the two groups.

95% confidence limits was based on the *t*-distribution if within-treatment variances were similar, and by means of an extension to Satterthwaite's rule for variances which were significantly different (Satterthwaite, 1946).

Results

Between January and November 1981, 106 patients were entered in the trial. There were 3 dropouts, 2 associated with failure of compliance, and one man who complained of a light-headed sensation which he attributed to the treatment agent. All 3 had received cimetidine. One hundred and three patients completed the trial, 53 (39 men and 14 women) received ranitidine and 50 (39 men and 11 women) received cimetidine. The background data of patients completing the trial are shown in Table 1. The drug groups were evenly matched apart from the duration of dyspepsia which was on average 5–7 years in the ranitidine group and 13 years in the cimetidine group.

After 4 weeks, 42 (79%) patients on ranitidine and 37 (74%) on cimetidine had healed. This difference is not significant. After 8 weeks, 52 (98%) on ranitidine and 43 (86%) on cimetidine had healed. This difference is statistically significant ($P < 0.05$). In view of the difference in the duration of the dyspeptic history between the ranitidine- and cimetidine-treated groups, healing rates were compared according to the

length of history. There was no difference between groups with histories of less than or greater than 5 years (Table 2). In addition, there were no significant differences between smokers and non-smokers (Table 3) and between men and women, although the healing rate for men on ranitidine at 8 weeks (100%) was significantly better than those on cimetidine (87%) ($P < 0.05$) (Table 4).

TABLE 3. Healing rates for smokers and non-smokers on ranitidine and cimetidine

	Treatment	Healed 4 weeks	Healed 8 weeks
Smokers			
$n = 39$	Ranitidine	31 (79%)	38 (97%)
$n = 31$	Cimetidine	22 (71%)	27 (87%)
	Total	53 (75%)	65 (93%)
Non-smokers			
$n = 14$	Ranitidine	11 (79%)	14 (100%)
$n = 19$	Cimetidine	15 (79%)	16 (84%)
	Total	19 (78%)	30 (90%)

Differences between smokers and non-smokers are not statistically significant.

TABLE 4. Healing rates for men and women on ranitidine and cimetidine

	Treatment	Healed 4 weeks	Healed 8 weeks
Men			
$n = 39$	Ranitidine	32 (82%)	39 (100%)
$n = 39$	Cimetidine	28 (72%)	34 (87%)
	Total	60 (77%)	73 (94%)
Women			
$n = 14$	Ranitidine	10 (71%)	13 (93%)
$n = 11$	Cimetidine	9 (82%)	9 (82%)
	Total	19 (76%)	22 (88%)

Differences between men and women are not significant. The healing rate for men on ranitidine (100%) at 8 weeks is significantly different from the rate on cimetidine (87%) ($P < 0.05$).

Unwanted effects

These were minimal. One patient declined to continue treatment with cimetidine, attributing extreme lethargy to the effects of the drug. One man, receiving cimetidine, complained of severe, central

TABLE 2. Healing of duodenal ulcers stratified by duration of dyspepsia

	Ranitidine		Cimetidine	
	at 4 weeks	at 8 weeks	at 4 weeks	at 8 weeks
Dyspepsia <5 yrs	27/34 (79%)	33/34 (97%)	14/19 (74%)	15/19 (79%)
Dyspepsia >5 yrs	15/19 (79%)	19/19 (100%)	23/31 (74%)	28/31 (90%)

The healing rates on ranitidine are not significantly different from those on cimetidine at 4 weeks but are significantly different at 8 weeks ($P < 0.05$).

abdominal pain for 3 days. Subsequently he was found to have a raised blood sugar and glycosuria which were transient although the treatment medication was continued. Cholecystogram and ultrasound examination of the biliary tract were negative for gallstones. Endoscopy showed the duodenal ulcer to have healed satisfactorily. We believe that this was a mild bout of pancreatitis which resolved spontaneously. Although there have been a few case reports of acute pancreatitis in patients receiving cimetidine, the condition may not be drug related (Arnold, Doyle and Bell, 1978). Results of experimental studies in rats have shown conflicting results (Joffe and Lee, 1978; Szabo and Goldman, 1978). One patient on ranitidine and one on cimetidine felt general malaise, but in both cases the condition resolved while the patients continued taking the treatment agent.

Laboratory investigations

Data for assessing changes in laboratory measurements were analysed if measurements were made at Visit 1 (pretreatment) and at Visit 3 if this was 21–35 days after Visit 1. There were no significant differences between the two groups for either visit for haemoglobin, platelet count, total white count, serum bilirubin, urea or aspartate transaminase levels and there were no significant changes between visits. In the cimetidine treatment group, the mean serum creatinine level rose from 93 to 102 mmol/litre, whereas the level remained at 92 mmol/litre in the ranitidine group. This observation has been made previously (Larsson et al., 1980) and is not thought to be clinically important. A slight fall in gamma glutamyl transaminase levels in the ranitidine group was matched by a slight rise in the cimetidine-treated

groups. The difference was of statistical, but not clinical, significance.

Discussion

The present study confirms the effectiveness of ranitidine and cimetidine in the healing of duodenal ulceration. The healing rate for ranitidine was similar to that for cimetidine at 4 weeks, and at 8 weeks was significantly better ($P<0.05$). Some early studies are shown in Table 5 (Berstad et al., 1980; Gibinski et al., 1981; Walt et al., 1981; Dobrilla et al., 1981; Peden et al., 1981). A previous report from this centre involving 50 patients, showed healing rates for ranitidine of 92% at 4 weeks and 100% at 8 weeks compared with a healing rate of 29% for placebo-treated patients at 4 weeks (Lee, Costello and Fielding, 1982). The healing rates for ranitidine are comparable to those reported for cimetidine (Gray et al., 1977; Northfield & Blackwood, 1977; Bardhan et al., 1977). Clearly, ranitidine is at least as effective as cimetidine in the short-term healing of duodenal ulceration.

Previous reports have shown conflicting results in ulcer healing rates in men and women. Peden et al. (1981) reported that women were less likely than men to heal duodenal ulcers after 4 weeks' treatment with H_2 receptor antagonists. This trend had become apparent in more recent studies and selection factors may have been relevant. In contrast, no difference was noted between men and women in two studies involving placebo and H_2 blockers (Porro et al., 1981) and low-dose antacid (Massarrat and Eisenmann, 1981) although, in this latter study, the trend was in favour of women. A favourable effect for women was found in a trial involving placebo, cimetidine and pirenzipine (Sonnenberg et al., 1981). At the high

TABLE 5. Early trials of ranitidine in short-term healing of duodenal ulceration

Author	Country	Number	Ranitidine dose (mg/day)	Length of treatment (weeks)	Percentage healed on ranitidine	Percentage healed on compared agent
Berstad et al. (1980)	Norway (Multi-centre)	50	200	4	92	46 (placebo)
Gibinski et al. (1981)	Poland (Multi-centre)	168	300	3	82	45 (placebo)
Walt et al. (1981)	U.K. (Multi-centre)	103	300	4	77	84 (cimetidine 1 g/day)
Dobrilla et al. (1981)	Italy (Single-centre)	40	160	4	83·3	29·4 (placebo)
Peden et al. (1981)	U.K. (Single-centre)	40	320	4	78	45 (cimetidine 800 mg/day)
Lee et al. (1982) (Present report)	U.K. (Single-centre)	103	300	4	78	74 (cimetidine 1 g/day)
				8	98	86 (cimetidine 1 g/day)

healing rates for ranitidine and cimetidine reported in the present study, no difference in healing rates was found between men and women. Similarly, the present report shows no difference between smokers and non-smokers in contrast to several studies which have reported impaired healing rates in smokers (Massarrat and Eisenmann, 1981; Sonnenberg *et al.,* 1981; Korman *et al.,* 1981). At the healing rates relevant to currently used ulcer healing agents, very large numbers may be needed to detect differences.

Choice of agent, therefore, may depend on other factors such as compliance, unwanted effects and relapse rates after healing. Cimetidine has been shown to affect the hepatic metabolism of a number of drugs including antipyrine and aminopyrine (Staiger *et al.,* 1980; Henry *et al.,* 1980), warfarin and phenindione (Hetzel, Birkett and Miners, 1979), chlordiazepoxide and diazepam (Patwardham *et al.,* 1980), phenytoin (Hetzel *et al.,* 1981) and propranolol (Heagerty *et al.,* 1981). In addition, cimetidine produces an elevation of serum prolactin levels after intravenous injection (Nelis and Van de Meene, 1980; Kleist *et al.,* 1981). Ranitidine has been reported as showing more prolonged gastric acid suppression than cimetidine in a man with Zollinger–Ellison syndrome in whom gynaecomastia regressed and sexual activity improved when ranitidine was substituted for cimetidine (Mignon *et al.,* 1980). The increased potency of ranitidine has been found useful in patients with life-threatening gastric hypersecretion resistant to cimetidine (Danilewitz, Tim and Hirschowitz, 1982). Like histamine, cimetidine has an imidazole ring and it may be that some of its unwanted effects are associated with its ring structure. Ranitidine has a nitrofuran ring and is a specific H_2 receptor antagonist. Cimetidine has been in use for over 5 years and has an excellent tolerance and safety record. However, there are reservations about anti-androgenic activity and alterations in drug metabolism. These effects do not occur with ranitidine and there may be clinical situations where ranitidine is the preferred agent.

Acknowledgments

References

ARNOLD, F., DOYLE, P.J. & BELL, G. (1978) Acute pancreatitis in a patient treated with cimetidine. *Lancet,* **i,** 382.

BARDHAN, K.K., SAUL, D.M., BALMFORTH, G.V., MARUYAMA, T., DUTHIE, H.L., FUSSEY, I.V., HEADING, R.C., FETTES, M., LOGAN, R.F.A., HOLDSWORTH, C.D., LANGMAN, M.J., DRONFIELD, M.W., LARKWORTHY, W., SMITH, P.M., EDWARDS, J.L., WYLIE, J.H.,

HAGGIE, S.J. & HAWKINS, B.W. (1977) The effect of cimetidine on duodenal ulceration. In: *Cimetidine* (Ed. by Burland, W.L. & Simkins, M.A.), p. 260, Excerpta Medica, Amsterdam.

BERSTAD, A., KETT, K., AADLAND, E., CARLSEN, E., FRISLID, K., SAXHAUG, K. & KRUSE-JENSEN, A. (1980) Treatment of duodenal ulcer with ranitidine, a new histamine H_2 receptor antagonist. *Scandinavian Journal of Gastroenterology,* **15,** 637.

DANILEWITZ, M., TIM, L.O. & HIRSCHOWITZ, B. (1982) Ranitidine suppression of gastric hypersecretion resistant to cimetidine. *New England Journal of Medicine,* **306,** 20.

DOBRILLA, G., DE PRETIS, G., FELDER, M. & CHILOVI, F. (1981) Endoscopic double blind controlled trial of ranitidine *vs* placebo in the short-term treatment of duodenal ulcer. *Hepatogastroenterology,* **28,** 49.

GIBINSKI, K., NOWAK, A., GABRYELEWICZ, A., SZALAJ, W., HASIK, J., KLINCEWICZ, H., POKORA, J., RADWAN, P.,r05 KOSECKI, P. & PACHLEWSKI, J. (1981) Multicentre double blind clinical trial on ranitidine for gastroduodenal ulcer. *Hepatogastroenterology,* **28,** 216.

GRAY, G.R., MCKENZIE, I., SMITH, I.S., CREAN, G.P. & GILLESPIE, G. (1977) Oral cimetidine in severe duodenal ulceration. *Lancet,* **i,** 4.

HEAGERTY, A.M., DONOVAN, M.A., CASTLEDON, C.M., POHL, J.F., PATEL, L. & HEDGES, A. (1981) Influence of cimetidine on pharmacokinetics of propranolol. *British Medical Journal,* **282,** 1917.

HENRY, D.A., MACDONALD, I.A., KITCHINGMAN, G., BELL, G.D. & LANGMAN, M.J.S. (1980) Cimetidine and ranitidine: a comparison of effects on hepatic drug metabolism. *British Medical Journal,* **281,** 775.

HETZEL, D., BIRKETT, D. & MINERS, J. (1979) Cimetidine interaction with warfarin. *Lancet,* **ii,** 639 (Letter).

HETZEL, D.J., BOCHNER, F., HALLPINE, J.F. & SHEARMAN, D.J.C. (1981) Cimetidine interaction with phenytoin. *British Medical Journal,* **282,** 1512.

JOFFE, S.N. & LEE, F.D. (1978) Acute pancreatitis after cimetidine administration in experimental duodenal ulcers. *Lancet,* **i,** 383 (Letter)

KLEIST, D. VON., GRAF, K.J., DOUGHERTY, F.C. & HAMPEL, K.E. (1981) Effects of cimetidine and ranitidine on gastric transmural potential difference and on prolactin secretion in man. *Hepatogastroenterology,* **28,** 210.

KORMAN, M.G., SHAW, R.G., HANSKY, J., SCHMIDT, G.T. & STERN, A.I. (1981) Influence of smoking on healing rate of duodenal ulcer in response to cimetidine or high-dose antacid. *Gastroenterology,* **80,** 1451.

LARSSON, R., BODEMAR, G., KAGEDAL, B. & WHELAN, A. (1980) The effects of cimetidine (Tagamet) on renal function in patients with renal failure. *Acta medica Scandinavica,* **208,** 27.

LEE, F.I., COSTELLO, F.T. & FIELDING, J.D. (1982) Ranitidine compared with placebo in the short-term healing of duodenal ulcer. In: *The Clinical Use of Ranitidine.* (Ed. by J.J. Misiewicz and K.G. Wormsley) p. 131. Medicine Publishing Foundation Symposium Series 5. Medicine Publishing Foundation, Oxford.

MASSARRAT, S. & EISENMANN, A. (1981) Factors affecting the healing rate of duodenal and pyloric ulcers with low-dose antacid treatment. *Gut,* **22,** 97.

MIGNON, M., VALLOT, B.J., MAYEUR, T.H. & BONFILS, S. (1980) Ranitidine and cimetidine in the Zollinger–Ellison syndrome. *British Journal of Pharmacology,* **10,** 173.

NELIS, G.F. & VAN DE MEENE, J.G.C. (1980) Comparative effect of cimetidine and ranitidine on prolactin secretion. *Postgraduate Medical Journal,* **56,** 478.

NORTHFIELD, T.C. & BLACKWOOD, W.S. (1977) Controlled clinical trial of cimetidine for duodenal ulcer. In: *Cimetidine* (Ed. by Burland, W.L. & Simkins, M.A.), p. 272. Excerpta Medica, Amsterdam.

PATWARDHAM, R.V., YARBOROUGH, G.W., DESMOND, P.V., JOHNSON, R.F., SCHENKER, S. & SPEEG, K.V. (1980) Cimetidine spares the glucuronidation of lorazepam and oxasepam. *Gastroenterology,* **79,** 912.

PEDEN, N.R., BOYD, E.J.S., SAUNDERS, J.H.B. & WORMSLEY, K.G. (1981) Ranitidine in the treatment of duodenal ulceration. *Scandinavian Journal of Gastroenterology*, **16**, 325.

PEDEN, N.R., BOYD, E.J.S. & WORMSLEY, K.G. (1981) Women and duodenal ulcer. *British Medical Journal*, **282**, 866 (Letter).

PORRO, G.B., PRADA, A., PETRILLO, M. & LAZZARONI, M. (1981) Women and duodenal ulcer. *British Medical Journal*, **283**, 235 (Letter).

SATTERTHWAITE, F.E. (1946) *Biometrics Bulletin*, **2**, 100.

SNEDECOR, G.W. & COCHRAN, W.G. (1967) *Statistical Methods,* 6th edn, p. 253. Iowa State University Press, Ames, Iowa.

SONNENBERG, A., MULLER-LISSNER, S.A., VOGEL, E., SCHMID, P., GONVERS, J.J., PETER, P., STROHMEYER, G. & BLUM, A.L. (1981) Predictors of duodenal ulcer healing and relapse. *Gastroenterology*, **81**, 1061.

STAIGER, C., SIMON, B., WALTER, B. & KATHER, H. (1980) Influences of ranitidine on antipyrine pharmacokinetics in healthy volunteers. *Digestive Diseases & Sciences*, **25**, 894.

SZABO, S. & GOLDMAN, H. (1978) Cimetidine and pancreatitis: lessons from animal experiments. *Lancet*, **ii**, 266 (Letter).

WALT, R.P., TROTMAN, I.F., FROST, R., GOLDING, P.L., SHEPHERD, T.H., RAWLINGS, J., HUNT, R.H., COLIN-JONES, D., MILTON-THOMPSON, G.J. & MISIEWICZ, J.J. (1981) Comparison of twice daily ranitidine with standard cimetidine treatment of duodenal ulcer. *Gut*, **22**, 319.