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Single nocturnal dose of an H_2 receptor antagonist for the treatment of duodenal ulcer

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SUMMARY Twenty four hour intragastric acidity and nocturnal acid output have been measured over five separate 24 hour periods in each of 12 patients with duodenal ulcer receiving either placebo, cimetidine 400 mg bd, cimetidine 300 mg nocte, ranitidine 150 mg bd, or ranitidine 300 mg nocte. In these doses ranitidine was significantly more effective at decreasing intragastric acidity and nocturnal acid output than cimetidine. There was no significant difference between twice daily ranitidine and night time ranitidine or between twice daily cimetidine and night time cimetidine in the reduction of intragastric acidity. Nocturnal acid output was controlled significantly better with ranitidine at night, twice daily dosage of ranitidine, and cimetidine at night, than by the twice daily dosage of cimetidine. It is suggested that a single nocturnal dose of cimetidine or ranitidine should be evaluated in a clinical trial.

Cimetidine was introduced in the United Kingdom for the treatment of duodenal ulcer with a recommended dose of 200 mg tds and 400 mg nocte (1 g/day).[1] More recently a dose of 400 mg bd has been shown to be equally effective at lowering intragastric acidity[2] and ulcer healing.[3 4] Ranitidine is also recommended in a twice daily dose of 150 mg for ulcer healing[5 6] and both of these drugs have been given effectively as a single night time dose to prevent ulcer relapse.[7 8]

Measures which decrease intragastric acidity over a 24 hour period are known to result in ulcer healing.[9 10] Dragstedt suggested that nocturnal hypersecretion was the most important single factor in the pathogenesis of duodenal ulcer[11] and we have recently shown that although there is little variation in an individual's response to cimetidine during the daytime, overnight, patients who show a poor clinical response to cimetidine treatment also show little decrease in hydrogen ion (H^+) activity.[12] These data and our knowledge that a single night time dose of an H_2 receptor antagonist can prevent duodenal ulcer relapse, suggest that a larger dose may be effective primary treatment. During the daytime food partially buffers intragastric acidity and therefore a morning dose of drug may be unnecessary. To investigate this hypothesis, we have studied intragastric acidity over a 24 hour period comparing twice daily ranitidine with twice daily cimetidine and both drugs given as a single large bedtime dose.

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Methods

PATIENTS

Twelve patients with an endoscopically proven duodenal ulcer in remission were each studied over five separate 24 hour periods receiving either placebo, cimetidine 400 mg bd, ranitidine 150 mg bd, cimetidine 800 mg nocte, or ranitidine 300 mg nocte. Treatments were randomised, taken single blind and administered at 2100 on the day before the study and at 0900 and 2100 on the study day for the twice daily dosage, and at 2100 on the study day for the once daily regimen. All subjects gave their informed consent and the study was approved by the Hospital Ethical Committee.

The study design was similar to that previously reported from our Department.[1] Patients were admitted to a specially allocated ward at 0730 having fasted from midnight. A 10 French gauge naso-

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gastric Salem sump tube was passed and position checked by water aspiration. Patients ate identical meals at the same time on each study day and the number of cigarettes and drinks consumed was recorded and repeated on subsequent study days.

Throughout the study, a sample of gastric juice was taken hourly for estimation of pH using a glass electrode (Radiometer, Copenhagen) calibrated with buffers at pH 4 and 7 before each hourly batch of measurements. At 0100 the stomach was emptied and continuous aspiration applied overnight using a mechanical pump at −50 mm of Hg, interrupted by manual aspiration every 20 minutes. The hourly volume of gastric secretion was recorded, a 5 ml aliquot taken for titration to pH 7 with 0·1 N sodium hydroxide using an autoburette (Radiometer, Copenhagen) and acid output calculated.

For the purposes of statistical analysis, pH was converted to hydrogen ion activity (H^+). Statistical comparison of H^+ activity was performed using a Fisher's significant differences test (with $p<0·05$) which takes into account all possible comparisons between treatments. Analysis of nocturnal acid output on different treatments was performed using a Friedman rank sum multiple comparison procedure.

Results

INTRAGASTRIC ACIDITY

The results of the five treatments are shown in Fig. 1. Twice daily ranitidine decreased mean 24 hour H^+ activity by 63% ($p<0·05$), twice daily cimetidine by 30% ($p<0·05$), night time ranitidine by 62% ($p<0·05$), and night time cimetidine by 40% ($p<0·05$). Twice daily ranitidine was significantly better at reducing mean 24 h H^+ activity than twice daily cimetidine ($p<0·05$) (Fig. 2) and night time ranitidine provided significantly better control of acidity than night time cimetidine ($p<0·05$) (Fig. 3). Cimetidine 800 mg was not significantly different

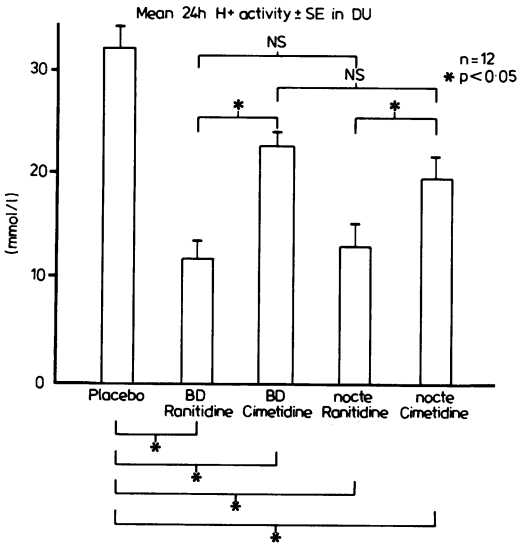

Fig. 1 *Mean 24 hour hydrogen ion activity ± SE for five treatments.*

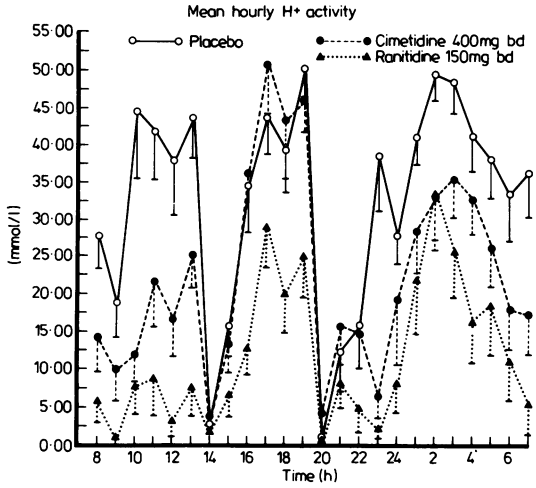

Fig. 2 *Mean hourly H^+ activity ± SE over 24 hour period after placebo, cimetidine 400 mg bd, and ranitidine 150 mg bd.*

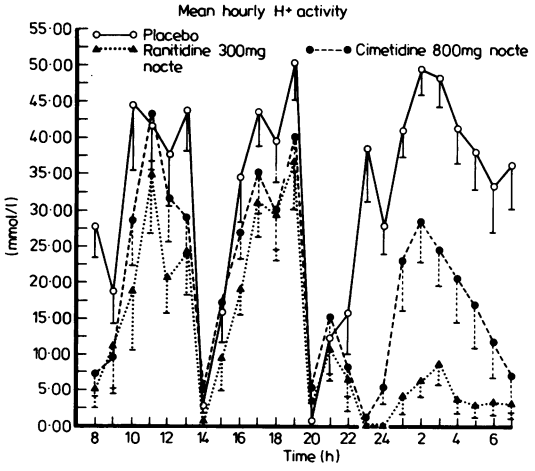

Fig. 3 *Mean hourly H^+ activity ± SE over the 24 hour period after placebo, cimetidine 800 mg nocte, and ranitidine 300 mg nocte.*

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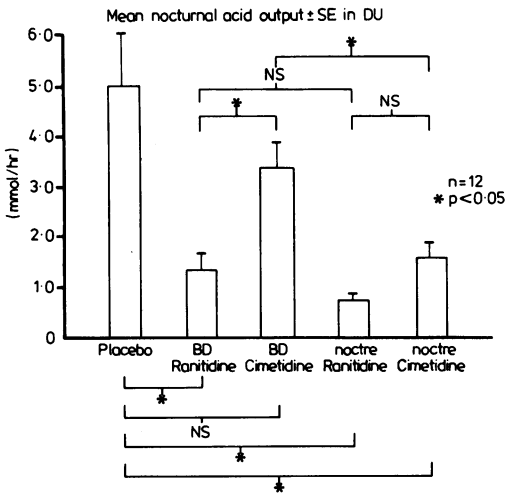

Fig. 4 *Mean nocturnal acid output ± SE for five treatments.*

from 400 mg bd and there was no significant difference between the two ranitidine treatments.

Reduction in H^+ activity during the morning (0900–1300) was 53% with twice daily cimetidine, 86% with twice daily ranitidine, 20% with night time cimetidine, and 50% with night time ranitidine. Although after lunch twice daily ranitidine reduced H^+ activity by 29% there was little reduction with the other treatments (Figs 2 and 3). Overnight, however, reductions were 34% with twice daily cimetidine, 54% with twice daily ranitidine, 56% with night time cimetidine, and 85% with night time ranitidine.

NOCTURNAL ACID OUTPUT

The results of the five treatments are shown in Figure 4. Cimetidine 400 mg bd decreased nocturnal acid output from 5·1 mmol/h to 3·7 mmol/h (NS), ranitidine 150 mg bd to 1·4 mmol/h ($p<0·05$), cimetidine 800 mg nocte to 1·6 mmol/h ($p<0·05$), and ranitidine 300 mg nocte to 0·8 mmol/h ($p<0·05$). Night time cimetidine and the two regimens of ranitidine were all significantly more effective at decreasing acid output than cimetidine 400 mg bd. There was no significant difference between twice daily ranitidine, night time cimetidine, and night time ranitidine.

Discussion

Nocturnal acid output and 24 hour H^+ activity were controlled better by ranitidine 150 mg bd than by cimetidine 400 mg bd and although ranitidine 300 mg nocte was better than cimetidine 800 mg nocte at decreasing mean 24 hour intragastric acidity, there was no difference between these latter two treatments at decreasing nocturnal acid output. Although nocturnal acid output was controlled better by cimetidine 800 mg nocte than cimetidine 400 mg bd, there was no significant difference between ranitidine 300 mg nocte and ranitidine 150 mg bd. There was also no significant difference in decreasing 24 hour H^+ activity between the two ranitidine treatments or between the two cimetidine treatments.

Twice daily cimetidine was better than night time cimetidine at decreasing H^+ activity during the morning but there was little difference between these two treatments after lunch. Overnight, the large single night time dose of cimetidine had a much greater effect on acid output and H^+ activity compared with the twice daily dose of this drug. Although there was a difference in decreasing H^+ activity between twice daily ranitidine and night time ranitidine during the morning, this was not as marked after lunch, and overnight, night time ranitidine was much better than twice daily ranitidine. Thus a single large nocturnal dose of an H_2 receptor antagonist is at least as effective at controlling both 24 hour H^+ activity and nocturnal acid output than a twice daily regimen.

Our results confirm our previous observation that twice daily doses of ranitidine[13] and cimetidine[14] are effective at decreasing 24 hour intragastric acidity although the decrease is not as great as our previous reports. This was probably because in the present study, half of the patients met our criteria of poor clinical response to cimetidine.[12] These patients had ultimately healed their ulcers with a variety of medical treatments other than H_2 receptor blockade. The previous poor response to cimetidine may also explain why the twice daily regimen of cimetidine had a decreased effect on H^+ activity and acid output in contrast with the twice daily ranitidine dosage. There have been three previous reports of ranitidine healing cimetidine resistant ulcers[15–17] but these were not controlled studies.

Blackwood and Northfield[18] showed that although cimetidine 800 mg had an increased and more prolonged effect on intragastric pH than the 400 mg dose both these regimens inhibit nocturnal acid output by a similar degree (92·7% and 94·2% respectively). This degree of acid inhibition is much greater than our report in patients showing a poor clinical response to treatment[19] when we failed to observe a significantly greater effect after increasing the dose of cimetidine from 1 g/day to 2 g/day.

Maintenance therapy with cimetidine 800 mg nocte has been shown to have a lower relapse rate[20]

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than with the 400 mg dose[17] and Fitzpatrick *et al* have suggested that maintenance therapy with cimetidine 400 mg nocte has mainly an antacid effect whereas cimetidine 800 mg nocte results in a real reduction of relapse rate.[21]

Cimetidine and ranitidine may increase serum prolactin[22 23] and by using a large nocturnal dose the risk of prolactin release might be increased in some patients. A total daily dose of cimetidine 800 mg nocte, however, is less than the 1 g/day originally recommended for cimetidine[1] and while using an 800 mg nocte dose for maintenance therapy, Blackwood *et al* reported no adverse events.[20] In addition, Burland *et al*[24] found no increase in serum prolactin after an 800 mg dose of cimetidine in healthy subjects.

On placebo, H^+ activity was lower during the daytime than during the overnight period which is when patients classically complain of pain relieved by food. Food buffering is more physiological than pharmacological control of acid secretion and the morning dose of an H_2 receptor antagonist may therefore be unnecessary.

If the concept of 'no acid no ulcer' is correct,[25] using a large single nocturnal dose of either cimetidine or ranitidine provides practical as well as theoretical advantages; patients would find a single dose more convenient and acceptable and compliance is likely to be better. Our study has shown that a single night time dose of an H_2 receptor antagonist is as effective as a twice daily regimen of these drugs in reducing H^+ activity and acid output and we suggest that a large single nocturnal dose of treatment be evaluated by clinical trial.

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Books

1985 Year book of digestive diseases Edited by N J Greenberger, F G Moody. (Pp. 495; illustrated; £41.00). Chicago: Year Book Medical Publishers Inc, 1985.

This is the second in the series of a compilation of original papers that have been selected and abstracted by two distinguished American gastroenterologists, one a physician and the other a surgeon. Each paper is reduced to a summary of the original paper, sometimes accompanied by a key Table or Figure, and followed by a comment from one of the editors. The layout, typography, and indexing are excellent, and make this a very easy way to keep up with what has been going on across the spectrum of clinical gastroenterology.

In no way can this anthology be described as comprehensive; the reduction of a year's publishing output to 250 papers inevitably reflects personal choice and national preoccupations. Others might choose differently – I would like to have seen the inclusion of more pathophysiology – but the book gains precisely because it is a personal selection, and is enlivened by the incisive and critical comments of the authors. It is a pity it is so expensive, at least for British gastroenterologists.

DAVID WINGATE

Manual of paediatric gastroenterology Edited by J H Tripp and D C A Candy. (Pp. 168; illustrated; £8.95.) Edinburgh: Churchill Livingstone, 1985.

This is a practical manual for clinicians for the practice of paediatric gastroenterology. It gives a practical didactic account without any references and this does not permit the reader to check upon what authority the views stated are based. The approach to management is very practical, however, and will be of particular value to new senior house officers in paediatrics. The book is full of lists and will be most helpful as a quick source of reference and should be available in busy children's departments and casualty departments for rapid referral. It should also be a useful aid to general practitioners. Its non-academic practical approach does limit, however, its educational value to stimulate the enquiring mind.

J A WALKER-SMITH

News

British Society of Gastroenterology

The Spring meeting of the British Society of Gastroenterology was held at the University of Lancaster from 9–11 April 1986, under the Presidency of Dr G P Crean. The first day was devoted to the BSG/Glaxo International Teaching Day, consisting of four symposia on the theme of 'Controversies in gastroenterology'. Special interest (endoscopy, pathology, surgery, and basic science) groups met during the first half of the second morning, before the start of the main scientific meeting. The plenary session included two 'State of the Art' Lectures (Dr P M Smith and Professor A S McNeish) and the 1986 Research Medal Lecture (Dr P J Ciclitira) as well as six free papers. The social programme included not only a civic reception and the conference dinner but also a cabaret evening; the highlight of the latter was a group from the Scottish Fiddle Orchestra under the 'mis-direction' of no less a person than the President of the Society.

BSG Research Award 1987

A three page summary of personal research work is invited by the Award Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 1987 Award. A bibliography may also be submitted if desired. The Award consists of a medal and £100 prize. Entrants must be 40 years or less (on 31 December 1987) but need not be a member of the BSG. All (or a substantial part) of the work must have been performed in the UK or Eire. The recipient will be required to deliver a 40 minute lecture at the Plenary Session of the Spring meeting in 1987. Applications (*six* copies) should be made to: The Honorary Secretary, BSG, 3 St. Andrew's Place, London NW1 4LB. *BY 1 DECEMBER 1986.*

Leeds Course in Clinical Nutrition

To be held from 1–5 September 1986 in the Dept. of Medicine, St James's University Hospital, Leeds. Further details from Mr T D Bilham, Dept. of Adult and Continuing Education, The University, Leeds LS2 9JT.

Correction

In the paper by Gledhill *et al* entitled 'Single nocturnal dose of an H_2 receptor antagonist for the treatment of duodenal ulcer', *Gut* 1983; **24:** 904–908; the dose quoted in the Summary, cimetidine 300 mg nocte should have read 800 mg nocte as in the remainder of the paper.