Changes in nocturnal and peak acid outputs after duodenal ulcer healing with sucralfate or ranitidine

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Abstract
Changes in basal and stimulated acid secretion after duodenal ulcer healing have been previously shown to be influenced by the nature of the treatment. This study aimed to determine possible changes in nocturnal acid secretion on duodenal ulcer healing in patients treated with sucralfate or ranitidine. Nocturnal acid output and peak acid output in response to pentagastrin stimulation were studied in 20 patients before and after duodenal ulcer healing with sucralfate (n = 9) or ranitidine (n = 11). Details regarding cigarette smoking were obtained from each subject. Median 10 hour nocturnal acid output fell significantly (p < 0.05) from 82.4 (29.1–188.3) mmol (median range) to 45.2 (14.7–144.4) mmol after healing with sucralfate, and rose significantly (p < 0.05) from 54.7 (16.8–74.3) mmol to 86.2 (11.7–118.1) mmol after ulcer healing with ranitidine. Peak acid output fell from 39.6 (22.0–52.8) mmol/hour to 27.8 (13.8–38.2) mmol/hour (p < 0.01) after healing with sucralfate, and unchanged after healing with ranitidine. There was no correlation between smoking and nocturnal acid output. These results provide further evidence that acid secretion decreases with sucralfate healing and remains the same or may even increase after ranitidine healing.

Ten hour nocturnal acid output has recently been shown to increase by 77% after four weeks’ treatment with nizatidine 300 mg at night in patients with a healed duodenal ulcer. We have previously measured acid secretion after duodenal ulcer healing3 and found a fall in acid secretory responses after healing with sucralfate, but no change following healing with ranitidine. The aim of this study was to determine possible changes in nocturnal acid output on duodenal ulcer healing in patients treated with sucralfate or ranitidine.

Subjects and methods
Twenty six patients (18 men and eight women; median age 32 years; range 21–56 years) with an active, endoscopically proved duodenal ulcer who had received no treatment other than token antacids for at least three weeks were randomised to receive treatment with either sucralfate 2 g twice daily or ranitidine 300 mg at night for six weeks, or if unhealed, eight weeks. Each patient underwent a nocturnal acid secretory test before starting treatment and three days after endoscopic confirmation of ulcer healing and stopping treatment. Six weeks after withdrawal of treatment a further endoscopy was performed to assess early relapse rates. Details regarding cigarette usage were recorded. Serum gastrin values were not measured.

On each study night patients were admitted to the gastrointestinal clinic laboratory at 17.30, having had nothing to eat or drink from 13.00. At 17.45 a size 14, vented nasogastric tube was passed into the stomach and positioned in the most dependent part of the stomach. Residual gastric contents were aspirated and discarded. A standard meal was taken between 18.00 and 18.30, consisting of 37 g protein, 104 g carbohydrate, and 67 g fat with a total kcal value of 1200. Gastric contents were aspirated completely at 20.00. Thereafter, gastric juice was collected in hourly batches until 08.00 by continuous suction supplemented by manual aspiration. At 08.00 a subcutaneous injection of pentagastrin (6 g/mg/kg) was given, and gastric juice was collected in 15 minute batches for the following hour. The H+ concentration was determined by titration to pH 7 using 0.2 mol/l NaOH. Hourly acid output was measured in each hourly collection period overnight, and nocturnal acid output was calculated for the 10 hour (22.00–08.00) period to conform to the method used by Fullarton et al.4 The contents aspirated during the 20.00–22.00 hours periods contained residual food. Peak acid output was calculated by doubling the sum of the two maximum consecutive 15 minute collections after injection of pentagastrin.

The results are presented as median and range and statistical analyses were performed using the signed rank test. Fisher’s exact test was used in the analysis of the smoking data. The study was approved by the local hospital ethics committee and informed consent was obtained from each patient.

Results
Twenty six patients had endoscopic ulcer healing after six or eight weeks’ treatment with either ranitidine (n = 11) or sucralfate (n = 9). Four patients (two taking ranitidine and two sucralfate) whose ulcers failed to heal after eight weeks’ treatment were excluded from analysis. Two further patients who had been taking sucralfate were excluded because of default (n = 1) or poor compliance due to nausea (n = 1).

Comparison of treatment groups
Table I shows that the ranitidine and sucralfate treated groups were comparable with regard to age, sex, and ulcer size.

Effect of treatment and ulcer healing on nocturnal acid output
Changes in hourly acid output before and after...
ulcer healing with ranitidine or sucralfate are shown in Figure 1. The 10 hour nocturnal acid output data for individual patients is shown in Figure 2; the median 10 hour nocturnal acid output increased from 54.7 (16.8–74.3) mmol to 86.2 (11.7–118.1) mmol (p<0.05) after ranitidine treatment and fell from 82.4 (29.1–188.3) mmol to 45.2 (14.7–144.4) mmol (p<0.05) following treatment with sucralfate. The increase in the nocturnal acid output in the ranitidine treated patients was mainly the result of a significant increase in acid concentration, while the fall in nocturnal acid output in the sucralfate treated patients was linked to a significant fall in volume (Table II).

EFFECT OF TREATMENT AND ULCER HEALING ON PEAK ACID OUTPUT

The peak acid output fell from 39.6 (22.0–52.8) mmol/hour to 27.8 (13.8–38.2) mmol/hour (p<0.01) after ulcer healing with sucralfate, while the pretreatment value of 24.0 (11.4–37.6) mmol/hour was unchanged at 27.8 (10.0–37.4) mmol/hour after ranitidine healing. Pretreatment values were, however, significantly higher in the sucralfate than in the ranitidine treated groups (p<0.01).

SMOKING AND CHANGES IN NOCTURNAL ACID OUTPUT ON HEALING

There was no correlation between smoking and nocturnal acid output, or between smoking and changes in nocturnal acid output on healing in the entire group. The nocturnal acid output was increased in eight of 15 smokers and in two of five non-smokers. In the sucralfate treated group, however, the nocturnal acid output increased in only one of seven smokers, whereas in the ranitidine treated group it increased in seven or eight smokers (p<0.02). In the ranitidine treated group, six of eight patients with an increased nocturnal acid output on healing smoked more than 10 cigarettes a day, compared with none of three patients in whom the nocturnal acid output fell on healing (Fig 2).

Table II: Volume and concentration of nocturnal acid secretion (10 hour) before and after ulcer healing in sucralfate and ranitidine groups

<table>
<thead>
<tr>
<th></th>
<th>Sucralfate group</th>
<th>Ranitidine group</th>
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<tbody>
<tr>
<td>H' concentration (mmol/l)</td>
<td>Volume (ml)</td>
<td>H' concentration (mmol/l)</td>
</tr>
<tr>
<td>Active Ulcer (median)</td>
<td>90-6 (37-2-104.5)</td>
<td>919 (440-1985)</td>
</tr>
<tr>
<td>Healed Ulcer (median)</td>
<td>65.7 (32-4-106.0)</td>
<td>629 (251-108.8)</td>
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Discussion

The influence of duodenal ulcer healing on acid secretion is controversial. Levin et al., in 1948, found no change in 12 hour nocturnal acid output in patients studied before and after duodenal ulcer healing. Recent controlled endoscopy studies have also failed to show a significant

Figure 2: Cigarette consumption and nocturnal acid output (10 hour) for individual patients before and after duodenal ulcer healing with ranitidine or sucralfate.
difference in acid secretion in patients with active and healed ulcers, although there was a tendency towards reduced acid secretion in the healed duodenal ulcer groups in two of them. These results contrast with the findings of Bodenar et al and Achord, who showed significantly higher acid secretory responses in patients with active than with healed duodenal ulcer, and with those of Kapur and Bardhan who found increased nocturnal intragastric acidity in patients with active, as opposed to healed, duodenal ulcer.

The effect of drug treatment on acid secretion is less contentious, at least in healthy volunteers. Aadland and Berstad and Frislid et al reported a transient increase in acid secretion in control subjects after 8 weeks treatment with cimetidine 1 g/day and ranitidine 150 mg twice daily, respectively, and Nwokolo et al showed rebound gastric hyperacidity in healthy subjects after 35 days' treatment with full dose cimetidine, nizatidine, and famotidine. The effect of H2 receptor blockers on acid secretion in patients with healed duodenal ulcer is less certain, and may be dose dependent. Jones et al reported increased responses to graded doses of imipramidine after three months' maintenance treatment with ranitidine 150 mg at night in duodenal ulcer patients in remission, but we were unable to confirm their findings in an almost identical study. Fullarton et al, however, found a convincing increase in nocturnal acid secretion in a similar group of patients after four weeks' treatment with full dose nizatidine (300 mg at night). Despite the good evidence for increased acid secretion after full dose H2 receptor blockade in volunteers and in patients with healed duodenal ulcer, several studies have been unable to show any change in acid secretory responses after healing of an active duodenal ulcer with an H2 receptor antagonist. Duodenal ulcer healing after treatment with sucralfate, on the other hand, is associated with a significant fall in acid secretory responses. The failure of acid secretion to fall on duodenal ulcer healing after treatment with H2 receptor blockers may be construed as indirect evidence of an increased parietal cell responsiveness after this treatment. The significant falls in both 10 hour nocturnal acid output and peak acid outputs after duodenal ulcer healing with sucralfate in this study support the concept that acid secretion is reduced after duodenal ulcer healing. In addition, the significant increase in nocturnal acid output after ulcer healing with ranitidine provides further evidence of increased acid secretion after healing with an H2 receptor blocker. The fall in peak acid outputs after healing with sucralfate was more noticeable than that in previous studies. The magnitude of the fall may have been influenced by the fact that the peak acid outputs was measured immediately after completion of the nocturnal study.

Replicate tests of nocturnal acid secretion, incidentally, show an average intraindividual variation of 23% personal communication. This is appreciably lower than the changes in median values encountered in the present study. The change after healing was +58% in the ranitidine treated, and -45% in the sucralfate treated groups.

Parietal cell responsiveness is usually assessed on the basis of dose response studies where the ratio of the low dose acid output:high dose acid output expressed as a percentage, is calculated, or the ED50 – the dose required to produce 50% of the maximum acid output – is determined. All these measurements, however, are somewhat arbitrary. They are based on the view that changes in parietal cell responsiveness are more likely to be reflected by the response to low dose than by high dose stimulation. The stimulatory factors involved in nocturnal acid output are unclear, but it is reasonable to presume that nocturnal acid output is a composite measure including the postcibal response at the beginning of the study (Fig 1), basal secretion during the latter part of the collection and, possibly, variations in autonomic and hormonal activity during the early hours of the morning. One can but speculate as to whether nocturnal acid output provides a measure of parietal cell responsiveness.

Two further points remain to be clarified. The first is whether changes in nocturnal acid output have any clinical relevance. Recent evidence suggests that patients with increased parietal cell responsiveness on duodenal ulcer healing are more likely to relapse. If nocturnal acid output can be accepted as a measure of parietal cell responsiveness then it may be useful in predicting patients at risk of relapse, in a manner analogous to the use of suppression of 24 hour acidity with H2 receptor blockers as a predictor of response to treatment. The low early relapse rate in this study precludes a conclusion. Secondly, does the nocturnal acid output provide a more sensitive index of the acid secretory status in ranitidine treated patients? Previous studies of basal acid output, responses to low dose penta-gastrin or histamine, or modified sham feeding and maximal pentagastrin or histamine stimulation failed to show a significant change in acid secretory responses after duodenal ulcer healing with an H2 receptor blocker. In this study, again, no change was found in response to maximal pentagastrin stimulation (peak acid outputs) but an increase in nocturnal acid output was noted. The striking increase in nocturnal acid output in duodenal ulcer patients in remission after treatment with an H2 receptor blocker, coupled with the findings in the present study, suggest that the nocturnal acid output may be a more sensitive index of changes after H2 receptor blockade.

Several views have been advanced to identify the cause of 'acid rebound' after treatment with an H2 receptor blocker. The current favoured view is that the 'up regulation' of both the H2 and gastrin receptors, with increased responsiveness to physiological stimuli once treatment is withdrawn. Hypergastrinaemia induced by prolonged acid inhibition has also been suggested as a possible mechanism for acid hypersecretion after the withdrawal of therapy, but studies with various H2 receptor blockers have shown that the raised gastrin values during treatment revert to normal before rebound acid hypersecretion becomes apparent.

It may be construed that the smoking data in the present study offer some support for the suggestion that smoking contributes to aug-
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