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A prospective comparison of the effects of placebo, ranitidine and highly selective vagotomy on 24 h ambulatory intragastric pH in patients with duodenal ulcer

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Twenty-four hour ambulatory intragastric pH (24 h IGpH) recording, a highly reproducible technique, was used to compare the effects of ranitidine and highly selective vagotomy (HSV) in 20 patients who had been referred for surgical treatment of duodenal ulcer. The 24 h IGpH was recorded when they were taking either placebo or ranitidine 300 mg at 10 pm, and again 4 to 13 weeks after elective HSV. Median 24 h IGpH and 24 h hydrogen ion activity (24 h $[H^+]$) were calculated for each patient. Median (quartile) 24 h IGpH was 1·4 (1·3–1·6) with placebo, 2·2 (1·8–2·7) after ranitidine and 2·6 (1·8–3·7) after HSV. IGpH was significantly higher after both ranitidine ($P<0·0001$) and HSV ($P<0·0001$) than after placebo, but IGpH after ranitidine did not differ from IGpH after HSV ($0·5>P>0·4$). HSV reduced 24 h $[H^+]$ by a median 68 per cent (quartiles, 47–82 per cent) whereas ranitidine reduced it by only 50 per cent (34–69 per cent, $0·1>P>0·05$). The 24 h pH recording was then analysed as two distinct periods; 'daytime' (8 am to midnight) and 'night-time' (midnight to 8 am). HSV reduced daytime $[H^+]$ by a median 77 per cent (59–93 per cent) whereas ranitidine reduced it by only 30 per cent (13–45 per cent, $P<0·0001$). HSV reduced night-time $[H^+]$ by a median 57 per cent (40–83 per cent) but ranitidine reduced it by a median 92 per cent (78–98 per cent, $P<0·01$). Thus, HSV inhibits gastric acidity more during the day than at night, whereas raniditine given at 10 pm effectively suppresses night-time acidity but is much less effective in suppressing daytime acidity. However both HSV and ranitidine will heal more than 90 per cent of duodenal ulcers. Hence, contrary to Dragstedt's teaching, suppression of nocturnal acidity is not of crucial importance for the healing of duodenal ulcers.

Keywords: Duodenal ulcer, nocturnal acid, highly selective vagotomy, ranitidine, ambulatory pH monitoring

Reduction of gastric acid output is the mainstay of medical and surgical treatment of duodenal ulcer. Dragstedt believed that suppression of nocturnal acid output was particularly important. In 1943, he and Owens reported[1] that transthoracic truncal vagotomy dramatically reduced the copious overnight secretion of acid that they had observed before operation in three patients with duodenal ulcer. This seminal work not only rekindled worldwide interest in the use of vagotomy for duodenal ulcer, but created an enduring impression that inhibition of overnight secretion was more important for the healing of ulcers than inhibition of secretion during the day. More recent work[2] which showed that a single 300 mg dose of ranitidine given in the evening was as effective in ulcer healing as two 150 mg doses given morning and evening lent further weight to this idea.

In the present study, intragastric pH was monitored over a 24 h period in control subjects and in patients with duodenal ulcer to study the effect of ranitidine and highly selective vagotomy (HSV). The findings cast doubt on the idea that overnight secretion is of paramount importance in the pathogenesis and therapy of duodenal ulceration.

** Mr T. Gledhill was tragically killed in a sailing accident on 9 April 1988 during the course of this paper's preparation*

Patients and methods

Two groups of subjects were studied. Firstly, 28 healthy male volunteers were studied to assess the reproducibility of serial recordings of 24 h intragastric pH. Secondly, 20 consecutive patients referred for elective operative treatment of duodenal ulcer were studied to assess the effects of ranitidine and HSV. All subjects gave informed consent before the first recording was commenced.

Measurement of 24 h ambulatory intragastric pH

Intragastric pH (IGpH) was monitored using the Medilog 1000 system (John Caunt Scientific Ltd, Oxford, UK), which employs an intragastric radiotelemetry capsule[3] (Remote Control Systems Ltd., London, UK), which incorporates both a glass pH electrode and a cotton thread reference electrode.

The telemetry capsule transmits a continuous, frequency-modulated radio signal to an aerial worn wrapped around the trunk at the level of the xiphoid. A fabric belt holds the aerial in position and two shoulder straps prevent the aerial sliding down the trunk. We showed previously that use of this belt virtually abolishes signal loss during recording of ambulatory intragastric pH with this system[4]. Information is relayed to a data recorder worn on a belt around the waist and the radio signal is sampled every 6 s, thus 14 400 measurements of gastric pH are obtained from each patient during a 24 h period.

Before the start of each IGpH recording, the system was calibrated with the telemetry capsule in buffers of pH 1·2 and 7·0 at 37°C.

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Calibration was repeated after every recording to check that the performance of the telemetry capsule had not altered. The entire 24 h recording was then transferred via a desktop computer to magnetic floppy disc for storage and analysis.

Day-to-day variation in 24 h intragastric pH

Twenty-eight healthy male volunteers of mean age 23 years (range 21–32) with no previous history of peptic ulcer disease had 24 h IGpH recorded on two occasions separated by an interval of 1–5 weeks.

Each subject arrived 45 min before commencement of the pH recording, having fasted for the previous 3 h. The telemetry capsule was tied to a tether and swallowed. The free end of the tether was attached to the skin of the cheek with adhesive tape to prevent onward passage of the telemetry capsule from the stomach. The length of the tether was calculated for each subject from his height, (50 cm for a height of 150 cm, increased 1 cm for every 7·5 cm that the subject's height exceeded 150 cm) and was fixed for each subject for the duration of the study.

When the capsule was in the stomach, the equipment was assembled and pH recording commenced. The subject then went home and returned at the same time the next day.

During the 24 h recording each subject kept a diary of food and fluid intake and the amount of tobacco smoked. The time of going to bed and rising was also recorded. Diet, smoking and sleeping patterns were duplicated, as far as possible, on the second occasion of IGpH recording.

Effects of ranitidine 300 mg nocte *and of highly selective vagotomy on intragastric pH in patients with duodenal ulcer*

Twenty patients, of median age 33 years (range 22–59), who had been referred for elective operation for duodenal ulcer were studied. In each the diagnosis of duodenal ulcer had been verified endoscopically within the previous 6 months. In 13 patients, the indication for operation was frequent attacks of pain or dyspepsia associated with relapse of the ulcer which was confirmed endoscopically; these patients had suffered with duodenal ulceration for a median 11 years (range 1–27). In the remaining seven patients, the indication for surgery was failure of their duodenal ulceration to heal despite 3 months continuous therapy with full dose anti-ulcer medication; these patients had suffered with duodenal ulcer for a median 7 years (range 2–30). In each patient 24 h IGpH was recorded on three occasions.

Before operation, 24 h IGpH was recorded twice in each patient, once when taking placebo and once when on ranitidine 300 mg. Anti-ulcer medication was stopped for 48 h before each of these recordings and the medication was ingested at 10 pm on two consecutive nights: the night before, and the night of IGpH recording.

All patients recorded details of their food and fluid intake and amount of tobacco smoked during each recording, and they were asked to go to bed at 11 pm and to rise at 7–7.30 am. Their actual bedtime and time of rising were recorded, as was the exact time at which the medication was taken. By these means, diet, smoking and sleeping pattern were kept constant for each IGpH recording. Each patient provided a 10 ml urine sample during every IGpH recording; this was stored at −20°C for assay of urinary ranitidine.

Each patient was allowed a 7–14 day interval between the two pre-operative IGpH recordings and the sequence of the placebo and ranitidine IGpH recordings was allocated in a randomized, single-blind manner. For all recordings of IGpH, patients who were working night shifts were studied 7 full days after their last night shift.

A standard insulin test was performed 7–10 days postoperatively following a technique we have previously described[5].

Each patient had 24 h IGpH recorded on a third occasion, 4–13 weeks after HSV, when the diet, smoking and sleeping pattern were identical to those of the pre-operative recordings. No medication, however, was taken on this occasion.

Analysis of data

Each 24 h IGpH recording was analysed to give median and quartile 24 h pH values. In the patients with duodenal ulcer, the 24 h record was also split into 'daytime' (8 am–midnight) and 'night-time' (midnight–8 am): median and quartile, daytime and night-time pH values were also calculated. The 24 h hydrogen ion activity (24 h $[H^+]$) was expressed as the area under the curve of hydrogen ion activity *versus* time. This was computed as the sum of the hydrogen ion activities equivalent to each of the 14 400 pH values provided by a 24 h recording. Daytime $[H^+]$ and night-time $[H^+]$ were similarly computed.

The effects of ranitidine and vagotomy on IGpH were calculated for each patient as the change in 24 h, daytime, and night-time $[H^+]$ compared with the corresponding $[H^+]$ when no active medication (placebo) was taken.

The effects of ranitidine and vagotomy on IGpH were compared by means of non-parametric statistics (Kruskal–Wallis one-way analysis of variance[6]), differences being considered statistically significant when $P < 0{\cdot}05$. As the use of tests which place weight on the magnitude of the difference between variables is not appropriate to comparisons of logarithmic variables, direct comparison of median IGpH values is not appropriate. To avoid this, all median IGpH values were converted to their equivalent hydrogen ion activity before comparisons between groups were made. However, because the use of hydrogen ion activities in graphs and text is cumbersome, the equivalent pH values have been quoted in preference.

The results of the insulin test were expressed as Hollander's criteria[7] and as peak acid response to insulin minus basal acid output.

Graphical presentation of data

Data are represented graphically as scatter plots on which group median values are indicated where appropriate.

Results

The tests were well tolerated by all subjects and no side-effects of the medication or of the IGpH recording procedure were noted. Patients' compliance with instructions was good and all patients took the tablets within 15 min of the time requested. Each patient with duodenal ulcer provided the required urine specimen, and a gas–liquid chromatographic assay showed that ranitidine was present in the urine of each patient who was taking ranitidine and in none of the samples from patients taking placebo.

The median data loss per 24 h IGpH recording over the entire study was 0·5 per cent (quartiles 0·07–2·1 per cent).

Day-to-day variation in 24 h intragastric pH in normal subjects

The median (quartile) 24 h IGpH of 28 normal subjects was 1·5 (1·5–1·7) on the first recording and 1·6 (1·4–1·8) on the second. Median 24 h IGpH on the two occasions did not differ significantly ($0{\cdot}975 > P > 0{\cdot}95$). Likewise, 24 h $[H^+]$ did not differ between the two recordings ($0{\cdot}8 > P > 0{\cdot}7$).

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Insulin tests. The insulin test was not performed in two patients because one suffered from insulin dependent diabetes and the other experienced an episode of fast atrial fibrillation which required cardioversion on the third postoperative day. For the remaining 18 patients the test was positive by Hollander's criteria in only 3, and the median peak acid response to insulin minus basal acid output was only 0·02 mmol/h.

24 h acidity. The median (quartile) 24 h IGpH in 20 patients with duodenal ulcer (*Figure 1*) was 1·4 (1·3–1·6) on placebo, 2·2 (1·8–2·7) on ranitidine 300 mg *nocte* and 2·6 (1·8–3·7) after HSV. Median 24 h IGpH was significantly higher on ranitidine and after HSV than on placebo ($P < 0{\cdot}0001$, $P < 0{\cdot}0001$ respectively). Median 24 h IGpH on ranitidine did not differ significantly from IGpH after HSV ($0{\cdot}5 > P > 0{\cdot}4$), although median hydrogen ion activity after HSV was one-quarter of that after ranitidine.

Median (quartile) suppression of 24 h $[H^+]$ (*Figure 2*) was 50 per cent (34–69) after ranitidine and 68 per cent (47–82) after HSV, but the difference was not quite significant ($0{\cdot}1 > P > 0{\cdot}05$).

Night-time acidity (midnight to 8 am). Median night-time IGpH (*Figure 3*) was 1·2 (1·0–1·4) on placebo, 5·8 (2·8–6·9) on ranitidine and 1·7 (1·4–2·8) after HSV. Both ranitidine and HSV raised night-time IGpH significantly compared with placebo ($P < 0{\cdot}0001$ and $P < 0{\cdot}001$ respectively). Median night-time IGpH was significantly higher after ranitidine than after HSV ($P < 0{\cdot}001$).

Median night-time suppression of $[H^+]$ (*Figure 4*) was

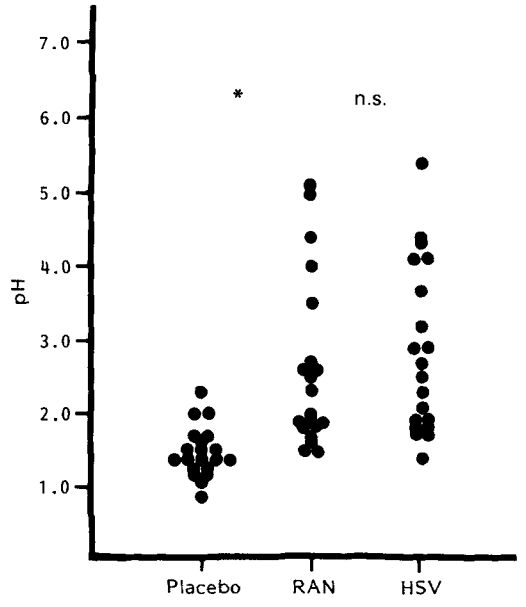

Figure 1 *Median 24 h intragastric pH with placebo, ranitidine 300 mg* nocte *(RAN) and after highly selective vagotomy (HSV) in 20 patients with duodenal ulcer. *P < 0·0001, placebo* versus *RAN and placebo* versus *HSV; n.s., not significant, RAN* versus *HSV*

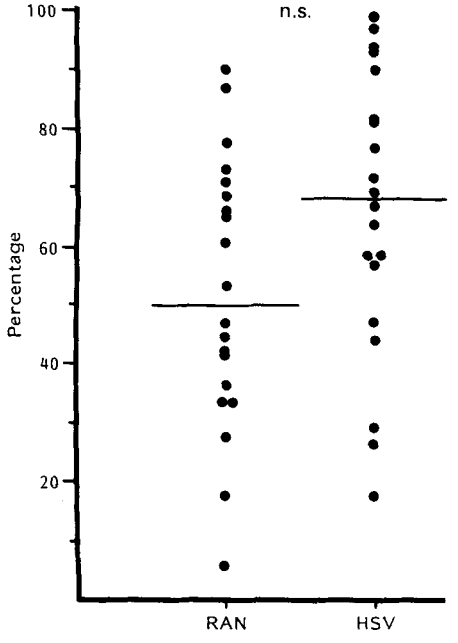

Figure 2 *Twenty-four hour acid suppression after ranitidine 300 mg* nocte *(RAN) and after highly selective vagotomy (HSV) in 20 patients with duodenal ulcer. Lines indicate median values. n.s., Not significant, RAN* versus *HSV*

92 per cent (78–98) after ranitidine and 57 per cent (40–83) after HSV ($P < 0·01$).

Daytime acidity (8 am to midnight). The median daytime IGpH (*Figure 5*) was 1·6 (1·4–1·7) on placebo, 1·8 (1·6–2·1) on ranitidine and 2·7 (2·0–3·8) after HSV. Median daytime IGpH was significantly higher after ranitidine ($P < 0·02$) and HSV ($P < 0·0001$) than after placebo. Also, median daytime IGpH after HSV was significantly higher than after ranitidine ($P < 0·001$).

Median daytime suppression of $[H^+]$ (*Figure 6*) was 30 per cent (13–45) after ranitidine and 77 per cent (59–93) after HSV ($P < 0·0001$).

Discussion

Using a highly reproducible technique, we have shown that ranitidine, given as a 300 mg *nocte* dose, is a more potent suppressor of night-time acidity than is HSV, whereas HSV is a more potent suppressor of daytime acidity than is ranitidine. Over a 24 h period there was no significant difference between suppression of acid after HSV and suppression after ranitidine, 300 mg *nocte*: nevertheless suppression by HSV was much greater than suppression by ranitidine and was almost significant ($0·05 < P < 0·1$).

Of the 20 patients studied, 18 had a standard insulin test performed between 7 and 10 days after HSV. The test was positive by Hollander's criteria in only three cases and the median peak acid response to insulin minus basal acid output

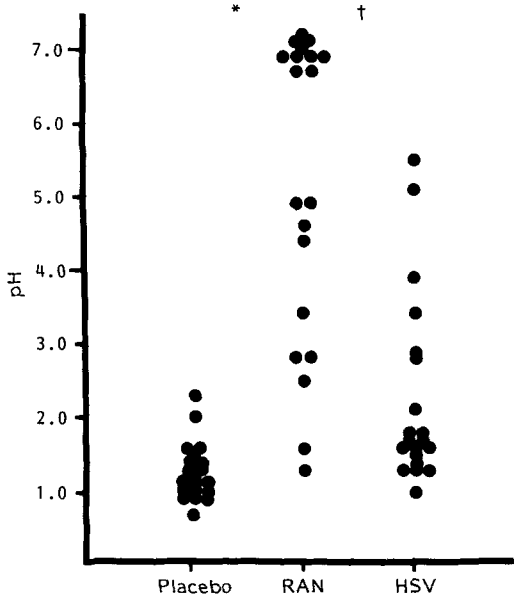

Figure 3 *Median night-time (midnight–8 am) intragastric pH with placebo, ranitidine 300 mg* nocte *(RAN) and after highly selective vagotomy (HSV) in 20 patients with duodenal ulcer. *P < 0·0001, placebo* versus *RAN; †P < 0·001, placebo* versus *HSV and RAN* versus *HSV*

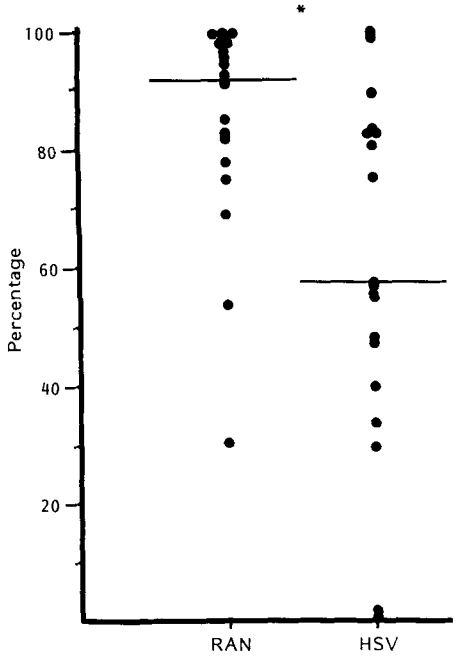

Figure 4 *Night-time (midnight–8 am) acid suppression after ranitidine 300 mg* nocte *(RAN) and after highly selective vagotomy (HSV) in 20 patients with duodenal ulcer. Lines indicate median suppression. *P < 0·01, RAN* versus *HSV*

was 0·02 mmol/h (quartiles 0–0·41 mmol/h). Most of the vagotomies seem to have been complete; thus our results, in particular the low overnight intragastric pH after HSV, cannot be attributed to incomplete vagotomy.

Other workers who have studied the effects of surgery and drugs on 24 h ambulatory intragastric acidity have measured IGpH by hourly aspiration of small aliquots of gastric juice[8], by continuous nasogastric suction to remove gastric juice in its entirety[9] or by intragastric titration to pH 5·0 with dilute alkali[10]. Direct comparison of our results with the findings of these workers is not valid as any technique involving aspiration of gastric juice, or intragastric titration, will raise antral pH and release gastrin. Thus, discrepancies between our findings and those of others may arise from these methodological differences: aspiration methods of measuring IGpH create an artefactual gastrin stimulus to acid secretion whereas non-aspiration techniques do not. Our technique is unable to measure the volume of acid secreted by the stomach and so acid output cannot be calculated. The non-aspiration techniques, like that described here, minimally disrupt gastric physiology, measure pH every 6 s and are highly reproducible[11] (M. J. Rogers *et al.*, unpublished results) a feature that is poorly documented for other methods of monitoring 24 h ambulatory IGpH.

Using a non-aspiration technique to study 24 h ambulatory intragastric pH in healthy males, Merki *et al.*[12] reported a median 24 h IGpH of 2·5 (quartiles 2·3–3·0) after ranitidine 300 mg at 7 pm. This finding is in good agreement with our observation, median 2·2 (quartiles 1·8–2·7), in patients with duodenal ulcer.

The pattern of intragastric acidity we have observed after ranitidine may have been influenced by the timing of the ranitidine dosage which was given at 10 pm. We used ranitidine 300 mg *nocte* because it is a simple regimen, in widespread clinical use, which has been shown to be as effective in healing duodenal ulcers as a 150 mg b.d. regimen[2]. Since ranitidine has a half-life in plasma of 3 h[13] and its action to suppress acid secretion is of about 4 h duration, a *nocte* dose of ranitidine might be expected to suppress nocturnal acid powerfully, but to provide little suppression of acid after 8 am the next morning. Vagotomy, in contrast, would be expected to give some degree of acid suppression over the entire 24 h period. The median hourly suppression of intragastric acid after HSV and ranitidine (calculated as the reduction in hourly $[H^+]$ by each treatment in each patient) is illustrated in *Figure 7*. Raniditine is seen to provide powerful suppression of acid overnight but little acid suppression after midday next day, whereas HSV affords

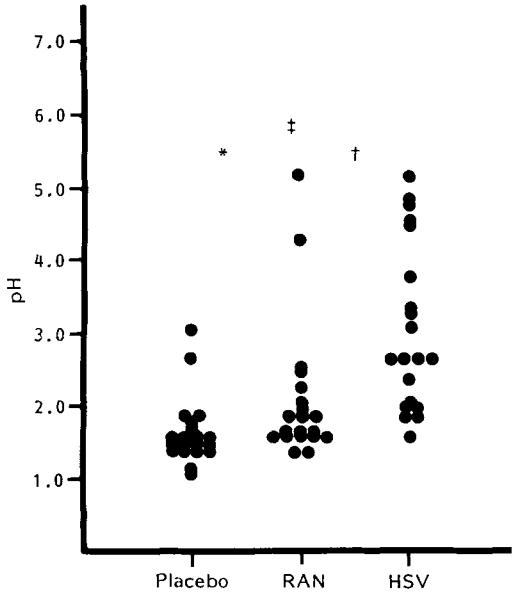

Figure 5 *Median daytime (8 am–midnight) intragastric pH after placebo, ranitidine 300 mg* nocte *(RAN) and after highly selective vagotomy (HSV) in 20 patients with duodenal ulcer.* * $P<0·02$, *placebo* versus *RAN;* † $P<0·001$, *RAN* versus *HSV;* ‡ $P<0·0001$, *placebo* versus *HSV*

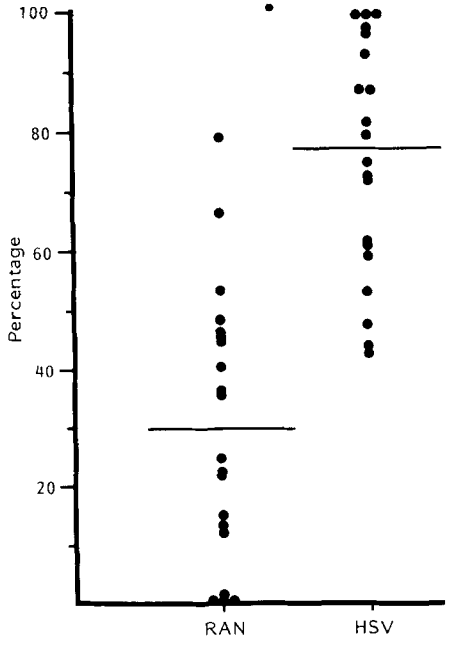

Figure 6 *Daytime (8 am–midnight) acid suppression after ranitidine 300 mg* nocte *(RAN) and after highly selective vagotomy (HSV) in 20 patients with duodenal ulcer. Lines indicate median acid suppression.* * $P<0·0001$, *RAN* versus *HSV*

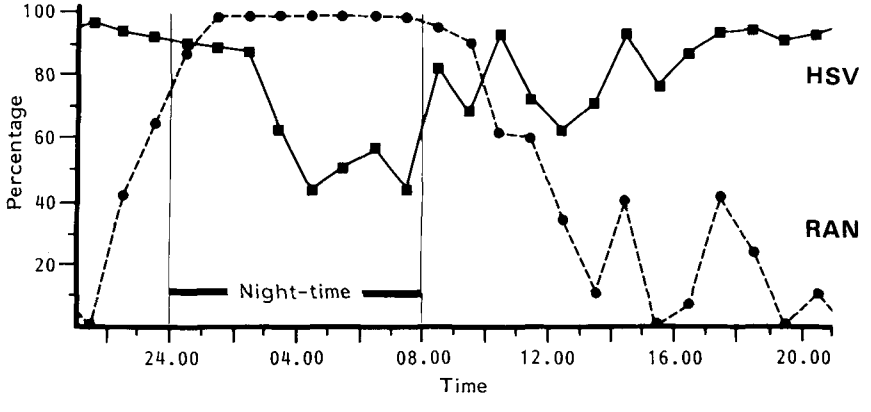

Figure 7 *Median percentage hourly acid suppression seen after ranitidine 300 mg* nocte *(RAN) and after highly selective vagotomy (HSV) in 20 patients referred for elective operation for duodenal ulcer. Ranitidine was taken at 10 pm; the night-time period (midnight–8 am) is indicated*

significant inhibition of acid over the entire 24 h, but gives greater suppression of daytime acid than of night-time acid—a finding that is at variance with Dragstedt's[1] ideas about the mode of action of truncal vagotomy.

If suppression of night-time acidity is the *sine qua non* for healing duodenal ulcers, treatments known to be potent in healing duodenal ulcers would be expected to have similar suppressive effects on night-time acid. We have found, however, that HSV and ranitidine gave markedly different degrees of suppression of night-time acidity. Thus the finding that two equally potent ulcer-healing regimens have such disparate effects on night-time acidity constitutes strong evidence against the hypothesis that night-time acidity is of crucial importance.

If powerful suppression of nocturnal acidity is not of critical importance for the healing of duodenal ulcers how can we explain the potent ulcer healing effect of the 300 mg *nocte* ranitidine regimen? Our hypothesis is that inhibition of 24 h intragastric acidity is of fundamental importance in healing duodenal ulcers; H_2 receptor antagonists are more effective in suppressing nocturnal acidity than daytime acidity, but they heal duodenal ulcers via their effect on 24 h acidity. HSV is more effective in suppressing daytime acidity than night-time acidity but its ulcer healing effect relates to its effect on 24 h acidity.

In summary, we have found that, contrary to Dragstedt's teaching[1], vagotomy suppresses daytime acidity more effectively than night-time acidity. Furthermore, the disparate effects of ranitidine and HSV on night-time acidity contrasts with their similar effect in healing duodenal ulcers. Hence, suppression of nocturnal acidity is not of major importance in the healing of duodenal ulcers.

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