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Rebound nocturnal hypersecretion after four weeks treatment with an H_2 receptor antagonist

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SUMMARY **Daytime intragastric pH, fasting and meal stimulated serum gastrin and nocturnal acid output were studied in eight male duodenal ulcer patients before, during and two days after completing nizatidine 300 mg nocte (20 00 h) for four weeks. Median nocturnal acid output (mmol/10 h) decreased during treatment to 11·6 (range 0·4–26·7) compared with pretreatment value of 39·4 (9·8–91·2); median acid inhibition 77% ($p<0·01$) which was strongest between 24 00 and 04 00 h. Two days after discontinuing treatment, nocturnal acid output increased to 74·1 (11–181). Compared with the pretreatment value this represents median rebound hypersecretion of 77% ($p<0·05$), caused by increased H^+ concentration and volume of secretion. Overall median daytime intragastric pH (09 00–21 00 h) was unchanged on the final day of treatment and two days after completing therapy, compared with the pretreatment values. Fasting serum gastrin measured between 09 30 and 10 00 h and the integrated gastrin response to an OXO breakfast taken at 10 00 h were also similar during and after treatment, compared with pretreatment values. The rebound nocturnal hypersecretion may be relevant to the high ulcer relapse rates after stopping H_2 receptor antagonists.**

Nizatidine is a new H_2 receptor antagonist which is four times more active on a molar basis than cimetidine and of similar potency to ranitidine.[1,2] In addition, nizatidine has a shorter duration of action (plasma half life 1·5 h)[3] than either cimetidine (1·9 h) or ranitidine (2·5 h).[4] Although the effects of single doses of nizatidine on basal and stimulated acid secretion are known[3,5,6] the effect of longer term therapy has not been studied. In the assessment of a new H_2 receptor antagonist it is important to show adequate suppression of nocturnal acid secretion as this has established benefit in ulcer healing.[7] This study was designed to determine the effect of four weeks nizatidine treatment on nocturnal gastric acid output, daytime intragastric pH and serum gastrin.

Methods

PATIENTS

Eight male subjects (median age 43 years, range 29–79) with a past history of endoscopically confirmed duodenal ulcers were studied while in clinical remission. None of the patients had received H_2 receptor antagonist therapy within two weeks of starting the study. Their mean weight was 76 kg (range 52–89), and seven were cigarette smokers. Six patients had previously undergone multiple gastric secretion tests as part of a previous study.

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STUDY DESIGN

Each patient was studied before starting nizatidine therapy, on the final day of a 28 day course of nizatidine 300 mg taken at 20 00 h, and again two days after completion of therapy. On each occasion daytime intragastric pH, fasting serum gastrin, integrated gastrin response to a standard OXO breakfast and nocturnal acid output were studied. To ensure study compliance each patient was contacted on their penultimate day of treatment and regular capsule counts were carried out.

DAYTIME INTRAGASTRIC pH

Daytime intragastric pH was monitored between

09 00 h and 21 00 h. On the post-treatment study day this was from 37 h–49 h after taking the last dose of nizatidine. For this a combined glass electrode (Radiometer GK 2802C) was passed perorally into the body of the stomach and its position confirmed radiologically. It was connected to a Digitrapper MkII (Synectics Medical) solid state recorder which registers pH every four seconds. The electrodes were calibrated at the start and completion of each recording using standard buffers of pH 1·07 (Synectics 5002) and 7·01 (Synectic 5001). On each study day patients were given standard meals (700 kcal each) at 12 30 and 17 30 h. Including the 40 kcal OXO breakfast each patient's total daily energy intake therefore was 1440 kcal. Smokers documented their cigarette consumption on their first study day and smoked an identical number on subsequent study days.

SERUM GASTRIN RESPONSE

Between 09 30 h and 10 00 h and with the patients fasted since the previous evening, three 10 ml venous blood samples were taken at 15 minute intervals for plasma gastrin estimation. On the post-treatment study day this was from 37·5–38 h after taking the last dose of nizatidine. At 10 00 h the patients took a standard OXO breakfast (40 kcal) consisting of two beef cubes (OXO Ltd, Croydon, England) dissolved in 200 ml water at 50°C. Further venous blood samples were obtained at 10 minute intervals for 90 minutes. Each sample was immediately centrifuged and the plasma stored at −20°C. Plasma gastrin estimation was done by radioimmunoassay using antibody R98 which has a lower limit of detection of 5–10 pg/ml.[8]

NOCTURNAL ACID OUTPUT

At 22 00 h, one hour after removing the intragastric electrode, a size 14F vented gastric tube (Andersen Inc, N York) was passed into the body of the stomach and its position confirmed by water recovery test. This was continuously aspirated overnight (22 00–08 00 h) and the gastric collections analysed as hourly aliquots. H^+ concentration was calculated for each hour by titration against 0·1 N NaOH to pH 7 using an autotitrator (Radiometer ETS 822). Hourly acid output (vol×conc) was calculated for each hour overnight (22 00–08 00). Nocturnal output (mmol) was expressed as total acid output from 22 00–08 00 h (mmol/10 hours). On the post-treatment day this was from 50–60 h after taking the last dose of nizatidine.

STATISTICAL ANALYSIS

The intragastric pH data were transferred from the Digitrapper MkII recorder (Synectics Medical) to an IBM compatible computer (Amstrad PC 1512 HD20) and analysed using the EsopHogram and GastrograpH programs (ver 5·0, 1987, Gastrosoft Inc). For each complete study day – that is, before, during, and after nizatidine therapy, median pH profiles were created by combining individual median values at 10 minute intervals throughout the 12 hour study period (09 00–21 00 h) using the Statphac program (version 2·07, 1987, Gastrosoft Inc). Integrated median pH curves were then created for each study day. In addition, for each individual median pH values were calculated for (a) 30 minute intervals from 09 00–21 00 h, (b) the time period 09 00–13 00 h termed morning pH, (c) the period 13 00–21 00 h termed afternoon pH, and (d) each complete study day. This was facilitated by using a compatible statistical package for analysis of pH data (StatpHac, ver 2·07, 1987 Gastrosoft Inc). Statistical comparisons between paired data were performed for each of these study periods using the one-sided Wilcoxon's signed-rank sum test. Significance was taken at the 5% level ($p \leq 0{\cdot}05$).

For analysis of the fasting gastrin data, the mean value of the three fasting samples was calculated for each individual for each study day. The integrated gastrin response to the OXO meal was calculated by estimating the area under the plasma gastrin time curve (AUC) using the trapezoid method.[9]

Statistical comparison of the results on the different study days was performed using the two sided Wilcoxon's rank-sum test. The study was approved by the local hospital Ethical Committee

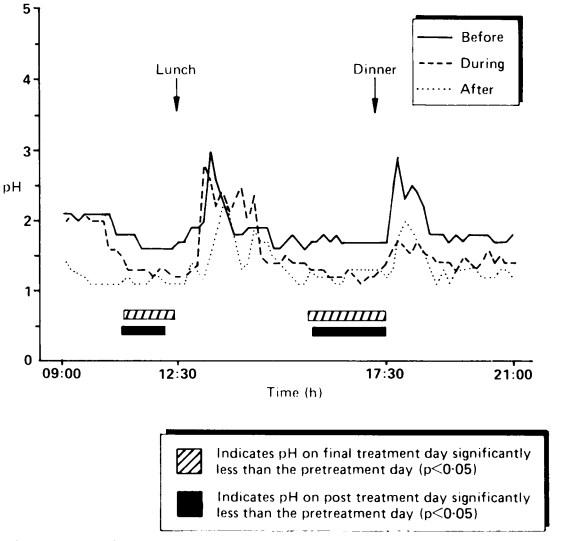

Fig. 1 *Median daytime (09 00–21 00 h) intragastric pH before, during and two days after four weeks' nizatidine 300 mg nocte (20 00 h).*

and all patients gave written fully informed consent before entry.

Results

DAYTIME INTRAGASTRIC pH

The overall daytime (09 00–21 00 h) median intragastric pH value pretreatment was 1·8 (range 1·0–3·2) which was similar to that on treatment (1·3: range 1·2–2·3) and to that post-treatment (1·7 range 1·1–1·7) (Fig. 1). Likewise the median morning (09 00–13 00 h) and afternoon (13 00–21 00 h) pH values were unchanged during and after nizatidine therapy compared with the pretreatment study day (Fig. 1). When the paired median pH values were analysed for each 30 minute interval, however, the intragastric pH was significantly lower on the final day of treatment over the mid-morning (11 00–12 30) and mid-afternoon (16 00–17 30) periods compared with the same pretreatment time periods ($p<0·05$) (Fig. 1). There was also a significantly lower median pH over similar time periods (10 45–11 45 and 16 15–17 35 h) two days after treatment compared with the same pretreatment time periods ($p<0·05$) (Fig. 1).

SERUM GASTRIN RESPONSE

The median fasting serum gastrin pretreatment was 36 pg/ml (range 27–58) and remained similar on therapy at 44 (22–75) and two days post-therapy at 35 (20–63).

The median integrated gastrin response (pg/ml/min) to the OXO meal before treatment was 4875 (range 4225–7375). This was not significantly altered on treatment being 5950 (range 3900–10 000) ($p=0·1$) (Fig. 2) or two days after treatment being 5200 (range 3000–9300) ($p=0·07$) (Fig. 2).

NOCTURNAL ACID OUTPUT

Median nocturnal acid output (mmol/10 h) was decreased during nizatidine therapy at 11·6 (range 0·4–26·7) compared with the pretreatment value of 39·4 (9·8–91·2), representing a median acid inhibition of 77% ($p<0·01$) (Fig. 3). This inhibition was because of a similar reduction in the volume and H^+ concentration of secretion (Table) and was most pronounced between the hours of 24 00 and 04 00 h (Fig. 4). Two days after completion of therapy, however, median acid output was increased at 74·1 (range 11–181) compared with pretreatment values ($p<0·05$) representing a median rebound hypersecretion of 77% (Fig. 3). This rebound hypersecretion occurred throughout the entire night time study period of 22 00–08 00 h (Fig. 4), and was accounted for by an increase in both H^+ concentration and volume of secretion (Table).

Discussion

This study has demonstrated that a 28 day course of nizatidine 300 mg at 8 00 pm effectively inhibits nocturnal acid secretion without causing any suppression of daytime intragastric pH. The return of normal acidity 12 hours post-dosing is consistent with the plasma half life of the drug.[3] Maintenance of a normal daytime intragastric pH may be important when considering longterm drug therapy as prolonged hypoacidity has been shown to alter the gastric microflora with production of nitrosamines which

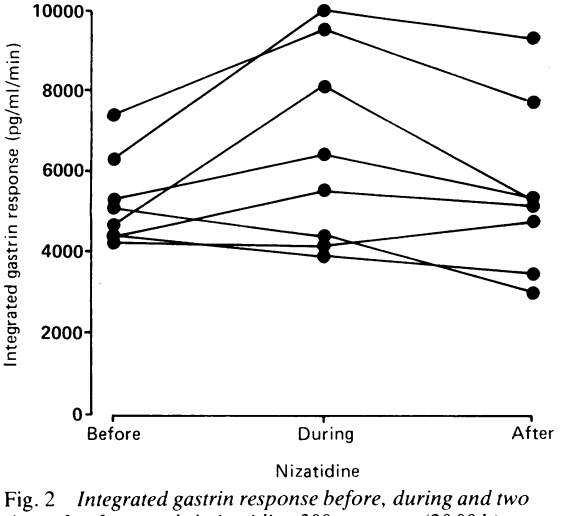

Fig. 2 *Integrated gastrin response before, during and two days after four weeks' nizatidine 300 mg nocte (20 00 h).*

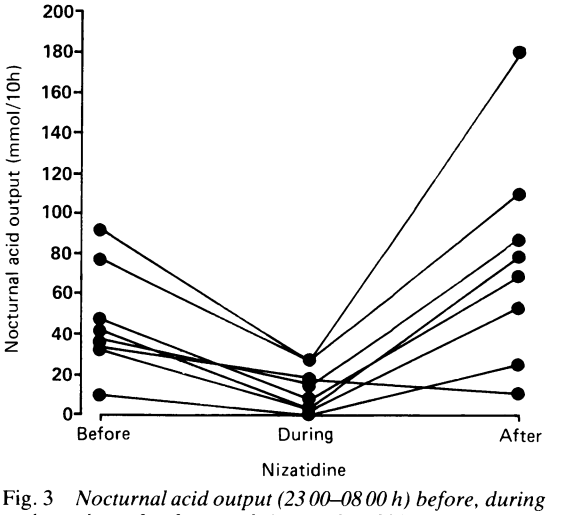

Fig. 3 *Nocturnal acid output (23 00–08 00 h) before, during and two days after four weeks' nizatidine 300 mg nocte (20 00 h).*

Table *Hourly acid output, H⁺ activity and volume of gastric secretion before, during and after four weeks nizatidine*

	Pre	*During*	*Post*
Acid output (mmol)	3·9 (1–9·1)	1·2 (0·4–2·7)	7·4 (1·1–18·1)
H^+ activity (mmol/l)	63·6 (49–77)	28·3 (1·4–44)	84·0 (25–94)
Volume (ml)	61·7 (12–128)	38·8 (22–101)	85·2 (31–221)

All values represent median with ranges.

may act as carcinogens.[10,11] The effect of acid inhibitory agents on serum gastrin concentrations is also important when considering longterm therapy. In rats longterm high dose treatment with the potent acid inhibitory agent omeprazole resulted in the development of gastric carcinoid tumours which was thought to be the result of the effects of prolonged hypergastrinaemia.[12] In our study daytime fasting and meal stimulated gastrin concentrations were not significantly increased after a one month course. It has previously been assumed that an increase in gastrin concentrations during treatment with acid inhibitory agents was related to acid inhibition,[13,14] however, doubt now exists.[15]

The rebound acid hypersecretion noted two days after completion of therapy is of particular interest as increased ulcer relapse rates have been noted after healing with H_2 receptor antagonists compared with other ulcer healing drugs.[16–18] Rebound hypersecretion has been reported in clinical trials with other H_2 antagonists[19,20] although the evidence is unconvincing. Brown *et al*, in an uncontrolled study, showed a small increase in basal acid output after four weeks cimetidine therapy in nine patients compared with pretreatment values.[19] Binder *et al* also showed a small increase in basal acid output in a randomised controlled study involving 57 patients after two weeks' cimetidine therapy but not after four or six weeks' treatment.[20] The majority of previous studies have not demonstrated rebound hypersecretion with H_2 antagonists but this may be because most have only studied maximal secretory capacity with high dose stimulants.[13,21,22] In our study we chose to look at nocturnal acid output as it is known to play an important role in duodenal ulcer disease and is a reproducible measure of basal output.[23] Nocturnal acid output has been used to assess the efficacy of single doses of H_2 receptor antagonists[24–26] but to our knowledge has not previously been examined before, during, and after withdrawal of a full therapeutic course.

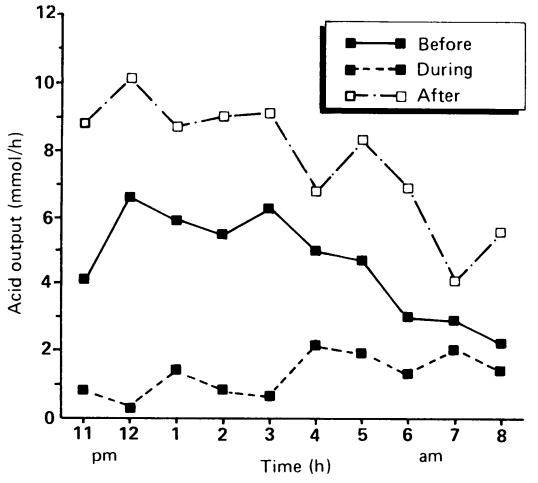

Fig. 4 *Hourly nocturnal acid output before, during, and two days after four weeks' nizatidine 300 mg nocte (20 00 h).*

The mechanism of the rebound hypersecretion noted in this study is not clear. Boyd *et al* have shown that acid output is suppressed by approximately 15% in volunteers subjected to their first intubation test compared with subsequent tests.[23] This is unlikely to explain our increased secretion on the third test day as six of our eight patients had undergone previous tube tests and the rebound noted amounted to 77%. Hypergastrinaemia induced by prolonged acid inhibition with associated parietal cell hyperplasia has been suggested as a possible mechanism for acid hypersecretion after H_2 receptor antagonist withdrawal. This sequence of events, however, has only been demonstrated in rats after high doses of metiamide[27] and not in man.[28] H_2 receptor antagonist withdrawal after a one month course has been shown to increase meal stimulated gastrin response in man[14] although the underlying mechanism remains unknown. In rat studies prolonged acid inhibition with either high dose ranitidine or omeprazole has been shown to produce hypergastrinaemia with an associated enterochromaffin-like cell hyperplasia although after discontinuation of treatment serum gastrin levels returned to control values within one week.[29] Moreover, although potent acid inhibitory agents such as omeprazole have been shown to produce hypergastrinaemia this may not necessarily exert trophic effects on the parietal cells.[30] In our own study there was no evidence of rebound hypergastrinaemia to explain the rebound hypersecretion.

Another cause of the rebound nocturnal hypersecretion could be 'up-regulation' of the histamine receptor on the parietal cell. Aadland and Berstad noted an increased acid output in response to low dose histamine 60 hours after a four week course of cimetidine compared with pretreatment values in healthy volunteers suggesting an increased sensitivity

('up-regulation') of the H_2 receptor after prolonged H_2 blockade.[31] In a later study to confirm the physiological significance of this 'up-regulation' Frislid *et al* showed an increase in meal stimulated acid output compared with pretreatment values 60–64 h after cessation of four weeks' ranitidine.[32] Most recently, Jones *et al* showed an increase in H_2 receptor sensitivity to the H_2 agonist impromidine in duodenal ulcer patients after three months' ranitidine treatment.[33]

If 'up-regulation' of H_2 receptors explains the rebound nocturnal hypersecretion then a similar effect would be expected during the day. The fact that we found no significant lowering of overall intragastric daytime pH post-treatment does not exclude rebound daytime hypersecretion as pH is only a measure of hydrogen ion activity and not acid output as was studied during the night. There were, in fact, time periods in mid-morning and mid-afternoon when the pH was significantly lower on the post-treatment study day compared with the equivalent pretreatment study periods providing some evidence for daytime rebound hyperacidity. The lower pH values demonstrated on the final day of treatment during mid-morning and mid-afternoon periods compared with identical pretreatment time periods are particularly interesting. The very short half life of nizatidine may allow rebound hyperacidity to occur during the day while still taking night time treatment. Such an effect, however, during treatment with nizatidine does not appear to be clinically adverse as ulcer healing rates and symptom relief are similar to other H_2 receptor antagonists.[34,35]

Although H_2 antagonists have transformed the management of acute duodenal ulcer disease the high relapse rates noted after discontinuation of therapy remain a concern. Further investigation of alterations in gastric function after healing courses of H_2 antagonist therapy are required to establish whether they may be contributing to the relapse rate.

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