Comparison of the effects of gastric antisecretory agents in healthy volunteers and patients with duodenal ulcer

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SUMMARY Thirty published studies of the clinical pharmacology of gastric antisecretory agents in normal volunteers and duodenal ulcer patients were reviewed. The aim was to investigate the relationship between antisecretory effect in the two populations. There was a significant correlation between effect in patients and normal subjects for suppression of 24 hour intragastric acidity (r=0.732; p=0.0068), nocturnal intragastric acidity (r=0.861; p=0.0033) and nocturnal acid output (r=0.964; p=0.0069). The regression lines for 24 hour and nocturnal acidity were very similar. The expected antisecretory effect of a particular dosage regimen in patients with duodenal ulcer can be predicted mathematically from data derived from studies in normal volunteers.

Antisecretory drugs are the agents most frequently prescribed for the treatment of duodenal ulcer. Prior to a new agent being investigated in controlled clinical trials, the antisecretory effects of different dose schedules are defined in clinical pharmacological studies. Such studies have been done both in normal volunteer subjects and in patients with healed duodenal ulcer. It is logistically easier to do this type of study in normal subjects. The relevance of such studies for future clinical use had not been established, as duodenal ulcer patients tend to secrete more acid than non-ulcer subjects.1 It is therefore not known whether results from studies in normal subjects can be extrapolated to duodenal ulcer patients. The aim of this investigation was to analyse the results of studies of antisecretory drugs on 24 hour and nocturnal intragastric acidity and nocturnal acid output in normal volunteers and duodenal ulcer patients to see if the two populations were distinct.

Methods

The reported clinical pharmacological studies of the effects of antisecretory drugs on 24 hour and nocturnal intragastric acidity and nocturnal acid output were reviewed.2-31 For some agents, a number of different dosage schedules have been investigated, not all of which have subsequently been developed for clinical use; all were considered. Where the same dose schedule has been studied in both normal volunteers and duodenal ulcer patients, the results were compared. Simple linear regression analysis was performed with the significance level of the correlation coefficient (r) being measured by the F-test.

Results

We identified 12 dose regimens where 24 hour intragastric acidity had been measured in both normal volunteers and duodenal ulcer patients. These were cimetidine 200 mg tid + 400 mg nocte, cimetidine 400 mg bd, cimetidine 800 mg nocte, cimetidine 1200 mg nocte, cimetidine 200 mg qid, ranitidine 150 mg nocte, ranitidine 300 mg nocte, famotidine 40 mg nocte, omeprazole 40 mg per day, and pirenzepine 75 mg bd. The relationship between the two groups is shown in Figure 1. There is a highly significant correlation between the degree of suppression in the two groups (r=0.732; p=0.0068).

For nocturnal intragastric acidity, nine dose regimens had been investigated in both groups. These were cimetidine 200 mg tid + 400 mg nocte, cimet-
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dine 400 mg bd, cimetidine 800 mg nocte, cimetidine 1200 mg nocte, ranitidine 150 mg nocte, ranitidine 300 mg nocte, famotidine 40 mg nocte, oxmetidine 400 mg bd and SK&F 93479 40 mg nocte. The relationship is shown in Figure 2. Again, there was a highly significant correlation (r=0.861; p=0.0033).

The similarity of the regression lines for 24 hour and nocturnal intragastric acidity (Figs 1, 2) is striking. The extrapolated intercepts on the Y axis are 22.1 and 20.9 respectively. These are not significantly different from each other (p=0.993). The slopes of the regression lines are 0.678 for 24 hour acidity and 0.776 for nocturnal acidity. Again, these do not differ significantly from each other (p=0.269).

The relationship between the two groups can be described mathematically using the equations of these lines. For 24 hour intragastric acidity,

\[
\% \text{ suppression in DU subjects} = \frac{\% \text{ suppression in normal subjects} - 22.1}{0.678}
\]

For nocturnal intragastric acidity,

\[
\% \text{ suppression in DU subjects} = \frac{\% \text{ suppression in normal subjects} - 20.9}{0.776}
\]

For nocturnal acid output, there were only five regimens which had been assessed in both groups. These were cimetidine 400 mg bd, cimetidine 800 mg nocte, cimetidine 1200 mg nocte, ranitidine 150 mg nocte and pirenzepine 100 mg nocte. Despite the small numbers, there was still a significant correlation (r=0.964; p=0.0069).

**Discussion**

This study has shown that the effect of antisecretory drugs in the doses evaluated in normal volunteers is closely related to their effect in patients with duodenal ulcer. The degree of suppression in normal volunteers is greater than that in duodenal ulcer patients. It is generally believed that duodenal ulcer patients have a greater acid secretory capacity than non-ulcer subjects, and it has recently been shown that ulcer subjects secrete more acid than normal controls throughout a 24 hour period. Although the effects of antisecretory agents are proportionately less in ulcer patients, it seems that commonly prescribed dose regimens of H2 receptor antagonists are sufficient to reduce acid secretion to levels seen in non-ulcer subjects. Patients with duodenal ulcer are not less sensitive to the effects of antisecretory drugs, but their acid secretion seems to be set at a higher level. This may be a manifestation of the increased parietal cell mass seen in these patients.
Nocturnal acid secretion is an important factor in duodenal ulcer pathogenesis. In a recent analysis of antisecretory drugs in duodenal ulcer, we found that the degree of suppression of nocturnal intragastric acidity was more strongly correlated to healing rates than was suppression of 24 hour acidity.

In summary, because the antisecretory effects of drugs in normal subjects are so well correlated with their effects in ulcer patients, new drugs or new regimens for existing drugs may be adequately investigated in normal volunteer subjects. Studies of nocturnal acidity may be adequate, as the correlation between groups is stronger than with 24 hour acidity and as it is nocturnal acidity in duodenal ulcer patients which is best correlated with healing rates. This approach should facilitate future research and development of antisecretory agents.

As an example, using the equation of the line in Figure 2, a drug which suppresses nocturnal intragastric acidity by 70% in normal subjects is likely to produce a suppression of 63-3% in patients with duodenal ulcer.

References
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