Do H₂ receptor antagonists have to be given at night? A study of the antisecretory profile of SKF 94482, a new H₂ receptor antagonist which has a profound effect on daytime acidity

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SUMMARY Evening dosing has become standard for H₂ receptor antagonists, because available agents inhibit nocturnal basal acid secretion more effectively than daytime stimulated secretion. We studied the optimal time of administration of a new high affinity long acting H₂ receptor antagonist, SKF 94482, for the suppression of intragastric acidity using intragastric telemetry. Sixteen healthy subjects received SKF 94482 200 mg or placebo at 07 30, 17 30, and 21 30 h during four separate studies. Time (h) above pH 4 was (mean (SD)) 1.1 (1.2) on placebo, 7.8 (5.0) on SKF 94482 given at 07 30, 5.75 (3.6) on SKF 94482 given at 17 30, and 6.1 (2.9) when given at 21 30. All treatment regimens were effective in increasing time above pH 4 ($p < 0.01$). The efficacy of the morning dose of SKF 94482 indicates that the best time to give H₂ receptor antagonists depends on their pharmacological properties.

Since the introduction of cimetidine there has been a constant rationalisation of dose and time of administration of the H₂ receptor antagonists. This has resulted from a better appreciation of their effect on intragastric acidity and the role of acid suppression in duodenal ulcer healing. While available H₂ receptor antagonists have a profound effect on basal nocturnal acid secretion^{1–4} they are less effective in the inhibition of naturally stimulated daytime acid.^{1,3,5} The efficacy of targetting the H₂ receptor antagonists to the nocturnal time period has been borne out in individual trials of duodenal ulcer healing^{6,7} and by a meta-analysis designed to study the relationship between acid suppression and ulcer healing.⁸ The proton pump blocker omeprazole, however, in doses of 20 mg/day or greater, can achieve higher healing rates than the H₂ receptor antagonists, which may result from the addition of daytime to nocturnal acid suppression.^{9–11} The potent prolonged acid suppression of omeprazole is also associated with a significant increase in serum gastrin,¹² which has been the subject of considerable debate^{13–16} in view of the possible deleterious consequences.

Using a three dimensional model to explore the relationship between acid suppression and ulcer healing, increasing the duration of suppression – that is, the number of hours spent above any given threshold pH – accelerated the rate of healing up to 16 hours.¹⁷ Thus extending the duration of acid suppression afforded by H₂ receptor antagonists beyond the nocturnal period might significantly improve ulcer healing, perhaps without the effect on gastrin from suppression of acid throughout the whole 24 hour period.

SKF 94482 is a new H₂ receptor antagonist which in *in vitro* and animal studies has a high affinity for the H₂ receptor and a potent and unusually long duration of action on acid secretion. The drug has a low bioavailability of approximately 7%, a half life of 15–32 hours and when given orally is twice as potent as ranitidine. We studied the optimal time of administration and duration of effect of this new drug by its effect on 24 hour intragastric acidity.

Methods

SUBJECTS

In a blinded, placebo controlled, randomised, latin square, crossover study SKF 94482 200 mg was

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administered at 07 30, 17 30, and 21 30 in 16 healthy male volunteers mean age 26 years (PAO >20 mmol/l). Drug regimens were administered for seven days, with the gastric acidity studies taking place on the sixth and seventh day of each regimen. There was no washout period between each regimen, because it was predicted that steady state was already reached by day 6. Only 15 of the planned 16 subjects were enrolled in the study because of a lack of study drug. All subjects gave written informed consent and the study was approved by the ethics committee of McMaster University Medical Center.

Throughout the study the subjects were encouraged to maintain the meal schedule used on the study days when intragastric acidity was recorded. Meals were standardised for time (breakfast 08 15, coffee 11 15, lunch 13 15, tea 16 15, dinner 18 15, night snack 22 15) and content as per an agreed protocol of an International 24 h Gastric Acid Study Group. The subjects reported to the investigational laboratory at 1600 on day 6 of each regimen when a combination glass pH electrode (440 M4, Ingold AG, Urdorf, Switzerland) was placed in the stomach. The tip was positioned in the body of the stomach by fluoroscopy (first visit), and the distance from the tip of the probe to the nares carefully measured for placement on future study days. Intragastric pH was recorded at six second intervals (14400 readings) and stored on portable solid state dataloggers (Gastrograph, MIC AG, Solothurn, Switzerland; Proxima II, Mui Scientific, Toronto, Canada). Electrodes and the recorder were calibrated before each study at 20°C using commercial buffer solutions of pH 7.00, 4.00, and 2 (Ingold AG), after each run calibration was repeated to assess electrode drift. Each subject used the same recorder and probe for all study days. Fasting serum gastrin was measured at the start of the study and at 0700 on day 7, the end of each study regimen.

DATA PROCESSING

At the conclusion of each study data were uploaded from the dataloggers to an IBM compatible personal computer. Encoded data were translated and manipulated, producing data files consisting of the means of each minute of readings (1440 datapoints in 24 hours), which were then used in all subgroup calculations. Five standard time periods were considered separately: 24 hour period (1700–1700), night (2200–0659), morning (0700–1159), afternoon (1200–1659), and evening (1700–2159). Changes in pH over time were summarised by calculating several response variables. Each response variable was calculated separately for the standardised time period for each subject and study day. Response variables calculated were: average (mean)

pH response over time, median response over time, and duration of time in hours spent above pH 4. The response variables were analysed for coefficient of skewness and kurtosis and the mean response over time was found to be normal in distribution. Median response over time was also calculated but was found to have greater coefficients of skewness and kurtosis, although giving substantially the same overall results, therefore results of medians are not represented here and means (SD) are shown. Random block analysis of variance was used for assessment of statistical significance of mean response between groups. Where there was a significant treatment effect, the Student-Newman-Keul's range test was used to make all possible comparisons among treatment groups; significance was assessed at the 1% level. Serum gastrin was not normally distributed, therefore the analysis of gastrin by drug was undertaken using Kruskal-Wallis and Friedman non-parametric statistics.

Results

All subjects tolerated the medication and procedures well, one subject had a less than two-fold rise in serum alanine transferase on liver function testing, for the three weeks of the study that he took SKF 94482, which returned to normal one week after the end of the study. One study period of the 60 individual study days was lost because of a fault in the recording equipment and was excluded from the analysis.

TWENTY FOUR HOUR ACIDITY

The mean of all subjects by treatment is shown as a continuous pH profile in Fig. 1. Mean 24 hour pH was 1.7 (0.4) on placebo, which was raised to 3.3 (1.0) on treatment following the morning dose; to 3.0 (0.8) with the evening dose and 3.1 (0.7) with the night time dose. All the SKF 94482 regimens were effective ($p < 0.01$) in increasing the time pH was above 4, and raising the mean and median pH when compared with placebo, but no drug regimen was different from another. Summary mean total data are represented graphically as notched box whisker plots (Fig. 2). Duration of time spent above pH 4 is summarised in the Table.

Table Duration (h) above pH 4

	24 h	Even (1723)	Noct (2307)	Morn (0712)	A'noon (1217)
Plac	1.1 (1.2)	0.2 (0.2)	0.4 (0.7)	0.2 (0.3)	0.1 (0.2)
200 B	7.8 (5.0)	0.7 (0.8)	3.5 (2.5)	2.2 (1.6)	1.4 (1.5)
200 E	5.75 (3.6)	0.9 (0.8)	3.2 (1.9)	0.9 (0.8)	0.6 (0.6)
200 N	6.14 (2.9)	0.5 (0.2)	4.2 (2.1)	1.0 (0.9)	0.5 (0.4)

Fig. 1 Mean pH profile smoothed by 5 point moving average, to show trends between therapy more clearly.

Fig. 2 Notched box whisker plot for 24 hours. Annotation is: the central line is the group median, the box encloses the middle 50% of the data values, the whiskers 1.5 times the interquartile range, outliers beyond this are represented a single points. Notches on the boxes represent the 95% CI on the median if the CI is wider than the interquartile range the box has a folded over appearance.

Night

All drug regimens were significantly more effective than placebo ($p < 0.01$) but did not differ from each other. The mean pH on placebo was 1.6 (0.6) increasing to 3.6 (1.4) with the morning dose, 3.6 (1.0) with the evening dose, and 4.0 (1.2) with the night time dose. Box whisker plots summarise the data in Fig. 3a.

Morning

All drug regimens were significantly more effective ($p < 0.01$) than placebo (1.84 (0.05)). The morning dose was slightly more effective (3.8 (1.2)) than the other two (2.9 (0.8) evening, 2.9 (0.8) night), $p < 0.05$. Box whisker plots are shown in Fig. 3b.

Afternoon

Only the morning dose (3.2 (1.1)) was significantly different from placebo 1.7 (0.4) ($p < 0.01$). Mean pH for the evening dose was 2.5 (0.6) and for the night dose 2.5 (0.6). Box whisker plots summarise the data in Fig. 3c.

Evening

The morning dose raised pH to 2.5 (0.9) and evening dose to 2.8 (0.7) compared with placebo 1.7 (0.4) ($p < 0.01$), the night time dose showed a significant response at pH 2.1 (0.5) when compared with

Fig. 3 Notched box whisker plots for: (a) night time; (b) morning; (c) afternoon; (d) evening.

placebo at the 5% level. These data are summarised in Fig. 3d.

The duration of action of SKF 94482 given at any of the three time points is such that a significant effect is seen 14–20 hours after administration.

SERUM GASTRIN

The data for serum gastrin are displayed as box whisker plots in Fig. 4. All active regimens doubled

serum gastrin from initial and placebo values and this increase was statistically significant ($p < 0.01$). No single value, however, extended outside our normal range (< 180 pg/ml).

Discussion

This study indicates that the time of administration of a single dose of SKF 94482 might be less critical than

Fig. 4 Notched box whisker plot for serum gastrin (pg/ml).

for other H_2 receptor antagonists. This drug has a long duration of action, as pH is still significantly raised above that of placebo between 14 and 20 hours after administration. This, together with the efficacy of the morning dose in inhibiting daytime and food stimulated acid secretion suggests that a different therapeutic approach can be taken with this compound compared with existing H_2 receptor antagonists.

Nocturnal administration of H_2 receptor antagonists has led to equivalent or improved healing rates compared with standard regimens in duodenal ulcer⁶⁻⁸ this has been ascribed to the pharmacological properties of the currently available agents which are most effective in inhibiting the prolonged basal acid secretion occurring at night.^{1,3,5} When currently available H_2 receptor antagonists are given in a single dose the duration of suppression is limited to 10 hours.^{2,5} Thus there is little effect on daytime acidity after nocturnal dosing. As duration of suppression above a target pH can be correlated with duodenal ulcer healing¹⁷ the greater duration of action of SKF 94482 might be expected to lead to improved healing rates over existing H_2 receptor antagonists. Particularly useful might be the effect of addition of good nocturnal acid suppression to the daytime suppression that can be achieved by a single morning dose. Omeprazole, in doses greater than 20 mg od, has a profound effect on intragastric acidity and excellent

duodenal ulcer healing rates,^{9,10} but is associated with hypergastrinaemia.¹² Perhaps in an attempt to reduce this effect on gastrin, omeprazole is being advocated at a 20 mg dose, this is, however, associated with a much more variable antisecretory response¹² with correspondingly less impressive duodenal ulcer healing rates.¹⁸

There is a gap between the duration of action of famotidine and ranitidine and the higher doses of omeprazole, which allows a potential window for therapy. An agent within this window might give rise to improved healing rates and a reduction in treatment failures without resulting in the two-fold rise in fasting serum gastrin seen with omeprazole.¹⁹ Although a complete gastrin response profile was not performed in this study, the fact that no subject had a serum gastrin outside the normal range at the end of one weeks treatment with SKF 94482, would support this contention.

Recent evidence has incriminated postprandial acid reflux rather than nocturnal reflux in the pathogenesis of erosive oesophagitis.^{20,21} It might therefore be expected that any H_2 receptor antagonists with the ability to control daytime acidity effectively might be more effective than conventional H_2 receptor antagonists, as has been for omeprazole.^{22,23} The similarly prolonged duration of action of SKF 94482 with its effect on daytime acidity may make this a useful agent in this disease.

A pharmacodynamic study of this type can only indicate possible optimal times of dose administration. This study has provided no information on the inhibition of acid volume or output, both of which may have an important role in peptic ulceration. Dose response studies and formal trials of efficacy in healing of peptic ulcer are required for full evaluation of this drug.

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