pH-feedback controlled infusions of ranitidine are no more effective than fixed-dose infusions in reducing gastric acidity and variability in antisecretory responses

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- 1 The antisecretory responses to pH-feedback controlled (maximum dose 800 mg 24 h⁻¹) and fixed-dose (0.25 mg kg⁻¹ h⁻¹) continuous infusions of ranitidine were compared in a randomised, placebo-controlled, cross-over study in 10 healthy male volunteers.
- 2 To assess tolerance during repeated dosing with ranitidine, the same infusion regimens were given before and after 6 days oral dosing with ranitidine 300 mg four times daily.
- 3 With the pH-feedback controlled infusion of ranitidine the median % time (interquartile range) with pH > 4 in the 24 h period was 57% (45–76) before and 23% (17–34) after 6 days oral dosing ($P < 0.001$). The respective values with fixed-dose infusion were 51% (38–63) and 26% (15–32) ($P < 0.002$).
- 4 The median 24 h doses (interquartile range) of ranitidine given by feedback-controlled infusion before and after 6 days oral dosing were 675 mg (542–728) and 749 mg (709–760), respectively ($P < 0.01$). The dose of ranitidine given by fixed-rate infusion was 423 mg (393–502) on both study days ($P < 0.001$ vs feedback infusion).
- 5 Plasma gastrin concentrations remained slightly elevated after 6 days of oral ranitidine dosing, whereas pancreatic polypeptide plasma levels remained unchanged.
- 6 The antisecretory efficacy of infusions of ranitidine is significantly decreased by circadian stimuli and tolerance. Individually-adapted infusions of high doses of ranitidine were not superior to fixed-dose infusion of 0.25 mg kg⁻¹ h⁻¹ in overcoming this variability.

Keywords H₂-receptor antagonists ranitidine pharmacodynamics
dose-response gastrin pancreatic polypeptide feedback infusion pump
tolerance

Introduction

Control of intragastric pH with intravenous H₂-receptor antagonists in critically ill patients is characterised by considerable variability of individual pH-response (Albin *et al.*, 1985; More *et al.*, 1985; Reid & Bayliff, 1986). This variability is undesirable, as constant elevation of intragastric pH above 4 is considered to reduce the risk of stress ulceration (Ballesteros *et al.*, 1990; Peura & Johnson, 1985; Rovers & Souney, 1989; Stothert *et al.*, 1980).

Variability in the response to H₂-receptor antagonists may be due to individual differences in regulatory mechanisms and pharmacokinetics, interaction with secretory stimuli, the diurnal secretory drive and the development of tolerance with repeated dosing (Frislid

& Berstad, 1984; Grant *et al.*, 1989; Johnston & Wormsley, 1988; Merki *et al.*, 1990a,b; Moore & Halberg, 1986; Wilder-Smith *et al.*, 1990a).

Pharmacodynamic studies have demonstrated a dose-response relationship of the antisecretory effect of ranitidine (Jones *et al.*, 1987; McIsaac *et al.*, 1990). A reduction in the variability of antisecretory response would therefore be expected with higher doses of ranitidine, or an optimisation of the mode of drug administration. Continuous infusions of H₂-receptor antagonists have been shown to raise intragastric pH more consistently than repeated bolus injections (Ballesteros *et al.*, 1990; Rovers & Souney, 1989).

The purpose of this randomised, cross-over study in

12 healthy volunteers was to examine, whether individually pH-feedback-adapted infusions of up to 800 mg ranitidine per day could reduce the individual diurnal variability in pH-response and the tolerance seen with fixed-rate infusions of conventional doses of ranitidine.

Methods

Twelve healthy male subjects of mean age ($\pm$ s.d.) 26.3 ± 3.2 years and mean weight 72.3 ± 10.4 kg were recruited. They had no history of gastrointestinal disease, took no concurrent medication and had no clinically significant abnormal haematological or biochemical tests. The three-way cross-over study was third-party blinded, i.e. subjects and staff directly involved in the study were not aware of the treatment regimens, as these were prepared by an independent doctor. Subjects were randomised to receive an infusion of 0.9% NaCl (placebo), a fixed-dose infusion of ranitidine ($0.25 \text{ mg kg}^{-1} \text{ h}^{-1}$) or a pH-feedback controlled infusion of ranitidine (maximum dose $800 \text{ mg } 24 \text{ h}^{-1}$) on days 1 and 8 of each study arm. Intra-gastric 24 h pH-metry was performed concomitantly, beginning at 08.00 h on study days 1 and 8. To maintain high ranitidine plasma concentrations, oral ranitidine 300 mg, or placebo was given four times daily (08.00, 12.00, 18.00 and 22.00 h) on study days 2 to 7. During pH-measurements only sips of water were allowed between the standardized meals (08.30, 12.00 and 17.00 h). Five volunteers were smokers. They smoked the same number of cigarettes on each study day. Subjects were confined to the research ward on days 1 and 8, but were at home from day 2 to 7. Compliance was determined by checking the tablet dispensers on day 8. The minimum washout period between regimens was 14 days. pH-metry was performed using combined glass electrodes (Ingold 440 M4, Urdorf, Switzerland) placed in the gastric body and Gastrojet® microprocessor feedback units (Medical Instruments Corporation, Solothurn, Switzerland). The feedback unit has been described and validated previously (Hannan *et al.*, 1990; Merki *et al.*, 1990b, 1991). Briefly, it comprises a 24 h solid-state datalogger, which registers 5 s pH medians, coupled with a pH-controlled infusion pump. The pump has 11 freely programmable infusion rates, between which the processor chooses to maintain the intra-gastric pH above a predetermined target. Maximum and minimum 24 h infusion doses were 800 mg and 80 mg, respectively, and a target pH of 4 was used in this study. In the fixed-dose regimen all 11 infusion rates were programmed at the same rate ($0.25 \text{ mg kg}^{-1} \text{ h}^{-1}$). All infusion regimens were given by feedback pump via a catheter placed in a forearm vein. On days 1 and 8, between 08.00 and 12.00 h, 11 blood samples for the measurement of gastrin and pancreatic polypeptide were drawn from a catheter in a cubital vein. Samples were centrifuged and immediately stored at -20°C until analysis. The analytical methods have been published previously (Meyer *et al.*, 1981; Witzel *et al.*, 1979).

The median pH and the % of time with $\text{pH} > 4$ of the total 24 h (08.00–08.00 h), fed (09.00–20.00 h) and fasting (20.00–08.00 h) periods were predefined for comparison on days 1 and 8 and between active drug

regimens using the Wilcoxon-signed-rank test. The doses of ranitidine given on study days and the area-under-the-curve (AUC) values of gastrin and pancreatic polypeptide were compared with the Wilcoxon-signed-rank test. Significance levels of $P < 0.05$ were assumed.

All subjects gave their written, informed consent and Ethics Committee approval was gained for the studies.

Results

Ten subjects completed the study. One subject missed a study day and another was excluded because of dizziness, nausea and tiredness (placebo regimen). No other side-effects were seen.

Intra-gastric acidity

Box-Whisker plots of the median pH-values for the 24 h, fed and fasted time periods are shown in Figure 1. Figures 2 and 3 represent the group median pH-time-profiles. The median percentage (interquartile range) of time with $\text{pH} > 4$ in the total 24 h, fed and fasting periods with either feedback or fixed-dose infusions are shown in Table 1. With placebo treatment, the % of time of $\text{pH} > 4$ in the 24 h period was 7% (3–10) on day 1 and 11% (3–14) on day 8 (not significant). There were no significant differences in the % of time of $\text{pH} > 4$ with the feedback and fixed-dose regimens on any study day in any time period and all values were significantly higher than those obtained with placebo treatment ($P < 0.001$).

In the fed period the median % of time with $\text{pH} > 4$ during placebo treatment was 13% (5–16) on day 1 and 12% (5–27) on day 8 (not significant). The results with ranitidine were significantly different from those with placebo on the first study day ($P < 0.002$), but not on day 8.

The fasting median % of time with $\text{pH} > 4$ on days 1 and 8 with placebo was 0% (0–1) on day 1 and of 2% (0–8) on day 8 (not significant). These values were significantly lower than those obtained with either ranitidine regimen ($P < 0.001$).

Doses of ranitidine

The median doses of ranitidine given by feedback and fixed-dose infusion are shown in Table 2.

Table 1 Median percentage (interquartile range) of time of $\text{pH} > 4$ with pH-feedback controlled and fixed-dose infusions of ranitidine 1 day before and after 6 days oral dosing with ranitidine 300 mg four times daily in 10 healthy volunteers. The total 24 h, fed and fasted time periods are shown

Feedback		Fixed-dose	
Day 1	Day 8	Day 1	Day 8
24 h: 57% (45–76)	23% (17–34) ¹	51% (38–63)	26% (15–32) ²
Fed: 71% (38–84)	23% (15–36) ²	51% (35–76)	18% (13–24) ²
Fast: 51% (39–68)	27% (21–32) ³	51% (39–63)	28% (15–42) ²

¹Day 1 vs day 8: $P < 0.001$.

²Day 1 vs day 8: $P < 0.005$.

³Day 1 vs day 8: $P < 0.01$.

No significant differences between feedback and fixed-dose on any day.

Gut hormones

With ranitidine feedback infusion, the mean AUC ($\pm$ s.d.) of plasma gastrin concentrations was 78 ± 36 pmol l^{-1} h on day 1 and 104 ± 66 pmol l^{-1} h on day 8 ($P < 0.03$). The corresponding AUC of gastrin concentrations was 86 ± 52 pmol l^{-1} h on day 1 and 101 ± 45 pmol l^{-1} h on day 8 with fixed-dose infusions ($P < 0.2$). During placebo dosing, gastrin levels were unchanged (day 1 51 ± 19 pmol l^{-1} h, day 8 57 ± 25 pmol l^{-1} h). The mean gastrin concentration-time profiles are shown in Figure 4. There were no significant differences in gastrin concentrations between the two ranitidine infusion groups on days 1 and 8.

The AUC of plasma pancreatic polypeptide concentrations did not change significantly from day 1 to day 8 with any infusion regimen. In the group given feedback infusions, the mean AUC ($\pm$ s.d.) of pancreatic polypeptide was 236 ± 114 pmol l^{-1} h on day 1 and 246 ± 66 pmol l^{-1} h on day 8. Corresponding values with fixed-dose infusion were 227 ± 148 pmol l^{-1} h and 248 ± 92 pmol l^{-1} h. The respective results with placebo were 203 ± 70 pmol l^{-1} h and 173 ± 75 pmol l^{-1} h. There were no significant differences between the ranitidine and placebo on days 1 and 8. Polypeptide concentrations rose sharply post-prandially in all treatment groups (Figure 5).

Discussion

The individual antisecretory response to H_2 -receptor antagonists varies considerably in critically ill patients (Albin *et al.*, 1985; More *et al.*, 1985; Reid & Bayliff, 1986). Because elevation of intragastric pH to levels greater than 4 is considered to reduce the risk of stress-induced mucosal lesions, reduction of this variability in response may afford improved prophylaxis against bleeding (Ballesteros *et al.*, 1990; Peura & Johnson, 1985; Rovers & Souney, 1989; Stothert *et al.*, 1980). To investigate whether higher doses of individually-adapted infusions of ranitidine can reduce this variability and the loss of antisecretory efficacy seen with prolonged dosing, we compared pH-feedback regulated dosing with fixed-dose infusions in healthy volunteers. There were no significant differences in the antisecretory effect of the two ranitidine infusion regimens, in either the fed or fasted time periods, or before or after 6 days of oral dosing with ranitidine 300 mg four times daily. The programmed target pH of 4 was attained as frequently with the lower doses of ranitidine given by fixed infusion, as it was with the doses of over 600 mg $24 h^{-1}$ given by feedback-controlled infusion.

The antisecretory effect of ranitidine was mitigated considerably by several factors in this study. The well-documented interaction between food ingestion and H_2 -receptor blockade (Frislid & Berstad, 1984; Johnston *et al.*, 1988; Merki *et al.*, 1990a) was particularly prominent following the early evening meal. In the following fasted period, the maximal diurnal acid-secretory drive interfered markedly with H_2 -receptor blockade, which was accentuated by the omission of the late-night snack used in other studies (Merki *et al.*, 1990a,b; Moore & Halberg, 1986).

Figure 1 Box-Whisker plots of median gastric pH in the a) 24 h, b) fed (09.00–20.00 h) and c) fasted (20.00–08.00 h) periods. Feedback d1 vs d8 $P < 0.003$ for all periods, fixed-dose d1 vs d8 $P < 0.005$ for all periods, feedback vs fixed-dose not significant d1 and d8, feedback and fixed-dose vs placebo d1 and d8 $P < 0.02$ for all periods.

Figure 2 Group ($n = 10$) median pH-time profiles on day 1 of feedback-controlled or fixed-dose infusions of ranitidine or placebo. Mealtimes were 08.30, 12.00 and 17.00 h.

Figure 3 Group ($n = 10$) median pH-time profiles on day 8 of feedback-controlled or fixed-dose infusions of ranitidine or placebo after 6 days oral dosing with ranitidine 300 mg four times daily. Mealtimes were 08.30, 12.00 and 17.00 h.

Table 2 Median doses (interquartile range) of ranitidine given 10 healthy volunteers by pH-feedback controlled and fixed-dose infusions 1 day before and after 6 days oral dosing with ranitidine 300 mg four times daily

<i>Feedback</i>		<i>Fixed-dose</i>
<i>Day 1</i>	<i>Day 8</i>	<i>Days 1 and 8</i>
24 h: 675 mg (542–728) ¹	749 mg (709–760)	423 mg (393–502) ^a
Fed: 326 mg (243–354) ²	359 mg (345–361)	199 mg (171–214) ^a
Fast: 341 mg (309–358) ³	375 mg (370–382)	217 mg (209–221) ^a

¹Feedback infusion dose day 1 vs day 8: $P < 0.01$.

²Feedback infusion dose day 1 vs day 8: $P < 0.002$.

³Feedback infusion dose day 1 vs day 8: $P < 0.02$.

^aFeedback vs fixed-dose on all days and in every time period $P < 0.001$.

Further factors may contribute to the wide variability of pH-response to H_2 -receptor antagonists, including differences in pharmacokinetics (Grant *et al.*, 1989; McFayden *et al.*, 1990) and tolerance. The rapid and considerable development of tolerance during oral dosing with H_2 -receptor antagonists corroborates earlier results in healthy volunteers (Rogers *et al.*, 1990; Smith *et al.*, 1990; Wilder-Smith *et al.*, 1990a,b). It is noteworthy, that in the fed period after 6 days oral dosing no difference was seen in the percentage of time of pH > 4 between the two ranitidine and placebo infusion regimens.

Past studies have shown some of the individual variability in antisecretory effect can be reduced by higher

Figure 4 Mean plasma gastrin concentration ($\pm$ s.d.) profiles on day 1 (—) and day 8 (.....) with a) ranitidine feedback-controlled, b) ranitidine fixed-dose and c) placebo infusions. A meal was given at 08.30 h.

Figure 5 Mean plasma pancreatic polypeptide concentration ($\pm$ s.d.) profiles on day 1 and day 8 with a) ranitidine feedback-controlled, b) ranitidine fixed-dose and c) placebo infusions. A meal was given at 08.30 h.

H₂-receptor blocker doses, but the overall antisecretory response remains relatively unpredictable (Colleen *et al.*, 1987; Gledhill *et al.*, 1984; Jones *et al.*, 1987; McIsaac *et al.*, 1990). In the present study, greater doses of ranitidine maintained the intragastric pH above 4 longer than lower doses in some individuals, but not in others. Overall, however, an increase in the intravenous 24 h dose of ranitidine from 423 mg to over 600 mg did not result in significantly longer maintenance of the pH target of 4. It therefore appears, that in this study the maximum pharmacological efficacy of ranitidine may have already been reached with the lower doses given by fixed-dose infusion.

Most dose-response studies with ranitidine have investigated the suppression of acidity at doses lower than those used here. A clear dose-response relationship exists with single oral doses up to 300 mg (Jones *et al.*, 1987; Konturek *et al.*, 1980a; McIsaac *et al.*, 1990). However, at higher doses several authors have seen minimal or no further enhancement of antisecretory effect (Fimmel *et al.*, 1985; McIsaac *et al.*, 1990; Merki *et al.*, unpublished results; Walt *et al.*, 1981). Comparison of the antisecretory effects of continuous infusions of ranitidine of 0.125 mg kg⁻¹ h⁻¹ and 0.25 mg kg⁻¹ h⁻¹

and of 150 mg 24 h⁻¹ and 300 mg 24 h⁻¹ have shown no significantly better pharmacodynamic results for the higher doses (Ballesteros *et al.*, 1990; Marchant *et al.*, 1988; Morris *et al.*, 1988). The suppression of acid output with stepped doses of ranitidine up to 0.5 mg kg⁻¹ h⁻¹ during histamine or pentagastrin stimulation are difficult to compare with measurements of basal acidity (Kett *et al.*, 1980; Konturek *et al.*, 1980a,b). H₂-antagonists with a greater maximum efficacy than ranitidine may be more successful in overcoming the variability in pH-response. This is implied by the results of recent studies performed in healthy subjects using identical feedback infusion devices with high doses of famotidine (Hannan *et al.*, 1990, 1991). Tolerance, however, was not investigated in these trials.

The processes behind tolerance are unclear, but adaptive changes in the gastrohormonal system or regulation at the receptor level are putative mechanisms. In previous studies investigating tolerance in healthy volunteers, plasma gastrin concentrations were consistently elevated and remained so, despite increasing intragastric acidity due to tolerance (Rogers *et al.*, 1990; Smith *et al.*, 1990; Wilder-Smith *et al.*, 1990b). This was reproduced in the present study. On day 8 with both

ranitidine infusion regimens, gastrin levels—especially postprandially—were higher than on day 1, despite significantly greater intragastric acidity due to tolerance. This divergence may be attributed to several factors, such as disturbance of the acute feedback between intragastric acidity and gastrin with repetitive dosing, or by changes at the G-cell or at the receptor level on the parietal cell (Bertaccini & Coruzzi, 1988). Alternatively, the persistent hypergastrinaemia may be an epiphenomenon, not causally implicated in the development of tolerance.

There were no changes in plasma pancreatic polypeptide concentrations after 8 days of continuous ranitidine dosing. Pancreatic polypeptide secretion is thought by some to be an indicator of vagal activation

(Rigaud *et al.*, 1988). Plasma concentrations of pancreatic polypeptide may, however, not reflect changes in local vagal activation at the parietal cell. Postprandial polypeptide release was remarkably reproducible and plasma concentrations returned to pre-stimulus values after approximately 3 h.

In conclusion, individually adapted infusions of doses of over 600 mg 24 h⁻¹ of ranitidine were unable to compensate for the diurnal variability of antisecretory effect or the tolerance with protracted oral dosing in healthy volunteers.

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