Individual and group dose-responses to intravenous omeprazole in the first 24 h: pH-feedback-controlled and fixed-dose infusions

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- 1 Individual responses to intravenous boli of omeprazole have shown considerable variability. Data on the individual responses to the new omeprazole infusion formulation are lacking.
- 2 Individual dose-responses in the first 24 h of fixed-dose and pH-feedback-controlled infusions of omeprazole were assessed in two randomised, third-party blinded, cross-over studies, using two separate groups of eight healthy subjects. In study A, feedback-controlled infusions of omeprazole (target pH 5, dose range 0–12 mg h⁻¹) and fixed-dose infusions (8 mg h⁻¹) were compared, both with an initial bolus of 80 mg. Omeprazole plasma concentrations were measured. Study B assessed the effect on individual pH-control of a loading bolus of either 40 mg or 80 mg omeprazole, followed by feedback-controlled infusions.
- 3 Study A: the median % time of pH > 5 was 71.2 (total range: 48.9–83.2) with feedback infusions and 57.9 (28.0–95.3) with fixed-dose infusions ($P = 0.06$). The mean 24 h infusion doses were 173.1 mg (44.5–253.1) in the feedback group and 192 mg in the fixed-dose group. The AUC of omeprazole plasma concentrations ranged widely, but correlated with the % time of pH > 5 during fixed-dose infusions. Study B: initial boli of 40 mg and 80 mg of omeprazole resulted in similar 24 h median % of time with pH > 5, 69.2 (49.9–78.8) and 69.6 (44.4–87.7), respectively. Mean omeprazole doses infused by feedback pump were 187.6 mg (83.1–253.6) after 40 mg boli and 159.9 mg (61.8–227.0) after 80 mg boli.
- 4 Feedback titration of omeprazole infusion doses demonstrated the individual variability in dose-responses in the initial 24 h and reduced this variability compared with fixed-dose infusions. The correlation between individual antisecretory effect and the AUC of omeprazole indicates that differences in omeprazole kinetics are an important factor in the variation of response.

Keywords omeprazole infusion intravenous feedback-controlled pump
plasma concentrations variability gastric pH

Introduction

The antisecretory effect of single intravenous doses of omeprazole has been shown to be dose-dependent and repeated intravenous dosing increases the efficacy of omeprazole [1–6]. The initial interindividual variability in dose-responses to intravenous omeprazole is considerable, especially in the fasting state [1–9]. Increasing the dose may augment the response in some individuals, but not in others [1–3]. This may

be due to differences in pharmacokinetics and metabolism, counterregulatory mechanisms or demographic data, such as age [10, 11].

Recently, two studies using half-hourly gastric juice aspiration have demonstrated that the variability seen with individual boli can be reduced with continuous infusions of omeprazole [9, 12]. However, it remains unclear, whether higher doses of intravenous

omeprazole will increase antisecretory response in a given individual, or which patient only requires low doses to attain a specified pH target. Furthermore, the variability in diurnal dosing requirements during continuous infusion is unknown. In many studies only group data, rather than individual results, are shown.

The individual dose-responses in the first 24 h with fixed-dose and pH-feedback-regulated infusions of omeprazole were therefore studied in healthy volunteers in the fasted and food-stimulated states. A pH feedback-regulated infusion pump was used to titrate the individually required doses of omeprazole. Additionally, the effect of different loading doses of omeprazole before continuous infusion was assessed.

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Methods

Two consecutive studies were undertaken in two different groups of eight healthy volunteers (four male and four female each, mean age (range): Study A: 24.3 years (21–26), Study B: 25.4 years (22–33)). Exclusion criteria were a history of gastrointestinal disease or surgery, concurrent medication, known hypersensitivity to omeprazole, clinically relevant biochemical or physical abnormality and drug abuse. All subjects gave their written informed consent and the University of Berne Ethics Committee approval was given for the study. Both studies were randomised, third-party blinded, two-way crossover and there was a washout period of 10 days between the treatment periods.

The basic conditions were identical in both trials. A combined glass pH electrode (Ingold 440M3) was positioned transnasally with the tip in the gastric body and an intravenous catheter was inserted into a forearm vein 1 h before the beginning of the 24 h study period at 20.00 h. Patients had fasted since their last meal at 12.00 h. pH-measurements and omeprazole infusions (4 mg ml⁻¹ infusion formulation, Astra Hässle AB, Sweden) began simultaneously at 20.00 h. The fasting period lasted from 20.00 h until 08.00 h the next morning. Intravenous hydration was maintained with 1000 ml 0.9% NaCl. In the fed period from 08.00 to 20.00 h, standardised meals (pH between 5 and 6) were given at 08.00, 12.00, 16.00 and 18.00 h. No further food or drink, except for small sips of tap water, were allowed. Smoking or chewing gum were prohibited. Subjects remained in the research ward for the entire study duration.

The pH electrodes were connected to the micro-processor-controlled feedback infusion unit (Gastrojet®, Medical Instruments Corp., Solothurn, Switzerland), comprised of a 24 h solid-state datalogger, which registers 5 s pH medians, and the infusion pump. The unit has been validated previously [13–16]. Briefly, the pump has 11 freely programmable infusion rates, between which the processor chooses to maintain the intragastric pH above a pre-

determined target. For individually feedback-titrated infusions the highest and lowest infusion rates in these studies were 12 and 0 mg h⁻¹, respectively. The maximum omeprazole dose given by pump was consequently limited to 280 mg. When a fixed-dose infusion was given, all 11 infusion rates were set at the same rate of 8 mg h⁻¹. A target pH of 5 was programmed throughout all study arms. The individual study regimens were as follows:

Study A

In both study arms a loading dose of 80 mg omeprazole was infused over 30 min beginning at 20.00 h. In one arm a fixed-rate infusion of 8 mg h⁻¹ was given by feedback pump for 24 h. In the other arm the pH-feedback infusion pump was allowed to titrate the doses required by each individual volunteer to maintain the target pH. For pharmacokinetic evaluation, blood samples were taken through an indwelling catheter in the second forearm at the times shown in Figure 3. Samples were centrifuged, the plasma separated and stored in plastic tubes at -20° C until analysis by liquid chromatography [17].

Study B

Volunteers were given a loading dose of 40 mg or 80 mg omeprazole as a short infusion over 30 min via the forearm vein at the start of the study at 20.00 h. Subsequently, the pH-feedback infusion pumps administered the doses of omeprazole required to maintain the target pH.

The volunteers were classified as extensive or poor metabolisers of omeprazole according to their mephenytoin hydroxylation index [18, 19].

Statistical analysis

The % time of pH > 5 and the median pH were pre-defined for confirmative analysis for the 24 h, fasting period (first 12 h), fed period (second 12 h) and the initial 2 h. The Wilcoxon-signed rank test and the Holm-Bonferroni correction for multiple testing were used to test the hypothesis that feedback-controlled infusions would control gastric pH better than fixed-dose infusions [20]. The doses of omeprazole infused in the above-defined time periods and the area-under-the-curve (AUC) values of the plasma omeprazole concentrations were compared confirmatively with the Student's *t*-test for paired samples. Hourly comparisons of doses were evaluated descriptively.

Results

Study A

The data from all eight volunteers were complete, although two had to repeat one study arm due to equipment failure.

The individual and group percentages of time with

Table 1 Median percentage of time with pH > 5 with pH-feedback-controlled (Feedb) and fixed-dose (Fixed) infusions in the 24 h, fasted and fed periods and the time taken from the start of the study to reach pH 5 (study A). Individual and median group values are shown

Number	Median percentage time with pH > 5						Time to pH 5 (min)	
	24 h		Fast		Fed		Feedb	Fixed
	Feedb	Fixed	Feedb	Fixed	Feedb	Fixed		
1	80.7	95.3	78.1	92.5	83.3	98.2	94	50
2	69.2	47.6	48.1	29.0	90.4	66.2	68	94
3	73.1	63.4	65.8	67.9	80.4	59.0	107	65
4	83.2	92.1	96.4	96.4	70.0	87.7	25	24
5	80.8	76.5	79.6	77.1	82.1	76.0	21	20
6	48.9	28.0	55.3	4.9	42.6	51.0	53	133
7	58.9	38.9	52.4	50.9	65.5	27.0	93	36
8	66.2	52.4	78.7	38.4	53.6	66.5	32	278
All ¹	71.2	57.9	71.9	59.4	75.2	66.4	61	58

¹Group median values.

pH > 5 and the median pH are shown in Tables 1 and 2, respectively. The group median % time of pH > 5 tended to be greater with the feedback infusion in the 24 h ($P = 0.06$, NS), fasting (NS) and fed periods (NS). The median pH was higher with feedback infusions only in the 24 h period ($P < 0.05$). The pH-time profiles are plotted in Figure 1. The median time taken to reach a pH of 5 was 61 min (range: 21–107) with the feedback pump and 58 min (range: 20–278) with fixed-dose infusions (NS) (Table 1).

The doses of omeprazole given are shown in Table 3. In the fasting period the mean dose of omeprazole given by feedback infusion was significantly greater than the dose given by fixed-dose infusion ($P < 0.05$). There were no significant differences in the mean applied doses in the 24 h and fed periods. The hourly time-profiles of the doses are plotted in Figure 2. The mean hourly doses were significantly higher with feedback-controlled infusions ($P < 0.05$) from 21.00 to 23.00 h. Subsequently, the group mean doses given by constant rate infusion were consistently greater, although the difference was only significant from 08.00 to 09.00 h and 19.00 to 20.00 h ($P > 0.05$). There was a significant correlation between the 24 h omeprazole dose applied by feedback pump and the % time of pH > 5 ($r = -0.83$, $P < 0.01$).

The AUC of omeprazole plasma concentrations are shown in Table 3. The median AUC (range) was 74.9 $\mu\text{mol l}^{-1} \text{h}$ (31.6–149.3) in the feedback infusion group and 76.8 $\mu\text{mol l}^{-1} \text{h}$ (31.8–149.0) in those given fixed-dose infusions. There were no significant correlations between the AUC of omeprazole and omeprazole doses. The AUC correlated with % time of pH > 5 during fixed-dose ($r = 0.7$, $P < 0.05$), but not during feedback-controlled ($r = 0.23$) infusions. Individual plasma concentration profiles are illustrated in Figure 3. All seven volunteers tested were extensive mephenytoin hydroxylators.

Study B

The data from all eight volunteers were complete. The percentages of time of pH > 5 can be seen in Table 4. The median pH in the 24 h time periods is

Table 2 Individual and group median 24 h pH in study A (feedback vs fixed-dose infusion) and study B (40 mg vs 80 mg loading bolus followed by feedback infusion)

Number	Study A		Study B	
	Feedback	Fixed-dose	40 mg	80 mg
1	5.5	5.8	5.6	5.1
2	5.3	4.9	5.3	5.6
3	5.5	5.4	5.3	5.6
4	6.5	6.5	5.5	5.6
5	5.7	5.5	5.2	5.4
6	4.9	4.5	5.3	6.1
7	5.1	4.7	4.9	4.8
8	5.5	5.0	5.5	5.3
Median:	5.5*	5.2*	5.3	5.5

* $P < 0.05$.

listed in Table 2. There were no significant differences in any time period between the 40 mg and 80 mg bolus groups in group median pH or time of pH > 5, although there was a trend to more sustained pH > 5 in the fasted period with an 80 mg bolus. The pH-time profiles are shown in Figure 4. To attain a pH > 5 required a median time of 29 min (range: 20–46) with a loading bolus of 40 mg and 22 min (range: 3–142) with 80 mg ($P = 0.08$, NS) (Table 4). The mean group doses of omeprazole infused were similar in the 24 h, fasted and fed time periods (Table 5), although in the hourly dose-time profiles they were consistently higher after a 40 mg loading bolus, this was significant from 21.00 to 24.00 h and from 4.00 to 5.00 h ($P < 0.05$) (Figure 5).

The six volunteers tested for their mephenytoin hydroxylation capacity were extensive metabolisers.

Adverse events

Overall, four volunteers complained of bloating and epigastric discomfort, two described lower abdominal pain and one subject had headache during the study.

Figure 1 Individual (thin lines) and group median (thick line) pH-time profiles in eight healthy subjects with a) feedback-regulated and b) fixed-rate infusions of omeprazole (study A). A loading bolus of 80 mg was given in both groups.

Table 3 Individual and group doses of omeprazole infused in the 24 h, fasted and fed periods and the area under the curve of plasma omeprazole concentrations (study A). Doses do not include the loading bolus

Number	Doses of omeprazole (mg)			AUC ($\mu\text{mol l}^{-1} \text{ h}$)	
	24 h	Fast	Fed	24 h	
	Feedback-controlled infusion			Feedback	Fixed-dose
1	134.3	99.0	35.3	111.8	149.0
2	193.9	136.1	57.7	149.3	137.4
3	157.6	103.6	54.0	31.6	49.6
4	44.5	17.3	27.3	71.7	143.2
5	185.2	114.3	70.9	78.0	74.1
6	253.1	124.3	128.8	58.3	31.8
7	228.6	131.1	97.3	58.3	41.5
8	187.3	90.2	97.1	78.6	79.5
Group	173.1 $\pm$ 64	102.0 $\pm$ 38*	71.1 $\pm$ 35	72.8 (49.4–107.3)	76.1 (46.1–125.7)
	(means $\pm$ s.d.)			(geometric means (95% CI))	
<i>Fixed-dose infusions (8 mg h⁻¹)</i>					
All	192.0	96.0*	96.0		

* $P < 0.05$, feedback vs fixed dose infusions.

Figure 2 Individual (thin lines) and group mean (thick line and circles) hourly dosage-profiles in eight healthy subjects with feedback-regulated infusions of omeprazole (study A). The fixed-rate infusion dose was 8 mg h^{-1} (dashed line and squares).

Figure 3 Individual profiles of plasma omeprazole concentrations with a) feedback and b) fixed-dose infusions of omeprazole.

Table 4 Median percentage of time with pH > 5 and the time taken from the start of the study to reach pH 5 following a loading bolus of 40 mg or 80 mg omeprazole and subsequent pH-feedback-controlled infusions (study B): individual and median group values in the 24 h, fasted and fed period are shown

Number	Median percentage time with pH > 5						Time to pH 5 (min)	
	24 h		Fast		Fed		40 mg	80 mg
	40 mg	80 mg	40 mg	80 mg	40 mg	80 mg		
1	77.0	57.8	69.2	47.9	84.9	67.6	46	142
2	65.5	70.5	58.2	58.8	72.8	82.3	29	22
3	64.7	80.9	66.3	86.9	63.1	75.0	28	10
4	72.4	85.0	76.8	88.8	68.1	81.2	39	22
5	66.0	68.8	51.3	59.3	80.7	78.2	40	32
6	78.8	87.7	81.7	83.3	75.8	92.2	23	3
7	49.9	44.4	43.5	81.0	56.2	7.9	26	27
8	74.7	65.4	60.9	63.2	88.4	67.5	20	21
All ¹	69.2	69.6	63.6	72.1	74.3	76.6	29	22

¹Group median values.

Figure 4 Individual (thin lines) and group median (thick line) pH-time profiles in eight healthy subjects with an initial loading bolus of a) 40 mg or b) 80 mg omeprazole, followed by feedback-regulated infusions of omeprazole (study B).

Table 5 Individual and mean ($\pm$ s.d.) doses of omeprazole infused by pH-feedback-controlled pump in the 24 h, fasted and fed periods following a loading dose of 40 mg or 80 mg omeprazole (study B). Doses do not include the loading bolus

Number	Doses of omeprazole (mg)					
	24 h		Fast		Fed	
	40 mg	80 mg	40 mg	80 mg	40 mg	80 mg
1	184.2	155.5	122.5	143.2	61.7	12.3
2	223.2	227.0	131.5	120.5	91.7	106.5
3	193.5	61.8	101.8	61.8	91.7	0.0
4	205.5	73.3	112.1	46.7	93.5	26.6
5	178.8	219.9	135.5	113.5	43.3	106.4
6	83.1	96.7	70.0	67.1	13.1	29.6
7	253.6	218.3	134.5	77.1	119.1	141.2
8	178.9	226.9	127.1	128.1	51.8	98.8
All	187.6	159.9	116.8	94.8	70.7	65.2
	± 49	± 73	± 22	± 36	± 34	± 54

Figure 5 Individual (thin lines) and group mean (thick line and circles) hourly dosage-profiles in eight healthy subjects with an initial loading bolus of a) 40 mg or b) 80 mg omeprazole, followed by feedback-regulated infusions of omeprazole (study B).

Discussion

A median pH of greater than 5 was achieved in the volunteer group in the first 24 h with fixed-dose and pH-feedback controlled infusions of omeprazole. This would seem to imply, that the target pH of 5 was consistently and reliably achieved, irrespective of the dosing regimen used. However, inspection of the individual percentage of time of pH > 5 revealed a variable response. The individual percentage of time of pH greater than 5 in the 24 h period varied between 28 and 95% during constant rate infusions (study A). In the fasting period the range was even wider, spanning from 5 to 96%. By titrating the individual momentary dose-requirements with a pH-feedback controlled pump, the inter- and intraindividual variability in the % of time with pH > 5 was reduced, but this was often not reflected in the group median values. However, in a few subjects a pH of 5 could not be consistently maintained in the first 24 h, even with daily doses of omeprazole close to 300 mg titrated by feedback-regulated pump. Our group results cannot be directly compared with the only other published study with fixed-rate infusions, because half-hourly aspirations for pH-measurements in fasted duodenal ulcer patients were used, mean results were reported and the study began in the morning [12].

The individual doses administered by feedback-controlled infusion varied severalfold, with a general tendency to higher doses in the initial fasting period and lower doses in the fed period than with the fixed-dose infusion. The higher dosage requirements in the first 12 h can be attributed to the lesser efficacy of omeprazole when parietal cells are unstimulated and the progressively greater action of omeprazole with repeated dosing, as well as the circadian rhythm of acid secretion [2, 4, 5, 11, 21–23]. In the early afternoon a majority of subjects demonstrated a second peak in feedback-regulated omeprazole doses, possibly related to the waning of the loading bolus effect.

The initial bolus of 80 mg omeprazole improved the consistency of the antisecretory effect in most subjects in the subsequent fasting period compared with the 40 mg bolus and drug requirements were reduced in the majority of individuals in this period (study B). The time taken to attain a pH of 5 was marginally shorter after a bolus of 80 mg in the group as a whole, but the latencies ranged from 3 to 142 min and in three cases the larger bolus did not result in a faster achievement of the target pH. Using

exactly the same protocol and doses, but different volunteers in study A and B, the time to pH 5 varied widely, giving different group results. Secondary factors, such as gastric emptying, may well confound this initial response time. A trend to better pH-control with greater boli has been demonstrated by some investigators, but not by others [5–7, 9].

The variability in antisecretory responses and dose-requirements with omeprazole infusions may be due to differences in metabolic capacity. Intraindividually, higher omeprazole doses resulted in greater AUCs. However, similar doses led to widely divergent AUCs in different individuals. Omeprazole is largely metabolized by the hepatic cytochrome P450 enzyme system and there seem to be extensive and poor metabolizers of omeprazole. The differences in metabolism are probably due to genetically determined capacities of S-mephenytoin 4' hydroxylase [24]. Extensive metabolizers may show a decreased antisecretory response compared with poor metabolizers after bolus administrations [3, 25, 26]. In our present study all 13 volunteers tested were classified as extensive metabolizers, indicating the variability in response is not primarily due to differences in metabolism.

The AUC of omeprazole plasma concentrations correlates with the acid inhibition after oral or bolus dosing [25–33]. This correlation probably relies on the initial availability of omeprazole in blocking the proton pumps [32, 34, 35]. During steady state infusions, the response will depend on the turnover or availability of pumps and the plasma omeprazole concentration to block them. The AUC of omeprazole at steady-state would consequently be expected to correlate with the antisecretory effect, as illustrated by the correlation between AUC and the percentage of time of pH > 5 during fixed-dose infusions in the present study. Other factors, such as gastric emptying, may influence the direct correlation between pharmacokinetics and acidity measurements.

Continuous infusions of omeprazole resulted in good overall antisecretory effect in the first 24 h of dosing. The favourable group results, however, mask the individual variability in initial response. Individual feedback dose titration was able to demonstrate the wide range of dose requirements and reduced the variability in pH-response. The variability in the first 24 h is likely to decrease with more prolonged application.

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