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Effect of single and repeated intravenous doses of omeprazole on pentagastrin stimulated gastric acid secretion and pharmacokinetics in man

J B M J JANSEN, P LUNDBORG, L C BAAK, J GREVE, M OHMAN, C STÖVER, K RÖHSS, AND C B H W LAMERS

From the Departments of Gastroenterology and Hepatology, St Radboud Hospital Nijmegen and University Hospital Leiden, The Netherlands, Hässle AB, Mölndal, Sweden.

SUMMARY Single intravenous doses of 10, 20, 40, and 80 mg and repeated once daily intravenous doses of 10 and 20 mg omeprazole induced a powerful and long lasting inhibition of pentagastrin stimulated gastric acid secretion (PAO) in healthy male volunteers. Single intravenous doses of 10, 20, 40, and 80 mg omeprazole inhibited PAO by 30% ($p<0.01$), 45% ($p<0.01$), 61% ($p<0.01$), and 80% ($p<0.01$), respectively when measured 1·5 h after dose, and by 20% (NS), 27% (NS), 36% ($p<0.01$) and 59% ($p<0.01$), respectively when measured 24 h after dose. Six days after repeated once daily intravenous doses of 10 and 20 mg omeprazole, PAO was inhibited by 63% ($p<0.01$) and 82% ($p<0.01$), respectively when measured 1·5 h after dose, and by 32% ($p<0.01$) and 43% ($p<0.01$), respectively when measured 24 h after dose. The inhibition of PAO by 10 mg administered intravenously as a single bolus injection was comparable with the inhibition by 20 mg as a single oral dose. Repeated once daily administration of 10 mg intravenously and 20 mg orally also resulted in comparable reductions in PAO. The reduction in PAO after repeated once daily oral administration of 20 mg was comparable with the effect of a single intravenous dose of 40 mg. Terminal half lives were short, but significantly ($p<0.05$) prolonged after a single intravenous injection of 80 mg. Repeated once daily intravenous administration of 10 and 20 mg did not result in prolongation of terminal half lives. It is concluded that intravenous administration of omeprazole causes a potent and long acting inhibition of pentagastrin stimulated gastric acid secretion in man. Its potency is augmented after repeated once daily administration.

Omeprazole, a substituted benzimidazole, has been shown to possess a powerful inhibitory action on gastric acid secretion by selective inhibition of the gastric proton pump (H^+/K^+ATPase) in the secretory membrane of the parietal cell.[1,2] The inhibition by omeprazole is dose dependent, long lasting,[3] and increases during the first days of repeated administration.[4–6] Clinical studies have shown that omeprazole is very effective in the treatment of patients with the Zollinger-Ellison syndrome,[7–9] peptic ulcer disease,[10–14] and reflux oesophagitis.[15] Data in man are based on studies with orally administered omeprazole. In some conditions, however, it is advantageous to inhibit gastric acid secretion *via* the intravenous route of administration – for example, in unconscious patients or those with upper gastrointestinal bleeding. We therefore investigated the effect of single and repeated doses of once daily intravenous omeprazole on pentagastrin stimulated gastric acid secretion as well as on drug pharmacokinetics. Furthermore, comparison was made with single and repeated oral administration of omeprazole.

Address for correspondence: Dr J B M J Jansen, Dept of Gastroenterology, University Hospital Leiden, Building 1 C4-17, PO Box 9600, 2300 RC Leiden, The Netherlands.

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Methods

SUBJECTS

Ten healthy male volunteers (median age 25 years, range 22–33) were included and completed the single dose study, while nine other healthy male subjects (median age 25 years, range 22–32) participated in the study on the effect of repeated once daily intravenous and oral doses of omeprazole. The studies were approved by the local ethical committees on experimental investigations in humans. Written informed consent was obtained from all subjects.

STUDY DESIGN

The single and repeated dose studies were done at separate centres using identical techniques and equipment. Studies were conducted as crossover, randomised and open trials. in the single dose study, each subject received single intravenous doses of placebo, 10, 20, 40, and 80 mg omeprazole and single oral doses of placebo and 20 mg omeprazole at intervals of at least one week. In the repeated dose study, single doses of intravenous and oral placebo were given in random order at intervals of at least two days, and then 10 and 20 mg intravenous and 20 mg oral omeprazole once daily for six days, also in random order and at intervals of at least one week. Acid secretion tests were started 1·5 and 24 hours after intravenous and six and 24 hours after oral drug administration (the sixth dose in case of repeated administration) in both studies. Blood samples for determination of omeprazole in plasma were taken at regular intervals. Blood and urine samples for a routine laboratory screen were collected at the pre-entry assessments and after the last experiment in the single dose study and at the end of each period in the repeated dose study.

DOSE, DOSAGE FORM AND ADMINISTRATION

The intravenous omeprazole formulation consisted of freeze dried omeprazole and solvent (polyethylene glycol 400 40%, sodiumdihydrogenphosphate 1·3 mg/l, disodiumhydrogenphosphate 0·3 mg/l). Immediately before use, the solvent was added to the freeze dried drug and thoroughly mixed. The final solution (4 mg/ml) was infused over five minutes in all experiments. The pure solvent was used as placebo. Enteric coated granules containing 20 mg omeprazole or an equivalent amount of placebo, dispensed in hard gelatin capsules were used in the oral experiments.

GASTRIC ACID SECRETION

Gastric acid secretion was measured with correction for pyloric losses using phenol red saline perfusion as previously described.[3] Basal acid secretion was collected in 15 minute samples during 30 minutes, followed by the collection of stimulated gastric acid secretion in 15 minute samples for one hour during continuous intravenous infusion of pentagastrin (1·5 μg/kg/h).

BLOOD SAMPLING

Blood samples for the determination of omeprazole in plasma were taken before and again at regular intervals for three to four hours and seven to eight hours after intravenous and oral drug administration (the sixth dose in case of repeated administration), respectively. Plasma omeprazole concentrations were analysed at the Department of Bioanalytical Chemistry, Hässle AB, using HPLC as previously described.[16]

CALCULATIONS

Peak acid output (PAO, mmol/h) in response to pentagastrin stimulation was calculated as the sum of the highest two consecutive 15 minute samples multiplied by two and the effect of omeprazole was expressed as percentage reduction in mean PAO compared with placebo.

The terminal half life ($t_{1/2}$) of intravenous omeprazole was determined from the individual regression lines of the log plasma concentration time curves during the elimination phase. The area under the plasma concentration time curve (AUC) was calculated using the trapezoidal rule and, in the case of intravenous administration, adding the area to infinity (last concentration$\times t_{1/2} \times 0{\cdot}693^{-1}$). Linear regression analysis was used on data obtained in the single dose study to determine the correlation between drug induced inhibition of gastric acid

Table 1 *The effect of single doses of omeprazole and placebo on pentagastrin stimulated PAO (mmol/h) and the percentage reduction of PAO during administration of omeprazole in 10 male healthy volunteers*

	Day 1		*Day 2*	
Dose omeprazole	*PAO (mmol/h)*	*PAO (% inhibition)*	*PAO (mmol/h)*	*PAO (% inhibition)*
placebo iv	38·1±3·0		38·4±4·0	
10 mg iv	26·6±2·3	30	30·7±3·2	20
20 mg iv	21·1±3·5	45	27·9±4·3	27
40 mg iv	14·7±3·5	61	24·7±3·1	36
80 mg iv	7·8±2·8	80	15·9±3·3	59
placebo orally	41·6±4·0		36·3±4·6	
20 mg orally	28·2±2·4	32	29·6±3·2	18

On day 1 the PAO was determined 1·5 h after intravenous administration and six hours after oral administration, respectively, while on day 2 the PAO was measured 24 h after both intravenous and oral administration of omeprazole. PAO results are expressed as mean±SEM.

secretion and intravenous dose after logit transformation according to:

$$\ln\left(\frac{\%\text{ reduction in PAO}}{100-\%\text{ reduction in PAO}}\right)=a\ln(\text{dose})+b.$$

The results from this regression analysis were used to estimate which intravenous dose was equipotent to 20 mg oral omeprazole.

STATISTICAL ANALYSIS

Statistical evaluations were made using Wilcoxon's matched-pairs rank-signed test for comparisons within each study and Mann-Whitney test for comparisons between studies. The statistical evaluation of gastric acid secretion data was carried out using values of PAO. A p value $<0{\cdot}05$ was considered statistically significant.

Results

SINGLE DOSE STUDY

Intravenous administration of omeprazole induced a long lasting dose dependent inhibition of pentagastrin stimulated gastric acid secretion. The results are presented in Table 1. Once daily intravenous administration of 10, 20, 40, and 80 mg omeprazole resulted in a maximal reduction in mean PAO (measured 1·5 h after dose) of 30% ($p<0{\cdot}01$), 45% ($p<0{\cdot}01$), 61% ($p<0{\cdot}01$), and 80% ($p<0{\cdot}01$), respectively. Corresponding values for minimal reduction (measured 24 h after dose) were 20% (NS), 27% (NS), 36% ($p<0{\cdot}01$), and 59% ($p<0{\cdot}01$), respectively. A single oral dose of 20 mg omeprazole resulted in a maximal reduction (measured six hours after dose) of 32% ($p<0{\cdot}05$) and a minimal reduction (measured 24 h after dose) of 18% (NS). There was a statistically significant relationship between maximal as well as minimal reduction in mean PAO and dose and the following linear regression lines were found to fit the obtained data after logit transformation:

Maximal effect: In (reduction/100−reduction)= 1·0485×In(dose)−3·3126 (r=0·9964)

Minimal effect: In (reduction/100−reduction)= 0·8048×In (dose)−3·3406 (r=0·9733).

Using these regression lines, it was calculated that a single oral dose of 20 mg omeprazole induced the same maximal reduction in mean PAO as that of 11·6 mg intravenous omeprazole, while the minimal effect after the oral dose was somewhat lower and corresponded to 10 mg intravenous omeprazole (Fig. 1).

The plasma omeprazole concentration time curves after different intravenous doses are presented in Figure 2, and the areas under the plasma concentration-time curves and terminal half lives are presented in Table 2. There were only small non-systematic variations in terminal half lives for doses up to 40 mg, while the $t_{1/2}$ was significantly higher ($p<0{\cdot}05$) for 80 mg intravenous omeprazole. There was a linear increase in median AUC with increasing intravenous doses although a disproportionally great increase was seen between 40 mg and 80 mg for some subjects (Fig. 3). The AUC values after 20 mg oral omeprazole were in the same range as those after intravenous doses of 10 mg.

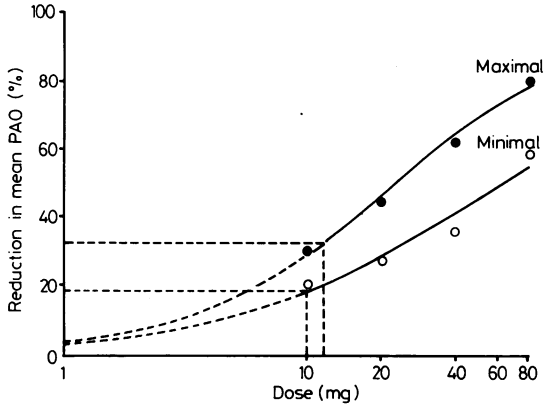

Fig. 1 *Percentage inhibition of pentagastrin stimulated PAO measured 1·5 h (maximal effect) and 24 h (minimal effect) after single intravenous doses of 10, 20, 40, and 80 mg omeprazole in 10 healthy male volunteers. From the linear regression lines after logit transformation: In (% reduction in PAO/100−% reduction in PAO)=a In (dose)+b, it was calculated that a single oral dose of 20 mg omeprazole induced the same maximal reduction in PAO as a single bolus injection of 11·6 mg, while the minimal effect after an oral dose of 20 mg corresponded with an intravenous bolus injection of 10 mg.*

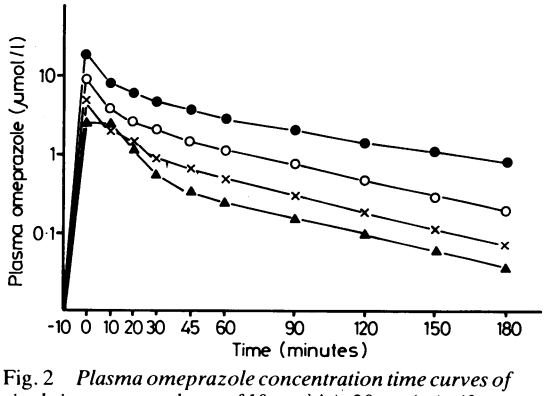

Fig. 2 *Plasma omeprazole concentration time curves of single intravenous doses of 10 mg (▲), 20 mg (×), 40 mg (○), and 80 mg (●) omeprazole in 10 healthy male volunteers.*

Table 2 *The area under the plasma concentration-time curves (AUC) and the terminal half lives (t½) after single doses of intravenous and oral omeprazole in 10 healthy male volunteers*

	AUC (μmol/h/l)	t½ (h)
10 mg iv	1·493±0·515	0·71±0·06
20 mg iv	2·099±0·255	0·68±0·04
40 mg iv	4·423±0·380	0·74±0·07
80 mg iv	12·007±1·713	0·99±0·10
20 mg orally	1·022±0·138	

Data are expressed as mean±SEM.

REPEATED DOSE STUDY

Repeated once daily intravenous administration of 10 and 20 mg omeprazole for six days resulted in a maximal reduction in PAO of 63% ($p<0·01$) and 82% ($p<0·01$), respectively and in a minimal reduction of 32% ($p<0·01$) (Table 3). The maximal and minimal reduction in mean PAO were 60% ($p<0·01$) and 37% ($p<0·01$), respectively after repeated once daily oral administration of 20 mg omeprazole. Data on pharmacokinetics of omeprazole at repeated administration are presented in Table 4 and the plasma profiles are presented in Figure 4. There were no statistically significant differences between the two doses studied as regards terminal half lives. The terminal half lives after repeated administration were significantly shorter, however ($p<0·05$) than those seen after corresponding single doses. The AUC values for 10 and 20 mg intravenous omeprazole after repeated administration were in the same range and not statistically different from those obtained after corresponding single doses. The mean UAC after repeated oral administration of 20 mg omeprazole was significantly lower ($p<0·01$) than that after repeated intravenous administration of 10 and 20 mg as well as that after a single oral dose of 20 mg.

Table 3 *Effect of repeated once daily administered doses of omeprazole and placebo for six days on pentagastrin stimulated PAO (mmol/h) and the percentage reduction of PAO during administration of omeprazole in nine healthy male subjects*

	Day 6		Day 7	
Dose omeprazole	*PAO (mmol/h)*	*PAO (% inhibition)*	*PAO (mmol/h)*	*PAO (% inhibition)*
placebo iv	46·1±3·3		48·7±2·2	
10 mg iv	17·1±2·9	63	33·0±2·0	32
20 mg iv	8·4±2·6	82	28·0±2·0	43
placebo orally	46·2±4·8		45·9±4·4	
20 mg orally	18·4±3·1	60	28·9±1·6	37

On day 6 the PAO was determined 1·5 h after intravenous administration and six hours after oral administration, respectively, while on day 7 PAO was measured 24 h after both intravenous and oral administration of omeprazole. PAO results are expressed as mean±SEM.

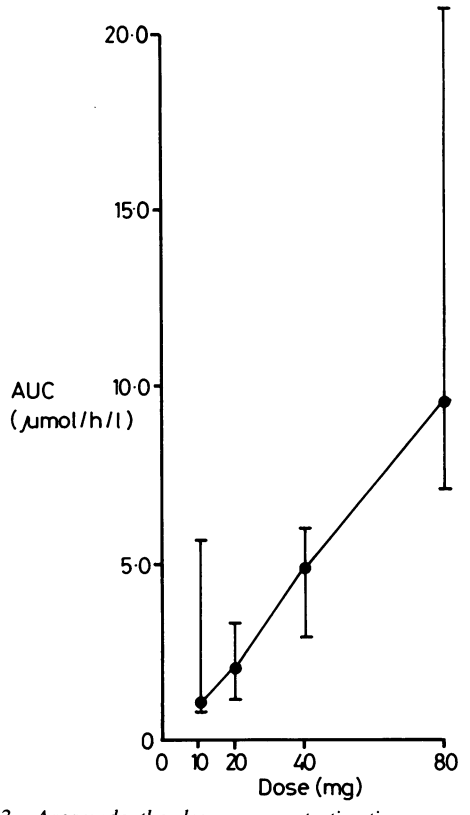

Fig. 3 *Area under the plasma concentration time curve (AUC) after single intravenous doses of 10, 20, 40, and 80 mg omeprazole in 10 healthy male volunteers. Values are expressed as median and range.*

Discussion

Intravenous administration of omeprazole induced a potent dose dependent inhibition of pentagastrin stimulated gastric acid secretion in man. Both maximal and minimal inhibition of pentagastrin stimulated PAO after single oral administration of 20 mg omeprazole were approximally equivalent to that of 10 mg omeprazole administered intravenously within the same subjects. This indicates that omeprazole has a long duration of action, which seems to be independent of the route of administration. These data are in conflict with a previous study, suggesting that single doses intravenously administered omeprazole have a shorter duration of action on intragastric acidity than expected from data obtained

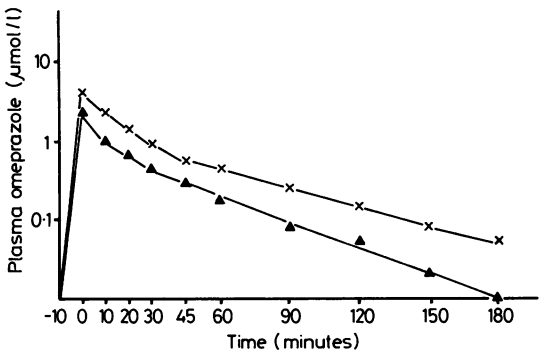

Fig. 4 *Plasma concentration time curves after repeated once daily intravenous doses of 10 mg (▲) and 20 mg (×) omeprazole in eight healthy male volunteers.*

during oral administration.[17] The suggestion of a local effect of orally administered omeprazole is therefore not in line with the results presented in this paper. In that study, only the effect of intravenously administered omeprazole was studied and compared with data on orally administered omeprazole obtained from the literature. This may explain the apparent difference in response to oral and intravenous omeprazole in that study, because most of the data obtained with orally administered omeprazole in the literature are based on studies with repeated dosing of which a cumulative effect on the inhibition of gastric acid secretion has been reported, exaggerating the effect of single oral dose administration.[4-6] This cumulative effect after repeated oral dosing was also observed in the present study. Furthermore, this study showed that repeated once daily doses of omeprazole administered intravenously, also have a cumulative inhibitory effect on pentagastrin stimulated gastric acid secretion in man. The maximal inhibition of PAO after repeated once daily intravenous administration of 10 and 20 mg omeprazole was approximally twice as pronounced when compared with the inhibition of PAO obtained after comparable single intravenously administered doses. The maximal inhibition of PAO obtained after repeated once daily oral administration of 20 mg omeprazole was comparable with the inhibition of PAO after a single intravenous dose of 40 mg.

Table 4 *The area under the plasma concentration-time curves (AUC) and terminal half lives (t½) after repeated once-daily doses of intravenous and oral omeprazole in nine healthy male volunteers*

	AUC (μmol/h/l)	*t½ (h)*
10 mg iv	0·895±0·040	0·49±0·04
20 mg iv	1·949±0·120	0·56±0·08
20 mg orally	0·586±0·070	

Data are expressed as mean±SEM.

The terminal half life of intravenous administered omeprazole was short and not significantly different for single bolus injections of 10, 20, and 40 mg. The terminal half life was, however, significantly prolonged after a bolus injection of 80 mg. This might indicate a non-linear kinetic for omeprazole in doses somewhere above 40 mg, which might be caused by interaction with the hepatic microsomal cytochrome P-450 mono-oxygenase system by the drug.[18] Although the AUC's obtained after single and repeated once daily intravenous doses of 10 and 20 mg omeprazole were in the same range, the terminal half lives were significantly shorter in the repeated dose study. Furthermore, considerable differences existed between the AUC's after single and repeated oral administration of 20 mg omeprazole. An explanation for differences in pharmacokinetics between the single and repeated dose study is not apparent, but the observed great interindividual variations in drug metabolism may be responsible for the differences obtained from studies performed on different populations.

We conclude that intravenous administration of omeprazole causes a potent and long lasting inhibition of pentagastrin stimulated gastric acid secretion in man. 10 mg of omeprazole administered as an intravenous bolus injection is equipotent to a single oral dose of 20 mg. The potency of intravenous omeprazole is augmented after repeated once daily administration. Repeated oral administration of 20 mg omeprazole resulted in a reduction in PAO which was comparable with that achieved after administration of a single bolus injection of 40 mg. The terminal half life of intravenously administered omeprazole is short. When compared with the other doses, the terminal half life after a single dose of 80 mg was significantly prolonged. This non-linear difference in terminal half lives for intravenous doses of 10, 20, 40, and 80 mg is probably explained by an augmented interaction with the hepatic cytochrome P-450 mono-oxygenase system in doses somewhere above 40 mg.

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