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Pharmacodynamics and kinetics of omeprazole MUPS 20 mg and pantoprazole 40 mg during repeated oral administration in Helicobacter pylori*-negative subjects*

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SUMMARY

Background: Omeprazole has become available in a tablet formulation, a Multiple Unit Pellet System (MUPS) containing a large number of small individually enteric-coated micropellets.

Aim: To compare the acid-inhibitory effect of omeprazole MUPS 20 mg with pantoprazole 40 mg and to describe the pharmacokinetics of both drugs following administration on day 1 and day 6.

Methods: Randomized, two-way crossover study. Sixteen *Helicobacter pylori*-negative healthy subjects, whose gastric acidity fell below pH 4 for 70% of a 24-h baseline period were included. Intragastric pH was measured continuously.

Results: On day 1 both drugs significantly raised median 24-h gastric pH compared to baseline. Median pH and percentages of time above pH 3 and 4 on day 1 and day 6 of administration were not significantly different, with the exception of median daytime pH on day 6, which was significantly higher with omeprazole (4.65 vs. 4.05). *AUC* and C_{max} of omeprazole were significantly increased on day 6. *AUC* and C_{max} of pantoprazole were not significantly increased.

Conclusions: No significant difference in acid-inhibitory effect on day 1. On day 6 median daytime pH was significantly higher with omeprazole MUPS, but the percentages of time spent above pH 3 and 4 were not significantly different. The significant increase in bioavailability of omeprazole may contribute to the increased effect on day 6.

INTRODUCTION

Omeprazole and pantoprazole are substituted benzimidazole derivatives. These agents, which are activated in the acidic compartment of the parietal cell, inhibit gastric acid secretion by binding to active proton pumps (H^+-, K^+-ATPase) in the secretory membrane of the parietal cell. The duration of the inhibitory effect of these drugs is due to the prolonged binding to the proton pump.[1–3] Substituted benzimidazole derivatives are rapidly eliminated from plasma and are extensively metabolized by cytochrome P-450 enzymes in the liver.[3, 4]

Recently omeprazole became available in a tablet formulation, a Multiple Unit Pellet System (MUPS), which contains a large number of small individually enteric-coated micropellets of omeprazole. MUPS tablets disintegrate rapidly in the stomach and the micropellets may empty more easily into the duodenal channel than conventional enteric-coated tablets.[5, 6] The relatively

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new proton pump inhibitor pantoprazole is administered as an enteric-coated tablet.

The recommended dose of omeprazole for the treatment of peptic ulcer disease and reflux disease is 20 or 40 mg o.d. The standard dose pantoprazole for both indications is 40 mg q.d.s. The pharmacodynamics of omeprazole capsules and pantoprazole tablets have been compared in several studies. Hartman *et al.* compared omeprazole 20 mg capsules with pantoprazole 40 mg tablets in a crossover study in healthy subjects with an unknown *Helicobacter pylori* status.[7] To make the study double-blind, two tablets of pantoprazole (20 mg) or one capsule of omeprazole (20 mg) were encapsulated using identical hard gelatine capsules. In that study pantoprazole 40 mg was significantly more effective than omeprazole 20 mg in raising 24-h median pH and daytime median pH both after single and repeated administration. However, with respect to healing rate, omeprazole 20 mg capsules and pantoprazole 40 mg tablets have similar efficacy in the treatment of reflux oesophagitis and duodenal ulcer.[8, 9]

The aim of the present study was to compare the pharmacodynamic effect on gastric pH of omeprazole MUPS 20 mg with pantoprazole 40 mg enteric-coated tablets following single (day 1) and repeated (day 6) oral administration and to describe the pharmacokinetics of both medications on these days.

METHODS

Subjects

Healthy subjects, between 18 and 40 years old, with normal physical examination and laboratory screening tests (haemoglobin, white blood cell total count, serum glucose, serum creatinine, total bilirubin, serum alkaline phosphatase, serum ASAT and/or ALAT) were recruited for the study. They were eligible for inclusion if their *H. pylori* serology (ELISA) was negative, and if their 24-h baseline gastric pH measurement was < pH 4 for more than 70% of the time (more than 16.8 h) at the time of enrolment.[10] Individuals were excluded from the study if they were pregnant, if they had gastrointestinal disorders, which might impair drug absorption, if they had a body weight more than 15% from ideal, and if they had a history of alcohol or drug abuse.

With the exception of oral contraceptives and the occasional use of paracetamol (acetaminophen) the subjects took no medication other than the study medication. Smokers were not excluded, but were instructed to refrain from smoking during the pH-monitoring studies. All subjects gave written informed consent and the study was conducted in accordance with the Declaration of Helsinki. The local Ethics Committee approved the study protocol.

Study protocol

This was a randomized, two-way crossover, investigator-blind study performed in the Leyenburg Hospital from April 1998 to October 1998. The study was designed to include 16 healthy *H. pylori*-negative subjects whose intragastric pH was below pH 4 for more than 70% of the time during a 24-h baseline period.

After inclusion each subject was assigned to one of the two 6-day dosing periods during which the subject received either omeprazole MUPS 20 mg o.d. or pantoprazole 40 mg o.d. Dosing periods were separated by washout periods of at least 14 days. The effect of both drugs on gastric acidity was assessed by 24-h intragastric pH monitoring on day 1 and day 6 of administration.

During the days of pH monitoring subjects stayed at a special research room in the clinic. Subjects arrived at the pH laboratory of the clinic by 08:00 hours. A venous catheter was inserted and the first blood sample was drawn. A nostril was anaesthetized with xylocaine spray and the 'personal' pH-measuring assembly was inserted and positioned, such that the pH electrode was located in the gastric corpus, 5–10 cm below the oesophagogastric junction as determined by the pH-drop. The insertion depth was recorded. In subsequent pH studies in the same subject, this same insertion depth was used. Recordings started at 08:30 hours. After the pH recording was started, the subjects took the first dose of the study medication immediately before the standard breakfast. Standard meals (breakfast, lunch and dinner) were prepared in the hospital and subjects were instructed to eat their lunch at 14:00 hours, and dinner at 18:00 hours. Blood samples (5 mL) for determination of omeprazole and pantoprazole plasma concentrations were drawn at pre-dose and at 30, 45, 60, 90, 120, 150, 180, 210 min, and at 4, 5, 6, 7, 8 and 9 h after dose. The venous catheter was removed after the last blood sample. From 23:00 hours the subjects remained in fasting condition and slept. They arose again between 07:00 and 07:30 hours the next day. The pH electrode was removed at 08:30 hours and the position of the

assembly was checked prior to removal. On the pH measurement days the use of tap water, tea and non-carbonated mineral water was restricted to a total of 2 L. Other beverages were not permitted.

Plasma concentrations of omeprazole and pantoprazole were determined by means of liquid chromatography techniques at Bio-analytical Chemistry, Astra Hässle AB, Mölndal, Sweden.[11]

Data analysis and statistical evaluation pH data

Twenty-four-hour pH-metry was performed as previously described.[12]

Evaluation of pH data was performed as previously described.[12, 13] Data were analysed using the SPSS statistical package. Wilcoxon's matched pairs signed rank test was used for comparison between treatment regimens. Median pH values over the whole 24-h period, day- and night-time, and cumulative percentages of time during which pH was above thresholds 3 and 4 over these time periods, were compared.

The significance level of each test was set at 0.05 (two-sided). *P*-values are presented as calculated for each test, no correction being made for multiple testing.

Pharmacokinetic data

Pharmacokinetic parameters were derived by non-compartmental analysis using WinNonlin software (version 3.1, Scientific Consulting Inc.). For each individual the following parameters were derived separately on day 1 and 6 of drug administration: time prior to the first measurable concentration (T_{lag}), time of maximum observed concentration (T_{max}), and the maximum observed concentration (C_{max}). The terminal rate constant (k) was determined by log-linear regression of the terminal phase of the plasma concentration–time curve. The terminal half-life ($T_{½}$) was calculated as follows: $T_{½} = 0.693/k$. The area under the concentration–time curve (*AUC*) and the area under the first moment curve (*AUMC*) were estimated by the linear-logarithmic trapezoidal method up to the last measured data point with extrapolation to infinity using k. The ratio of plasma clearance and bioavailability (*Cl/F*) was calculated by dividing the dose by the *AUC*. The ratio of the volume of distribution based on the terminal phase and bioavailability (*V/F*) was calculated by dividing *Cl/F* by k. Mean residence time (*MRT*) was the ratio of *AUMC* and *AUC*.

Differences in pharmacokinetic parameters between day 1 and 6 and differences in pharmacokinetic parameters between omeprazole and pantoprazole were evaluated using Wilcoxon's matched pairs signed rank test. The level of significance was set at 0.05.

RESULTS

Eighteen healthy subjects (11 women, seven men, aged 20–30 years) were screened. The serology (ELISA) was positive in one subject. One subject discontinued with the study after the baseline measurement. Sixteen subjects (nine women, seven men) with a mean age of 24.7 years (range 21.4–30 years), a mean weight of 73 kg (range 55–97 kg) and a mean height of 175.6 cm (range 157–192 cm) fulfilled the inclusion criteria and were randomized. Both drugs were well-tolerated and there were no clinically relevant adverse events.

Group median pH-time curves and interquartile ranges (25th–75th percentile) for baseline and the two treatment regimens during the first (day 1) and second (day 6) 24-h recording period are shown in Figure 1. The percentages of time spent above pH thresholds 1–7 for baseline and the two treatment regimens during the entire recording period, day- and night-time on day 1 and day 6 are shown in Figure 2. Inter-individual variation in response to the different dosing regimens is shown in Figure 3. Median pH values and median percentages of time spent above pH thresholds 3 and 4, for baseline and the two treatment regimens during the entire recording period, and day- and night-time on day 1 and day 6 are shown in Table 1. Differences in pharmacokinetic parameters between day 1 and 6 and differences in pharmacokinetic parameters between omeprazole and pantoprazole are displayed in Table 2. Median plasma concentrations of omeprazole and pantoprazole on day 1 and day 6 of administration are shown in Figure 4.

Compared to baseline, both drugs significantly increased median gastric pH and the percentages of time spent above pH 3 and 4 over the whole first 24 h of administration. During the night-time period, percentages of time above pH thresholds 3 and 4 were not significantly increased with pantoprazole. There were no significant differences between omeprazole and pantoprazole in median pH values or time spent above pH thresholds 3 and 4 for either the whole first 24 h period or day- or night-time period. On day 6 of

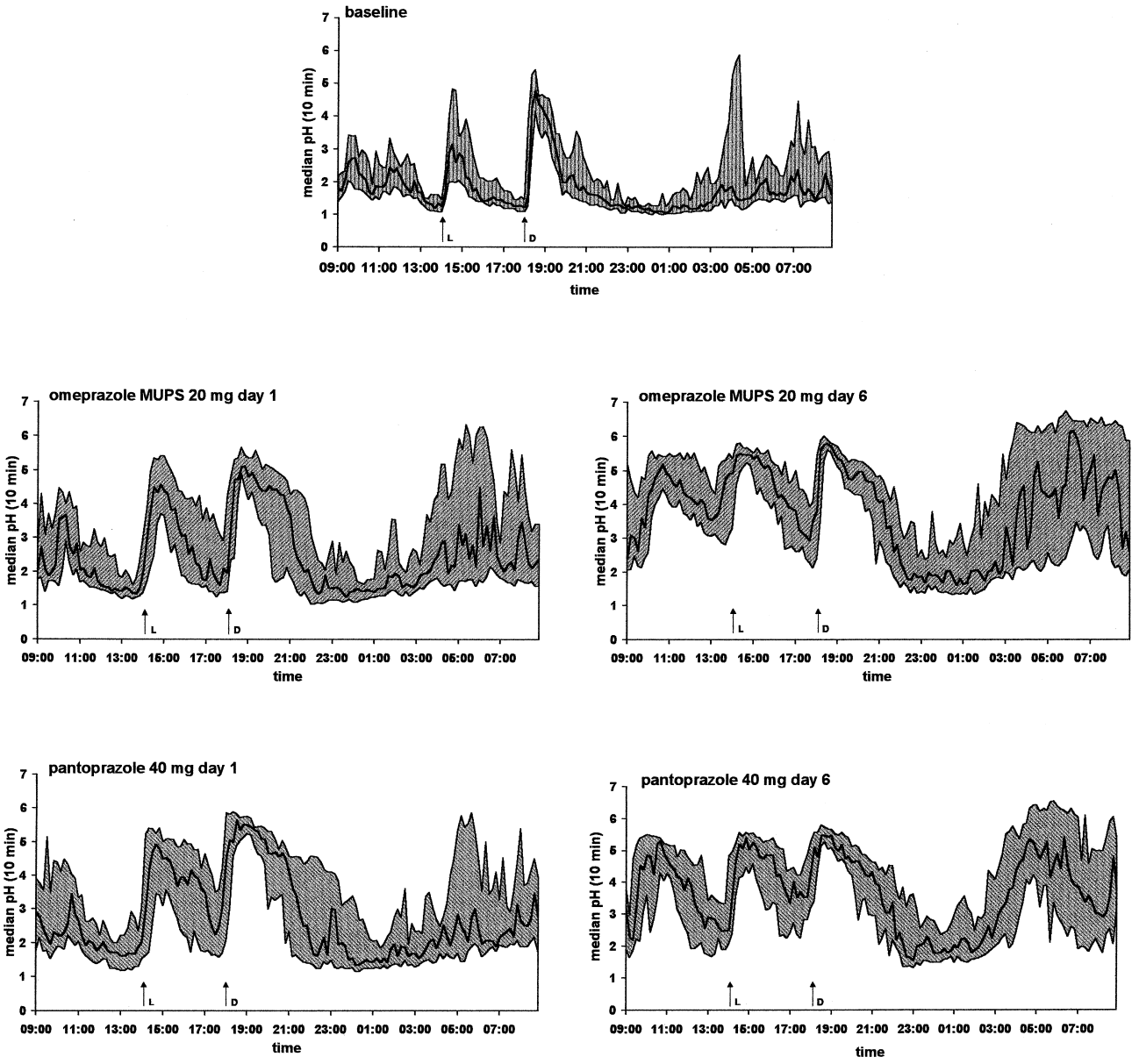

Figure 1. pH–time curves for baseline and the two treatment periods (day 1 and day 6 of administration). Median pH and 25th–75th percentile (shaded area). Arrows: L = lunch, D = dinner.

administration, median pH over the day period was significantly higher with omeprazole MUPS, but there were no significant differences between omeprazole and pantoprazole in the percentages of time spent above pH thresholds 3 and 4.

On day 6 of omeprazole administration, C_{max}, $T_{½}$, and *AUC* were significantly increased in comparison with the values on day 1, whereas *Cl/F* and *V/F* were reduced. No pharmacokinetic differences were observed between day 1 and day 6 of administration for pantoprazole. T_{lag} and $T_{½}$ of omeprazole were smaller than the corresponding values of pantoprazole. No significant differences were observed for T_{max} and *MRT* on day 1 and day 6, between omeprazole and pantoprazole.

DISCUSSION

This direct comparative study in *H. pylori*-negative subjects showed no significant differences between omeprazole MUPS 20 mg and pantoprazole 40 mg after

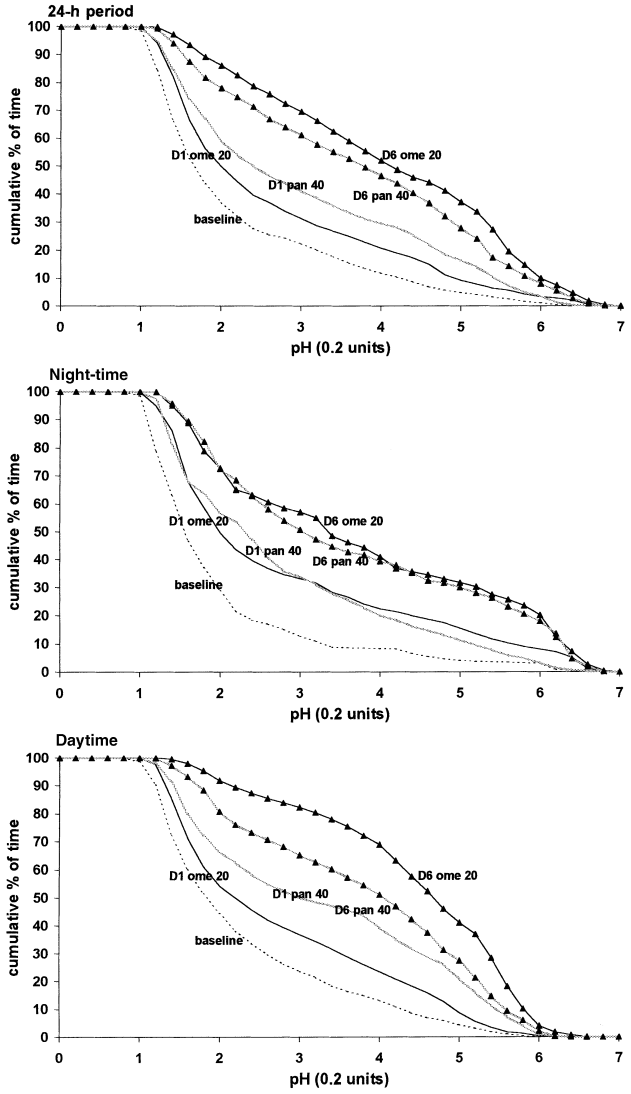

Figure 2. Cumulative percentages of time spent above pH thresholds during time periods. D1 = day 1, D6 = day 6, ome 20 = omeprazole MUPS 20 mg, pan 40 = pantoprazole 40 mg.

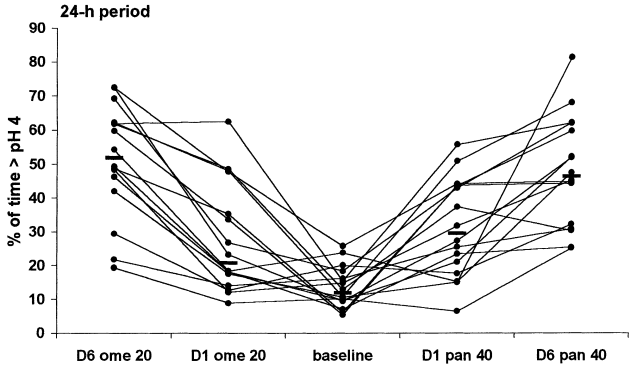

Figure 3. Individual responses of the 16 subjects to omeprazole MUPS 20 mg o.d. and pantoprazole 40 mg o.d. on day 1 and day 6 of administration (24-h period). D1 = day 1, D6 = day 6, ome 20 = omeprazole MUPS 20 mg, pan 40 = pantoprazole 40 mg.

single dose administration. After repeated administration median pH over the day period was significantly higher with omeprazole MUPS, but there were no significant differences between omeprazole and pantoprazole in the percentages of time spent above pH thresholds 3 and 4.

The pharmacokinetic parameters in this study are consistent with data obtained in other studies for both omeprazole and pantoprazole.[6, 14, 15] The time interval between dosing and the first measurable concentration of omeprazole MUPS was significantly shorter than the lag time of pantoprazole, but there was no significant difference in acid-inhibitory effect during the daytime on day 1 of administration. *AUC* and C_{max} of omeprazole MUPS 20 mg were significantly higher on day 6 than on day 1 (74% and 68%, respectively). This effect has been described earlier.[14, 15] Possible reasons for the increase in bioavailability upon repeated administration may be saturation of first-pass metabolism and a stepwise decrease in gastric acid delivered into the duodenum.[16] The increased bioavailability and decreased clearance is reflected in the decrease in *V*/*F* and *Cl*/*F*. For pantoprazole, *AUC* and C_{max} following repeated administration were comparable to those after the first dose, indicating that bioavailability remained constant after the first dose. The clinical relevance of the increase in *AUC* with repeated dosing of omeprazole remains unclear. However, it can be speculated that the increase in *AUC* may contribute to the increase in the pharmacodynamic effect on day 6 of administration.

In the present study median gastric pH on day 6 over the daytime period was significantly higher with omeprazole MUPS. In a previous direct comparative study of omeprazole MUPS 20 mg and pantoprazole 40 mg, median gastric pH on day 7 of administration was not significantly different. However, on day 1, median gastric pH was significantly higher with pantoprazole.[17] The clinical relevance of significant differences in median pH over time periods is limited, when percentages of time spent above pH thresholds 3 and 4 in those time periods do not differ significantly. According to the studies of Burget, Bell and Howden *et al.*, healing of peptic ulcer disease or erosive oesophagitis with antisecretory drugs is correlated with both the duration of gastric acid suppression over the 24-h

Table 1. Pharmacodynamic data of omeprazole MUPS 20 mg and pantoprazole 40 mg. Median pH values, median percentage of time above pH 3 and 4 and (25th–75th percentile)

	Baseline	Omeprazole MUPS Day 1	Pantoprazole Day 1	Ome MUPS vs. panto Day 1	Omeprazole MUPS Day 6	Pantoprazole Day 6	Ome MUPS vs. panto Day 6
Median pH							
24 h	1.6 (1.5–1.9)	1.95 (1.7–3.7)	2.4 (1.8–3.7)	0.178	4.05 (3.5–4.7)	3.7 (2.9–4.5)	0.289
night	1.5 (1.3–2.2)	2.0 (1.6–2.8)	2.3 (1.6–2.75)	0.234	3.3 (2.0–5.2)	3.05 (2.1–4.0)	0.469
day	1.84 (1.6–2.0)	2.1 (1.7–4.0)	3.0 (1.9–4.2)	0.125	4.65 (3.6–5.0)	4.05 (3.2–4.8)	0.038
% > pH 3							
24 h	22.4 (16.3–26.6)	31.3 (22.8–56.6)	41 (25.4–62)	0.148	69.5 (53.4–79.5)	61 (49–74.5)	0.569
night	12.8 (5.0–35.8)	33.2 (14.5–48)	33.9 (7.3–46.2)	0.796	57.1 (19.2–65.3)	50.8 (24.9–71.3)	0.959
day	23.7 (19.2–29.5)	36.9 (26.3–64.3)	50 (33.8–72.3)	0.07	82.2 (60.1–88.1)	65.2 (54.4–85.6)	0.255
% > pH 4							
24 h	11.9 (9.5–17.7)	20.8 (14.9–44.7)	29.5 (18.4–43.7)	0.109	51.9 (43.1–62.2)	46.4 (31.2–61.5)	0.438
night	8.3 (1.2–26.5)	22.5 (6.5–32.1)	20.1 (0.2–30)	0.056	41.0 (12.4–56.3)	39.3 (16.7–49.9)	0.836
day	13.1 (9.0–15.9)	23.6 (15.3–49.9)	39.3 (25.3–55.8)	0.1	68.9 (42.5–74.1)	51.2 (36–69.3)	0.109

Table 2. Pharmacokinetic data of omeprazole MUPS 20 mg and pantoprazole 40 mg. Median values and interquartile ranges (25th–75th percentile)

	Omeprazole MUPS Day 1	Omeprazole MUPS Day 6	Omeprazole MUPS Day 1 vs. day 6	Pantoprazole Day 1	Pantoprazole Day 6*
T_{lag} (h)	0.0§ (0.0–0.56)	0.0† (0.0–0.25)	0.724	0.63§ (0.5–1.00)	0.5† (0.0–1.31)
T_{max} (h)	0.75 (0.5–2.5)	0.75 (0.5–1.5)	0.636	1.5 (0.94–2.00)	1.0 (1.0–3.25)
C_{max}	0.47 (0.2–0.64)	0.79 (0.59–0.84)	0.003	2.69 (2.4–3.39)	3.29 (2.30–3.55)
AUC (mg · h/L)	0.65 (0.38–1.00)	1.13 (0.83–2.01)	0.001	4.34 (3.13–7.04)	4.21 (2.58–6.27)
Cl/F (L/h)	31 (18–52)	18 (10–25)	0.008	9.2 (5.7–12.8)	9.5 (6.2–15.5)
V/F	31 (25–41)	21 (19–26)	0.001	17 (13–22)	16 (11–23)
$T_{½}$ (h)	0.81‡ (0.64–1.00)	0.91# (0.75–1.39)	0.047	1.33‡ (1.12–1.49)	1.11# (1.00–1.34)
MRT (h)	2.2 (1.7–3.4)	1.8 (1.6–3.2)	0.438	2.8 (2.2–3.8)	2.6 (2.1–5.6)

*For pantoprazole no significant differences between day 1 and day 6.
P-values omeprazole vs. pantoprazole: § = 0.011; † = 0.03; ‡ = 0.001; # = 0.001.

period and the degree of gastric acid suppression.[18–20] The percentage of time spent above pH threshold 3 is more important for ulcer healing than further elevation of gastric pH. Healing rates at 8 weeks of (erosive) reflux oesophagitis are directly correlated with the duration of gastric acid suppression above pH 4. In our study there is no significant difference between omeprazole MUPS 20 mg and pantoprazole 40 mg in the percentages of time spent above pH 3 and 4 on day 1 and day 6 of administration. The percentages of time spent above pH 3 and 4 on day 6 of omeprazole 20 mg MUPS administration are comparable with the values of these variables found in a previous study with omeprazole 20 mg capsules.[12] This indicates that the omeprazole 20 mg MUPS formulation performs as well as the omeprazole 20 mg capsules formulation. Therefore, it is not surprising that in clinical studies omeprazole 20 mg capsules and pantoprazole 40 mg tablets have similar efficacy with respect to healing rates in the treatment of duodenal ulcer and reflux oesophagitis.[8, 9] Furthermore, more recently Mulder *et al.* showed that omeprazole MUPS 20 mg and pantoprazole 40 mg have similar efficacy in symptom relief at 4 weeks in the treatment of reflux oesophagitis grade I to IV.[21]

In conclusion, this direct comparative study demonstrates that the acid-inhibitory effects of omeprazole MUPS 20 mg and pantoprazole 40 mg are not significantly different on day 1 of administration. On day 6 of administration, median daytime pH was significantly higher with omeprazole MUPS. The clinical relevance of

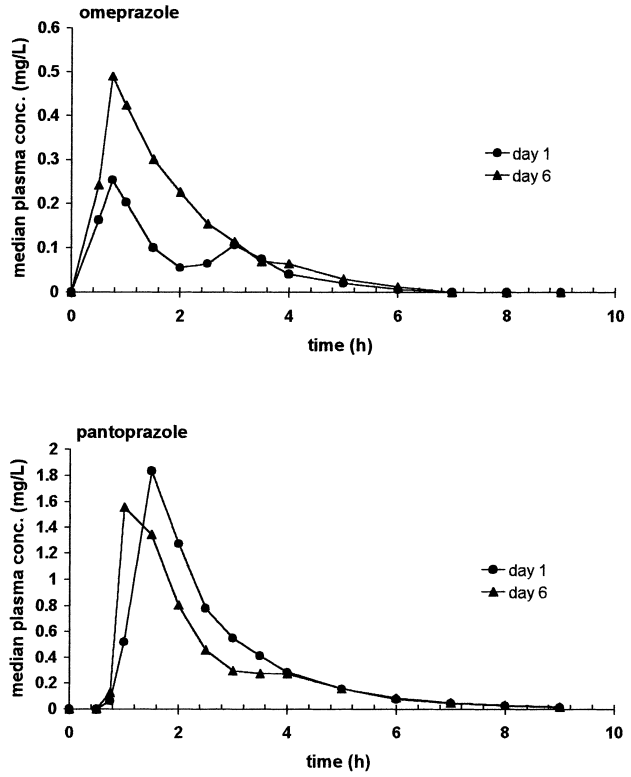

Figure 4. Time profiles of median plasma concentrations of omeprazole MUPS 20 mg and pantoprazole 40 mg on day 1 and day 6 of administration.

this difference is limited, since percentages of time spent above pH 3 and 4 in this period were not significantly different. The significant increase in bioavailability of omeprazole on day 6 of administration may contribute to the increased acid-inhibitory effect after repeated administration.

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