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Twenty-four-hour intragastric pH profiles and pharmacokinetics following single and repeated oral administration of the proton pump inhibitor pantoprazole in comparison to omeprazole

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SUMMARY

Background: Pantoprazole is a proton pump inhibitor characterized by a low potential to interact with the cytochrome P450 enzyme system in man. Its effect on intragastric pH following single and repeated oral intake was investigated in comparison to omeprazole by continuous intragastric pH-metry at doses recommended for treatment of peptic ulcer disease. *Methods*: Sixteen healthy male subjects underwent two dosing periods. From day 1 to day 7, they were given once daily by mouth 40 mg pantoprazole in one period and 20 mg omeprazole in the other period, according to a double-blind randomized crossover design. Twenty-four-hour intragastric pH was recorded and frequent blood samples for pharmacokinetic analysis were taken on day 1 and day 7. A placebo pH profile was obtained prior to each treatment period. *Results*: Pantoprazole was significantly more effective than omeprazole with regard to increase in 24-h and daytime pH, following both single (median 24-h pH: 1.45 vs. 1.3, $P < 0.05$; median daytime pH: 1.6 vs. 1.3, $P < 0.01$) and repeated (median 24-h pH: 3.15 vs. 2.05, $P < 0.01$; median daytime pH: 3.8 vs. 2.65, $P < 0.05$) oral intake. As compared to the first dose, repeated administration of both drugs markedly increased the effect on intragastric pH. With pantoprazole, steady-state serum concentrations were obtained after the first dose, but not with omeprazole. Both drugs were well tolerated without relevant changes in vital signs of clinical laboratory parameters. *Conclusion*: Pantoprazole 40 mg is significantly more effective than omeprazole 20 mg in raising intragastric pH.

INTRODUCTION

Pantoprazole is a proton pump inhibitor with a low potential to interact with the cytochrome P450 system both in animals[1] and in man.[2, 3] Its potency to inhibit gastric acid secretion has already been shown with the aspiration technique during pentagastrin stimulation.[4–6] In patients suffering from acid-related diseases 40 mg was shown to be the optimal therapeutic dose,[7] and high healing rates and rapid pain relief have been established in gastric and duodenal ulcers as well as in gastro-oesophageal reflux disease.[8–10] In comparison to ranitidine, pantoprazole accelerates healing and symptom relief in gastroduodenal ulcers, and in reflux oesophagitis it also improves the rate of healing.[8] With regard to gastric ulcer patients, pantoprazole 40 mg seems to be even more effective than omeprazole 20 mg.[9] Furthermore, pantoprazole was highly effective in healing ranitidine-resistant peptic ulcers, and long-term maintenance therapy was well tolerated.[11]

It was the aim of this study to investigate the intragastric pH profiles following single and repeated oral administration of pantoprazole 40 mg in comparison to omeprazole 20 mg under the conditions of normal life.

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The doses chosen reflect the recommendations for treatment of peptic ulcer disease.

ETHICS

The study was approved by an ethics committee, and performed according to the revised Declaration of Helsinki and in compliance with the rules of Good Clinical Practice. The subjects were given comprehensive verbal and written information, and written informed consent was obtained before the start of the study.

SUBJECTS AND METHODS

Subjects

Protocol-correct data from 16 subjects had to be available for the statistical evaluation. In total, 18 male subjects were admitted to the study. All were assessed as healthy based on physical examination, medical history and routine clinical laboratory screening. Two were withdrawn for reasons not related to the treatment. Sixteen completed the whole study. Their age ranged from 21 to 35 (median: 29) years, their body weight ranged from 60 to 88 (median: 74) kg.

Study design

The study was performed by the contract house Institut für klinische Pharmakologie according to a randomized two-period crossover design. Each subject underwent two dosing periods of 9 days each in randomized order. On days −2 and −1 of both periods, placebo was administered orally. From days 1 to 7, the subjects were given once daily by mouth 40 mg pantoprazole in one period, and 20 mg omeprazole in the other period under double-blind conditions. During each period, the subjects stayed at the Institut für klinische Pharmakologie. Blood was taken on days 1 and 7 of both periods, before and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12 and 24 h after intake of drug. Both dosing periods were separated by a washout period of at least 2 weeks.

Medication

Pantoprazole. 45.11 mg pantoprazole sodium sesquihydrate (two enteric-coated tablets each containing 22.56 mg), corresponding to 40 mg pantoprazole (Byk Gulden Pharmaceuticals, Konstanz, Germany).

Omeprazole. One capsule containing 20 mg omeprazole, as enteric-coated granules (commercially available, Antra, Astra Chemicals, Wedel/Hamburg, Germany).

To obtain double-blindness, two tablets of pantoprazole or one capsule of omeprazole were filled in identical hard gelatine capsules. Identical placebo capsules were also provided by Byk Gulden Pharmaceuticals.

Dietary

Medication was administered under fasting conditions around 09.00 h in the morning together with 200 mL tap water. Breakfast, lunch and dinner were identical on each study day with pH-metry (days −2, 1, 7) and taken 2, 6 and 10 h after oral administration.

pH-metry

Intragastric pH was recorded continuously over 24 h using a DL 7-recorder (Autronic GmbH, Karlsruhe, Germany) and glass electrodes (LOT 440-M4, Ingold, Urdorf, Switzerland). Before use, the electrodes were calibrated at pH 4 and 1. The electrodes were inserted through the nose up to the pH-decrease when passing the cardia. Then they were pushed forward for another 5–7 cm. The length of the probe for each volunteer was documented in order to attain the same gastric region for all measurements.

Pharmacokinetic analysis

Pantoprazole-Na serum concentrations were determined by reversed-phase HPLC using a gradient technique and UV-detection at a wavelength of 286 nm.[12] Sample workup was performed on-line by direct injection of 200 μL of untreated serum on a precolumn. The limit of quantitation was 0.03 mg/L. Serum concentrations were expressed as pantoprazole-Na.

Omeprazole serum concentrations were analysed using the same HPLC method as for pantoprazole-Na, the only difference being the wavelength used for UV-detection, which was chosen at 301 nm for omeprazole. The equation for the calibration line was: $Y = 0.9938 \times X - 0.0032$. The accuracy at these concentrations ranged between −22.7% (0.015 mg/L) and +3% (0.2 mg/L). The limit of quantitation was set at 0.01 mg/L, the accuracy and precision at this concentration being 21 and 6.0%. The recoveries at concentrations between 0.1 and 2 mg/L were between 101.0%

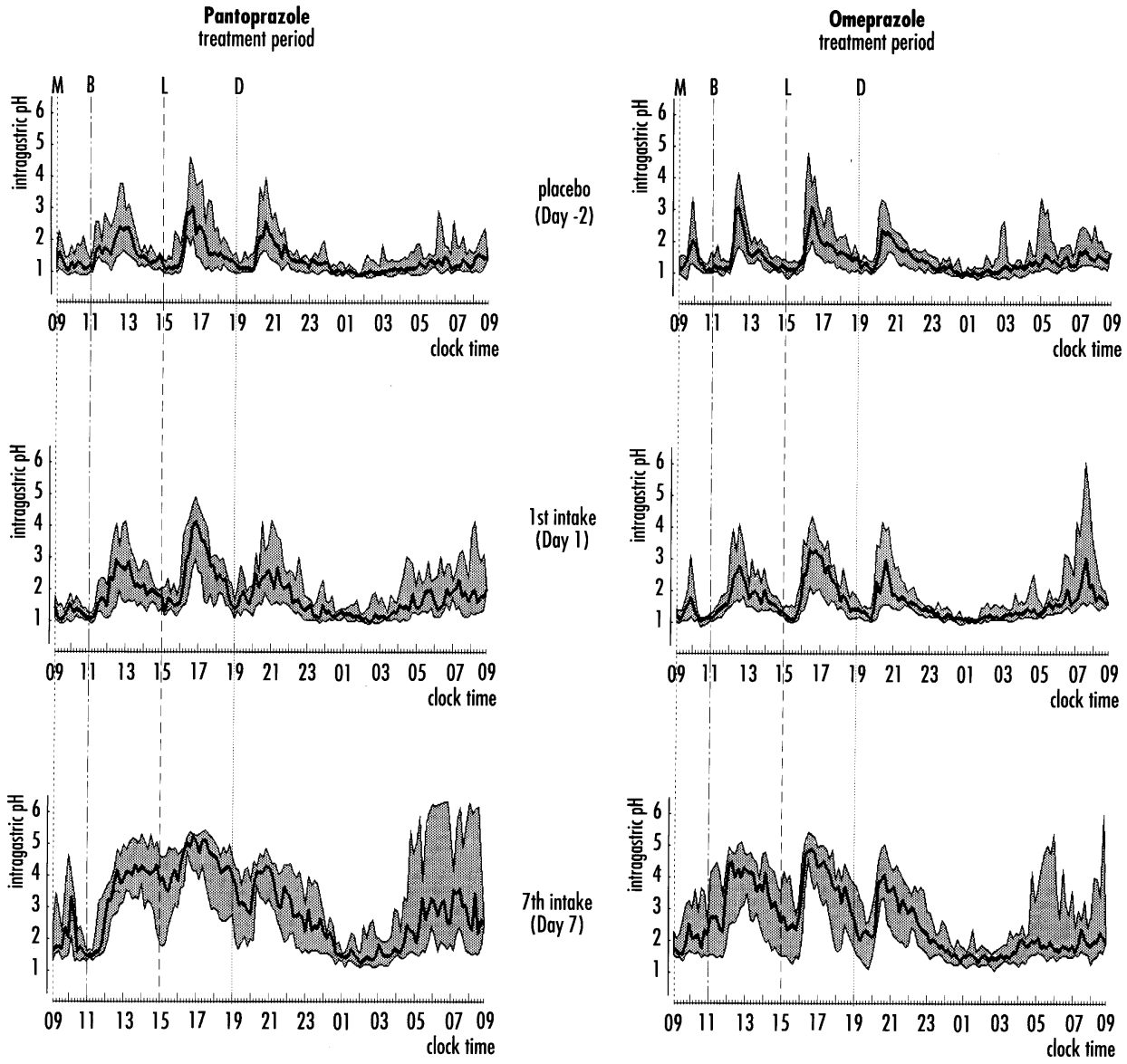

Figure 1. Median pH profiles ($n = 16$, first/third quartile) after placebo and the first and seventh oral intake of pantoprazole 40 mg and omeprazole 20 mg. M = medication (placebo: day −2; drug: days 1–7), B = breakfast, L = lunch, D = dinner.

(0.1 mg/L) and 106.4% (1.0 mg/L). The precision was determined at 0.1, 0.5 and 2.0 mg/L and gave coefficients of variation of 2.47, 1.05 and 1.53%, respectively.

Statistical evaluation

Efficacy. The median pH of the following time intervals was calculated for each subject and each profile:

total: 0–24 h post-administration (09.00–09.00 h);
day: 0–14 h post-administration (09.00–23.00 h);
night: 14–21 h post-administration (23.00–06.00 h).

Confirmative inference statistical analysis was performed for the 24-h intervals. Separate analyses for day and night were only considered as supportive data.

The comparison between the two treatments in terms of verum minus placebo was done non-parametrically with regard to the two-period crossover design using the test

Table 1. Intragastric pH after single and repeated oral intake of pantoprazole and omeprazole

Time after intake (clock time)	Treatment	Pantoprazole 40 mg Median $N = 16$	Pantoprazole 40 mg 68% range	Omeprazole 20 mg Median $N = 16$	Omeprazole 20 mg 68% range	Test
0–24 h (09.00–09.00)	Placebo	1.20	1.10–1.60	1.20	1.00–1.50	
	First intake	1.45	1.40–1.90	1.30	1.10–1.50	*
	Seventh intake	3.15	1.90–3.80	2.05	1.40–3.30	**
0–14 h (09.00–23.00)	Placebo	1.40	1.10–2.00	1.40	1.10–1.60	
	First intake	1.60	1.40–2.80	1.30	1.20–1.60	**
	Seventh intake	3.80	2.20–4.50	2.65	1.50–4.20	*
14–21 h (23.00–06.00)	Placebo	1.00	0.90–1.40	1.00	0.70–1.20	
	First intake	1.15	1.10–1.90	1.10	0.90–1.20	N.S.
	Seventh intake	1.50	1.20–2.50	1.40	1.10–2.20	N.S.

Koch's crossover test procedure based on differences drug–placebo. * $P < 0.05$, ** $P < 0.01$, N.S. = not significant.

procedure described by Koch[13] for single dose and steady state separately.

In order to compare the results of this study with published data on omeprazole, the per cent reduction of intragastric acidity was additionally calculated. This was done by transfering the pH values of each experiment to hydrogen ion activity using the formula: $\text{mmol/L} = 10^{-\text{pH}} \times 1000$. Then, the arithmetic mean was calculated for each experiment and group medians were derived thereof.

Pharmacokinetics

The following pharmacokinetic characteristics were determined for both pantoprazole-Na and omeprazole: area under the concentration–time curve (AUC), maximum serum concentration (C_{max}), the time of its occurrance (t_{max}) and terminal elimination half-life ($t_{\frac{1}{2}}$).

C_{max} and t_{max} were obtained directly from the concentration–time profiles. The area under the concentration–time curve ($AUC_{0-\infty}$ on day 1, $AUC_{0-24\,h}$ on day 7) was determined by the trapezoidal rule as described previously.[14]

Relative bioavailability (day 7 vs. day 1) of both pantoprazole and omeprazole was assessed by the individual ratios test/reference of the corresponding AUCs (extent of absorption) and C_{max} values (rate of absorption). Point estimates and shortest 90% confidence limits after logarithmic transformation were given for the ratios of the population medians of day 7 (test) and day 1 (reference).

RESULTS

Safety and tolerability

Both drugs were well tolerated. There were no clinically relevant changes in vital signs, ECG or clinical laboratory parameters nor were there relevant adverse events.

Efficacy

The reliability of the method used is shown by almost identical pH profiles and pH values following the placebo administration preceding each active dosing period (Figures 1 and 2, Table 1). Following the first dose, only a slight increase in median pH was observed with both drugs (Figure 1 and Table 1), however, pantoprazole was significantly more effective than omeprazole. The median reduction of intragastric acidity was 21% with omeprazole and 37% with pantoprazole.

Repeated once daily administration led to pharmacodynamic accumulation of the effect on intragastric pH. On day 7, a marked increase in 24-h and daytime median pH was observed, which was significantly in favour of pantoprazole (Figure 1 and Table 1). In terms of median acidity, this means 80% reduction with omeprazole, while with pantoprazole 98% reduction was calculated for the 24-h period.

During the night, the pH values decreased to almost placebo level. Only a slight increase in median pH of about 0.5 pH units in comparison to placebo was observed without statistically significant differences be-

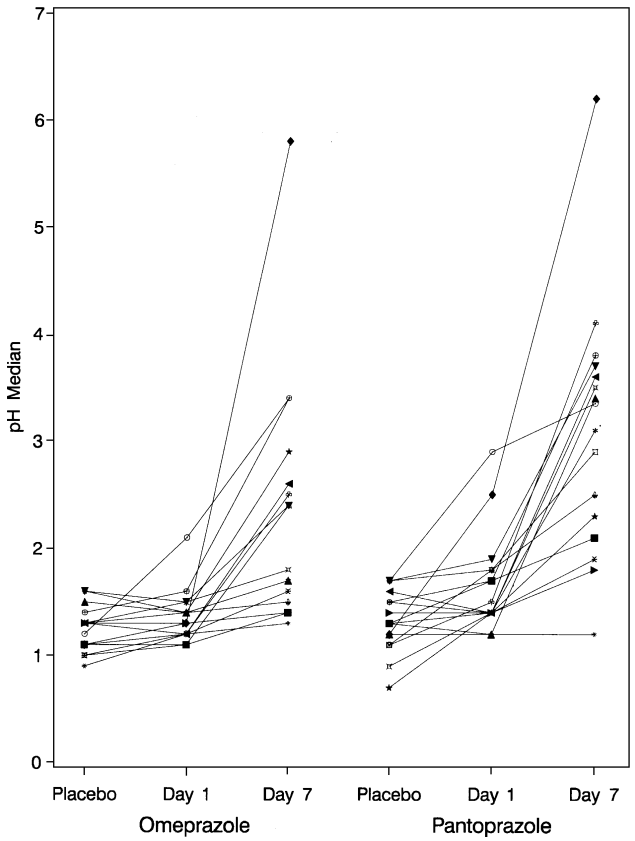

Figure 2. Individual median 24-h pH values following placebo and the first and seventh daily oral intake of omeprazole and pantoprazole.

tween the two drugs. In the early morning, pH increased again with both drugs, the increase observed with pantoprazole being higher than with omeprazole.

Individual 24-h median pH values are shown in Figure 2. The course of the median pH values was similar in both treatment periods within subjects, but, in general, the increase caused by pantoprazole was higher than that with omeprazole. Thus the individual data support the central tendency found in the statistical analysis.

Pharmacokinetics

The pharmacokinetic characteristics of pantoprazole following repeated administration (day 7) were similar to those after the first dose (day 1), while with omeprazole a 41% increase in AUC and a 32% increase in C_{max} were observed. The point estimates (90% confidence intervals) for AUC and C_{max} were 1.05 (0.91, 1.21) and 1.21 (0.97, 1.50) for pantoprazole, and 1.41 (1.09, 1.84) and 1.32 (1.04, 1.68) for omeprazole, respectively. Maximum serum concentrations were observed after about 3 h with pantoprazole and after about 1 h with omeprazole. $t_{\frac{1}{2}}$ was less than 1 h for both drugs (Table 2).

Compared with pantoprazole, administration of omeprazole seemed to be followed by a greater variability of the serum concentration–time profiles (Figure 3).

DISCUSSION

The pH-elevating effect of both pantoprazole 40 mg and omeprazole 20 mg increased during repeated once daily administration. The results were significantly in favour of pantoprazole following both single and repeated administration. Increasing the dose of omeprazole from 20 to 40 mg reveals similar pH values compared with pantoprazole 40 mg.[15] Consistently, treatment with 40 mg pantoprazole appears to result in slightly higher healing rates in duodenal ulcer (95 vs. 91% with omeprazole 20 mg at 4 weeks, N.S.) and in gastric ulcer

Table 2. Pharmacokinetic characteristics of pantoprazole-Na and omeprazole

	Pantoprazole 40 mg		Omeprazole 20 mg	
	Day 1	Day 7	Day 1	Day 7
	Geometric mean (68% range)		Geometric mean (68% range)	
$AUC_{0-\infty}$ or $AUC_{0-24\,h}$ (mg × h/L)	1.99 (1.14–3.47)	2.09 (1.34–3.26)	0.20 (0.13–0.32)	0.28 (0.14–0.56)
$t_{\frac{1}{2}}$ (h)	0.92 (0.73–1.16)	0.78 (0.53–1.15)	0.50 (0.40–0.64)	0.58 (0.42–0.81)
C_{max} (mg/L)	1.33 (0.69–2.58)	1.34 (0.48–3.69)	0.139 (0.08–0.25)	0.184 (0.10–0.32)
	Median (68% range)		Median (68% range)	
t_{max} (h)	2.75 (2.50–3.50)	3.00 (2.00–3.00)	1.25 (0.50–2.00)	1.00 (0.50–2.50)

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