Pharmacokinetics and effect on caffeine metabolism of the proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole

Tommy Andersson, Johan Holmberg, Kerstin Röhss & Anders Walan

Clinical Research & Development, Astra Hässle AB, Mölndal, Sweden

Aims To study the pharmacokinetics of three proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole, as well as any potential influence on CYP1A2 activity (measured by means of rate of caffeine metabolism) of these compounds at single dose and repeated dose administration.

Methods Fourteen healthy males, classified as 12 extensive metabolizers (EMs) and two poor metabolizers (PMs) according to the urinary S/R mephenytoin ratio, completed this open, randomized, three-way cross-over study. In each of the three 7-day treatment periods either omeprazole (20 mg), lansoprazole (30 mg) or pantoprazole (40 mg) in therapeutically recommended doses was administered once daily, and the pharmacokinetics of the proton pump inhibitors as well as the rate of caffeine metabolism was measured on days 1 and 7.

Results In the EMs there was an increase in AUC from day 1 to day 7 for omeprazole. In the PMs the AUC of both omeprazole and lansoprazole was unchanged during repeated dosing, while for pantoprazole there was a tendency to a slight decrease. The AUC at steady state was for all three proton pump inhibitors 5 fold higher in PMs compared with EMs, indicating that the same proportion of the dose, irrespective of compound, is metabolized by CYP2C19. No induction of CYP1A2 was evident for any of the compounds in either EMs or PMs.

Conclusions The ~5 fold difference in AUC between EMs and PMs indicates that approximately 80% of the dose for all three proton pump inhibitors is metabolized by the polymorphically expressed CYP2C19. None of the three proton pump inhibitors, administered in therapeutically recommended doses, is an inducer of CYP1A2—neither in PMs nor in EMs.

Keywords: pharmacokinetics, omeprazole, lansoprazole, pantoprazole

Introduction

Omeprazole, a proton pump (H^+ , K^+ -ATPase) inhibitor, has been used for over a decade in the treatment of gastric acid related diseases. Based on more than 200 million patient treatments, it has been demonstrated that omeprazole is a safe drug with no reported dose related side effects. Omeprazole is mainly metabolized by a polymorphically expressed cytochrome P450 (CYP) enzyme, CYP2C19 [1–7]. Thus, the metabolic capacity of a certain portion of the population (~3% Caucasians and ~15% Asians), defined as poor metabolizers (PMs), is decreased and these individuals exhibit 5 to 10 fold higher than average plasma concentrations of the drug. The reason why they metabolize omeprazole slowly is that their livers do not express a functional form of CYP2C19. This particular enzyme has been shown to be the main enzyme involved in the formation of the major metabolite of omeprazole, hydroxy-omeprazole [6, 7]. The formation of another metabolite, omeprazole sulphone, has been reported to be mainly mediated by CYP3A4 [6, 7]. Moreover, it has been suggested that, in PMs, omeprazole 40 mg daily can slightly

(~30%) induce CYP1A2 [8]. This potential property of omeprazole is possibly dose/concentration dependent, and it has been indicated that rapid/extensive metabolizers (EMs) need 120 mg omeprazole daily to give similarly induced levels of CYP1A2 as seen after omeprazole 40 mg to PMs [8–11]. In these studies the rate of caffeine metabolism has been used as an indicator of CYP1A2 activity. Omeprazole in doses of 20 to 40 mg daily does not influence the metabolism of other CYP1A2 substrates, such as phenacetin and theophylline [12–16].

Both lansoprazole [17–19] and pantoprazole [20–22] seem to be dependent on the same CYP isoforms for their major metabolism as omeprazole. The difference in AUC of lansoprazole and pantoprazole between a PM and an average EM seems to be relatively similar to that reported for omeprazole, indicating that about the same proportion of the total metabolism of all three compounds is dependent on CYP2C19. The formation of hydroxy-lansoprazole and a dealkylated metabolite of pantoprazole is thus mediated by CYP2C19 while the formation of the sulphones of these compounds, as for omeprazole, is dependent on CYP3A. It has also been reported that the metabolism of theophylline is slightly induced after lansoprazole treatment 30–60 mg [23, 24] and, since theophylline is a substrate for CYP1A2, this indicates an induction of CYP1A2 by lansoprazole. In contrast

Correspondence: Dr Tommy Andersson, Clinical Research & Development, Astra Hässle AB, S-431 83 Mölndal, Sweden.

to this, it has been shown that the metabolism of caffeine was not affected by lansoprazole treatment 30 mg daily [11].

However, these properties of the proton pump inhibitors, i.e. the same degree of CYP2C19 dependence and the potential for a slight CYP1A2 inductive capacity have hitherto not been studied in the same individuals. This study was performed in order to compare in the same individuals, including both EMs and PMs, the three proton pump inhibitors, both after single dose and at steady state, with respect to pharmacokinetics and effect on CYP1A2 activity.

Methods

Fourteen healthy males, classified as 12 extensive metabolizers [EMs] and two poor metabolizers (PMs) according to the urinary S/R mephenytoin ratio [25], ranging in age from 22 to 32 years and in weight from 68 to 86 kg, completed this open, randomized, three-way cross-over study. The study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty of the University of Göteborg and by the Swedish Medical Products Agency. Written informed consent was received from all subjects prior to participation.

Each of the three treatment periods had a duration of 7 days and were separated by a wash-out period of at least 2 weeks. In each treatment period either omeprazole, lansoprazole, or pantoprazole was administered orally once daily in doses of 20, 30, and 40 mg, respectively, which are the therapeutically recommended dosages for these compounds. The pharmacokinetics of each compound were studied on days 1 and 7. The potential effect on CYP1A2 was measured as the change in the rate of caffeine metabolism, using the caffeine breath test [8, 9] as well as urinary caffeine metabolite ratio [26, 27], before start of treatment and on days 1 and 7.

Alcohol and all medications, including 'over the counter' drugs, were prohibited for the 2 days prior to and during each of the three treatment periods. All subjects were told to abstain from all food and liquids after 22.00 h on the day prior to each investigational day (days 1 and 7 in each period). On these days standardized meals were served at the laboratory at standardized times. Moreover, food (e.g. chocolate) and beverages (e.g. coca-cola and coffee) that could influence the performance of the caffeine breath test were avoided at least during 1 day prior to each caffeine breath test. Food known to be inducers of CYP1A2, i.e. grilled food, broccoli, cabbage and most other cruciferous vegetables were also avoided at least 1 week prior to start of the study and until the study was finished. The amount of physical exercise was kept constant during the study.

Drug administration

All drugs were administered as commercially available formulations: Omeprazole (Losec[®], Astra AB, Sweden) 20 mg was given orally as enteric coated granules in capsules; lansoprazole (Lanzo[®], Leaderle, Orion-Farmos, Sweden) 30 mg was given orally as enteric coated granules in capsules; and pantoprazole (Rifun[®], Schwarz Pharma, Germany) 40 mg was given orally as acid-resistant tablets. All three formulations were taken with 200 ml of tap water in the morning after an overnight fast.

Caffeine, 3 mg kg⁻¹ body weight, was given orally as [¹³C]-(N-3-methyl)-caffeine dissolved in 200 ml tap water. This is a stable, non-radioactive isotope (molecular weight 195.2; specific ¹³C content at the N-3-methyl group, 0.99; Cambridge Isotope Laboratories, MA, USA). At pre-entry and on study days 1 and 7 the caffeine dose was administered 2 h after drug intake (at maximum plasma concentrations) in order to detect any potential acute influence (i.e. inhibition on day 1) or long-term influence (i.e. induction on day 7) of the proton pump inhibitors on the caffeine metabolism.

Pharmacokinetics

On days 1 and 7 blood samples were drawn 5 min before (reference sample) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9 and 10 h after drug administration from an indwelling cannula in a forearm vein. All blood samples were collected in heparinized tubes, centrifuged, and the plasma transferred and stored frozen (-20°C) until analysis. The plasma samples were analysed for omeprazole at Bioanalytical Chemistry, Astra Hässle AB, using liquid chromatography with u.v.-detection [28]. The limit of quantitation for omeprazole was 20 nmol l⁻¹ (CV = 10–15%). Lansoprazole and pantoprazole were determined using similar methods. For determination of lansoprazole a mobile phase consisting of 0.20% of ammonium hydroxide (25%) and 2.5% of methanol, in dichloromethane, was used and a wavelength of 283 nm. The limit of quantitation was 25 nmol l⁻¹ (CV < 20%). The repeatability at 2700 and 270 nmol l⁻¹ (n = 10) was 0.3 and 0.7%, respectively. For determination of pantoprazole a mobile phase consisting of 0.18% of ammonium hydroxide (25%) and 3% of methanol, in dichloromethane, was used and a wavelength of 289 nm. The limit of quantitation was 25 nmol l⁻¹ (CV < 20%). The repeatability at 2500 and 250 nmol l⁻¹ (n = 10) was 1.3 and 1.1%, respectively.

The area under the plasma concentration *vs* time curve (AUC) for omeprazole, lansoprazole and pantoprazole were calculated using the log linear trapezoidal method. The AUC was extrapolated to infinity by adding the residual area obtained by dividing the last measured plasma concentration (*C_t*) with the rate constant (*λ_z*) as determined by log-linear regression analysis of the terminal slope of the plasma concentration *vs* time curve. Plasma elimination half-life (*t_{1/2,z}*) was calculated as ln2/*λ_z*. The observed maximum plasma concentration (*C_{max}*) and time to reach *C_{max}* (*t_{max}*) were recorded.

Caffeine breath test

Within 1 week prior to the first dose administration as well as on days 1 and 7 the subjects arrived at the laboratory for a caffeine breath test. On days 1 and 7 the caffeine dose was administered 2 h after the dose of omeprazole, lansoprazole or pantoprazole. At selected intervals during 8 h subsequent to ingestion of the caffeine dose, breath samples were collected in plastic bags (approximately 2.5 l). Two aliquots of the breath samples were immediately transferred into evacuated vials (Vacutainer[®]) and stored at room temperature until analysis. The samples were analysed for amount of

^{13}C -labelled CO_2 in the breath at Bioanalytical Chemistry, Astra Hässle AB, using isotope ratio mass spectrometry [8].

The cumulative ^{13}C elimination of the ^{13}C test dose was calculated according to the trapezoidal rule up to the last time point of $^{13}\text{CO}_2$ collection. The rise in the breath (expressed as per ml) of ^{13}C -labelled CO_2 over the baseline curve at pretreatment, as measured up to 8 h after administration of the caffeine dose, was compared with that following 1 day and 1 week's treatment with omeprazole, lansoprazole and pantoprazole. A potential change in this measure during treatment relative to that of the baseline would indicate a change in caffeine clearance, which in turn would indicate an altered activity of hepatic CYP1A2 [8].

Caffeine metabolites in urine

Urine was collected during two consecutive 3 h periods after the caffeine administration, i.e. 2–5 and 5–8 h after drug administration. Urine volumes were recorded and 10 ml aliquots were acidified to $\text{pH} < 3.5$ with a citrate buffer and stored frozen (-20°C) until analysis. Caffeine metabolites in urine were determined by gradient elution LC and MS detection at Bioanalytical Chemistry, Astra Hässle AB. The chromatographic column was Microspher C18, $3\ \mu\text{m}$, $50 \times 4.6\ \text{mm}$ (Chrompack, the Netherlands). The mobile phases used consisted of 1.5% acetonitrile, ammonium acetate $5\ \text{mmol l}^{-1}$ and formic acid 0.1%, in water (mobile phase I) and 10% acetonitrile, ammonium acetate $5\ \text{mmol l}^{-1}$ and formic acid 0.1%, in water (mobile phase II). The mobile phase was 10% of phase II at the start of the run and a linear gradient to 100% of phase II in 5 min. The flow-rate was $1\ \text{ml min}^{-1}$. The mass spectrometer was an API-1 (Perkin-Elmer/Sciex) equipped with pneumatically assisted electrospray. The molecular ion of the analytes were detected in the negative-ion mode and selected-ion monitoring. The urine samples were diluted 20 times with mobile phase I and $50\ \mu\text{l}$ of the mixture was injected onto the column. The limit of quantitation was $3\ \mu\text{mol l}^{-1}$ for both AFMU, 1U, 1X and 17U with a CV of 10.2, 12.3, 11.2 and 10.9%, respectively. The repeatability at $60\ \mu\text{mol l}^{-1}$ was 5.9, 3.9, 4.2 and 2.9%, respectively ($n = 10$). External quantitation was used at three levels with a non-linear, quadratic calibration procedure.

In each urine sample the amounts of 1-methylxanthine (1X), 1-methyluric acid (1U), 5-acetylamino-6-formyl-amino-3methyl uracil (AFMU), and 1,7-dimethyluric acid (17U) were determined. According to Campbell *et al.* [26] and Grant *et al.* [27] the activities of the enzymes CYP1A2, N-acetyl transferase (NAT2), and xanthine oxidase (XO), respectively, correspond to the following urinary metabolite ratios, which were calculated:

$$\begin{aligned}\text{CYP1A2: } & \frac{\text{AFMU} + 1\text{X} + 1\text{U}}{17\text{U}} \\ \text{NAT: } & \frac{\text{AFMU}}{1\text{X}} \\ \text{XO: } & \frac{1\text{U}}{1\text{X}}\end{aligned}$$

Statistical evaluation

For EMs, the data were analysed using an ANOVA with factors subject, period, treatment and study day on log transformed variables. The values of the pharmacokinetic variables on day 1 were compared with those on day 7. A comparison between control values and values obtained on days 1 and 7, respectively, was performed for the caffeine breath test and the urinary caffeine metabolite ratios. These comparisons were performed separately for each study drug by means of calculating 95% confidence intervals for the corresponding mean ratios. The caffeine metabolite ratios between day 1 and day 7 *vs* control were compared between the three different treatments by means of 95% confidence intervals and corresponding values. In these calculations Student's *t*-distribution and the mean square error from the ANOVA were used.

Descriptive statistics for all the variables are given.

Due to the limited number of PMs ($n = 2$), only descriptive statistics for the variables are given for these individuals.

Results

Pharmacokinetics

The median plasma levels in both EMs and PMs at steady state (day 7) of omeprazole, lansoprazole and pantoprazole are shown in Figure 1a–c. The pharmacokinetic parameters on both day 1 and day 7 are presented in Table 1.

For all acid pump inhibitors the plasma levels at steady state in PMs were higher than those in EMs, i.e. the mean AUC was approximately 5 fold higher in PMs than in EMs, irrespective of compound tested (5.4, 5.9, and 6.5 fold higher for omeprazole, lansoprazole, and pantoprazole, respectively). In the EMs, there was a 76% (95% CI = 46–113%) increase in AUC from day 1 to 7 for omeprazole. No increase was observed for lansoprazole and pantoprazole. In the PMs, the AUC was unchanged for both omeprazole and lansoprazole, while for pantoprazole there seemed to be a slight decrease. In EMs, the mean plasma elimination half-life ($t_{1/2,z}$) was slightly below 1 h for omeprazole and slightly above 1 h for lansoprazole and pantoprazole. In PMs, the mean $t_{1/2,z}$ was 2.4 h, 3.8 h and 6.3 h for omeprazole, lansoprazole and pantoprazole, respectively. Thus, the difference in $t_{1/2,z}$ between PMs and EMs was 2.5 fold, 3.5 fold, and 5 fold for omeprazole, lansoprazole and pantoprazole, respectively. Finally, the mean time to reach maximum plasma concentration was 1.5 h for both omeprazole and lansoprazole in both EMs and PMs, while it seemed to be slightly longer for pantoprazole (2.2 h).

Caffeine breath test

The results from the caffeine breath test, with cumulative ^{13}C elimination following treatment with the different proton pump inhibitors, are presented in Table 2. The ratios for {day 1 value/control value} were 0.97 (95% CI = 0.88–1.07), 0.92 (0.83–1.01), and 0.92 (0.84–1.02) for omeprazole, lansoprazole, and pantoprazole, respectively. The corresponding figures for the ratios for {day 7 value/

Figure 1 Median plasma concentration *vs* time profiles at steady state (day 7) of **a**) omeprazole (20 mg), **b**) lansoprazole (30 mg), and **c**) pantoprazole (40 mg), in extensive (EMs, ●, *n* = 12) and poor metabolizer (PMs, ○, *n* = 2).

control value} were 0.94 (0.85–1.04), 0.95 (0.87–1.05), and 0.94 (0.85–1.03), respectively. Thus, no effect on this parameter was observed for any of the proton pump inhibitors, either on day 1 or on day 7, indicative of lack of effect on CYP1A2 activity.

Caffeine metabolites in urine

The {day 1 value/control value} for the urinary metabolite ratio measuring the CYP1A2 activity was 0.97 (95% CI 0.86–1.09), 0.92 (0.82–1.04), and 0.98 (0.86–1.10) for omeprazole, lansoprazole, and pantoprazole, respectively. The corresponding figures for the {day 7 value/control value} were 0.96 (0.85–1.08), 0.99 (0.88–1.12), and 0.91 (0.81–1.03), respectively. The {day 1/control value} of the urinary metabolite ratio mirroring the xanthine oxidase activity was 0.99 (0.89–1.09), 0.97 (0.88–1.07), and 1.07 (0.97–1.18), for omeprazole, lansoprazole, and pantoprazole, respectively. The corresponding figures for {day 7 value/control value} were 1.02 (0.92–1.12), 1.05 (0.95–1.16), and 0.99 (0.90–1.10), respectively. Thus, the measures

mirroring the CYP1A2 and xanthine oxidase activities were not changed on days 1 and 7 following omeprazole, lansoprazole or pantoprazole treatment, compared with control values (Table 3). These two ratios exhibited rather small variation compared with the ratio for *N*-acetyltransferase activity, which exhibited a coefficient of variation (i.e. s.d./mean) of almost 100%. Moreover, this ratio was increased for all three proton pump inhibitors on day 7 compared with control; 38% (15–66%) for omeprazole, 46% (21–75%) for lansoprazole, and 44% (20–74%) for pantoprazole. For pantoprazole, it was increased also on day 1 (24%, 3–49%). For omeprazole and lansoprazole no change was observed on day 1 *vs* control value (1.06, 0.88–1.27 for omeprazole; 1.02, 0.85–1.23 for lansoprazole).

Discussion

Previous studies and isolated published and unpublished observations have indicated a similar degree of dependence on the polymorphically expressed CYP2C19 for the metabolism of the three proton pump inhibitors omeprazole, lansoprazole, and pantoprazole [1, 17–22, 29]. In the present study it was demonstrated, in the same individuals, that the difference in AUC between EMs and PMs actually is the same (5 fold) for omeprazole, lansoprazole and pantoprazole. Since the difference in AUC between EMs and PMs is 5 fold, the amount of drug metabolized by CYP2C19 can be estimated to be 80% in EMs, which previously has been suggested [30]. It was also indicated in this study, in both EMs and PMs, that none of the three proton pump inhibitors induced CYP1A2 activity following administration of therapeutically recommended doses of these compounds.

The AUC of omeprazole increased in EMs during repeated dosing, which is in agreement with previous reports [29, 31]. In the two PMs, the AUC of neither omeprazole nor lansoprazole changed during repeated dosing, which also is in agreement with previous reports [29, 32]. The explanation for this discrepancy between EMs and PMs is probably that CYP2C19 is inhibited in EMs by omeprazole during repeated dosing which results in an increased AUC, but in PMs, which lack activity of this enzyme, no such inhibition and subsequent increase in AUC can occur [29]. Surprisingly, though, for pantoprazole there was a tendency to a slight decrease in AUC during repeated dosing in PMs. This may be indicative of an induction of its metabolism by pantoprazole in these individuals, and since the major metabolism of the acid pump inhibitors in PMs probably is CYP3A mediated, it may be indicative of a CYP3A induction. Furthermore, since the *t*_{1/2} of pantoprazole in these PMs seemed to be similar or even longer on day 7 *vs* day 1 this might be induction of the intestinal CYP3A. Only two slow metabolizers participated in this study but, since our experience is that there is very little variation in metabolism between PMs, especially with regard to omeprazole, the results obtained in this study may be representative for this group of individuals. An induction of CYP3A activity has previously been suggested for omeprazole and lansoprazole in *in vitro* experiments in human hepatoma cell lines [33]. However, this has never been verified *in vivo*, and, especially for omeprazole, several interaction studies with CYP3A substrates demonstrate the contrary—no effect

Table 1 Pharmacokinetic parameters following different treatments. Mean and s.d. (median and range for $t_{\max}$) for the extensive metabolizers ($n=12$) and individual data for the two poor metabolizers.

		Omeprazole		Lansoprazole		Pantoprazole	
		Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
EMs							
$t_{\max}$		1.0	1.5	1.5	1.5	2.0	2.0
(h)		(1–5)	(1–2.5)	(1–2)	(1–2)	(1–3.5)	(1.5–3.5)
$C_{\max}$		0.70	1.07*	2.25	2.21	5.73	5.44
($\mu\text{mol l}^{-1}$)		(0.36)	(0.59)	(0.71)	(0.68)	(1.07)	(1.42)
AUC		1.11	2.23*	5.01	4.87	9.93	9.51
($\mu\text{mol l h}^{-1}$)		(0.57)	(1.86)	(2.40)	(2.04)	(3.26)	(3.51)
$t_{1/2}$		0.7	0.9*	1.2	1.1	1.2	1.3
(h)		(0.3)	(0.2)	(0.4)	(0.3)	(0.3)	(0.3)
PMs							
$t_{\max}$	No. 1	2.0	1.0	1.5	2.0	4.0	2.5
(h)	No. 18	1.5	1.5	1.0	1.0	2.0	2.0
$C_{\max}$	No. 1	2.60	3.31	5.60	4.60	11.3	11.5
($\mu\text{mol l}^{-1}$)	No. 18	2.53	3.01	4.16	5.02	10.4	7.80
AUC	No. 1	11.6	13.0	36.2	31.0	71.2	60.2
($\mu\text{mol l h}^{-1}$)	No. 18	10.3	11.0	24.7	26.7	71.4	63.2
$t_{1/2}$	No. 1	2.2	2.7	5.4	4.0	4.3	6.6
(h)	No. 18	2.2	2.0	4.0	3.5	5.2	6.0

* = different from day 1 value ($P < 0.05$).**Table 2** Cumulative $^{13}\text{CO}_2$ elimination, expressed as per mille over baseline, following different treatments.

		Omeprazole		Lansoprazole		Pantoprazole	
	Control	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
EMs (<i>n</i> = 12)							
Mean	39	37	36	36	37	35	36
s.d.	9	9	8	10	9	8	6
PMs							
No. 1	26	32	35	31	29	21	29
No. 18	32	27	30	30	33	29	30

Table 3 Urinary caffeine metabolites ratios representing CYP1A2, *N*-acetyl-transferase (NAT) and xanthine oxidase (XO) enzyme activity. Mean and s.d. for the extensive metabolizers ($n=12$) and individual data for the two poor metabolizers.

		Control	Omeprazole		Lansoprazole		Pantoprazole	
			Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
EMs								
CYP1A2		4.3	4.3	4.1	4.2	4.3	4.2	3.9
		(1.4)	(1.7)	(1.3)	(2.3)	(1.8)	(1.5)	(1.5)
NAT		0.17	0.16	0.22*	0.20	0.25*	0.21*	0.26*
		(0.14)	(0.13)	(0.17)	(0.20)	(0.23)	(0.18)	(0.25)
XO		1.1	1.0	1.1	1.0	1.1	1.2	1.1
		(0.2)	(0.1)	(0.2)	(0.2)	(0.2)	(0.3)	(0.2)
PMs								
CYP1A2	No. 1	3.0	2.8	3.3	2.6	2.9	2.3	2.6
	No. 18	3.0	2.6	3.3	2.6	3.3	2.5	3.0
NAT	No. 1	0.12	0.12	0.14	0.13	0.09	0.15	0.14
	No. 18	0.45	0.51	0.36	0.52	0.52	0.58	0.49
XO	No. 1	0.87	0.88	0.86	0.76	0.95	0.82	0.86
	No. 18	1.03	0.88	1.01	0.96	1.03	1.06	0.90

* = different from control value ($P < 0.05$).

on CYP3A activity [30]. Even after very high doses of omeprazole, 120 mg daily, no tendency of induction of CYP3A was observed [34].

A substantial difference in AUC between the three proton

pump inhibitors was observed and in both EMs and PMs, the mean AUC at steady state was 2.5 fold and 5 fold higher for lansoprazole (30 mg) and pantoprazole (40 mg), respectively, as compared with that for omeprazole (20 mg). Since

similar inhibitory effects on gastric acid secretion have been reported following administration of these therapeutically recommended doses of the proton pump inhibitors [35], this observation may indicate that omeprazole is the most potent inhibitor of gastric acid secretion among these three compounds.

No induction of CYP1A2 was evident for any of the compounds following 1 week's treatment with therapeutically recommended doses of each of them, as observed in two independent tests of caffeine clearance—the caffeine breath test and the urinary ratio of caffeine metabolites. This is in agreement with previous reports for omeprazole, showing that no induction will occur with therapeutic doses of omeprazole [8, 10]. However, the variation in the previous studies in PMs with regard to induction by omeprazole was substantial (ranging from 13% to 63% induction) making it difficult to draw relevant conclusions. For lansoprazole and pantoprazole the phenomenon of induction has not been studied in PMs. The variation in the present material was not very pronounced for the methods used in the determination of CYP1A2 activity.

The mean ratios representing the activity of xanthine oxidase indicate that also this activity is unaltered by treatment with proton pump inhibitors, which is in agreement with previously reported results for omeprazole [10]. The urinary metabolite ratio corresponding to *N*-acetyl-transferase activity, on the other hand, was higher on day 7 for all three treatments compared to the control value. This is contradictory to what has previously been reported for omeprazole [10], but due to the high variation observed for this ratio in the present study it is difficult to draw any firm conclusions.

Conclusion

The difference in AUC between EMs and PMs was ~5 fold for all three proton pump inhibitors indicating that 80% of the total metabolism of these compounds are mediated by CYP2C19. No induction of CYP1A2 was evident for any of the compounds in neither EMs nor PMs.

We thank Maria Håkansson for excellent technical performance.

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(Received 10 July 1997,
accepted 4 December 1997)