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Age-related differences in the pharmacokinetics and pharmacodynamics of lansoprazole

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1 The pharmacokinetics and pharmacodynamics of lansoprazole, an antisecretory and antiulcer agent, were evaluated in 12 older (>60 years) and 12 younger (<60 years) healthy men.

2 Doses of lansoprazole (15 or 30 mg) or placebo were each given once daily for 7 consecutive days in this randomized, double-blind, three-way crossover study. Plasma concentrations and urinary excretion of lansoprazole and its metabolites, and gastric acid secretion were monitored after dosing on days 1 and 7 of each treatment period.

3 Within each age group, lansoprazole pharmacokinetics were linear. The mean clearance and elimination half-life of lansoprazole were about 40% lower and higher, respectively, in the older subjects (CL_0: 12–14 *vs* 20–24 l h^{-1}; $t_{½,z}$: 1.90–2.19 *vs* 1.26–1.44 h).

4 At each dose level, acid secretion was more inhibited in the older group. However, the AUC associated with a 50% decrease in acid secretion was similar (849 *vs* 892 ng ml^{-1} h) for both age groups. Multiple dosing decreased the maximum possible inhibition more in the older group than in the younger group.

5 Since the decrease in acid output associated with equivalent AUCs on day 1 was similar for the two age groups, the greater difference between day 1 and day 7 secretion in the older group indicates that recovery of secretory activity may decline with increasing age.

Keywords age lansoprazole pharmacokinetics pharmacodynamics

Introduction

Lansoprazole is a substituted benzimidazole with antisecretory and antiulcer activities [1]. Its mechanism of action is selective inhibition of the parietal cell membrane enzyme H^+,K^+-ATPase [1], commonly referred to as the 'proton pump'. Under acidic conditions in the parietal cells, lansoprazole is transformed into active metabolites, principally a cyclic sulphenamide (AG-2000) and a disulphide (AG-1812), which react with sulphydryl groups of the ATPase [2, 3]. Lansoprazole has a chiral centre, and the (+)- and (−)-enantiomers have similar antisecretory activities [4].

Lansoprazole is effective in treating various peptic diseases, especially those resistant to treatment with histamine H_2-receptor antagonists, including duodenal ulcer [5, 6], gastric ulcer [6, 7], reflux oesophagitis [8], and Zollinger-Ellison syndrome [9]. In these studies, healing rates of up to 95% occurred after a few weeks of once daily treatment. Another study showed that the healing rate of duodenal ulcer was dose related [10].

In healthy subjects, lansoprazole produced a dose-dependent and profound decrease in basal and stimulated gastric acid secretion [11]. A 60 mg dose produced almost total suppression, which was fully reversed within days after drug withdrawal. Morning dosing has been shown to be equivalent to or more effective than evening dosing in increasing the mean or median pH for a 24 h period and in increasing the percentage of time the pH is equal to or greater than 4 [12, 13].

Earlier studies of lansoprazole have measured its effect on acid secretion but have made no systematic study of its pharmacokinetics. The aims of this study were to characterize the pharmacokinetics of lansoprazole and the pharmacokinetic-pharmacodynamic relationship in healthy subjects. To determine any effects of patient age

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on the disposition and action of the drug the study was conducted in young and elderly individuals.

Methods

Subjects

A total of 24 healthy males were enrolled into the study; 12 subjects were assigned to a younger group (age range, 29 to 54 years; mean ± s.d., 38.0 ± 10.6 years) and 12 subjects to an older group (age range, 60 to 78 years; mean ± s.d., 64.8 ± 5.0 years). By design, the mean age of the older group was significantly greater ($P < 0.05$) than that for the younger group.

All subjects gave informed written consent and met the inclusion and exclusion criteria described in the study protocol, including the requirement of a peak acid output response to pentagastrin stimulation of >20 mmol h^{-1} for the younger subjects and >10 mmol h^{-1} for the older subjects. The study protocol was approved by the institutional review board at the study site. The younger subjects weighed 61.4 to 97.7 kg (mean ± s.d., 77.8 ± 12.0 kg), and the older subjects weighed 70.9 to 111.4 kg (mean ± s.d., 87.7 ± 10.5 kg). All 12 younger subjects and 11 older subjects normally consumed caffeinated beverages. Seven younger and four older subjects were smokers.

Study design and drug administration

This was a randomized, double-blind, three-period, complete crossover, placebo-controlled, multiple-dose study. Each subject received oral, single, daily doses of 15 mg lansoprazole, 30 mg lansoprazole, or matching placebo capsules for 7 consecutive days. The three treatment periods were each separated by a 1 week washout period. The order of treatment for each subject was randomized.

The dosage form consisted of 15 mg lansoprazole as enteric-coated granules in a capsule. The capsules (one 15 mg capsule and one placebo capsule for the 15 mg dose, two 15 mg capsules for the 30 mg dose, or two placebo capsules) were administered with 120 ml water. On days 2 to 6 of each treatment period, the capsules were given 2 h before breakfast, which was followed by a normal eating pattern. The procedure for drug administration on days 1 and 7 is described below.

Stimulation and measurement of acid secretion

Gastric acid secretion was measured after the first dose (day 1) and the last dose (day 7) of each treatment period. After a fast from 19.00 h the night before, the subjects were given the capsules with 120 ml water at 08.00 h and then continued to fast for the next 3 h. At that time a liquid meal (500 ml, pH 5.5, 40 g protein, 30 g fat, 30 g carbohydrate, 550 kcal, 768 mOsm) was instilled into the stomach during a 5 min period through an Anderson AN10 nasogastric tube (H.W. Anderson, Santa Monica, CA, USA), which had been fluoroscopically positioned in the antrum of the stomach. Gastric acid secretion was measured by automatic intragastric titration to pH 5.5, with 0.5 M sodium hydroxide as the titrant, at 30 min intervals during the next 4 h [14]. At 4 h after the first liquid meal, a second identical liquid meal was instilled. Gastric acid secretion was again measured for the next 4 h, so that acid secretion was measured for a total of 8 h after dosing on days 1 and 7.

Blood and urine sampling

Serial blood samples (6 ml each) were collected through an indwelling catheter (heparin lock) into heparinized collection tubes prior to dosing (0 h) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 h after dosing on days 1 and 7 of each regimen. Within 1 h of collection, the samples were centrifuged; the plasma was separated and stored frozen below −10° C until assayed. The total urine output of each subject was collected on days 1 and 7 at the following intervals: just before dosing (on day 1 only), 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h. To ensure the stability of lansoprazole, which is an acid-labile drug, urine was collected in containers containing sodium bicarbonate powder. When necessary, additional sodium bicarbonate was added to adjust the pH to 7 or above. The urine volume and pH were recorded, and a 25 ml aliquot was then stored at ≤−10° C until drug analysis.

Drug analysis

Plasma and urine samples were assayed for lansoprazole and its AG-1908, AG-1909, AG-1813, AG-1777, and AG-1907 metabolites using a modification of the specific h.p.l.c. method of Akoi *et al.* [15]. The principal change involved use of omeprazole, another substituted benzimidazole, as internal standard. The limits of detection of lansoprazole and its metabolites in plasma and urine were 10 and 25 ng ml^{-1}, respectively. Assay results for plasma and urine quality control samples, which were prepared and stored with study samples until analyses, showed intra- and inter-assay coefficients of variation within 2.4 and 5.0%, respectively, for plasma and within 3.5 and 5.6%, respectively, for urine. Lansoprazole and metabolites were stable in frozen human plasma and urine quality control samples as well as in their extracts reconstituted and standing at room temperature.

Pharmacokinetic analysis

The peak plasma concentration (C_{max}) and the time at which it was reached (t_{max}) were observed values. Values of AUC(0,24) were calculated using the linear trapezoidal rule. The elimination rate constant (λ_z) was calculated as the negative slope of the linear regression of ln concentration *vs* time in the terminal phase. The terminal elimination half-life ($t_{½,z}$) was calculated as $\ln 2/\lambda_z$. The oral clearance (CL_0) after single and multiple doses was calculated by dividing the dose by AUC(0,24). No urinary excretion rates were determined since lansoprazole is extensively metabolized by the liver and no unchanged drug was detected in the urine.

Analysis of variance (ANOVA) was used to evaluate the within-age group pharmacokinetics of lansoprazole

after single and multiple doses, to assess dose proportionality between the 15 and 30 mg doses within the same age group, and to compare lansoprazole pharmacokinetics in the older group with those in the younger group. Effects for age group, dosing days, sequences, subjects, regimens, periods and smoking were included in the model. Prior to such analyses, plasma drug concentrations after the 30 mg once daily regimen were normalized to a 15 mg dose for dose proportionality assessment. Comparisons of interest were performed by appropriate *F*-test. All *P* values less than or equal to 0.050 were deemed to be statistically significant. Also, non-parameteric 95% confidence intervals (CI) were calculated to assess the statistical significance of differences in the kinetic parameters of lansoprazole between young and elderly subjects.

Pharmacokinetic-pharmacodynamic modelling

Evaluation of the relationship between the pharmacokinetics of lansoprazole and inhibition of acid secretion was based on AUC(0,24) values and cumulative acid output over the 8 h sampling interval (3 to 11 h postdosing). AUC(0,24) values were used since drug concentrations 10 h after dosing contributed negligibly to the total AUC. Graphical observations and exploratory non-linear regression analysis of all data suggested than an inhibitory sigmoidal E_{max} model was appropriate using the following equations:

$$\frac{E}{E_0} = \frac{(EAUC_{50})^{\gamma}}{(EAUC_{50})^{\gamma} + AUC^{\gamma}} \quad \text{for day 1}$$

and

$$\frac{E}{E_0} = \frac{\delta\cdot(EAUC_{50})^{\gamma}}{(EAUC_{50})^{\gamma} + AUC^{\gamma}} \quad \text{for day 7}$$

where E is the measured pharmacologic effect after drug administration (gastric secretion, mmol per 8 h); E_0 is the baseline gastric acid secretion, the average for days 1 and 7 of placebo treatment since preliminary ANOVA results did not demonstrate any significant day or age-group·day interaction effects; δ is the adjustment factor for day 7 that accounts for the decline in secretory capacity after repetitive administration of lansoprazole; $EAUC_{50}$ is the AUC at which secretion is reduced to one-half of E_0, assuming agonist stimulation is equal to that during the placebo period; and the exponent γ is the sigmoidicity parameter that defines the steepness of the hyperbola.

The day 7 adjustment factor δ corrects for the cumulative effect of lansoprazole administration, which involves reduction of ATPase levels, and the opposing effects of compensatorily increased stimulation by the endogenous ATPase agonists such as histamine, gastrin, and acetylcholine. For day 7, $EAUC_{50}$ thus represents the AUC required to reduce acid secretion to one-half of $\delta\cdot E_0$.

An additive random error with zero mean and constant variance was assumed for each subject, and data for each subject were fitted using this model. PROC NLIN of SAS version 5.18 with Marquardt's method was used to fit the data. There were four observations for each subject, two for the 15 and 30 mg doses of day 1, and two for the 15 and 30 mg doses of day 7. Thus, there was one degree of freedom for error within the data set for each subject. Examination of the parameter estimates revealed that γ was close to 2 for almost all subjects. Therefore, the model described above was refitted for each subject by fixing $\gamma = 2$, resulting in a two-parameter model with two degrees of freedom for error for each subject. A younger subject was excluded from the pharmacodynamic analysis owing to an anomalous gastric acid secretion (E_0) and elevated gastrin plasma concentration on day 7 of the placebo regimen. Parameter estimates of $EAUC_{50}$ and δ obtained from the model were subjected to a weighted analysis of variance with sequence and age group as the main effects. The reciprocal of the within-subject mean squared error for each subject was used as the diagonal weight matrix.

The data were also subjected to population analysis with the NONMEM program version 4, level 1.1, with double precision (University of California, San Francisco, CA). The interindividual variabilities in $EAUC_{50}$ and δ as well as the intraindividual variability, or residual error, in the pharmacodynamic measurements were modelled with an additive model, each with a zero mean and variance.

Results

Pharmacokinetics

Mean plasma lansoprazole concentrations in the two age groups after the first and last oral doses of the 15 mg and 30 mg dosing regimens are shown in Figure 1. A mean lag time of approximately 30 min was observed in the oral absorption of lansoprazole in both age groups. Higher mean plasma drug concentrations and a prolonged elimination $t_{½}$ of lansoprazole after both the first and last dose of each dosing regimen was observed in the older group.

The mean pharmacokinetic parameters of lansoprazole are listed in Table 1 for each dose level and age group. Overall, the intragroup analyses indicated that the pharmacokinetics of lansoprazole were linear, since dose normalized values of C_{max}, t_{max}, $t_{½,z}$ and CL_0 were similar both between the first and last doses of each dosing regimen and also between the two dose levels. The only exception was that in the older subjects, the mean $t_{½,z}$ value after the last 15 mg dose was 15% longer than after the first dose (2.19 ± 1.23 h *vs* 1.90 ± 0.92 h; $P < 0.05$). For each dose level and dosing day, the rate of absorption, as reflected in mean C_{max} and t_{max} values, appeared to be age-independent. Although the mean C_{max} was approximately 14% higher in the older subjects, the difference was not statistically significant. However, the oral clearance of lansoprazole was 43% lower in the older subjects (12 ± 5 to 14 ± 10 l h^{-1} *vs* 20 ± 16 to 26 ± 17 l h^{-1}; 95% CI: 11%–75%). This decreased clearance was reflected in a 49% longer mean $t_{½,z}$ in the older group than that in the younger group (1.90 ± 0.92 to 2.19 ± 1.23 h *vs* 1.26 ± 0.43 to 1.44 ± 0.62 h; 95% CI: 30%–68%). No unchanged lansoprazole was excreted in

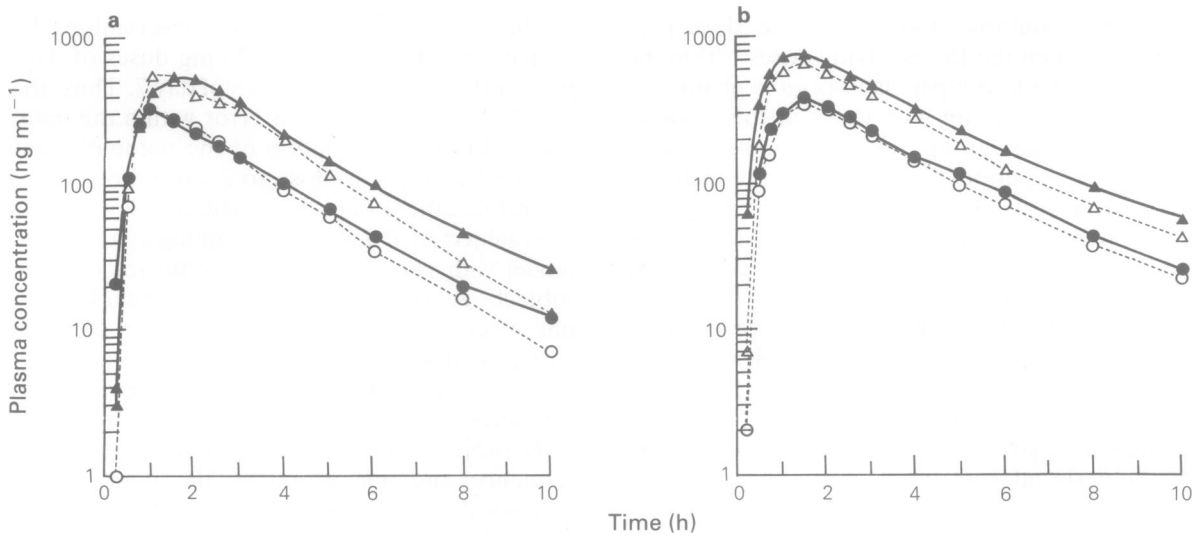

Figure 1 Mean plasma lansoprazole concentrations in younger (a) and older groups (b) after once daily dosing with 15 mg (○) and 30 mg (△) lansoprazole. ○, △, single-dose (day 1); ● and ▲, steady-state (day 7).

Table 1 Mean ± s.d. pharmacokinetic parameters of lansoprazole after oral once daily administration of 15 and 30 mg lansoprazole

	15 mg		*30 mg*	
Parameter	*Day 1*	*Day 7*	*Day 1*	*Day 7*
Younger group				
C_{max} (ng ml^{-1})	413 ± 199	396 ± 209	750 ± 331	739 ± 415
t_{max} (h)	1.15 ± 0.39	1.29 ± 0.74	1.48 ± 0.99	1.46 ± 0.65
AUC(0,24) (ng ml^{-1} h)	950 ± 593	1012 ± 855	1763 ± 1056	2074 ± 1466
$t_{½,z}$ (h)	1.32 ± 0.51	1.44 ± 0.62	1.26 ± 0.43	1.39 ± 0.58
CL_0 (l h^{-1})	24 ± 17	26 ± 17	24 ± 16	20 ± 16
Older group				
C_{max} (ng ml^{-1})	449 ± 150	429 ± 134	773 ± 248	946 ± 311
t_{max} (h)	1.46 ± 0.53	1.35 ± 0.34	1.56 ± 0.94	1.13 ± 0.47
AUC(0,24) (ng ml^{-1} h)	1334 ± 673†	1483 ± 720†	2678 ± 1144†	2862 ± 1085†
$t_{½,z}$ (h)	1.90 ± 0.92†	2.19 ± 1.23*'†	1.93 ± 0.81†	2.07 ± 0.85†
CL_0 (l h^{-1})	14 ± 6†	14 ± 10†	14 ± 7†	12 ± 5†

*Significantly different from corresponding value for day 1 within the same regimen and age group.
†Significantly different from corresponding value for younger group for same dosing day and regimen.

the urine of any subject. The plasma and urine concentrations of the metabolites were below the limits of detection.

Gastric acid secretion

Meal-stimulated acid secretion (mmol per 8 h) after the first two meals on days 1 and 7 for both age groups is shown in Figure 2. For the placebo treatment, no statistically significant differences due to day effects were found. Therefore, the mean for the first and last doses for each subject was calculated as the reference stimulated acid output in the absence of drug (E_0). Analysis of the mean secretion data after single and multiple doses of lansoprazole produced four general observations: 1) acid secretion was significantly more suppressed on day 7 than on day 1, 2) acid output was significantly more suppressed for the 30 mg regimen than for the 15 mg regimen, 3) the suppression was significantly greater in the older group, and 4) the relationship between percent suppression of acid secretion and lansoprazole dose was non-linear and was more characteristic of the hyperbolic E_{max} model commonly used to describe dose-response relationships. With these observations in mind, the relationship between the relative gastric acid secretion (E/E_0) and AUC was investigated using an inhibitory E_{max} model.

Pharmacokinetic-pharmacodynamic relationship

Preliminary analyses were conducted with a population regression approach where the E/E_0-AUC paired data for all subjects were included in a single analysis, ignoring the correlation of observations from the same subject. These analyses demonstrated that addition of a sigmoidicity factor, γ, significantly improved the quality of the regression, as did any term that allowed either $EAUC_{50}$ or E_{max} to shift as a function of repetitive dosing, thus accounting for the greater inhibition on day 7. The value of γ was about 2.

Attempts were made to employ the three parameter (γ, $EAUC_{50}$ and δ) sigmoidal E_{max} model in the non-linear regression of the data for each individual. In these exploratory analyses, the model was generally

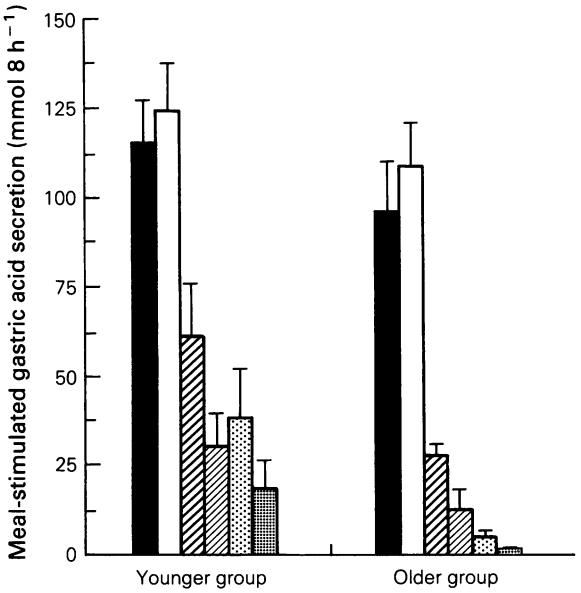

Figure 2 Mean ± s.e. mean total 8 h meal-stimulated gastric acid secretion after oral once daily administration of placebo (solid bars, single dose; open bars, steady state), 15 mg (light diagonal bars, single dose; dark diagonal bars, steady-state) and 30 mg (light half-tone bars, single dose; dark half-tone bars, steady-state) lansoprazole to younger and older subjects.

overparameterized (as evidenced from the correlation matrix of parameter estimations); γ was again found to be near 2 and was therefore fixed to this value for subsequent analyses. Data from one younger subject could not be fitted. The means of individual values and the population estimates of the pharmacodynamic parameters, $EAUC_{50}$ and δ, for the two subpopulations are presented in Table 2. As expected, the interindividual variabilities in $EAUC_{50}$ and δ were higher for the elderly group. The mean curves from the individual parameter estimates are plotted with the experimental data after single (Figure 3a) and repetitive (Figure 3b) dosing. The mean $EAUC_{50}$ values for the younger and

Table 2 Mean of individuals ± s.d. and population estimates of the pharmacodynamic parameters of lansoprazole in young and elderly subjects

Parameter	*Mean of individuals*	*Population estimate*	*Interindividual variability (% CV)*
Younger group			
$EAUC_{50}$ (ng ml^{-1} h)	892 ± 535	899 ± 332 (709–1159)*	37
δ	0.40 ± 0.22	0.45 ± 0.12 (0.32–0.58)*	27
Older group			
$EAUC_{50}$ (ng ml^{-1} h)	849 ± 425	756 ± 332 (566–936)*	44
δ	0.19 ± 0.22‡	0.19 ± 0.12 (0.04–0.38)*	62

‡Significantly different from corresponding value for younger group. *P* value obtained from the weighted ANOVA model with sequence and age group as the main effects.
*95% CI.

older groups (892 ± 535 *vs* 849 ± 425 ng ml^{-1} h) were similar, suggesting that for equivalent AUCs of lansoprazole, the reduction in acid secretion after a single dose was independent of age. The greater observed decreases in the older subjects after a single dose of either the 15 mg or 30 mg appeared to be solely associated with the higher AUCs in that group rather than greater intrinsic sensitivity to lansoprazole. Exploratory multiple linear regressions of $EAUC_{50}$ against several regressors, including age, lansoprazole clearance, smoking status, E_0, and baseline gastrin secretion, found no significant associations.

The mean δ for the younger group was 110% higher than that for the older group (0.40 ± 0.22 *vs* 0.19 ± 0.22, 95% CI: 11%–210%). However, when age (as opposed to age group) was used as a covariate, the linear association between δ and age yielded $P = 0.0935$. Analysis

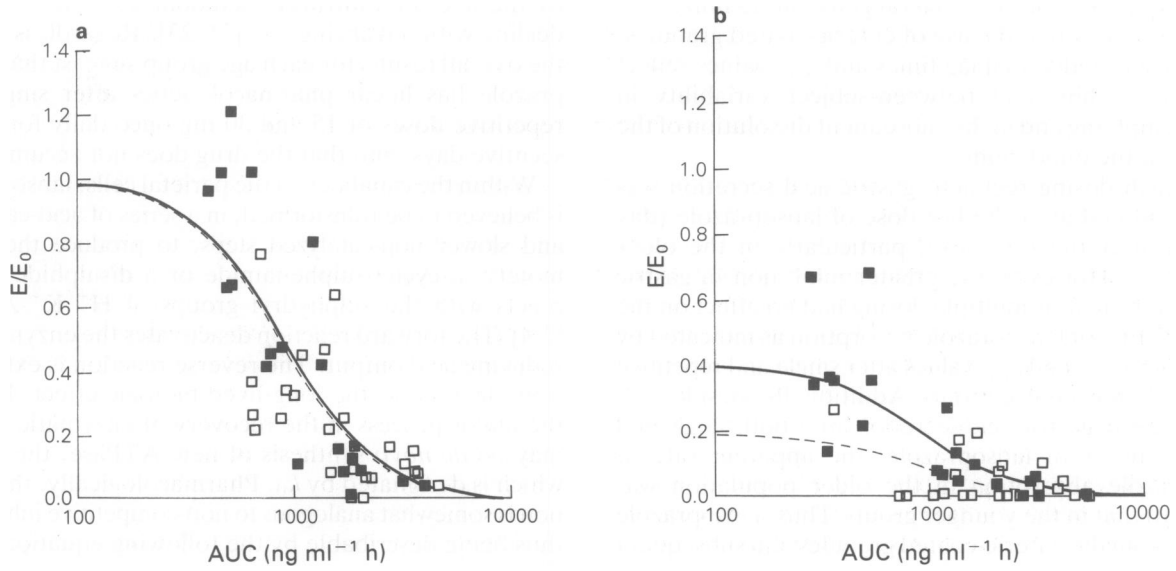

Figure 3 Individual data and mean regression curves of fractional acid secretion inhibition (E/E_0) *vs* lansoprazole area under the curve (AUC) in younger (■, —) and older (□, -----) subjects after a single dose (A) and repetitive dosing for 7 days (B).

of covariance revealed a significant positive association between δ and E_0. No other significant associations were detected. The finding of a lower mean δ in the older group reflects the experimental observation that the percent difference between day 1 and day 7 inhibition is greater in the older than in the younger group. This observation may be of practical significance, particularly when it is recognized that for each dose level inhibition was greater for the older group than for the younger group on day 1. The greater inhibition corresponds to the higher AUC for lansoprazole in the older group, putting their responses near the lower region of the AUC *vs* inhibition curve in which inhibition is less sensitive to increasing AUC.

The similarity between the population estimates of $EAUC_{50}$ and δ and the means of individual values (Table 2) validate the pharmacokinetic-pharmacodynamic modelling for each individual which was based on four data points.

Discussion

The substituted benzimidazoles, a new class of drugs that inhibit the parietal cell enzyme, H^+,K^+-ATPase, have very short half-lives in plasma [16, 17]. Lansoprazole is no exception, as our study has shown. However, the inhibition of acid secretion after lansoprazole administration continues well beyond the elimination of the drug, so that once a day dosing provides essentially continuous suppression of acid output [11]. Thus, although steady-state plasma drug concentrations are obtained with the first dose of lansoprazole, steady-state pharmacological effects are delayed.

Like omeprazole, the prototype proton pump inhibitor lansoprazole is an acid-labile drug that is extensively degraded in the acidic pH of the stomach. The potential for low and variable bioavailability due to acidity of the stomach or delayed gastric emptying has largely been obviated with the use of an enteric-coated formulation. In the present study, the age-independent lag time observed in individual plasma drug concentrations-time profiles of lansoprazole which ranged from 15 min to 2.5 h, was probably due the use of enteric-coated granules. The range of individual lag times and t_{max} values reflect both the within- and between-subject variability in gastric emptying and in the subsequent dissolution of the coating in the duodenum.

For each dosing regimen, gastric acid secretion was more inhibited after the last dose of lansoprazole (day 7) than after the first dose, particularly in the older population. However, the greater inhibition in gastric acid secretion after multiple dosing had no effect on the apparent rate of lansoprazole absorption as indicated by the similar C_{max} and t_{max} values after single and repetitive doses within each age group. Additionally, despite age differences in gastric acid secretion after both single and multiple doses of lansoprazole, the apparent rate of lansoprazole absorption in the older population was similar to that in the younger group. Thus, lansoprazole release from the enteric-coated granules and subsequent absorption, which occurs in the duodenum, were not affected by changes in gastric pH.

Preliminary results from another study (data on file, Abbott Laboratories) showed a high but relatively variable absolute bioavailability (F) of lansoprazole in young subjects administered the same dosage form used in this study, with a mean F of 0.81 ± 0.22 and 0.91 ± 0.52 for 15 and 30 mg single doses, respectively. Additionally, relatively low between-subject variability in lansoprazole disposition was observed after intravenous administration of a 15 mg dose to the same subjects, with individual $t_{½}$, clearance (CL), and volume of distribution (V_{ss}) values ranging between 0.52 and 0.89 h, 24 and 39 l h^{-1}, and 24 and 36 l, respectively. Thus, the between-subject variability in AUC values observed within each age group in our study may be mainly associated with differences in the extent of lansoprazole absorption rather than differences in its disposition. In this regard, we note that the intersubject variability in CL_o is greater than that in λ_z, the latter term being independent of the extent of absorption.

Despite the apparent variability in the extent of absorption, the kinetics of lansoprazole appear to be time invariant. For each dosing regimen and age group, differences in the $t_{½,z}$ values obtained following single and repetitive administrations were not statistically significant; the AUCs after multiple and single doses were similar, and there were no significant effects with period, regimen or sequence. Thus, despite the inhibition of acid secretion in each age group, the extent of lansoprazole absorption was similar following single and repetitive doses of either 15 or 30 mg once daily. The AUC for omeprazole appears to increase after repetitive administration, ostensibly as a result of increased absorption rather than decreased first-pass hepatic extraction [18]. The absolute bioavailability of lansoprazole is high (>85%) even for a single dose, whereas the bioavailability of single doses of omeprazole, also administered in enteric-coated dosage form, is approximately 50% [19]. Thus the bioavailability of lansoprazole appears to be less sensitive to inhibition of acid secretion following repetitive once daily doses, than is omeprazole [20].

The decreased oral clearance with age was not unexpected since lansoprazole is extensively metabolized by the liver and intrinsic metabolic clearances tend to decline with advancing age [21–23]. Regardless of age, the overall results for each age group suggest that lansoprazole has linear pharmacokinetics after single and repetitive doses of 15 and 30 mg once daily for 7 consecutive days, and that the drug does not accumulate.

Within the canaliculi of the parietal cells, lansoprazole is believed to be transformed, in a series of acid-catalyzed and slower non-catalyzed steps, to produce the active moiety, a cyclic sulphenamide or a disulphide, which reacts with the sulphydryl groups of H^+,K^+-ATPase [2,4]. The forward reaction deactivates the enzyme, thus reducing acid output. The reverse reaction is extremely slow, leading to the long-lived biologic effect. Indeed, the major process in the recovery of enzymatic activity may be *de novo* synthesis of new ATPase, the rate of which is designated by k_0. Pharmacologically, the situation is somewhat analogous to non-competitive inhibition, thus being describable by the following equation:

$$E = \frac{E_{max} \cdot EAUC_{50} \cdot Ag}{(EAUC_{50} + A)(Ag + E_{Ag50})}$$

where A is the concentration (or AUC) of the antagonist, and $EAUC_{50}$ is the concentration (or AUC) associated with 50% reduction in response (acid output). The terms Ag and E_{Ag50} are similarly defined, referring to the endogenous agonist(s). In the case of H^+,K^+-ATPase in the parietal cell, stimulation is thought to be mediated by gastrin, histamine and acetylcholine [24]. If the production of these agonists is unaffected by the antagonist, the equation above may be reduced to a simple inhibitory E_{max} model in which

$$E = \frac{E_0 \cdot EAUC_{50}}{(AUC + EAUC_{50})}$$

and

$$E_0 = \frac{E_{max} \cdot Ag}{(Ag + E_{Ag50})}$$

While this situation may hold for a brief period after acute exposure to the antagonist, it is generally not the case under chronic exposure, since feedback mechanisms often result in compensatory increases in agonist production. This was the case in the present study, in which serum gastrin concentrations increased significantly at day 7 (data not presented). In the non-linear regression model used for the present study, the term δ, which characterized differences in the maximum possible acid secretion between day 1 *vs* day 7, reflects several factors, including the increased output of agonist (e.g. gastrin), as well as a decrease in E_{max} arising from irreversible deactivation of H^+,K^+-ATPase.

In theory, the non-competitive inhibition model is not entirely appropriate for the description of the relationship between lansoprazole AUC and inhibition. Derivation of the equation requires the assumption that the number of functional ATPase units remains constant. In reality, the formation of the complex between a benzimidazole and ATPase is essentially irreversible, with a very slow recovery ($t_{½}$ around 1 day) of acid secretory activity [11]. The return of secretory capacity is thought to be mediated principally by synthesis of new ATPase [24]. In such a case, we might expect that the relationship between lansoprazole AUC and inhibition to be linear rather than hyperbolic. In fact, the results of the present study suggest a non-linear relationship, confirming similar observations *in vitro* and *in vivo* with omeprazole [25,26].

In interpreting this effect, we must first recognize that the active intermediate is formed in an acid catalyzed reaction. Inactivation of ATPase results in decreased acid output into canaliculi, which theoretically would reduce the rate and extent of formation of the sulphenamide or disulphide active intermediate. This means that fewer molecules of the active intermediate are available to react with, and thus deactivate the ATPase. Overall, the factors discussed above predict a complex non-linear relationship between AUC and inhibition. The fitting of the experimental data to the inhibitory sigmoidal E_{max} model therefore represents an empirical simplification of the underlying pharmacokinetics and pharmacodynamics.

If we assume that the rate of synthesis of H^+,K^+-ATPase is zero order (k_0), and that the rate of loss is first order, with a rate constant k_1, then the number of ATPase units at steady-state, $ATPase_{ss}$, in the absence of a proton-pump inhibitor is defined as: $ATPase_{ss} = k_0/k_1$. After administration of a single dose of lansoprazole, the number of functional ATPase units is reduced non-linearly as a function of the number of active intermediate molecules in the lumen of the vesicles. After concentrations of lansoprazole have peaked, recovery of acid secretory capability of the parietal cells is dependent on *de novo* synthesis of new receptors, and dissociation of the disulphide-linked complex. If synthesis is the dominant process, and if it occurs at a maximal zero order rate, the time course of the recovery process is described by:

$$ATPase = ATPase_{ss}\,(1 - f \cdot e^{-k_1 t})$$

where f is the $ATPase_{ss}$ fraction remaining after clearance of the dose. The quantity of ATPase increases until the next dose of lansoprazole is administered. That dose decreases the number of ATPase units to a level lower than that after the first dose, so that E_{max} is also decreased. Eventually, steady-state conditions are reached, and the time required to do so is dependent on the turnover rates of ATPase.

The relative and absolute quantities of active intermediate and ATPase determine the rate of their second order reaction. As ATPase declines, acid production and thus the rate of conversion of lansoprazole to the active intermediate also decrease. As noted above, a decreased second order rate for deactivation of ATPase increases the residence time of the active intermediate, allowing parallel pathways such as reaction with nucleophiles or washout to be more competitive in its elimination. As a result, the rate of decline in acid secretory activity may or may not reflect the rate of resynthesis. Certainly, at low rates of *de novo* synthesis, and high ratios of the active intermediate to ATPase, maximal inhibition will be reached rapidly. On the other hand, with exceptionally high turnover rates for ATPase, and subtherapeutic dosage, first-dose and steady-state inhibitions may not differ greatly.

The parameter δ was added to the model to quantify the differences in day 1 and day 7 inhibition. It reflects the relative decrease in ATPase units, and therefore E_{max}, in going from a single dose to steady-state conditions, yet it is dependent on several factors including the $AUC/EAUC_{50}$ ratio after a single dose, the ATPase synthesis rate and feedback increase in the amounts of endogenous agonists. The difference in δ between the two age groups was statistically significant, indicating that any or all of the above factors may be age-dependent. Although the resynthesis rate may be slower in the older population, recovery of acid secretory ability in the older group of the present study was essentially complete 1 week later, as was established through the analyses of variance of E_0 and the examination of potential carryover effects. For acid secretory activity to recover in 1 week, the apparent $t_{½}$ for the restoration of full secretory activity had to be 2 days or less.

In conclusion, a longer elimination $t_{½}$ and slower clearance of lansoprazole was observed in the older group compared with the younger group. Secretion of

gastric acid was more inhibited in the older group than in the younger group, especially after multiple dosing, The pharmacokinetic-pharmacodynamic relationship of lansoprazole can be described by an inhibititory sigmoidal maximum effect model, but in reality, is probably more complex than the model would suggest. The greater decrease in acid secretion after multiple dosing in the older group indicates that recovery of secretory activity (perhaps by *de novo* synthesis) may decline with advancing age.

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