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A bioavailability/bioequivalence study of two oral lansoprazole formulations after single administration to healthy volunteers

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Two oral lansoprazole formulations, containing encapsulated microgranules, Lasoprol® (test formulation) and Lanzor® (reference), were administered to 12 healthy volunteers of both sexes in a single dose of 30 mg lansoprazole in order to investigate their comparative bioavailability. No statistically significant differences, at the probability level of 90%, were observed neither for the maximal serum concentrations (1.12 : 1.22 μg/ml) nor for the area under the concentration-time curves (5.01 : 5.77 μg/ml · h), the parameter to which the inhibition of acid secretion induced by lansoprazole is directly related. The similar holds true for the value of time to reach the maximal concentration of lansoprazole in serum, although this parameter was previously described as less sensitive in comparative bioavailability studies. The terminal elimination half-lives were 4.56 h for Lasoprol® and 4.57 h for the reference formulation. The results indicate the bioequivalence and good tolerability of both lansoprazole formulations. The overall pharmacokinetic profile of the drug was comparable with the data previously reported by other investigators.

1. Introduction

Lansoprazole, 2-((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl) sulphinyl-benzimidazole, belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppresses gastric acid secretion by specific inhibition of the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. The effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus [1–3]. Similarly to its structurally related congener, omeprazole, lansoprazole is used in the treatment of peptic ulcer and gastro-oesophageal reflux disease and is given by mouth in an usual dose of 30 mg once daily [4]. It also has activity *in vitro* against *Helicobacter pylori* [5].

Lansoprazole is unstable at acidic pH, but when given as a suitable pharmaceutical formulation, e.g. an enteric-coated granule form, the absorption of the drug is rapid. Peak serum concentrations are achieved about 1.5 h after a dose by mouth; bioavailability is reported to be over 80% even with the first dose [6]. In a dose range from 15 mg to 60 mg the pharmacokinetics of lansoprazole is approximately linear [6]. It is nearly 97% bound to plasma proteins. It is extensively metabolized in the liver to hydoxylated sulfinyl and sulfone derivatives that have very little or no antisecretory activity. The elimination occurs primarily in feces *via* the bile; only 15% to 30% of a dose are excreted in urine, no unchanged lansoprazole is found. The elimination half-life is only about 1.5 h, but the acid inhibitory effect of lansoprazole lasts more than 24 h. The clearance of lansoprazole is decreased both in the elderly and in patients having a chronic hepatic disease [7–11]. Elimination half-life increases approximately 50%–100% in the geriatric population and up to 5 times in hepatically impaired subjects [6].

Two different pharmaceutical companies using encapsulated microgranules from different origin currently market lansoprazole in Yugoslavia. This paper describes a comparative bioavailability study of two oral lansoprazole formulations (capsules Lasoprol®, manufactured by Aegis Ltd., Cyprus, and Lanzor® capsules, Laboratoires Houde, France, which was used as the reference product) following single administration in healthy volunteers.

2. Investigations and results

The tolerability of the two formulations of lansoprazole was good. No adverse events were reported by the participants or revealed by clinical and laboratory findings.

The average lansoprazole serum concentrations versus time curves after oral administration of capsules Lanzor® and Lasoprol® are illustrated in the Fig.

Relevant pharmacokinetic parameters derived from the individual lansoprazole serum concentration-time profiles are summarized in Table 1, while the parameters for the assessment of bioequivalence are shown in Table 2.

After the single oral administration of lansoprazole 30 mg as Lanzor®, serum concentrations of the drug were maximal within a period of 1 to 2 h in 12 volunteers. Subject number 4 showed a maximum level at 2 h, 6 out of 12 subjects did so at 1.5 hours, whereas the rest 5 participants at the time T1 h. Intersubject variation between the times to reach peak concentrations of lansoprazole after the ingestion of a same dose of the test formulation, Laso-

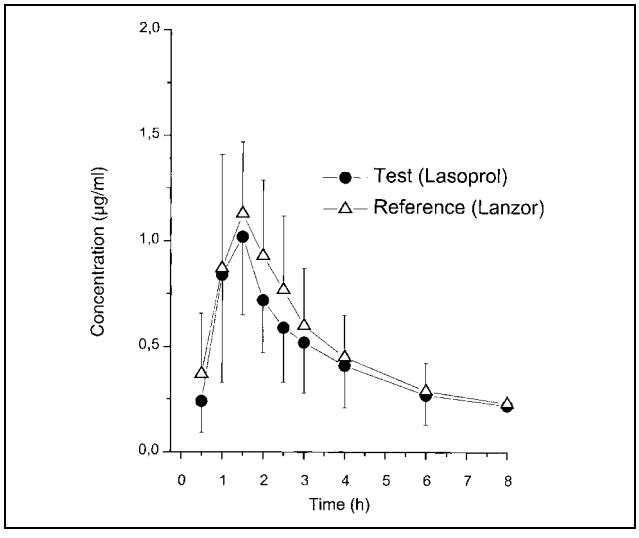

Fig. Serum concentration-time curves (mean ± SD) after administration of two oral lansoprazole formulations, 30 mg Lanzor® capsules (reference) and 30 mg Lasoprol® capsules (test), to 12 healthy volunteers

Table 1: Pharmacokinetic parameters obtained after administration of two formulations of lansoprazole 30 mg to 12 healthy volunteers

Parameter	Formulation	
	Lasoprol® (Test)	Lanzor® (Reference)
C_{max} (μg/ml)	1.12 ± 0.40	1.22 ± 0.43
t_{max} (h)	1.38 ± 0.31	1.33 ± 0.33
k_e (h^{-1})	0.1796 ± 0.0770	0.1864 ± 0.0772
$t_{1/2e}$ (h)	4.56 ± 1.90	4.57 ± 2.49
AUC^{0-8} (μg/ml · h)	3.49 ± 1.45	4.03 ± 1.46
$AUC^{0-\infty}$ (μg/ml · h)	5.01 ± 2.35	5.77 ± 2.92

C_{max} = maximal serum concentration; t_{max} = time to reach C_{max}; k_e = elimination-rate constant; $t_{1/2e}$ = elimination half-time; AUC^{0-8} = area under the concentration-time curve from 0 to 8 hours; $AUC^{0-\infty}$ = area under the concentration-time curve from zero to infinity
Data are presented as mean values ± SD

prol®, was very similar. Namely, four subjects showed maximum after 1 h, seven 1.5 h after dosing, and only the one volunteer at time T2 h.

The mean t_{max} as calculated from all 12 volunteers was 1.38 ± 0.31 h for the test formulation, and 1.33 ± 0.33 h for the reference product. Serum concentrations of lansoprazole declined very rapidly, with the terminal half-life ranging from 2.26 h to 8.24 h for Lasoprol® (mean 4.56 h) and from 2.09 h to 9.64 h for Lanzor® capsules (mean 4.57 h).

The analysis of parameters for the assessment of bioequivalence showed that there were no statistically significant differences between the formulations. The 90% confidence limits for C_{max} (0.7–1.08), AUC^{0-8} (0.84–1.08) and $AUC^{0-\infty}$ (0.86–1.09) were within the accepted critical ranges and, consequently, the bioequivalence of the two formulations of lansoprazole was demonstrated.

3. Discussion

The lack of data on intrasubject variability in published papers on lansoprazole bioavailability did not make it possible to perform a predetermination of sample size. Therefore, a total of 12 subjects, what is a minimal number of participants to assess bioequivalence according either to the Yugoslav Ministry of Health regulative or to the EC guideline [14], were chosen. A power analysis derived from the tables of Machin and Campbell [15] has shown that 11 subjects are sufficient with a power of 80%, while the calculations in the present study, based on the confidence interval approach for C_{max} and $AUC^{0-\infty}$, showed $n = 8$ and $n = 10$, with the power of 80%, to be the valid number of volunteers. Both results that have also been in a close agreement with the values tabulated by Diletti et al. [16, 17] confirmed the validity of the arbitrarily chosen sample size.

Parameters describing the absorption of lansoprazole observed in the present study were in agreement with values previously reported in the literature [1–4, 6, 9–11]. Oppositely, the mean elimination half-life of the drug was shown to be twice increased, e.g. approximately 4.5 h in this study in comparison to up to 2 h found in healthy volunteers by other investigators [1–4, 6–11]. This increase appeared, at least, as a consequence of wide variability of individual $t_{1/2e}$ values, which have ranged from 2 to nearly 10 h. Since the volunteers were not phenotyped or genotyped prior the study it is reasonable to attribute differences to genetic polymorphism of CYP2C19, a key enzyme involved in the hepatic elimination of lansoprazole [11]. Differences due to different composition and manufacturing processes of various lansoprazole formulations seem to be less likely.

Time to reach C_{max}, although not important for the overall therapeutic effect of drugs like lansoprazole, was very close after the ingestion of test and the reference formulation (1.38 : 1.33 h). A non-parametric statistical analysis showed that there were no significant differences between the treatments ($p = 0.0678$) and, thus, confirmed the similarity of tested drugs concerning the rate of their absorption.

With regard to the target parameters for the evaluation of individual bioequivalence after single administration, the C_{max} (log-transformed) as well as the values of log-transformed AUCs were not significantly different between the two formulations. However, the confidence interval for C_{max}-ratio were outside the 0.8 to 1.25 limits, and thus the CI was extended to 0.7–1.43, as supported by statements in the 9th draft of the European CPMP [12] and that of Steinijans and Hauschke [13]. This extended range can readily be accepted since the therapeutic index of lansoprazole is not narrow and its pharmacological effect, similarly to omeprazole [18], is not related to C_{max}. Concerning that the standard 90% confidence intervals, both for C_{max} and for AUCs lay within the acceptance range for bioequivalence the individual bioequivalence of Lasoprol® and Lanzor® capsules was concluded.

In conclusion, after single oral administration of lansoprazole to 12 healthy volunteers either as one 30 mg Lasoprol® capsule (test formulation) or the one 30 mg Lanzor® capsule (reference formulation), both containing an enteric-coated microgranule, the clinical and biological tol-

Table 2: Parameters for the assessment of bioequivalence

Lansoprazole pharmacokinetics	C_{max} (μg/ml)	t_{max} (h)	AUC^{0-8} (μg/ml · h)	$AUC^{0-\infty}$ (μg/ml · h)
Test formulation (Lanzor®)				
Mean	1.12	1.38	3.49	5.01
SD	0.40	0.31	1.45	2.35
Reference formulation (Lasoprol®)				
Mean	1.22	1.33	4.03	5.77
SD	0.43	0.33	1.46	2.92
Point estimator (%)	82.2[a]	86.1	95.2[a]	95.1[a]
90% Confidence interval	70.0–108.2	78.7–97.7	83.9–107.9	85.6–108.8
CV-intra (%)	11.7	38.6	9.4	11.4
Limits of bioequivalence (%)	70–143[b]	$p \leq 0.05$	80–125	80–125
p-Value	NS	NS ($p = 0.0687$)[c]	NS	NS

[a] Log-transformed data; [b] according to statements of CPMP [12] and Steinijans and Hauschke [13]; [c] Wilcoxon signed rank test
C_{max} = maximal serum concentration; t_{max} = time to reach C_{max}; AUC^{0-8} = area under the concentration-time curve from 0 to 8 h; $AUC^{0-\infty}$ = area under the concentration-time curve from zero to infinity; NS = not significant.

erability was excellent. The pharmacokinetic results obtained in this study showed that the formulations under the investigation were of comparative bioavailability and, thus, bioequivalent in terms of the rate and the extent of absorption. Since Lasoprol® is bioequivalent to Lanzor®, which is already marketed in Europe, their interchangeability by a prescriber could be authorized.

4. Experimental

4.1. Study population

Twelve normal subjects of both sexes, 6 males and 6 females, were enrolled in the study. The participants were aged between 21 and 50 years (mean 39.2 years), their weight varied from 55 to 105 kg (mean 74.1 kg), and height from 165 to 185 cm (mean 172.8 cm). All of them underwent a prestudy medical examination, ECG recording, and hematological and urine analysis 7 days prior to the clinical start.
Both the Ethics Committee and the Drug Commission of the Military Medical Academy, Belgrade, FR Yugoslavia approved the study on September 1997. All subjects gave written informed consent before participation.

4.2. Study design

The study was a single-dose study, open for the clinical part and blind for the analytical part, randomized, one-way crossover according to a Latin square design, with a washout period of at least three days. The washout period of minimum 72 h was considered sufficient because of the mean terminal half-life of less than 2 h reported for lansoprazole [1–4, 6–11].
Study participants were hospitalized at night preceding the trial and remained hospitalized until the 8 h blood sampling. They returned to the Clinic of Toxicology and Clinical Pharmacology, National Poison Control Centre, Military Medical Academy, Belgrade, on day 4 for further drug administration and blood sampling.
On each administration day participants were fasted overnight for 10 h. Capsules were administered by the oral route around 7 a.m. with 150 ml of water. The standardized hospital breakfast was served 4 h after drug administration and the regular lunch was consumed at 2 p.m.
Blood samples were collected just prior to drug administration (T0 h), and then at T0.5 h, T1 h, T1.5 h, T2 h, T2.5 h, T3 h, T4 h, T6 h and T8 h after lansoprazole dosing. Samples were centrifuged at 3000 rpm for 10 minutes immediately after collection, and the serum stored in tubes at $-20\,^{\circ}C$ until analytical determinations were performed.

4.3. Analytical determinations

The content of lansoprazole in serum was determined by HPLC using the extraction procedure previously reported by Avgerinos and Potsides [19] and the analytical technique described in details by Kilibarda et al. [20].
A reverse-phase column Pecosil C-18 (4.6×250 mm, particle size 10 µm; Perkin Elmer, USA) and a mobile phase consisted of an acetonitrile-0.1 mol $\cdot$ l^{-1} sodium acetate mixture (40 : 60 v/v, pH 7.6, adjusted with a drop of glacial acetic acid) was used. Quantification was performed at wavelength of 277 nm. To extract lansoprazole from the sample 9 ml of dichlormethane was added to 1 ml of serum, then mixed for 10 min and centrifuged at 3000 rpm for further 10 min. After the upper water phase has been removed by aspiration, an organic layer was evaporated to dryness in a water bath at $40\,^{\circ}C$. The residue had been reconstituted with 200 µl of methanol, mixed for 60 s by vortex, filtered through a 0.45 µm pore membrane filter. Finally, an aliquot of 20 µl was injected into the chromatographic system.
The assay was linear for concentrations of lansoprazole between 0.10 and 1.50 mg/l. Mean recovery was 88.35% with a coefficient of variation bellow 9%. The detection limit of the chromatographic method was 0.05 mg/l.

4.4. Pharmacokinetic analysis

The pharmacokinetic parameters were calculated according to standard methods, using the PHARM® 1.4 package (Simed SA, Paris-Crèteil, France) running on a personal computer. Maximal serum concentrations of lansoprazole (C_{max}) and time to reach maximal concentration (t_{max}) were obtained directly from the concentration-time curve data. Elimination rate constant (k_e) was estimated by log-linear regression analysis on data points that were visually assessed to be on the terminal log-linear phase. The terminal serum half-life ($t_{1/2e}$) was calculated according to the equation $t_{1/2e} = 0.693/k_e$. The area under the concentration-time curve from the time zero to time of last quantitative concentration (AUC^{0-t}) was calculated using the linear trapezoidal method. AUC from time zero to infinite time ($AUC^{0-\infty}$) was calculated as follows: $AUC^{0-\infty} = AUC^{0-t} + C_t/k_e$, where C_t is the last quantifiable concentration. The relative bioavailability (F_{rel}) of test lansoprazole formulation was calculated from the equation $F_{rel} = AUC^{0-\infty}$ of test drug/$AUC^{0-\infty}$ of reference drug. All the results are presented as mean value ± standard deviation (SD).

4.5. Statistical analysis

A multiplicative model was assumed for concentration-dependent parameters (C_{max}, AUC^{0-8}, $AUC^{0-\infty}$), implying a logarithmic normal distribution, whereas for the time-related parameter, t_{max}, an additive model with normal distribution of non-transformed data was assumed [21].
An analysis of variance for the crossover design has been performed with an evaluation of treatment, period and carry-over effects, the residuals of which were afterwards tested for normality as described by Chow and Liu [22]. The 90% standard confidence interval (CI) limits for relative treatment differences were calculated parametrically by geometric means based on logarithmic transformation of the intraindividual ratios of C_{max}, AUC^{0-8} and $AUC^{0-\infty}$. They had to fall into the bioequivalence range of 80–125% for AUC and into the wider acceptance range of 70% to 143% for C_{max} [12, 13]. The analysis of t_{max} was based on the non-parametric Wilcoxon signed rank test (level of significance $p = 0.05$) and was carried out using STATISTICA® 5.0 for Windows package (StatSoft, Inc., Tulsa, USA) running on a personal computer.
Point estimators were calculated as described by Chow and Liu [22] and Steinijans and Diletti [23], while coefficients of variation (CV-intra) were calculated according to Diletti et al. [16, 17] and Chou and Liu [22] for log-transformed and untransformed data, respectively.

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