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Research paper

Bioequivalence evaluation of lansoprazole 30-mg capsules (Lanfast® and Lanzor®) in healthy volunteers

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Abstract

The bioequivalence of two lansoprazole 30-mg capsules was determined in healthy human, adult volunteers after a single dose in a randomized cross-over study. The study was conducted at Pharmaconsult, Flemington Pharmaceutical Corp., New Jersey, USA. Reference (Lanzor®, Laboratoires Houde, Paris, France) and test (Lanfast®, Julphar, UAE) were administered to volunteers with 240 ml water after overnight fasting. Blood samples were collected at specified time intervals, plasma was separated and analyzed for lansoprazole using a validated HPLC method. The pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$ and elimination rate constant were determined from plasma concentration-time profile of both formulations and found to be in good agreement with previously reported values. The calculated pharmacokinetic parameters were compared statistically to evaluate bioequivalence between the two brands, using the statistical modules recommended by the Food and Drug Administration. The analysis of variance (ANOVA) did not show any significant difference between the two formulations and 90% confidence intervals fell within the acceptable range (80–120%) for bioequivalence. Based on these statistical inferences it was concluded that the two formulations exhibited comparable pharmacokinetic profiles and that Julphar's Lanfast is bioequivalent to Lanzor of Lab. Houde.

Keywords: Lansoprazole; Bioequivalence; Pharmacokinetics; High-performance liquid chromatography; Julphar

1. Introduction

Bioequivalence of two formulations of the same drug comprises equivalence with respect to the rate and extent of their absorption. While the area under concentration time curve (AUC) generally serves as the characteristic of the extent of absorption, the peak concentration (C_{max}) and the time of its occurrence (T_{max}), reflect the rate of absorption, especially in fast-releasing drug formulations [1,2]. The present study was conducted to evaluate the bioequivalence of two brands of lansoprazole 30-mg capsules in fasting, healthy human volunteers. Although several studies have been published regarding lansoprazole pharmacokinetics, very few of them have focused on the proof of bioequivalence between two formulations.

Chemically lansoprazole is 2-{(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl}sulfinylbenzimidazole, as shown in Fig. 1 [3]. It is a benzimidazole derivative with antisecretory and antiulcer activities. It inhibits the acid pump activity in the final stage of the enzyme process and therefore reduces the acid secretion of parietal cells. Lansoprazole is converted to active sulfonamide metabolites in the acidic environment of parietal cells; these metabolites inactivate H^+,K^+-ATPase [4]. In vitro, inhibition of H^+,K^+-ATPase activity and acid secretion by lansoprazole were found to be concentration dependent [5]. Although lansoprazole alone has a relatively low eradication effects on *Helicobacter pylori*, it may enhance the ability of other agents to eradicate the organism [6,7]. Orally 30 mg/day of lansoprazole provided effective symptoms relief and healing of duodenal ulcer in 75–100% of patients after 4 weeks of therapy in non-comparative and comparative trials [8]. In healthy volunteers, single and multiple oral doses of lansoprazole inhibited both basal and stimulated gastric acid secretions [9].

Since lansoprazole is acid-labile, it is usually adminis-

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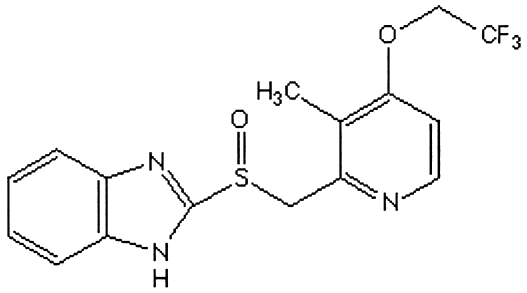

Fig. 1. Molecular structure of lansoprazole [3].

tered as capsules containing enteric coated granules to prevent gastric decomposition and to increase the bioavailability. Its absolute bioavailability is 80–91%, which may be decreased if administered within 30 min of food intake. It has high protein binding (97%) which is decreased in renal function impairment [7,10]. Lansoprazole has a half-life of about 1.5 h; renal impairment decreases the half-life. After oral administration peak concentration is achieved within 1–2 h; a single 30-mg oral dose gives a peak concentration of 750–1150 ng/ml [7]. Peak maxima (C_{max}) and bioavailability were not significantly altered by administration of multiple doses of the drug for 7 days [11] as compared to the first day of treatment although bioavailability showed marked inter-individual variability [11,12].

No significant difference was reported in the pharmacokinetics of lansoprazole in typical healthy individuals as compared to patient groups [13]. The peak blood levels over the dosage range of 15, 30, and 60 mg appear relatively dose-proportional. Time to peak concentration ranged from 1.0 to 2.0 h and half-life ranged from 1.3 to 2.1 h [12]. A significant difference was observed in half-life when compared in young (1.4 h) and elderly (1.9–2.9 h) subjects after multiple-day dosing. No effect of food on half-life was observed, although food delayed the time to peak concentration (3.3–3.7 h) [13]. Lansoprazole is extensively metabolized in the liver to two main excretory metabolites that are inactive [13,14]. In the acid environment, lansoprazole is converted to two active metabolites that inhibit the acid secretion by H^+,K^+-ATPase within the parietal cells canaliculus, but that are not present in the systemic circulation [14]. Therefore, in this study only the parent drug was estimated in plasma samples.

1.1. Objectives of the study

The purpose of this study was to determine the pharmacokinetic parameters of two brands of lansoprazole 30-mg capsules and then to compare these parameters statistically to evaluate the bioequivalence between the two brands. Lanfast® (Julphar, UAE) was used as test product while Lanzor® (Laboratoires Houde, Paris, France) was used as reference product.

2. Material and methods

2.1. Study products

Test product: Lanfast® – lansoprazole 30-mg capsules; Batch No. 0001; expiration date 10/97. Manufacturer: Gulf Pharmaceutical Industries – Julphar, UAE.

Reference product: Lanzor® – lansoprazole 30-mg capsules; Batch No. 147; expiration date 06/97. Manufacturer: Laboratoires Houde, Paris, France.

2.2. Study design

Considering the reported pharmacokinetic data [8] of lanosprazole, considering $\alpha = 0.05$, and the bioequivalence range (0.8–1.2) a total number of 26 volunteers is expected to be sufficient to obtain a statistical power greater than 80%. Based on this estimation 26 healthy male volunteers completed this pharmacokinetic study at Flemington Pharmaceutical Corp., NJ, USA. Their mean age was 25.1 ± 7.2 years with a range of 18–45 years, and mean body weight was 76.7 ± 10.9 kg with a range of 56.6–97.4 kg. Every subject completed an acceptable medical history, medication history, physical examination, an electrocardiogram, screens for HIV-1 and -2 antibody and hepatitis B surface antigen, and a urine drug screen prior to study initiation. Selected routine clinical laboratory measurements were performed during screening. Upon completion of study, the physical examination and clinical laboratory measurements were repeated. The subjects were instructed to abstain from taking any medication for 1 week prior to and during the study period. Informed consent was obtained from the subjects after explaining the nature and purpose of the study. The study protocols were approved by the Institutional Review Board (IRB) of PRACS Institute, Fargo, ND, USA.

2.3. Drug administration and sample collection

This study was based on a single-dose, randomized, two-treatment, two-period crossover design. In the morning of phase I, after an overnight fasting (10 h) volunteers were given single dose of either formulation (reference or test) of lansoprazole 30 mg with 240 ml of water. No food was allowed until 4 h after dose administration. Water intake was allowed after 2 h of dose; water, lunch and dinner were given to all volunteers according to a time schedule. The volunteers were continuously monitored by PRACS Institute staff throughout the confinement period of study. They were not be permitted to lie down or sleep for the first 4 h after the dose. Approximately 10 ml of blood samples for lansoprazole assay were drawn into heparinized tubes through indwelling cannula before (0 h) and at 0.33, 0.67, 1.0, 1.67, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0,8.0, 10, 12 and 16 h after dosing. The blood samples were centrifuged at 2400 rev./min for 15 min at 4°C; plasma was separated and kept frozen at −20°C until assayed. After a washout period of 7 days the

study was repeated in the same manner to complete the crossover design.

2.4. Chromatographic conditions

An HPLC method was developed and validated at PRACS Institute Analytical Laboratory Ltd. for lansoprazole assay in plasma samples. Lansoprazole reference standard was obtained from Chemo, Iberica, S.A.; internal standard Megestrol acetate from Sigma; acetonitrile (HPLC grade), methyl-*t*-butyl ether (HPLC grade), and methanol (HPLC grade) from Burdick and Jackson; and KH_2PO_4 (ACS grade) from Fischer Scientific.

HPLC system was an isocratic system consisting of a solvent delivery pump, diode array detector (Hewlett–Packard 1090), and a chromatograph (Hewlett–Packard 1090 Chemstation). The separation was performed by using a stainless-steel Dupont SB-CN column. The mobile phase consisted of 46% acetonitrile and 54% KH_2PO_4 buffer (pH 4.5) and was pumped at a flow rate of 1.5 ml/min. Effluent was monitored at a wavelength of 285 nm and corresponding peak areas were recorded.

The method was validated by following the international guidelines [15]. The limit of quantitation for lanosprazole was 20 ng/ml plasma; at this concentration the accuracy was 96.9% while precision was 12.7%. During validation within batch accuracy ranged from 92.5 to 107.0%, while within batch precision remained below 16.6%. The between batch accuracy was between 94.6 and 105.1% while precision remained below 12.7%. Short-term stability showed that lansoprazole is stable in plasma at least 16 h at room temperature, while long-term stability studies showed that lansoprazole is stable in plasma for at least 64 days when stored at −20°C.

2.5. Extraction of lansoprazole from plasma

A 1-ml aliquot of plasma was extracted with 6 ml of extraction solution containing internal standard (Megesterol acetate, 0.13 μg/ml in methyl-*t*-butyl ether). After mixing and centrifugation, the organic phase was removed and evaporated to dryness under nitrogen stream and residue was reconstituted in 100 μl of methanol; 10 μl was injected onto the HPLC system equipped with a diode-array UV detector and peak areas were recorded.

2.6. Pharmacokinetic analysis

Pharmacokinetic analysis was performed by means of a model independent method. The maximum lansoprazole concentration (C_{max}) and the corresponding peak times (T_{max}) were determined by the inspection of the individual drug plasma concentration-time profiles. The elimination rate constant (λ_Z) was obtained from the least-square fitted terminal log-linear portion of the plasma concentration–time profile. The elimination half-life ($T_{1/2}$) was calculated as $0.693/\lambda_Z$. The area under the curve to the last measurable concentration (AUC_{0-t}) was calculated by the linear trapezoidal rule. The area under the curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-t} + C_t/\lambda_Z$, where C_t is the last measurable concentration.

2.7. Statistical analysis

For the purpose of bioequivalence analysis AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were considered as primary variables. Bioequivalence was assessed by means of an analysis of variance (ANOVA GLM model) [16] for crossover design and calculating standard 90% confidence intervals [17–19] of the ratio test/reference (T/R). The products were considered bioequivalent if the difference between two compared parameters was found statistically insignificant ($P \geq 0.05$) and 90% confidence intervals for these parameters fell within 80–120%. The acceptance range for C_{max} may be wider than that for AUC, particularly for drugs having highly variable peak concentrations; the recommended range for C_{max} is 70–143% [20–22]. The Anderson–Huauck test [23–25] was also applied which computes the probability in the two one-sided *t*-test based on the null hypothesis.

3. Results and discussion

The mean concentration-time profiles for the two brands of lansoprazole 30-mg capsules are shown in Fig. 2. All calculated pharmacokinetic parameter values were in good agreement with the previously reported values [4–13]. The pharmacokinetic parameters for both formulations are shown in Table 1. For bioequivalence evaluation various statistical modules were applied to AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} as per current FDA guidelines [24]. Table 2 shows the results of the statistical analysis for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. Due to lack of normality of the ln-transformed data, the final conclusions of this study were based on the analysis done on the non-transformed data.

According to the mean plasma levels of the 26 subjects completing the study, the relative bioavailability was found

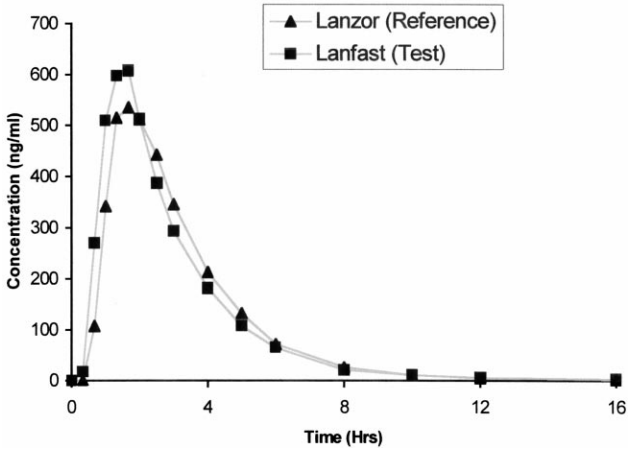

Fig. 2. Plasma concentration–time profile of lansoprazole 30-mg capsules.

Table 1
Pharmacokinetic parameters of the two brands of lansoprazole capsules

Volunteer no.	AUC_{0-t} (ng h/ml)		$AUC_{0-\infty}$ (ng h/ml)		C_{max} (ng/ml)		T_{max} (h)		λ_Z (/h)		$T_{1/2}$ (h)	
	Test	Ref.	Test	Ref.	Test	Ref.	Test	Ref.	Test	Ref.	Test	Ref.
1	5724.40	5204.49	6107.77	5479.24	775.71	1093.93	2.50	1.00	0.19	0.19	3.68	3.59
2	1518.37	1172.63	1559.37	1218.05	1088.93	448.64	1.00	4.00	0.66	0.77	1.06	0.90
3	1186.72	1720.13	1247.21	1753.86	549.46	650.23	2.00	3.00	0.67	0.66	1.04	1.06
4	805.70	2390.36	869.29	2445.39	259.24	1002.91	1.00	1.67	0.56	0.58	1.24	1.19
5	1155.86	762.54	1210.83	794.06	617.60	302.34	0.67	2.50	0.63	0.80	1.10	0.87
6	2380.60	3050.71	2449.14	3110.23	723.69	923.12	1.67	2.50	0.40	0.41	1.73	1.70
7	1077.61	1044.55	1101.32	1087.05	676.98	631.89	1.33	1.33	0.92	0.81	0.75	0.86
8	1755.64	1760.97	1811.35	1798.06	1027.63	899.53	1.33	1.33	0.80	0.72	0.86	0.96
9	973.11	1196.18	997.42	1220.28	726.50	842.71	1.00	1.33	0.86	0.97	0.81	0.72
10	689.05	702.22	728.86	730.07	402.61	498.46	1.33	2.50	1.00	1.10	0.70	0.63
11	1323.86	1399.50	1446.42	1470.66	517.65	720.23	1.67	1.67	0.48	0.63	1.46	1.09
12	1367.10	232.78	1404.92	382.08	724.68	101.81	1.67	2.50	0.79	0.31	0.88	2.26
13	3092.67	3354.46	3153.61	3435.88	1000.02	1130.11	1.33	1.33	0.43	0.41	1.61	1.70
14	1730.24	1475.54	1783.64	1537.40	859.90	739.26	1.00	2.00	0.70	0.75	0.99	0.92
15	1070.01	1381.20	1135.48	1414.83	704.49	674.09	1.67	1.33	0.79	0.74	0.88	0.94
16	1803.08	1454.36	1849.72	1516.90	1101.85	597.21	0.67	1.00	0.65	0.61	1.07	1.14
17	2507.96	2160.75	2575.22	2258.86	977.05	781.99	1.33	2.00	0.52	0.50	1.34	1.38
18	2051.32	1192.23	2089.22	1332.68	1040.51	465.25	1.67	1.67	0.60	0.51	1.16	1.36
19	1181.96	1220.58	1237.80	1266.78	558.82	699.28	1.67	1.33	0.86	0.90	0.81	0.77
20	1097.87	395.90	1118.80	439.70	804.68	249.90	1.33	1.67	1.06	0.96	0.65	0.72
21	1339.46	1431.47	1392.86	1476.91	653.11	705.10	2.00	1.33	0.73	0.67	0.95	1.03
22	3610.07	2995.25	3715.98	3095.12	1872.63	1093.00	0.67	1.33	0.48	0.48	1.45	1.45
23	847.34	869.04	879.00	911.96	623.53	523.03	1.00	1.33	0.80	0.80	0.86	0.86
24	1655.91	1436.13	1739.99	1508.53	864.15	865.76	1.00	1.33	0.58	0.62	1.20	1.12
25	1285.73	3253.84	1413.65	3337.19	708.90	1009.81	1.00	1.00	0.81	0.36	0.86	1.91
26	2044.78	1185.02	2121.10	1244.11	536.57	818.97	1.67	1.33	0.30	0.76	2.32	0.91
Mean	1741.40	1709.34	1813.08	1779.46	784.50	710.33	1.35	1.74	0.66	0.65	1.21	1.23
SD	1072.43	1099.15	1127.72	1131.09	307.51	265.86	0.45	0.71	0.21	0.22	0.63	0.62
%CV	61.58	64.30	62.20	63.56	39.20	37.43	33.48	40.82	31.70	33.33	51.72	50.51

to be 101.8, 101.9 and 110.4% on the basis of mean AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, respectively.

3.1. Area under the curve (AUC_{0-t})

The mean AUC_{0-t} was 1741 ng h/ml and 1709 ng h/ml for test and reference products, respectively; these values were in good agreement with reported ones [9,12]. On the basis of these values it was concluded that the two products did not show any unusual pharmacokinetics values for lansoprazole.

ANOVA did not show any significant differences for periods effects and treatment (formulations). 90% confidence interval also fell within the bioequivalence acceptance criteria. Two one-sided *t*-tests [23–25] were also performed on the ratio (r) of mean AUC_{0-t} of test to mean AUC_{0-t} of reference. These tests showed the $P(r < 0.8) = 0.0054$ and $P(r > 1.2) = 0.0167$; so both tests were rejected and it was accepted that the probability for the ratio (*T/R*) to lie within 0.8 and 1.2 was 0.98.

3.2. Area under the curve ($AUC_{0-\infty}$)

The mean $AUC_{0-\infty}$ was 1813 ng h/ml and 1779 ng h/ml for test and reference products, respectively; these values were in good agreement with reported ones [9,12]. These values again confirmed the conclusion that the two products did not show any unusual pharmacokinetics for lansoprazole.

Table 2
Statistical analysis of pharmacokinetic data[a]

	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}
ANOVA GLM (Prob. *F*)	> 0.30 (>0.30)	> 0.30 (>0.30)	> 0.31 (>0.3)
90% CI	88.1–115.6% (89.6–117.3%)	89.0–114.8% (91.1–117.2%)	93.0–128.1% (86.1–119.9%)
Two one-sided *t*-test probability[b]	0.98	0.98	0.81

[a] Values in parentheses indicate analysis for periods.
[b] Probability for *T/R* ratio (r) to be within 0.8 and 1.2.

ANOVA did not show any significant differences for periods effects and treatment (formulations). 90% confidence interval ranges also fell within the bioequivalence acceptance criteria. Two one-sided *t*-tests [23–25] were also performed on the ratio of mean $AUC_{0-\infty}$ of test to mean $AUC_{0-\infty}$ of reference. These tests showed the $P(r < 0.8) = 0.0038$ and $P(r > 1.2) = 0.012$; so both tests were rejected and it was accepted that the probability for the ratio (*T/R*) to lie within 0.8 and 1.2 was 0.98.

3.3. Peak plasma concentration (C_{max})

The mean C_{max} was 784 and 710 ng/ml for test and reference products respectively; these values were in good agreement with reported ones [9,12], assuring further the lack of any unusual pharmacokinetics for lansoprazole.

ANOVA did not show any significant difference; for periods effects the observed *F* value was 0.092 while table *F* value at corresponding degree of freedom was 4.26 ($P > 0.05$). In terms of treatment (formulations), no significant difference was observed; observed *F* value was 1.06 while table *F* value at corresponding degree of freedom was 4.26. 90% confidence interval ranges among the reference and test products also fell within the bioequivalence acceptance criteria for C_{max} (70–143%) [20–22]. Two one-sided *t*-tests [23–25] were also performed on
the ratio of mean C_{max} of test to mean C_{max} of reference. These tests showed the $P(r < 0.8) = 0.003$ and $P(r > 1.2) = 0.183$; probability for this ratio to be lie within 0.8 and 1.2 was 0.81.

For T_{max} the parametric point estimate of difference (test-reference) was −0.39 h, which showed an improved rate of bioavailability, though it was very close to acceptance limits (±20% of reference mean).

4. Summary and conclusion

The statistical comparison of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} clearly indicated no significant difference in the two brands of lansoprazole 30-mg capsules. 90% confidence intervals for the mean ratio (*T/R*) of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were entirely within the Food and Drug Administration acceptance range. Based on the pharmacokinetic and statistical results of this study, we can conclude that Lanfast 30-mg capsules (Julphar, UAE) is bioequivalent to Lanzor 30-mg capsules(Lab. Houde, France), and that the two products can be considered interchangeable in medical practice.

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