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“Bioequivalence Study of Esomeprazole in Healthy Adults, Human Subjects, Under Fasting Conditions.”

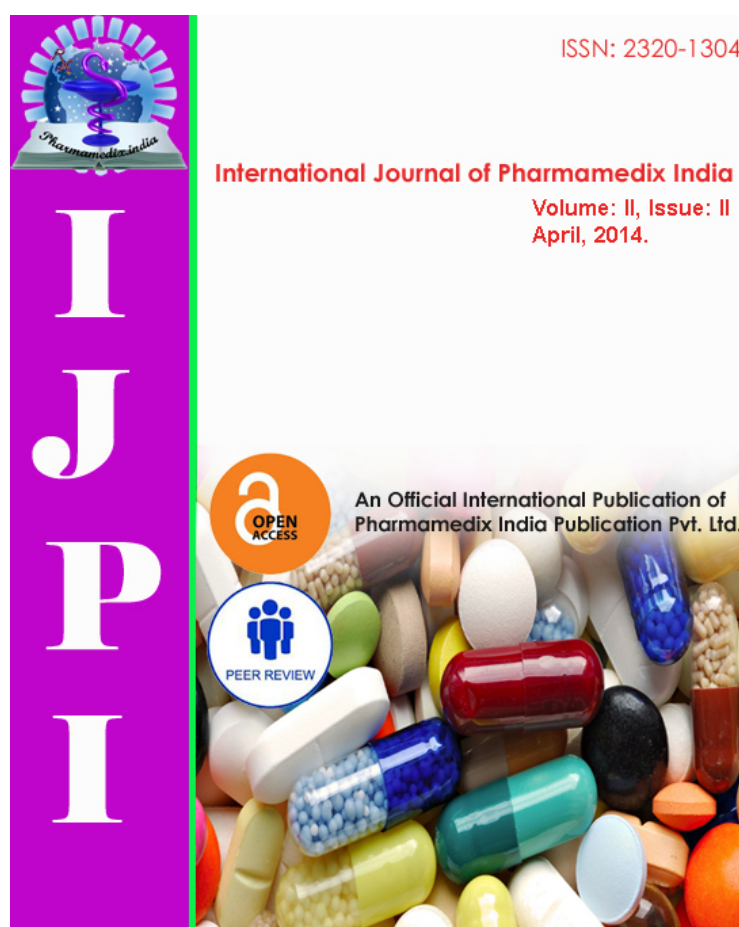
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Abstract:

This is an open label, randomized, balanced, two treatment, two period, two-sequence, single dose, crossover bioequivalence study in twelve (12) healthy adults, human subjects, under fasting conditions. In each treatment period, subjects received a single dose of esomeprazole 40 mg capsule. Treatment periods separated by a washout period of at least 05 days. The bioequivalence of a single capsule formulation of esomeprazole 40 mg given individually assessed by the geometric mean ratios of the area under the plasma concentration time curve (AUC) and observed maximum plasma concentration (C_{max}). ANOVA model performed on an untransformed and a natural log-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} taking into account - sequence, subject (sequence), period and treatment as variables. 90% Confidence interval for the ratio of the geometric least square means of natural log transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of Test and Reference formulations are within 80.0% to 125.0%, hence bioequivalence is established.

Keyword: Bioavailability and Bioequivalence studies, Proton pump inhibitors, Esomeprazole.

Introduction

International regulatory authorities¹ require that the final quality judgment of an oral dosage form be based on its in vitro dissolution profile and its in vivo bioavailability or bioequivalence evaluation. The latter is based on the premise that the concentration of the drug in the systemic circulation is at equilibrium with the concentration of the drug at the site of action and that the therapeutic effect of the drug moiety is a function of its pharmacodynamic-pharmacokinetic relationship.

Bioequivalence gained increasing attention during the last 40 years after it became evident that marketed products having the same amounts of the drug may exhibit marked differences in their therapeutic responses. Generally, these differences were well correlated to dissimilar drug plasma levels caused mainly by impaired absorption. The phenomenon are available in the literature, researchers correlated the bioavailability and clinical effectiveness of USP thyroid products^{2,3,4}, digoxin^{5,6}, tolbutamide⁷, prednisone^{8,9} and phenytoin¹⁰.

Consequently, on the basis of simple pharmacokinetic concepts and parameters, bioavailability and bioequivalence studies have been established as acceptable surrogates for expensive, complicated and lengthy clinical trials, and are used extensively worldwide to establish and ensure consistent quality and a reliable, therapeutically effective performance of marketed dosage forms.

Bioavailability reflects the extent of the systemic availability of the active therapeutic moiety and is generally assessed by measuring the 'area under the concentration time curve', the peak plasma concentration and the time to reach the peak plasma concentration. The extent of the systemic availability is determined by the extent of drug absorbed from the site of administration, and is influenced by the drug, the dosage form and the interaction of these with the complex environment of the absorption site. For a drug that obeys linear pharmacokinetics, the AUC and $C_{\max}$ values increase proportionately with the dose^[11]. Consequently, if two formulations of the same drug exhibit comparative AUC values, they are considered to have similar systemic availability. The bioavailability of an oral dosage form or a drug generally compared with an intravenous solution (100% standard), to determine the absolute

bioavailability. In case of drugs which obey non-linear kinetics, the changes in AUC and $C_{\max}$ values are not proportional to the dose administered¹¹. This is because either one or more of the processes which handle the drug i.e. absorption, distribution, metabolism and excretion are saturated i.e. their capacity has been exceeded within the therapeutic concentration range of the drug. In this situation, the plasma concentration-time profile cannot be used as an indicator of absolute bioavailability. The latter has to be then assessed by measuring the extent of the drug and its metabolites excreted in the urine.

The comparative bioavailability assessment of two or more formulations of the same active ingredient to be administered by the same route is termed bioequivalence. Bioequivalence studies compare both the rate and extent of absorption of various multisource drug formulations with the reference drug, on the basis that if two formulations exhibit similar drug concentration-time profiles in the plasma, they should exhibit similar therapeutic effects. For an unapproved generic dosage form to be marketed and accepted as therapeutically equal effective to the reference formulation, *in vivo*. Bioequivalence studies provide a quality

control tool to monitor production and manufacturing changes¹².

Esomeprazole is absorbed rapidly after oral administration¹³. Increase in systemic exposure, as shown by areas under the plasma-concentration time curves, are dose related after single doses, increasing in a nonlinear fashion¹⁴. Esomeprazole is metabolized extensively in the liver by two cytochrome P450 isoenzymes to metabolites devoid of antiseecretory activity. The drug is primarily metabolized by CYP2C19 to hydroxyl and desmethyl metabolites and to a lesser degree by CYP3A4 to sulfone metabolites.

The use of generic drugs has increased due to their effectiveness and the increasing variety of drugs that are now available as generic drug in the recent years. However, their use in clinical practice depends not only on their essential similarity (in formulation and composition, as determined by regulatory agencies), but also on their bioequivalence with their reference counterparts. Therefore, study of the comparative bioavailability of test and reference drugs is important for appropriate assessment by the scientific community. Two drugs are considered to be bioequivalent if they are pharmaceutically equivalent and their bioavailability is so similar that they are unlikely to produce

clinically relevant differences in regard to safety and efficacy¹⁵.

2. MATERIAL AND METHOD

2.1 Selection of subjects

All the subjects were undergo physical, hematological, serological and clinical screening procedures within 21 days prior to admission day in to the clinical facility for period I. The volunteers were sign the informed consent document prior to screening¹⁶.

2.2 Medical history

An evaluation of the volunteer's was included the following:

- Demography
- Subjects medical history (present and pass illness, history of allergies, and concomitant medications)
- Subjects surgical history
- Obstetric and gynecological history for female volunteers
- Significant family history
- Chocolate, tea, coffee, cola, alcohol and tobacco consumption patterns and any other addictive behaviors
- Physical (general and systemic) examination and investigations¹⁶

2.3 Inclusion criteria

Volunteers meeting following criteria were enrolled: Sex: male, Age: 18-45 years, volunteer with BMI of 18.50-24.90 (inclusive

both) kg/m² with weight of 50-80 kg, Healthy and willing to participate in the study, Volunteer willing to adhere to the protocol requirements and to provide written informed consent, Non-smoker or smoker who smokes less than 10 cigarettes per day¹⁷.

2.4 Exclusion criteria

The volunteers were excluded from the study based on the following criteria: Clinically relevant abnormalities in the results of the laboratory screening evaluation (including creatinine kinase), Clinically significant abnormal ECG or chest x-ray, Systolic blood pressure less than 100 mm Hg or more than 140 mm Hg and Diastolic blood pressure less than 60 mm Hg or more than 90 mm Hg, Pulse rate less than 50/minute or more than 100/minute, oral temperature less than 95 degree F or more than 98.6 degree F, Respiratory rate less than 12/minute or more than 20/minute, History of allergy to the test drug or any drug chemically similar to the drug under investigation, History of alcohol or drug abuse, Positive breath alcohol test, Recent history of kidney or liver dysfunction, History of consumption of prescribed medication since last 14 days or OTC medication since last 07 days before beginning of the study, Volunteers suffering from any chronic illness such as arthritis, asthma etc., HIV, HCV, HBsAg positive volunteers, opiate, tetra hydrocannabinol,

amphetamine, barbiturates, benzodiazepines, cocaine positive volunteers based on urine test, Volunteers suffering from any psychiatric (acute or chronic) illness requiring medications, Administration of any study drug in the period 0 to 3 months before entry to the study, History of significant blood loss due to any reason, including blood donation in the past 3 months, History of pre-existing bleeding disorder, Existence of any surgical or medical condition, which, in the judgment of the chief investigator and/or clinical investigator/physician, might interfere with the absorption, distribution, metabolism or excretion of the drug or likely to compromise the safety of volunteers, inability to communicate or co-operate due to language problem, poor mental development or impaired cerebral function¹⁷.

2.5 Sampling of blood

All blood samples were collected in pre-labeled tubes containing 5 IU dilute heparin in normal saline for each ml of blood. Samples were collected through an indwelling cannula placed in a forearm vein. The cannula was kept in situ as long as possible by injecting, about 0.5 ml of 5 IU/ml of heparin in normal saline solution to maintain the cannula patent. While sampling through the cannula, blood samples were collected after discarding first 0.5 ml of heparinized blood from the tubing of the

cannula. Tubes were shaken gently to ensure the proper mixing of blood with anticoagulant. The cannula was removed from the volunteers in each period before checkout or it was removed upon volunteer's request during study¹⁷.

2.6 Pharmacokinetic and statistical analysis

In order to investigate the relative bioavailability of the test drug

(esomeprazole) against the reference drug (esomeprazole), 90% confidence intervals were calculated for the intrasubject ratio (test/reference) of the geometric least square means of primary parameters (C_{max} , AUC_{0-t} , $AUC_{0-\infty}$)¹⁸. The pharmacokinetic parameters of esomeprazole (test) are summarized in Table 1 and the pharmacokinetic parameters of esomeprazole (reference) are summarized in Table 2.

Table 1: Plasma pharmacokinetic parameters of all the subjects for test drug (esomeprazole)

Pharmacokinetic parameters	Mean	Median	SD	CV (%)	Max	Min
C_{max} (ng/ml)	1145.36	1038.88	457.66	39.96	2278.24	611.39
T_{max} (hr)	3.04	3.00	0.53	17.46	4.00	2.25
AUC_{0-t} (ng-hr/ml)	37773.30	3135.20	2181.57	57.82	8443.66	1081.77
$AUC_{0-\infty}$ (ng-hr/ml)	3827.24	3160.09	2226.80	58.18	8650.363	1097.83
K_{el} (1/hr)	0.57	0.533	0.24	42.37	1.18	0.28
$T_{1/2}$ (hr)	1.40	1.30	0.53	37.84	2.52	0.58

Table 2: Plasma pharmacokinetic parameters of all the subjects for reference drug (esomeprazole)

Pharmacokinetic parameters	Mean	Median	SD	CV (%)	Max	Min
C_{max} (ng/ml)	1162.58	1174.52	444.11	38.20	2053.23	402.86
T_{max} (hr)	1.96	1.62	0.99	50.72	4.50	1.00
AUC_{0-t} (ng-hr/ml)	3483.06	3195.05	2213.32	63.55	9732.95	1005.42
$AUC_{0-\infty}$ (ng-hr/ml)	3531.13	3237.34	2255.47	63.87	9919.63	1019.29
K_{el} (1/hr)	0.58	0.54	0.25	42.48	1.09	0.27
$T_{1/2}$ (hr)	1.37	1.29	0.52	37.83	2.61	0.63

3. RESULTS

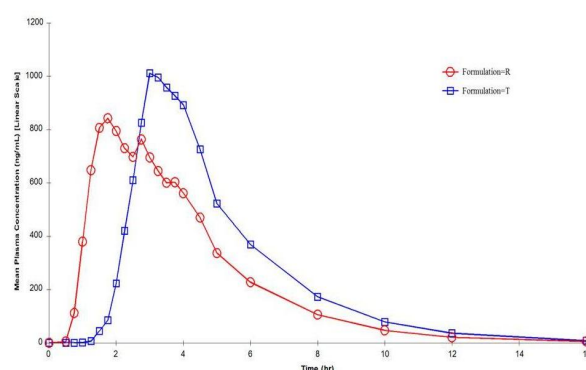
The mean (SD) C_{max} for test and reference drugs are 1145.35 (457.66) ng/ml and 1162.58 (444.11) ng/ml, respectively, were attained at T_{max} of 3.042 and 1.958 hours respectively. All subjects presented an $AUC_{0-t}/AUC_{0-\infty}$ ratio was greater than 80%. The mean elimination half life was 1.406 and 1.370 hours for test and reference drugs respectively. Analysis of variance (ANOVA) for crossover design was used to assess the effect of formulations, periods, sequences, and subjects on pharmacokinetic parameters. Sequence effect was tested against the between subject mean squares. All other effects were tested against the within subject mean error. No significant formulation, period or sequence effect was observed ($p>0.05$) for any of the pharmacokinetic parameters, but in case of subject variation, significant differences were observed for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ which are usual due to inter individual variations among subjects. Since, all of the tested pharmacokinetic parameters indicate the rate and extent of absorption of the administered drug from its dosage form; the insignificant differences between two formulations reflect the therapeutic equivalency of two formulations, test and reference.

Table 3: p-values of paired t-test

Parameters	p-value
C_{max} (ng/ml)	0.794
T_{max} (hr)	0.102

AUC_{0-t} (ng-hr/ml)	0.202
$AUC_{0-\infty}$ (ng-hr/ml)	0.202

The analytical method was specific, sensitive, accurate and precise. The chromatograms showed that both the peaks were completely resolved from one another and also from plasma components. Mean plasma drug concentration of esomeprazole for both test and reference drugs are presented in following figure.



The 90% CI for esomeprazole C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were 88.261% to 114.304%, 99.304% to 117.017% and 99.029% to 117.391%, respectively. All the values of the parameters were within the predetermined range of 80.0% to 125.0% according to the FDA requirement for bioequivalence.

Table 4: 90 % confidence intervals for different pharmacokinetic parameters

Parameters	Point estimate	Upper limit	Lower limit
C_{max} (ng/ml)	100.44	114.30	88.26
AUC_{0-t} (ng-hr/ml)	107.80	117.01	99.30
$AUC_{0-\infty}$ (ng-hr/ml)	107.82	117.39	99.02

4. DISCUSSION

To exclude any clinically important differences in the rate and extent at which the active entity of the drugs becomes available at the site of action, assessment of bioequivalence of test product to reference product is necessary. The current study had some limitations that should be considered. This was an open label study, so it might not address objectively the efficacy and safety profiles of the formulations tested. The study was also limited by inclusion of healthy male subjects who were administered a single dose in the fasted state, the result can not be extrapolated to a clinical setting. In the present study, food was strictly controlled and all subjects received the same standardized meal in two periods, thereby minimizing the effect of food consumption. These results remain to be tested for effect of food as well as in patient subjects.

This study examined the pharmacokinetic parameters and bioequivalence of two antiulcer drugs (esomeprazole capsules) in healthy human male subjects. The pharmacokinetic parameters calculated for both the test and reference drugs were not significantly different, which reflects the comparable pharmacokinetic characteristics of two drugs. All the 90% confidence intervals for important pharmacokinetics parameters were well within the FDA accepted limits for bioequivalence products (80.0%-125.0%). Both the formulations were

well tolerated and all 12 subjects completed the study without any incidence of adverse effects. So it can be concluded that the two drugs are bioequivalent in terms of rate and extent of absorption and hence interchangeable.

5. CONCLUSION

The mean (SD) C_{max} for test and reference drugs (esomeprazole) are 1145.35 (457.66) ng/ml and 1162.58 (444.11) ng/ml, respectively, were attained at T_{max} of 3.042 and 1.958 hours respectively. All subjects presented an $AUC_{0-t}/AUC_{0-\infty}$ ratio was greater than 80%. The mean elimination half life was 1.406 and 1.370 hours for test and reference drugs respectively.

The pharmacokinetic parameters were tested by paired t-test at 5% level of significance. It can be observed that all the p-values are greater than 0.05 indicating no significant difference among the parameters obtained for test and reference drugs (esomeprazole).

From the present study, it has been observed that the 90% confidence intervals of C_{max} (88.261% to 114.304%), AUC_{0-t} (99.304% to 117.017%) and $AUC_{0-\infty}$ (99.029% to 117.391%) are within the bioequivalence acceptance limits of 80.0% to 125.0% for antiulcer agents according to the FDA requirement for bioequivalence. Hence, the present study passed the required limits.

The study may help in the preliminary requirement for generic products to enter in

the market, development of new formulations of the existing drugs, control of quality of a drug product during the early stages of marketing in order to determine the influence of processing factors, storage and stability on drug absorption and determination of influence, patient related factors and possible interaction with other drugs on the efficiency of absorption

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