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Comparation of Bioavailability: Two Dexlansoprazole Formulations in Beagle Dogs after a Single Dose Administration

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Abstract

The study was performed to determine oral bioequivalence of generic dexlansoprazole and reference formulation (Dexilant) in healthy dogs. A 2 period crossover balanced design was used with a 7 days washout period between the doses. Dexlansoprazole was analyzed by LC-MS/MS in the presence of omeprazole as internal standard. The mean ratio of parameters C_{max} and AUC_{0-t} and 90% confidence intervals of correspondents were calculated to determine the bioequivalence. The means AUC_{0-t} for test and reference formulation were 4094.5 ug/L*h and 3684.9 ug/L*h, for $AUC_{0-\infty}$ were 4137.5 ug/L*h and 3709.6 ug/L*h and, for C_{max} 1643.0 ug/L and 1498.2 ug/L, respectively. Geometric mean of the test /reference Pharmaceuticals 30 mg formulation individual percent ratio was 99.3% for AUC_{0-t}, 100.6% for $AUC_{0-\infty}$ and 110.0% for C_{max}. The 90% confidence intervals were 84.0% ~ 117.5%, 85.3% ~ 118.7%, 85.0% ~ 142.3%, respectively. It was concluded that pharmacokinetic data for test formulation were similar enough to original innovator, both formulations had the delayed releasing and double peak characteristics in dogs according to the rate and extent of absorption.

Keywords: Bioequivalence; Dexlansoprazole; LC-MS/MS; Pharmacokinetics

Introduction

Helicobacter pylori (*H. pylori*), first isolated in 1984, was found parasitic in gastric mucosa, inducing upper gastrointestinal diseases such as gastritis, peptic ulcer, gastroesophageal reflux disease and gastric cancer. It was reported that early detection, timely and effectively take antibiotics could prevent and control upper digestive system diseases to a great extent. Years past *H. pylori* has been found to be a bacteria which is difficult to treat, and it also obtained the resistance of common used antibiotics [1-6].

Modern treatments are effective in managing the symptoms of the gastrointestinal disease, mainly through using antibiotics and PPIs. Dexlansoprazole is the R-enantiomer of lansoprazole. The reference formulation adopts an innovative Dual Delayed Release (DDR) delivery system, designing to extend the duration of drug exposure and maintain pharmacologically active levels of drug over a longer period of time, resulting in a dexlansoprazole plasma concentration–time profile with two distinct peaks. The levofloxacin-dexlansoprazole based quadruple therapy provides high *H. pylori* eradication for clarithromycin or dual clarithromycin and metronidazole resistant strains. This regimen could be used as an alternative first line therapy for *H. pylori* eradication. Dexlansoprazole appears to be effective in improving heartburn, regurgitation and maintained for the duration of the treatment [6,7].

The pharmacokinetic parameters for dexlansoprazole have been acquired fromclinical trials including healthy subjects and patients. For reducing the R&D risk and cost of a generic drug product, using Beagle dogs as the preclinical subjects to evaluate bioequivalence is an effective and fast way. In this study, a simple, rapid and sensitive LC-MS/MS method was developed and validated for the determination of dexlansoprazole 30 mg capsules after oral administration in beagle plasma, and it is helpful to make a forward clinical research.

Methods

Subjects

Six males and six females pure bred beagle dogs were purchased from Beijing Marshall Biotechnology Co. Ltd. (the qualification card number 11400600000678). The animal room was maintained at a temperature of 18-25°C, with a relative humidity of 40-70% and a 12 h light/dark cycle. Prior to the initiation of dosing, the dogs were quarantined for 2 weeks and then acclimatized to the study environmental conditions before use. The dogs were fed 300 g certified commercial diet (Vital River, Charles River China, PR China) at a fixed time per day and tap water *ad libitum* during the study. Each dog was individually housed in an elevated stainless-steel cage and exercised in compliance with the Animal Welfare Act requirements accordance with NIH guideline (NRC, 1996). The study was approved by the Ethical Committee of the Faculty of Veterinary Medicine and carried out in the Center for New Drug Safety Evaluation and Research of Hebei Medical University (GLP certificated lab.).

Drug products

The employed test formulation was dexlansoprazole manufactured by Pharmaceutical factory of Hebei Medical University 30 mg (lot number 140501) and the reference formulation was manufactured by Takeda Pharmaceuticals America Inc. 30 mg (lot number C20674).

Study design

The study was conducted in a randomized 2 period crossover balanced design with 7 days wash out period between the doses. During each period, the animals were fed at 5:00 pm, and after an overnight fast they received a single 30 mg capsule dexlansoprazole dose of either formulation at 8:00 am. All dogs proceed fast 3 h following the drug administration, but liquid consumption was permitted.

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Blood samples from a suitable leg vein were collected into vacuum heparin containing tube with scale before and 0.5,1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 h after administration of each dexlansoprazole 30 mg, and collect blood for 3 ml in each time point.

Drug analysis

Blood samples were cooled in a bath and centrifuged at 3000 rpm for at least 10 min at approximately 4°C. Sample tubes were frozen at -80°C, and maintained to that temperature until analysis (delivery to the analytical phase). All samples from a single beagle were analyzed on the same day in order to avoid inter assay variation.

Plasma concentrations of dexlansoprazole were determined by the HPLC coupled with tandem mass spectrometry (LC-MS/MS), in positive ion electrospray ionization mode, using a multiple monitoring (MRM) method andomeprazole as internal standard (IS) due to its similar extraction efficiency and ionization efficiency to dexlansoprazole. The transitions used were 369.8 → 252.0 for Dexlansoprazole and 345.9 → 198.0 for IS. This apparatus consisted of an SHIMADZU LC-30A liquid chromatography system, with pump, automatic injector, oven and SCIEX AB API4000Q-Trap mass spectrometer with ESI. Use liquid-liquid extraction obtaining the analytes from plasma samples. The method was validated for specificity, linearity, precision, accuracy, extraction recovery and matrix effect, stability and dilution integrity. The analytical column was a Synergi Fusion-RP C18, 4 μm, 50 × 3.0 mm (phenomenex). The mobile phase consisting of methanol (A) and Buffer (ammonium acetate 2 mM) (B) was delivered for separation of analytes using a gradient elution program at a flow rate of 0.5 mL/min. The gradient elution program was conducted as follows: 0-1.4 min, 65% A; 1.4-2.5 min, 65%-95% A. The auto-sampler was maintained at 4°C and the injection volume was 5 μL.

Pharmacokinetic analysis and statistical analysis

The pharmacokinetic parameters were calculated according to non-compartment model and were analyze dusing the DAS® Institute (Version 3.2.6): Including half-life ($t_{1/2}$), total body clearance/F (CLz/F), steady state apparent volume of distribution/F (Vz/F). Maximum concentration (C_{max}), time-to-maximum concentration (T_{max}) were obtained directly from the curves. Area under curve from zero to the last measurable plasma concentration point (AUC_{0-t}, t=12 h for p.o. administrations) and area under the plasma concentration-time curve from zero to time infinity ($AUC_{0-\infty}$) were calculated by applying the linear trapezoidal rule and ratio of $AUC_{0-t}/AUC_{0-\infty}$ ($R\_AUC_{(t/\infty)}$).

The bioequivalence between both formulations was assessed by calculating individual C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ together with their mean and 90% confidence intervals (CI) after log transformation of the data. The inclusion of the 90% CI for the ratio in the 80% to 125% range (for AUC_{0-t}, $AUC_{0-\infty}$) and 70% to 143% range (for C_{max}) was analyzed by nonparametric (DAS® Institute Version 2.1.1) and parametric (ANOVA) methods.

Results

Method validation

The calibration curves($r \geq 0.9960$, r was the correlation coefficient) were linear in the ranges of 5-1200 ng/mL by using least square linear regression analysis with a weight factor of $1/x^2$. The lower limit of quantification (LLOQ) for Dexlansoprazole in dog plasma was 5 ng/ml, respectively, based on a signal-to-noise ratio (S/N) of 10, and the intra-day precision (RSD%) was 4.54% (n=6) and accuracy (RE%) was 8%. The limit of detection (LOD) was 1 ng/ml, respectively based on an S/N of 3. The accuracy and precision of the method were evaluated by determining replicate QC samples (8, 200 and 800 ng/ml) on three days. The precision of intra and inter day RSDs were no more than 15.43%, and the accuracy ranged from -3.0% ~ 4.4% (Table 1), indicating acceptable precision and accuracy of the present method.

The extraction recoveries of dexlansoprazole (for the three quality control concentration of 8,200 and 800 ng/ml) and IS from beagle plasma were 109.48%, 93.79%, 95.63% and 92.90%, respectively. The matrix effect of dexlansoprazole (for the quality control concentration of 8,200 and 800 ng/ml) and IS were 105.61%, 106.08%, 99.06% and 111.16%. The stability of analytes in plasma of dexlansoprazole were accessed and found short term stability for 4 h (25°C), autosampler for 8 h (4°C) and long term stability for 6, 15, 30 days (-80°C) and during the one and three freeze and melt cycles (Table 2) indicated the good stability of dexlansoprazole during the study.

Pharmacokinetic and statistical analysis

The mean (± SD) plasma concentration time profile of the 2 formulations, shown in Figure 1, was similar.

Central and dispersion measures for all pharmacokinetic parameters for both formulations are shown in Tables 3 and 4. From this, the mean values of C_{max} were found to be 1498.2 (± 876.9 standard deviations [SD]) ng/mL for the reference product and 1643.0 (± 988.8) ng/mL for the test product. For T_{max} (h), the mean values were found to be similar to both the reference and test product and the value was 2.0 (1.7) h. The mean values of AUC_{0-t} were found to be 3684.9 (± 1761.5) ng.h/mL for reference and 4094.5 (± 3259.6) ng.h/mL for the test product. The mean $AUC_{0-\infty}$ was found to be 3709.6 (± 1770.5) ng.h/mL and 4137.5 (± 3251.0) ng.h/mL for the reference and the test product, respectively. Table 5 presents the ratios and the respective confidence intervals for bioequivalence analysis.

Discussion

Gastroesophageal reflux disease (GERD) is a clinical condition characterized by persistent retrograde movement of gastric contents into the esophagus that typically manifests as burning retrosternal pain and/or regurgitation. Atypical symptoms of GERD have been described and include chronic cough, vocal hoarseness, globus, water brash, and throat pain that can affect an individual's quality of life (QOL) and/or produce complications [8-10].

Proton pump inhibitors (PPIs) are the standard therapy for long-

Nominal Con. (ng/ml)	Measured Con. (Mean ± SD, ng/ml)	Accuracy (RE%)	Intra-day Run (RSD%)	Inter-day Run (RSD%)
8.00	8.19 ± 0.62	2.4	5.92	15.43
200	209 ± 11	4.4	3.69	11.37
800	776 ± 31	-3.0	3.25	7.74

Abbreviations: Con.=Concentration

Table 1: Precision and accuracy for dexlansoprazole in dog plasma.

Storage Conditions	Nominal Con. (ng/ml)	Measured Con. (Mean ± SD, ng/ml)	RSD (%)	RE (%)
4 h (25ºC)	8.00	7.17 ± 0.59	8.17	-8.46
	800	799 ± 28	3.46	0.46
Auto-sampler for 8 h (4ºC)	8.00	8.37 ± 0.33	3.99	6.76
	800	790 ± 41	5.15	-0.71
1 freeze and melt cycles	8.00	7.36 ± 0.53	7.21	-6.08
	800	732 ± 19	2.64	-7.96
3 freeze and melt cycles	8.00	8.01 ± 0.54	6.74	2.17
	800	774 ± 59	7.59	-2.72
6 days (-80ºC)	8.00	8.19 ± 0.72	8.79	4.55
	800	785 ± 8	0.99	-1.30
15 days (-80ºC)	8.00	8.91 ± 0.36	4.01	7.33
	800	754 ± 30	3.91	-1.44
30 days (-80ºC)	8.00	8.44 ± 0.66	7.82	7.74
	800	829 ± 39	4.71	4.27

Abbreviation: Con.=Concentration

Table 2: Stability of dexlansoprazole in dog plasma under different storage conditions.

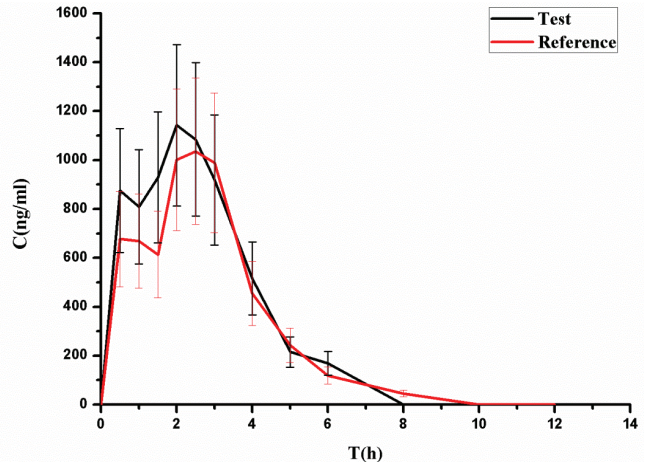

Figure 1: Mean plasma concentration-time profile of dexlansoprazole over the first 12 h after oral administration of the test formulation.

Parameters (Units)	Test		Reference	
	Means (Median)	Standard Deviation (Amplitude)	Means (Median)	Standard Deviation (Amplitude)
$AUC_{(0-t)}$ (ug/L*h)	4095	3260	3685	1762
$AUC_{(0-\infty)}$ (ug/L*h)	4138	3251	3710	1771
C_{max} (ug/L)	1643	989	1498	877
T_{max} (h)	2.0	1.2	1.7	1.1
$R\_AUC_{(t/\infty)}$ (%)	98.3	2.3	99.3	0.9
Vz/F (L/kg)	1.4	1.0	1.3	1.0
CLz/F (L/h/kg)	1.1	0.5	1.0	0.5
$T_{1/2}z$ (h)	0.9	0.4	0.8	0.3

Table 3: Mean pharmacokinetic of parameters dexlansoprazole of test and reference formulation (n=12).

Parameters (Units)	Test	Reference
	Geometric mean	Geometric mean
$AUC_{(0-t)}$ (ug/L*h)	3272.61	3294.04
$AUC_{(0-\infty)}$ (ug/L*h)	3340.75	3319.55
C_{max} (ug/L)	1400.08	1273.01

Table 4: Geometric mean pharmacokinetics parameters of dexlansoprazole of test and references formulation (n=12).

Parameters	Ratio T/R (%)	Lower Limit (%)	Upper Limit (%)
$AUC_{(0-t)}$	99.3	84.0	117.5
$AUC_{(0-\infty)}$	100.6	85.3	118.7
C_{max}	110.0	85.0	142.3

Table 5: Bioequivalence evaluation from the ratio means and the 90% geometric confidence interval of two formulations (n=12).

term management of GERD. Pharmacologic treatment options for GERD have been directed at suppression of gastric acid production in order to reduce both volume and acidity of gastric contents. Anti-secretory agents employed for the treatment of GERD include the histamine-2 receptor antagonists (H2RA) and proton pump inhibitors (PPI). H2RA possess a rapid onset of symptom control and effectively inhibit acid production; however, their use is limited by their brief duration of action and tachyphylaxis possibly owing to histamine-2 receptor up-regulation and enhanced gastrin secretion in the presence of histamine blockade. On the contrary, Proton pump inhibitors (PPIs) block the gastric H, KATPase via covalent binding at different cysteine residues and inhibit gastric acid secretion, and its activity cannot be replaced until a new proton pump is synthesized. Consequently, such agents are also used to treat acid-related conditions such as peptic ulcers, functional dyspepsia and their complications including bleeding, non-steroidal anti-inflammatory drug-induced gastrointestinal lesions, etc. Combine with antibiotics, PPIs are also used to eliminate *Helicobacter pylori*. PPIs have an excellent safety profile, and have become one of the most commonly prescribed class of drugs in both primary and specialty care [8,11-17].

Lansoprazole is substituted benzimidazoles that contain the asymmetric chiral sulfur atom in their chemical structure and therefore they exist in both form R- and S-enantiomers. Therefore, lansoprazole was initially used as a racemate. Since R-enantiomer of lansoprazole, dexlansoprazole, constitutes more than 80% of circulating drug after oral administration of racemic drug, provides lower clearance and 5-fold greater systemic exposure than the S-enantiomer. Dexlansoprazole is extensively metabolized in the liver by cytochrome P450 (CYP) enzymesystem, and mainly through CYP2C19. There are genetic differences in the activity of this enzyme, the pharmacokinetics and pharmacodynamics of PPIs are affected by genetic polymorphisms

of CYP2C19.That may cause the standard deviation in this experiment appears a bit large. The safety profile of dexlansoprazole MR is similar to that of lansoprazole. The extended pharmacodynamic effects, added convenience, and efficacy and safety of dexlansoprazole MR offer a novel approach to gastric pH control in patients with acid-related disorders [18-22].

Dexlansoprazole MR is a novel modified-release formulation of dexlansoprazole, an enantiomer of lansoprazole, which employs an innovative Dual Delayed Release (DDR) delivery system designed to prolong plasma concentration of dexlansoprazole and provide extended duration of acid suppression with once-daily (q.d.) dosing. The DDR delivery system have two distinct drug release periods in the digestive system, therefore extending plasma concentrations following oral administration. Dexlansoprazole MR capsules contain a mixture of two types of granules, each providing a different pH-dependent dissolution profile. One type of granule is designed to release drug fast after the granules reach the proximal duodenum, while the second is designed to release the remaining dose farther along the digestive system at the distal portion of the small intestine. As a result, dexlansoprazole MR produces a dual-peak PK profile, contrary to the single peak seen with conventional PPIs. To maintain prolonged plasma concentrations, dexlansoprazole MR releases drug over a longer period than conventional delayed release PPIs and thereby requires higher daily doses. Compared with lansoprazole, dexlansoprazole MR achieves higher AUCs without a commensurate increase in C_{max} [7,8,23].

The bioavailability of a pharmaceutical form refers to the extent and speed of absorption of the active principle in contained it. Two pharmaceutical forms are said bioequivalent when administered to the same individual, in the same experimental conditions and at the same dose, they show no significant differences in relation to bioavailability. In this study two formulations of dexlansoprazole had been evaluated. Washout period was adequate and there was no quantifiable concentration of the drugs in the second period of the study, indicating that there was no carryover effect from the first to the second period. The mean ratio of parameters C_{max} and AUC_{0-t} and 90% confidence intervals of correspondents were calculated to determine the bioequivalence [24].

The analysis method for the quantification of dexlansoprazole in human plasma mainly focus on the LC–MS/MS method, recently, RP-HPLC method has been developed and validated for its simple and stability. However, the LC–MS/MS methods appear several original advantages, such as high specificity and sensitivity. In this study by LC–MS method revealed some pharmacokinetic parameter of dexlansoprazole. The means AUC_{0-t} for test and reference formulation were 4094.5 ng.h/mL and 3684.9 ng.h/mL, for $AUC_{0-\infty}$ were 4137.5 ng.h/mL and 3709.6 ng.h/mL and, for C_{max} 1643.0 ng/mL and 1498.2 ng/mL, respectively. The ratios were 99.3% for AUC_{0-t}, 100.6% for $AUC_{0-\infty}$ and 110.0% for C_{max}. The 90% confidence intervals were 84.0% ~ 117.5% for AUC_{0-t}, 85.3% ~ 118.7% for $AUC_{0-\infty}$ and 85.0% ~ 142.3% for C_{max} [25].

The AUC_{0-t} and $AUC_{0-\infty}$ are both recognized as an uncontaminated measurement of the extent of absorption. The present study showed that 90% CI of mean AUC_{0-t} and $AUC_{0-\infty}$ (after log-transformation of individual ratios) were included into the bioequivalence range (80-125%), consequently, the two formulations of dexlansoprazole are equivalent for the extend of absorption.

The statistical comparison of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ clearly indicated no significant difference in the two formulations of dexlansoprazole 30 mg delayed release capsules. 90% confidence intervals for the mean ratio (T/R) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were entirely within CFDA acceptance range. Based on the pharmacokinetic and statistical results of this study, we can conclude that the generic dexlansoprazole used in this study was bioequivalent to the original innovator dexlansoprazole.

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