

Comparative Bioavailability of Two Tablet Formulations of Dipyridamole in Healthy Volunteers

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Abstract

The bioavailability of two dipyridamol tablet formulations of (Dipyridamole from Tolidaru and Persantin from Boehringer) was compared in 14 healthy male volunteers who received a single dose of 25 mg of the test (T) and the reference (R) products in a randomized balanced 2-way crossover design. Plasma samples were obtained over a 16 h interval and dipyridamole concentrations determined by HPLC with ultraviolet detection. The maximum plasma concentration (C_{max}), area under the plasma concentration time curve up to the last measurable concentration (AUC_{0-t}), as well as infinity ($AUC_{0-\infty}$), and the absorption rate ($C_{max}/AUC_{0-\infty}$) were analyzed statistically under the assumption of a multiplicative model. The time to maximum concentration (T_{max}) was analyzed assuming an additive model. The parametric confidence intervals (90%) of the mean values of the pharmacokinetic characteristics for T/R ratio were in each case well within the bioequivalence acceptable range of 80-125%. The test formulation was found bioequivalent to the reference formulation by the Schuirmann's two one-sided t tests and by Wilcoxon Mann Whitney two one-sided tests procedure. Therefore, the 2 formulations were considered to be equivalent.

Keywords: Dipyridamole; Comparative bioavailability; Pharmacokinetic parameters; Bioequivalent.

Introduction

Dipyridamole is widely used as a coronary vasodilator in patients with high blood pressure it is also a prophylactic agent in patients suffering from angina pectoris and an inhibitor of platelet aggregation in various thrombo-embolic conditions (1, 2). Dipyridamole also potentiates anti-metabolite activity in a dose-dependent manner (3). In view of the fact that the drug is known to have a delayed absorption pattern (4-6), studies on the bioavailability of newly developed tablet formulations are deemed essential. The objective of this study was to compare bioavailability of a new commercial dipyridamole tablet formulation

(Tolidaru Co., Tehran, Iran) relative to the reference formulation of persantin (Boehringer Ingelheim, Ridgefield, CT, USA) following a single dose administration to healthy adult male volunteers.

Experimental

In vitro analysis

The two dipyridamole brands were found to be similar in weight variation, disintegration time, dissolution, and assay as stipulated by the USP XXIII, as well as by the manufacturer.

Subjects

Fourteen healthy male adult volunteers participated in this study. Their mean age (\pm SD) was 35.5 ± 6.7 years with a range of 22-48 years,

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and a body weight of 77.5 ± 7.6 kg with a range of 64-91 kg. The volunteers were free from significant cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal and any acute or chronic disease or drug allergy as determined from their medical history, clinical examination, and laboratory investigation (hematology, blood chemistry, and urine analysis). The volunteers were asked to abstain from taking any medicine, including OTC drugs, for at least two weeks prior to and during the study. All subjects gave their written informed consent prior to participation in the study and after explaining the nature and purpose of this study.

Study design and blood sampling

Administration of the two products (test and reference) to the subjects was carried out by means of a two-way crossover design with a one-week washout period. Subjects were randomly divided into two equal groups and assigned to one of the two sequences of administration. Each subject received a single dose of 25 mg tablet of either brand with 240 ml of water after overnight fasting for at least 10 h. Subjects were allowed to eat a standard breakfast at 4 h, lunch at 8 h, and dinner at 12 h after drug administration. Beverages and food containing caffeine were not permitted over the entire course of the study. Volunteers were ambulatory during the study, but strenuous activity was prohibited. Blood samples (7 ml) from an antecubital vein were collected into citrate containing evacuated glass tubes before and at 0.33, 0.67, 1.33, 1.67, 2, 3, 4, 5, 6, 8, 10, 12, 14 and 16 hours post dosing. The plasma was then separated after centrifugation and stored frozen at -20°C until quantitative analysis.

Quantitative drug analysis

We have previously reported a method for measuring the concentration of dipyridamole in plasma (7). Briefly, the assay involved reversed-phase high performance liquid chromatography with ultraviolet detection at 280 nm and dipyridamole was extracted from plasma by a back-extraction procedure, with propranolol as the internal standard. All samples from a single volunteer were assayed on the same day to avoid inter-assay variation. The limit of dipyridamole quantitation in plasma was 5 ng/ml.

Pharmacokinetic and statistical analysis

The Pharmacokinetic characteristics for dipyridamole were determined from the plasma concentration-time data. The maximum plasma concentration (C_{\max}) and time to reach maximum plasma concentration (T_{\max}) were obtained directly from the plasma concentration-time data. The area under the plasma concentration time curve up to the last time (t) showing a measurable concentration (C_t) of the analyte (AUC_{0-t}) was determined by applying the linear trapezoidal rule. The apparent elimination rate constant (K_{el}) was calculated by the log-linear regression of the data points of describing a terminal log-linear decaying phase. The $\text{AUC}_{0-\infty}$ values (express the magnitude of absorption) were determined by adding the quotient of $*C_t$ and the appropriate k_{el} to the corresponding AUC_{0-t} , which is:

$$\text{AUC}_{0-\infty} = \text{AUC}_{0-t} + *C_t / K_{el}$$

Where $*C_t$ is the last detectable plasma concentration.

The sampling period covered more than 96% of the total AUCs for both brands T and R. The apparent elimination half-life ($t_{1/2}$) of dipyridamole in plasma was calculated by using the following equation:

$$t_{1/2} = (\ln 2) / K_{el}$$

The ratio of $C_{\max}/\text{AUC}_{0-\infty}$ was also computed and used as a measure for the rate of absorption. Bioequivalency between formulations was assessed by calculating individual C_{\max} , AUC_{0-t} , $\text{AUC}_{0-\infty}$, $t_{1/2}$ and K_{el} ratios (test/reference) and their inclusion into the 80-125% bioequivalence range were statistically analyzed by parametric (ANOVA for log-transformed data) and non-parametric (Wilcoxon rank sum test) methods (8, 9). Individual T_{\max} differences were analyzed by the Wilcoxon rank sum test.

Results and Discussion

Dipyridamole was well tolerated by the volunteers and all of them continued the test up to the end and were discharged in good health. Both formulations of dipyridamole were readily absorbed from the gastrointestinal tract of the

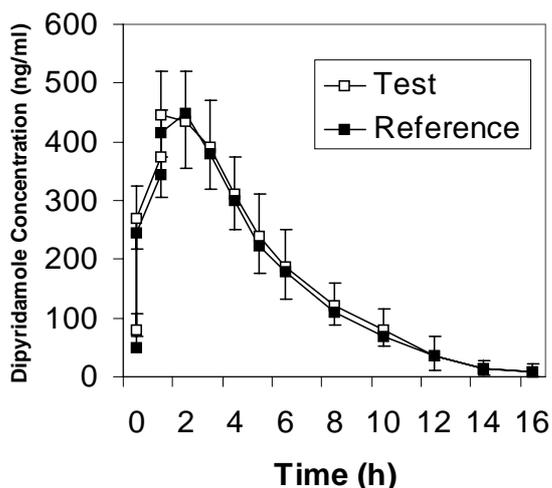


Figure 1. Mean plasma concentration time profiles of dipyridamole following oral administration of the 2 brands to 14 healthy volunteers.

volunteers. Dipyridamole was measurable at the first sampling time (0.33 h) in all volunteers following administration of the two brands. The mean plasma concentration time curves for the two brands are shown in figure 1. Fourteen ANOVA's were performed to compare dipyridamole plasma concentrations produced by the two formulations at each sampling time. There was no statistical difference between the two formulations at the fourteen time points. The parameters used to measure bioavailability were AUC_{0-t} and $AUC_{0-\infty}$, for the extent of absorption and $C_{max}/AUC_{0-\infty}$ for the absorption

Table 1. Mean pharmacokinetic parameters for dipyridamole after administration of the 2 formulations to 14 subjects.

| Parameter | Test Formulation | Reference Formulation |
|---|------------------|-----------------------|
| AUC_{0-t} (ng h ml ⁻¹) | | |
| Geom. mean | 2433.43 | 2357.96 |
| 90% CI | 1765.71-3326.45 | 1663.92-3317.51 |
| $AUC_{0-\infty}$ (ng h ml ⁻¹) | | |
| Geom. mean | 2567.04 | 2492.28 |
| 90% CI | 1917.63-3496.51 | 1875.26-3421.11 |
| C_{max} (ng/ml) | | |
| Geom. mean | 498.1 | 475.25 |
| 90% CI | 346.71-713.98 | 307.84-718.22 |
| K_{el} (h ⁻¹) | | |
| Geom. mean | 0.066 | 0.067 |
| 90% CI | 0.060-0.072 | 0.060-0.075 |
| $t_{1/2}$ (h) | | |
| Geom. mean | 10.4 | 10.3 |
| 90% CI | 9.53-11.51 | 9.3-11.54 |
| T_{max} (h) | | |
| Mean | 1.732 | 1.851 |
| ± SD | ± 0.796 | ± 0.653 |

rate and they were calculated in a model-independent manner. Table 1 shows the geometric mean values and the range for the above parameters. Results of the ANOVA test performed on the bioavailability data clearly indicated that there was no significant difference between formulations in none of the pharmacokinetic characteristics (AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , T_{max} , K_{el} , $t_{1/2}$ and $C_{max}/AUC_{0-\infty}$). There was neither any period and sequence effect on these parameters.

Table 2 shows the parametric 90% confidence intervals of the mean values of the pharmacokinetic characteristics as well as the point estimates for T/R ratio assuming multiplicative model. Non-parametric confidence intervals were also included. The confidence limits for the mean AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , K_{el} , $t_{1/2}$ and $C_{max}/AUC_{0-\infty}$ indicated that these values are entirely within the bioequivalence acceptable range of 80-125%. It could be seen from table 2 that the parametric point estimate of the difference (T-R) of T_{max} is 0.12 h and thus within the stipulated bioequivalence range of ±0.37 h. In conclusion, based on the pharmacokinetic and statistical results of this study, we can assume interchangeability of both preparations in clinical practice.

Table 2. Parametric and nonparametric 90% confidence intervals for the mean pharmacokinetic characteristics of dipyridamole formulations

| Model: multiplicative | T/R point estimate | Confidence limits | Level of confidence |
|----------------------------|--------------------|-------------------|---------------------|
| Parametric analysis* | | | |
| AUC_{0-t} | 103.2 | 93.9-112.8 | 90 |
| $AUC_{0-\infty}$ | 103.0 | 93.6-112.3 | 90 |
| C_{max} | 104.8 | 97.3-114.1 | 90 |
| K_{el} | 98.5 | 95.1-102.1 | 90 |
| $T_{1/2}$ | 100.1 | 96.5-102.9 | 90 |
| $C_{max} / AUC_{0-\infty}$ | 102.1 | 97.4-107.0 | 90 |
| Nonparametric analysis** | | | |
| AUC_{0-t} | 102.0 | 88.4-120.9 | 91.13 |
| $AUC_{0-\infty}$ | 101.7 | 88.7-121.4 | 91.13 |
| C_{max} | 105.2 | 91.9-119.3 | 91.13 |
| K_{el} | 98.9 | 92.8-103.3 | 91.13 |
| $T_{1/2}$ | 99.60 | 95.5-106.2 | 91.13 |
| $C_{max} / AUC_{0-\infty}$ | 100.8 | 94.4-109.5 | 91.13 |
| Model: additive | | | |
| T-R (h) point estimate | | Confidence limits | Level of confidence |
| Parametric analysis* | | | |
| T_{max} | 0.119 | -0.048-0.286 | 90 |
| Nonparametric analysis** | | | |
| T_{max} | 0 | -0.25-0.25 | 91.13 |

* = two 1-sided t tests, ** = two 1-sided Wilcoxon test

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