The importance of bioequivalence

ASSIGN BUSTER

Bioequivalence is defined as ” the absence of a significant difference in the rate & extent to which the active ingredient or active moiety in pharmaceutical equivalent or pharmaceutical alternative become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study” (Huixiao et al., 2009).

The importance of bioequivalence studies is increasing due to the large growth of the production and consumption of generic product (Vetchý et al., 2007). Bioequivalence also assess the relative bioavailability of two drug products & thus focuses on comparative drug product performance (Mei-Ling et al., 2001). The rationale of bioequivalence study is the monitoring of pharmacokinetic and pharmacodynamic parameters after the administration of tested drugs (Vetchý et al., 2007). A standard pharmacokinetic study is the conventional method for evaluating the pharmacokinetics of a drug in human subjects.

Deferiprone (DFP, Ferriprox™, Kelfer™, L1, CP20) was synthetic hydroxypyridinone iron chelator isolated from legume Mimosa paduca (Clarke and Martell 1992) to be taken orally, and bind iron in conditions of iron overload (Kontoghiorghes, G. J, 1985). Iron was essential to all species and there was no physiologic excretory pathway for this essential element (Andrews, 1999). In conditions of primary iron overload (eg, hemochromatosis) or secondary iron overload (eg, transfusion-dependant thalassemia), accumulation of this potentially toxic element results in massive iron accumulation and lead to generation of toxic free radical damage (Rund and Rachmilewitz 2005). DFP was used in the treatment of Thalassemia Major and was also used worldwide to treat cancer, leukemia,

hemodialysis and other diseases like detoxification metals, such as aluminum in hemodialysis patients (Paschalidis et al., 1999; Di-Ji et al., 2004). Deferiprone was the world’s first and only orally active iron chelating drug, which was effective and inexpensive to synthesize thus increasing the prospects of making it available to most thalassemia patients in third world countries who are not currently receiving any form of chelation therapy (Kontoghiorghes et al., 2004).

DFP is a bidentate chelator and has a two pka of 3. 6 and 9. 9 (Hider and Liu 2003) with strong iron binding properties of pFe3+ 19. 6 and pFe2+ 5. 6 thus binding it in 3: 1 complex indicating a high degree of relative specificity for trivalent iron (Clarke and Martell 1992; Tam et al 2003). It was a water soluble compound with partition coefficient of 0. 11 and has a molecular weight of 139 Da which made them move freely through cell membranes of the body. DFP absorbed rapidly and completely after oral administration. . Deferiprone appears in plasma within 5 to 10 minutes of ingestion and Peak plasma levels achieved within 1 hour after administration. Food reduces the rate of absorption but not the extent of absorption thus reducing the peak concentration with Cmax of about 100µmol/L in fasting state and about 85µmol/L (Matsui et al 1991; Al-Refaie et al 1995a). Deferiprone is metabolized to the inactive glucuronide that is the predominant form recovered in the urine (James et al., 2001). The drug was eliminated rapidly with a half-life of about 2 hours due to hepatic biotransformation. It was metabolized by glucuronidation and about 90% of the drug excreted in urine as glucuronide. Half-life was shorter in healthy subjects of about 1. 3 hours than that of thalassemia subjects having 2. 3 hours (Stobie et al 1993).

Most frequently occurring side effects are transient gastrointestinal symptoms (GI) such as nausea, vomiting, and abdominal pain (Cohen et al 2003).

OBJECTIVE

The purpose of this study was to evaluate bioequivalence of new tablet formulation of Deferiprone with Ferriprox® (Apotex, Canada).

MATERIALS AND METHODS

Materials

Two drug products of deferiprone 500 mg tablet were used for invivo bioequivalence study. One was the test product (“ Test”) manufactured locally and another was the Reference or innovators products. Deferiprone standard was supplied by Assistant Drug Controller, Ministry of Health, Islamabad. Acetonitrile and methanol HPLC grade were purchased from MERCK.

Study products

The test formulations were Ferrinil 500 mg tablet Batch No……. , expiry ……, and the reference product Ferriprox® 500 mg tablet Batch No…… expiry…… (Apotex INC., Canada).

Human subjects

The study was approved by the Ethics Committee of BeSt Center, Faculty of Biosciences, University of Veterinary and Animal Sciences, Lahore. Twelve healthy Pakistani male volunteers aged between 18-55 years were included in the study. All volunteers were in good health confirmed by physical and clinical laboratory examination including serology, hematology and

biochemical test. All volunteers were abstained from other drug intake and alcoholic preparations three weeks prior to and throughout the study. Those volunteers who had chronic smoking history, alcoholic intake and caffeine intake were excluded.

Study design

The study carried out was randomized, two-treatment, two-period, two-sequence, single dose crossover study with two weeks wash-out period. Each volunteer was in fasted state approximately 10 hours prior to the study. Each volunteer received a single dose of 1000 mg deferiprone with 240 ml of water. Blood samples were collected immediately before and 0. 25, 0. 5, 0. 75, 1, 1. 5, 2, 2. 5, 3, 4, 6, 8 and 12 hours after drug intake. A standardized lunch is consumed after blood sampling at 4 hours. The plasma were separated by centrifugation and stored at -80°C.

ANALYTICAL METHOD

The analytical method was modified by the method of Goddard et al. 1990 using validated HPL method

DATA ANALYSIS

The pharmacokinetic parameters of both test and reference drug were compared and was determined by taking Cmax and Tmax directly from the individual concentration versus time data. Elimination rate constant was determined from log-linear least squared regression of the terminal part of the plasma concentration versus time curve. Half-life was estimated from equation 0. 693/Kel. The area under the concentration versus time curve was calculated by linear trapezoidal rule.

The comparison of generic product of deferiprone 500 mg with innovator’s product was assessed using relevant pharmacokinetic parameters, Cmax, Tmax, AUC (0-t) and AUC (0-âˆž) and was transformed to logarithmic scale before statistical analysis. The difference of the mean corresponding log Cmax, log AUC(0-t) and log AUC(0-âˆž) between the two products will be determined by 2-way analysis of variance (ANOVA) for a crossover design at the significant level of Î± = 0. 05. The 90% confidence interval (CI) (two-one sided test) for the differences of the mean log Cmax, log AUC(0-t) and log AUC(0-âˆž) between the two products were calculated.

The two products are considered to be bioequivalent when 90% CI of the differences of all parameters were within WHO accepted range of 80%-125%.