Bioequivalence of Doxazosin Slow Release Tablets: A Pilot Study

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INTRODUCTION

Bioequivalence studies are carried out to compare the systemic exposure profile of a test drug product to that of a reference product.[1] Doxazosin is a potent quinazoline derivative and is effective for the treatment of hypertension and benign prostatic hyperplasia.[2]

AIM

To carry out a pilot bioequivalence study to assess comparative bioavailability between test product, doxazosin mesylate 8mg slow release tablets and reference product, Cardura®XL 8mg tablets.

METHOD

Method of Analysis

High-performance liquid chromatography method adapted from Sripalakit et al[3] for the detection of doxazosin in human plasma. Prazosin was used as the internal standard.

1. Extraction carried out twice with ethyl acetate
2. Chromatographic separation of doxazosin using a reversed-phase Apollo C_{18} column (250 x 4.6mm, 5µm) with mobile phase of methanol–acetonitrile–0.04M disodium hydrogen orthophosphate (22:22:56, v/v/v) adjusted to pH 4.9 with 0.9M orthophosphoric acid
3. Quantification by fluorescence detection (excitation wavelength = 246nm; emission wavelength = 389nm)
4. Construction of calibration curve

Pilot Study

1. Single dose reference and test products administered to two healthy individuals after overnight fasting
2. Blood samples collected at specified time intervals
3. Cross-over study with two-week wash out period
4. Plasma doxazosin concentrations and actual sampling intervals tabulated

RESULTS

Retention times for prazosin and doxazosin were approximately 4.4 and 13.4 minutes respectively. No significant interfering peaks from endogenous substances were observed with blank plasma extract. A linear standard calibration curve (Figure 1) in the concentration range 1 to 50ng/mL was obtained (correlation coefficient (r) = 0.9979, slope = 0.2038, intercept = –0.3216, lower limit of quantification = 1ng/ml).

Mean C_{max} of doxazosin in the two individuals was: 50.13 ± 1.04ng/mL at T_{max} of 6 hours for the generic and 28.91 ± 6.02ng/mL at T_{max} of 8 hours for the Cardura®XL. The $AUC_{(0\text{-}t48)}$ for Cardura® XL was 549.13 ± 95.13ng hr/mL, whilst the $AUC_{(0\text{-}t48)}$ for the generic was 1080.5 ± 72.43ng hr/mL. Relative bioavailability values of test product/reference product was 1.97 ± 0.22 based on $AUC_{(0\text{-}t48)}$ and 1.86 ± 0.4 based on C_{max} (Figure 2).

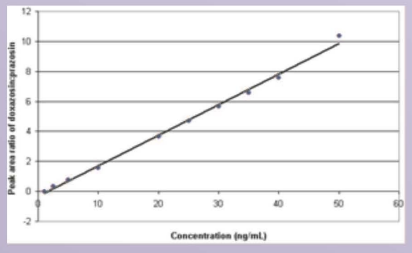

Figure 1: Standard Calibration Curve

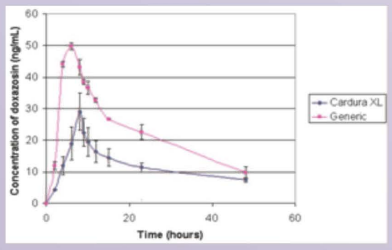

Figure 2: Mean plasma doxazosin concentrations following single oral doses of doxazosin 8mg test and 8mg reference product

CONCLUSION

The extraction method used involving ethyl acetate and the HPLC analysis are adequate to determine doxazosin in human plasma. The bioequivalence trial using this extraction and analytical method showed significant variance between test and reference product. Results from this pilot study are limited since it was carried out in only two individuals and significant intra and inter subject variability in absorption of doxazosin following administration of modified release oral formulations is possible.

REFERENCES

1. The European Agency for the Evaluation of Medicinal Products (EMEA). Investigation of bioavailability and bioequivalence. [cited 2009 Nov 30] Available from: URL: www.emea.europa.eu/pdfs/human/qwp/140198en.pdf (2000).
2. Goldsmith DR, Plosker GL. Doxazosin gastrointestinal therapeutic system: A review of its use in benign prostatic hyperplasia. Drugs 65(14): 2037-2047 (2005).
3. Sripalakit P et al. Validation and pharmacokinetic application of a method for determination of doxazosin in human plasma by high-performance liquid chromatography. Biomedical Chromatography 20: 729-735 (2005).