Poster Session 1 – Biopharmaceutics

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In-vitro and in-vivo evaluation of two formulations of olanzapine compared to Zyprexa

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Olanzapine is a new antipsychotic drug closely related to clozapine both in chemical structure and pharmacological effects that is only marketed as coated tablet. Due to the small proportion of the active component in the tablet and also its insolubility in water, formulation and manufacturing of its tablet dosage form needed special consideration (Bergemann et al 2004). The aim of this study was to evaluate in-vitro specifications and pharmacokinetic parameters of two formulations of olanzapine in comparison to Zyprexa 5 mg tablets as reference formulation. Olanzapine hasn't a monograph in the USP or BP, and because of this, in-vitro characters including weight variation, content uniformity, assay of active ingredient and dissolution rate were determined in accordance to pharmacopoeial comments. Dissolution profiles were compared for similarity to reference product by performing F2 test. In-vivo study was conducted as a single-dose, randomized, 2-way, open-label, crossover study in healthy subjects aged 20–29 years. The proposed protocol was approved by an Institutional Review Board (IRB) before the study was initiated. Subjects were randomized to receive (under fasting conditions) either the test or reference formulation of olanzapine (5-mg tablet) at study period 1 and the opposite formulation at study period 2. Study periods were separated by a washout period of at least 20 days. During each study period, 15 plasma extractions were made to determine olanzapine plasma concentrations and to calculate the pharmacokinetic properties of C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, mean residence time, and $t_{1/2}$. Plasma concentration of olanzapine was determined by a modified HPLC (Aravagiri et al 1997) method using an EC detector. Physical examination and subject interview were used to assess tolerability. All products met the pharmacopoeial specifications for weight variation, content uniformity, and assay. Dissolution behaviour of formulation A was similar to Zyprexa ($F2 = 54.3$) and formulation B was different from reference product ($F2 = 27$). Because of this, only product A was subjected to in-vivo study. The analytical method used was found to be linear over a range of 3–50 ng mL^{-1} of drug in plasma. Between day and within day coefficient of variation of different samples of the same concentration were lower than 5%. Mean recovery of plasma extraction procedure was greater than 95%. For both formulations, all subjects suffered from sedation and some of them had transient nausea. Mean (s.d.) C_{max}s of 44.0 (7.0) ng mL^{-1} and 44.7 (7.2) ng mL^{-1} for test or reference formulations, respectively, were attained at median T_{max}s of 3.2 and 3.5 h (respectively, for test and reference formulations). T_{max}, was not statistically different between the 2 formulations, and the 90% CI calculated for T_{max} for the difference of the medians was within the predefined range. The 90% CIs of the parameters (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$) also were within the predefined range; thus, the 2 formulations are considered bioequivalent.

Aravagiri, M., et al (1997) *Ther. Drug Monit.* **19**: 307–313
Bergemann, N., et al (2004) *Pharmacopsychiatry* **37**: 63–68