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Effect of multiple peak phenomena on Bioequivalence results

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Many drugs when given orally demonstrate multiple peak phenomena in their concentration – time profiles and the effects of this phenomenon on the results is considered in a cetirizine bioequivalence study.

Bioequivalence of test tablet with reference tablet were compared in 22 healthy volunteers who received two 10mg tablets of cetirizine in a randomized blind cross over design. Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 30 hours.RP-HPLC system consisted of a C_{18} Nucleosil column 100×4 mm and mobile phase: buffer KH_2PO_4(PH=3),methanol and acetonitrile (53:40:7), flow rate: 1.4ml/min, oxazepam as internal standard and UV detection at 235nm was performed.

The pharmacokinetic parameters mean±S.D of test tablet(Cetirizine):

$AUC_{(0-T)}$(2295.32±711.87)ng/ml*hr, $AUC_{(0-\infty)}$(3343.68±2402.76) ng/ml*hr, C_{max1}(288.00±114.71) ng/ml, C_{max2}(190.56±71.93) ng/ml, T_{max1}(0.76±0.33)hr and T_{max2}(3.84±2.05)hr.

The pharmacokinetic parameters mean±S.D of reference tablet (Zyrtec):

$AUC_{(0-T)}$(2846.16±1156.32) ng/ml*hr, $AUC_{(0-\infty)}$ (3693.68±2215.64) ng/ml*hr, C_{max1}(332.33±151.41) ng/ml, C_{max2}(299.52±113.01) ng/ml, T_{max1}(0.93±0.39)hr and T_{max2}(3.57±1.96)hr.

The 90% confidence interval are as follows: $AUC_{(0-T)}$:67.9-104.1%, $AUC_{(0-\infty)}$:67.4-118.2%, C_{max1}:66.5-110.7%, C_{max2}:69.7-110.0%, T_{max1}:63.0-99.5%, T_{max2}:84.5-130.5%. Therefore the two products were not bioequivalent (out of acceptable 0.8-1.25% range). E.g. three methods for evaluation of $AUC_{(0-\infty)}$ were applied.

Method A: final k_e after last peak, method B: mean k_e and method C: k_e calculated from final 4 or 5 points concentration – time curve. T-test between method A and B, A and C, B and C have demonstrated meaningful difference ($p<0.005$) between method A with B(0.017) and B with C($p<0.004$).

Multiple peak phenomena should be considered in bioequivalence studies and more details will be discussed.

Biography

Dr Sima Sadrai has completed her Ph.D from Tehran University of Medical Sciences 1995 about population pharmacokinetics of theophylline and postdoctoral studies from Uppsala University School of Pharmacy by Professor Mats Karlsson. She is associate professor in Tehran University of Medical Sciences. She has twenty two years teaching experience with special interest in pharmacokinetics modeling. She has published more than 20 papers and review in reputed journals.