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KARUNRAT TEWTHANOM : PHARMACOKINETIC AND BIOAVAILABILITY STUDY OF DIDANOSINE IN HEALTHY THAI VOLUNTEERS. THESIS ADVISOR: SUVATNA CHULAVATNATOL, Ph.D., KRISANA KRAISINTU, Ph.D., WANCHAI BUPPANHARUN, M.D., THAI BOARD OF INTERNAL MEDICINE. 113 p. ISBN 974-661-805-9

Didanosine (2',3'-dideoxyinosine, ddI) is an effective nucleoside antiretroviral drug used worldwide including Thailand. Pharmacokinetic and bioavailability data of this drug in Thai population have still not been available. This study was performed to investigate the pharmacokinetics and bioavailability of ddI original tablet (100 mg/tablet) and ddI buffered powders (original buffered powder, 167 mg/sachet and local buffered powder, 170 mg/sachet) in Thai healthy volunteers. Furthermore, bioequivalence assessment was conducted between ddI original buffered powder and ddI buffered powder produced locally.

Pharmaceutical evaluation in terms of content uniformity and content of active ingredient of ddI in each preparation revealed that all preparations met standard requirements of the USP XXIII and NF XVIII. Content uniformities (mean ± SD) were 100.43 ± 2.14, 104.17 ± 1.15 and 98.29± 3.34% for ddI original tablet, original buffered powder and local buffered powder, respectively, while contents of active ingredient were 97.98 ± 3.40, 102.76 ± 4.52 and 99.30 ± 2.35%, respectively. Eighteen healthy Thai volunteers with mean age of 22.56 ± 4.48 yrs participated in the study and were randomly assigned to receive a single dose of 200 mg original tablet, 167 mg of original buffered powder and 170 mg of local buffered powder of ddI after 10 hrs fasting. The study was crossover designed with a 1-week washout period. Five milliliters of blood were collected before and at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6 and 8 hrs after drug administration. Concentration of ddI in plasma samples was analyzed by HPLC. Mean ± SEM of pharmacokinetic parameters of ddI original tablet, original buffered powder and local buffered powder were as followed: peak plasma concentrations (C_{max}) were 786.06 ± 83.91, 659.92 ± 59.33 and 648.84 ± 49.71 ng/mL, times to peak plasma concentration (t_{max}) were 0.60 ± 0.06, 0.67 ± 0.04 and 0.58 ± 0.04 hr, half-lives ($t_{1/2}$) were 1.52 ± 0.14, 1.45 ± 0.25 and 1.91 ± 0.31 hrs, elimination rate constants (k) were 0.521 ± 0.04, 0.677 ± 0.10 and 0.464 ± 0.05 hr^{-1}, area under the concentration vs time curves at 0-8 hr (AUC_{0-8}) were 997.45 ± 89.86, 872.10 ± 84.43 and 801.13 ± 58.86 ngxhr/mL, area under the concentration vs time curves at 0-∞ ($AUC_{0-\infty}$) were 1,106.56 ± 103.49, 934.44 ± 87.12 and 903.42 ± 76.39 ngxhr/mL, mean residence times (MRT) were 2.11 ± 0.17, 2.05 ± 0.26 and 2.40 ± 0.37 hrs. No statistical differences were demonstrated ($p>0.05$) for any of pharmacokinetic parameters of ddI among the 3 preparations. The relative bioavailabilty (F) of local buffered powder was 116.00% compared with ddI original tablet and was 115.23% compared with original buffered powder. The 90% confidence interval of the ratios of mean of C_{max}, AUC_{0-8}, $AUC_{0-\infty}$ and t_{max} of local buffered powder and original buffered powder were 0.85-1.11, 0.80-1.04, 0.82-1.11 and 0.77-0.96, respectively. It can be concluded that pharmacokinetics of 200 mg ddI tablet, 167 mg ddI original buffered powder, and 170 mg ddI local buffered powder were not statistically different and ddI local buffered powder was bioequivalent to ddI original buffered powder, and may be used interchangeably if necessary.