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NONGLUCK KARUGANANT : PHARMACOKINETICS OF CEFTIBUTEN IN HEALTHY THAI VOLUNTEERS. THESIS ADVISORS : KORBTHAM SATHIRAKUL, Ph.D., AEUMPORN SRIGRITSANAPOL, Ph.D., ASDA VIBHAGOOL, M.D., M.A.C.P., WINAI WANANUKUL, M.D., CERTIFICATE OF CLINICAL PHARMACOLOGY AND TOXICOLOGY. 127 P. ISBN 974-661-681-1

Ceftibuten, an orally administered third generation cephalosporin, is promoted as an oral step down therapy from parenteral cephalosporin treatment in hospitalized patients with susceptible pathogens. There has not been a clinical trial for evaluation of its pharmacokinetics in Thai people. This study was performed to characterize the disposition of ceftibuten following 400 mg single doses to the healthy Thai volunteers. The time intervals over which plasma levels were maintained above the MIC_{90} of susceptible pathogens were also assessed because time interval is an important parameter correlating with efficacy of cephalosporins.

Thirteen healthy Thai male volunteers aged between 20-40 years participated in the study. All subjects were determined to be in good health by medical history, physical examination and routine laboratory tests (blood chemistry, hematology and urinalysis). Following an overnight fast, all volunteers received ceftibuten, each at a single dose of 400 mg. Blood samples were drawn immediately before (predose) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 and 16 hours after dosing. Urine was collected at 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 16 and 16 to 24 hours after dosing. Plasma and urine samples were stored at –70 °C until they were analysed by High Performance Liquid Chromatography.

The results showed that drug was highly and rapidly absorbed with a mean fraction of drug absorbed (F) of 0.82, a mean absorption lag time (t_{lag}) of 0.52 hrs and a mean time to maximum concentration (t_{max}) of 2.13 hrs. The peak concentrations in plasma (C_{max}) ranged from 14.4 to 24.7 μg/mL. Average ceftibuten pharmacokinetic parameters (±Standard deviations) were as follow : elimination half-life ($t_{1/2}$), 2.34±0.21 hrs; mean residence time (MRT), 5.07±0.58 hrs; area under the plasma concentration-time curve (AUC_∞), 100±14.9 μg.hr/mL; apparent volume of distribution (V_d/F), 0.24±0.04 L/kg; absorption and elimination rate constant (k_a, k) of 1.48±0.96 hr^{-1} and 0.30±0.03 hr^{-1}, respectively. Urinary recovery of unchanged form (%Ae) was 55.6±10.7% of administered doses within 24 hours. The renal clearance (CL_R) and apparent total body clearance (CL/F) were 2.21±0.41 and 4.06±0.63 L/h. C_{max}, t_{max}, k_a, k_e, t_{lag}, $t_{1/2}$, V_d/F, %Ae, CL/F of subjects in this study were found to be similar to those obtained from Western adult volunteers, except for the higher values of AUC_∞ and lower CL_R, which probably indicated that in healthy Thai volunteers drug was more slowly cleared via renal and higher in fraction of drug absorbed. In addition, elimination of ceftibuten also appeared slower in Thais when compared with Japanese. Ceftibuten maintained plasma levels above the MIC_{90} for 60-98% of the dosing interval against *E. coli*, *Klebsiella* spp., *Proteus* spp. and *H. influenzae* (Ampicillin-susceptible). *H. influenzae* (β-lactamase-positive) showed a duration of plasma levels above MIC_{90} of 40-88% of the dosing interval. Strains of *M. catarrhalis* and *S. pyogenes* showed the value of 30-70%, whereas strains of *H. influenzae* (β-lactamase-negative) and *S. pneumoniae* (penicillin-susceptible) showed less time above MIC_{90}, 20-40% of the dosing interval.

It was concluded that the use of 400 mg once daily dosage regimen is likely to provide effective concentrations of ceftibution which are sustained in the plasma for the majority of the dosing interval against the organisms mentioned above except *H. influenzae* (β-lactamase negative) and *S. pneumoniae*. This implies possible effectiveness of its role in parenteral to oral switch therapy, especially for the treatment of gram-negative sepsis in community acquired infection. However, the present study provided preliminary data that still needs further investigation in a number of Thai patients. Analysis of data which incorporates local MIC_{90} data should also be conducted.