Thesis title Pharmacokinetics and Bioavailability Studies of Metoprolol in Healthy Thai

Name Pornhatai Klaisit

Degree Master of Science (Pharmacy)

Thesis Supervisory Committee

Oraphan P. Matangkasombut, Ph.D.

Krisana Kraisintu, Ph.D.

Saming Kaojarern, M.D., Dip.in Clin Pharm.

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ABSTRACT

Metoprolol is a β_1-blocker without ISA is one of the most widely used β-blocker in the management of cardiovascular disorders including hypertension, angina pectoris and myocardial infarction. It was listed in the National Drug List of Thailand until 1992 it was replaced by atenolol. In general Chinese and Thai physicians prescribe β-blockers at a lower dose than those recommended in the Pharmacopoeia . This may be due to the differences in the body size or drug metabolism and/or the sensitivity of patients to the drug . Thus, it is essential to establish the pharmacokinetic profile of metoprolol in Thai subjects which would render the more appropriate dosage adjustment. Moreover, to enable clinicians choosing the most cost-effectiveness regimen with confidence of the quality of the locally produced ME tablet; bioavailability from three commonly used local manufacturers are compared to the innovator, "Betaloc®".

Twenty proven healthy Thai volunteers, ten males and ten females, age 21.85±1.01 years and body weight of 56.55±7.93 kg were participated in the present study. The tested drug was given in double blind randomized cross over fashion with at least 7 days for washout period. A single oral dose 1x100 ME tablet was given following an overnight fast and food was abstained for another 3 hours post dosing. Venous blood samples of approximately 5 ml were drawn at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hrs. Plasma were separated and frozen for analysis of ME and HM by HPLC within 3-5 days. RSTRIP non linear estimation program was used to estimate pharmacokinetic parameters. Pharmacokinetic parameters, i.e., Cmax, Tmax, $AUC_{0-\alpha}$, T1/2, Ka and Ke in males and females are 91.95, 129.54 ng/ml; 1.20, 1.55 hours; 384.21, 830.11 ng/ml/hr; 2.37,3.12 hours; 1.46,1.16 hr^{-1} and 0.34, 0.30 hr^{-1} respectively. Moreover, one female subject behave like a poor metaboliser, since, no metabolite (HM) can be detected.

The present pharmacokinetic data would provide a more appropriate mean for dosage adjustment of ME in Thai patients. However, one should bear in mind that there is a wide intersubject variation and sensitivity of male and female subjects to the drug may not be the same. Therefore, clinical responses are still coinsidered to be one of the most useful guide.

Bioequivalence study indicate that all three tested brands of ME tablets can be used interchangeably, provided that the product has been proved to complile with the pharmacopoeial standard, particularly the dissolution rate and the content uniformity.