CHAPTER 6

DISCUSSION

This study investigated the bioequivalence of metformin comparing between the test (generic metformin from GPO, Bangkok, Thailand) and the reference Glucophage® in healthy Thai male volunteers. The mean 90% CI for the ratios $\frac{\text{Test}}{\text{Reference}}$ of $AUC_{o-t,}$ $AUC_{o-\infty}$ and C_{max} were well within the bioequivalence range 80-125%. The stipulated bioequivalence range of difference T_{max} (Test-Reference) were ± 20% of the T_{max} of the reference formulation. A bioequivalence product should produce no significant difference to the reference in T_{max} and in natural log transformed data of the $AUC_{o-t,}$ $AUC_{o-\infty}$ and C_{max} tested.

The measurement of plasma metformin was performed by using HPLC with UV detection (37, 38). HPLC-UV was the method of choice in this study because of its high specificity and rapid and simple technique suitable for use in routine practice, therefore a number of studies reported the determination of metformin in blood sample and tablets by this method. The results of validation revealed that the assay covered wide range of concentrations with linearity and good precision, accuracy and recovery. Moreover, this condition could cover more than 80% of $AUC_{o-\infty}$ which were adequate to reflect the extent of absorption. Therefore, this HPLC-UV method was appropriate for analysis of metformin in plasma samples.

In this study, the pharmacokinetic parameters of metformin between the test and the reference product were compared. After dose administration, the plasma concentrations of metformin from both preparations increased rapidly and attained the peak levels at 2 h (mean 2.33 $\pm$ 0.76 h, range 1-4 h) and 2.25 h (mean 2.42 $\pm$ 0.78 h, range 1–4 h), for the test and the reference product, respectively. There was no significant difference of the T_{max} between two preparations and the mean (90% CI) for the T_{max} difference of –0.10 [(-0.33)-0.14] h, within the bioequivalence range of $\pm$ 0.48 h (20% of T_{max} of the reference). The average T_{max} obtained from this study

was in agreement with previous study (T_{max} of 2-3 h) (38, 41). Although metformin is a strong base and largely ionized in the physiological pH in the small intestine with a relative bioavailability of approximately 50% to 60% (31, 32), the large V_d of metformin (average 654 L) may be due to distribution to the hepatocytes, enterocytes and erythrocytes by organic cation transporter 1 (OCT1) (42).

The means (± SD) of the C_{max}, AUC_{o-t} and $AUC_{o-\infty}$ for the test versus reference product were 2798.52 ± 588.88 versus 2532.39 ± 688.49 ng/mL, 15184.41 ± 3119.26 versus 13845.77 ± 2737.93 ng.h/mL and 15440.55 ± 3103.47 versus 14065.67 ± 2754.49 ng.h/mL, respectively. The value of AUC from our study was slightly higher than those values reported in the literature (AUC 11600 ± 3840 ng.h/mL) whereas the value of C_{max} was two to three times higher than those values reported in the literature (C_{max}1600-1860 mg/mL) (41, 43) and product monograph (C_{max}600-1800 mg/mL). These may reflect a higher average body weight and a larger V_d of metformin in western subjects than in Thai subjects. Moreover, the differences in analytical methods from various studies may results in differences C_{max}, AUC values. The mean elimination $t_{1/2}$ of test product (3.31 ± 0.55, range 2.20-4.85 h) and reference product (3.52 ± 0.34, range 3.00-4.54 h) were similar and both were comparable to those values reported in the literature (average $t_{1/2}$ of 3.1 ± 0.7 h) (41).

Subject No. 7 showed abnormal peaks of metformin after receiving a reference product. This may be due to vasovagal symptom occurring after dosing and a delay in gastric emptying time which reduces the rate of drug absorption in the small intestine. In addition, subject No. 17 had mild light headedness which is reported in ≥ 1.0 - ≤ 5.0% of patients. This study also found that subject No. 16 had asymptomatic elevated liver enzymes on post study visit (study day 13) and returned to normal values on study day 25. However, metformin-associated hepatotoxicity is very rare and few cases have been reported in the literature due to metformin may inhibit gluconeogenesis in hepatic cells, may results accumulation of pyruvate that can be changed to lactate which causes hepatic cells damaged (44). No subjects reported sign and symptoms of other serious adverse drug reaction.

According to the ANOVA table (Table 18, 19, 20), the inter-subjects variability in the AUC and C_{max} were observed (p=0.000 and 0.0002, respectively). These

findings were expected since some volunteers may exhibit either extremely high (volunteer No 4, 8, 9, 15 and 17) or extremely low (volunteer No 10, 18, 19 and 24) of AUC and C_{max} values. However this study was conducted as a cross-over design and the pharmacokinetic parameters were measured in the same subject, intra-subject variability would be minimized since each subject would serve as his own control. The % CV of intrasubject estimated from S^2 obtained from the ANOVA were 12% and 15%, respectively, for the AUC and C_{max}. The power of test from this study was > 80% for all pharmacokinetic parameters (40). The AUC analysis in this study showed that the sampling time was adequate and the calculated AUC-extrapolation was less than 20% for all volunteers. Bioequivalence analysis showed no statistically significant differences between the two preparations. The mean (90% CI) for the ratios $\frac{\text{Test}}{\text{Reference}}$ for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were 1.09 (1.04-1.16), 1.10 (1.04-1.16) and 1.12 (1.04-1.20), respectively. These values were within the bioequivalence range of 0.8-1.25, thus, our study demonstrated the bioequivalence of the two preparations.

CONCLUSION

This study evaluated the bioequivalence of 850-mg oral formulations of the generic metformin manufactured by GPO, Thailand and the innovator Glucophage® in 26 healthy Thai male using a randomized, cross over design under fasting condition. The results showed that the 90% CI for the ratio $AUC_{o-t,}$ $AUC_{o-\infty}$ and C_{max} of the two preparations were within the acceptable range 0.80-1.25. In addition, the T_{max} difference was within the bioequivalence range of $\pm$ 20% of T_{max} of the reference product. Based on the above, we can conclude that generic metformin manufactured by GPO is bioequivalent to Glucophage®.