DISCUSSION

For most patients, acceptable bronchodilator response will be achieved if a once-daily theophylline product has oral bioavailability of 0.7-0.9 (70-90%)[35]. Since the relative bioavailability (F_{rel}) of Uni-Dur®, Theo-Dur® and Xanthium® with reference to the rapid release tablet (Franol®) were 85, 97 and 77 %, respectively, the three SRT products were considered effective in controlling asthma. Their relative bioavailabilities also correlated with the extent of absorption assessed by $AUCss_{0-24}$ (μg/ml.hr). The mean $AUCss_{0-24}$ of Theo-Dur® were significantly greater than those values of Uni-Dur® and Xanthium®. The result complied with the fact that Uni-Dur® and Xanthium® are ultraslow SRT products designed for once-daily dosing, while, Theo-Dur® is designed for 12-hour dosing. Since Uni-Dur® and Xanthium® are designed for very slow absorption, the possibility of incomplete bioavailability would be problematic because the duration of absorption might exceed the gastrointestinal transit time.

Although once-daily dosing of Theo-Dur® provided almost complete bioavailability, its absorption profile produced high peak concentration and excessive fluctuation in serum theophylline concentration (232%), about twofold higher than those values obtained from Uni-Dur® (137%) and Xanthium®(113%). The upper limit of fluctuation is usually accepted at 100% where fluctuation in serum theophylline concentrations can stay within therapeutic range of 10-20 μg/ml[13]. Nevertheless, Theo-Dur® has received approval from the US-FDA for once-daily administrations. This study showed that this recommendation should be applied to selected patients since patients with normal theophylline clearance will have greater fluctuation of Theo-Dur® and an increased risk of undesired effects. In this case, the

once-daily designed products with less fluctuation, Uni-Dur® and Xanthium®, are preferred.

There were no statistically different in the pharmacokinetic profiles of Uni-Dur® and Xanthium® with regard to the area under the curve at steady state, 0-24 hrs, the minimum and maximum theophylline concentrations as well as the fluctuation index. However, the average Tss_{max} of Uni-Dur® (10.05 ± 4.63 hr) were significant longer than Xanthium®(7.70 ± 1.69 hr). So the best time to administer the drug for controlling nocturnal symptoms (usually occurs at 02.00 AM to 06.00 AM) should be approximately 10 hr before the worst airflow period for Uni-Dur® (e.g. 06.00 PM ± 2 hr) and approximately 7–8 hr for Xanthium®(e.g. 08.00 PM ± 2 hr). Moreover, Uni-Dur® exhibited consistent extended-release absorption characterized by a long plateau-shape in serum theophylline concentration during the 4th to 16th hour after dosing. Uni-Dur®, a programmed cores sustained-release formulation in a scored tablet, provide the constancy of sustained-release characteristics by osmotic release of drug[18]. While Xanthium® is a bead-filled capsule that gets their sustained-release characteristics by the varying thickness of coating, which the thinner coating dissolving with faster rate than the beads with thicker coating. The limitation of bead coating may constrain a delay in the rate of its absorption and resulted in a decrease in the extent of absorption. The lower bioavailability of Xanthium® in this study is agreeable with previous study[23].

In this study, Uni-Dur® provided more stable serum theophylline concentration over a 24-hour period, therefore, the drug was considered to be the best choice for nocturnal asthma. Moreover, data from other studies showed that it has much less fluctuation in theophylline concentrations in approximately one-third of Uniphyl®, another once-daily designed product, and its adverse effect is less than Uniphyl®[24].

Regarding to the use of once-daily preparations, peak concentrations and the time to peak concentration should be monitored. These preparations may cause large fluctuations in concentrations over a dosing interval. Peak concentrations of these preparations usually occur ten hours after administration[35]. If these products are administered in the evening to control nocturnal asthma, a blood sample obtained early the following morning should be suitable. If the dose is taken in the morning, then serum concentrations should be obtained late in the afternoon or in the early evening. Once a reliable serum concentration has been obtained, dosage adjustment can be made accordingly. In most patients, serum concentrations will change in direct proportion to the change in dose. Occasionally patients will exhibit nonlinear kinetics and disproportionate increase in serum concentration will occur as the dose is increased. Therefore, whenever a change in the dose is made, serum concentrations should be monitored at steady state. Appropriate dosage selection coupled with monitoring of serum theophylline concentrations will allow for safe and effective use of theophylline with minimal risks of serious toxicity.

To assess the rate and extent of theophylline absorption, Wagner-Nelson absorption profiles were derived. This method assumes that the kinetic of the study drug being described by a linear one-compartmental model. Since the amount of drug absorbed is equal to the amount in the body plus the amount eliminated, knowing the elimination rate constant (K_e), the cumulative of absorption profile can be calculated from blood levels. In our study, accurate estimate of K_e could not be obtained from serum drug concentration-time curves of sustained-release products since their elimination phases were interfered by absorption rate-limited. Therefore, the K_e derived from a bioavailability study of immediate-release product (Franol®) were used. The result showed that during the first 6 hours the absorption process of Theo-Dur® was closed to zero-order (8.6% per hr), thereafter, followed by first-order. The absorption profile of Xanthium® complied with the first-order process. Xanthium®

was an ultraslow sustained-release formulation so the absorption process might exceed gastrointestinal transit time thus resulted in an incomplete absorption. The absorption profile of Uni-Dur® was a zero-order process for 0-4 hr, 4-15 hr and 15-24 hr with different rate of 7.5, 2.5 and 1% per hr, respectively. This indicated that Uni-Dur® possessed a unique characteristic of drug releasing pattern which resulted in zero-absorption profile complied with the absorption pattern previous reported[14;18]. The reason being a technologically advanced sustained-release formulation of Uni-Dur® that contains programmed cores in a scored tablet that exhibits its sustained release by osmotic difference. Moreover, this released pattern is free of food-related effects, therefore would produce reliable, predictable and sustained level of theophylline for 24 hours.

CONCLUSION

In conclusions, the 12-hour dosing SRT product, Theo-Dur®, was not recommended as a once-daily product in subject with normal theophylline clearance due to excessive fluctuation in serum theophylline concentration, although the drug exhibited better bioavailability. Xanthium® had the lowest relative extent of absorption because of its ultraslow release characteristic. Uni-Dur® had higher relative extent of absorption than Xanthium®, but did not reach statistically difference. However, Uni-Dur® had modest fluctuation in serum theophylline concentration and a long plateau-shaped concentration-time curve during the 4^{th}-16^{th} hour post dose. The reason may be due to a programmed core and a consistent release characteristic of the drug. Since a long plateau-shaped of serum theophylline concentration is useful to optimize lung function especially during the worst diurnal airflow period such as late night to early morning, Uni-Dur® may be more beneficial in controlling nocturnal asthma.