Thesis title	**Pharmacokinetics and Bioavailability of Phenytoin in Healthy Thais**
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ABSTRACT

Phenytoin is widely used as an antiepileptic drug worldwide. The unique properties of phenytoin such as poor water solubility and zero-order kinetics of phenytoin metabolism, together with difference in pharmaceutical formulations can result in dramatic changes in bioavailability of phenytoin capsule.

This research is performed to investigate the physical properties of 4 brands of phenytoin capsules (Dilantin®-the innovator product, local products-brand A, B and C). It was found that the innovator brand and brand B were within the standard range of dissolution test, content uniformity, and assay. Percent dissolution of brand A was much lower than standard values (17.7, 25.0, 29.4 at 30, 60 and 120 minutes, respectively). In contrast to brand C, percent dissolution was 77.1, 78.7 and 76.7 at 30, 60 and 120 minutes, respectively. This result showed that brand C was not formulated to be the extended form. Furthermore, the content uniformity and the assay of brand C were over the pharmacopoeia specification. This result revealed that phenytoin capsules available in Thailand did not have homogeneous pharmaceutical equivalence.

Three phenytoin brands, Dilantin®, brand A and brand B were selected for pharmacokinetic and bioavailability studies. The study was carried out in 16 healthy male Thai volunteers with the average age of 21 years old. A single oral dose of 300 mg (three capsules of 100-mg) phenytoin was given with 180 ml of water, following an 8-hour overnight fast. The tested drugs were given in a single blind randomized crossover fashion with at least 2 weeks for washout period. Venous blood samples of approximately 5 ml were drawn before medication and at 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hours, post dosing. Plasma were separated and phenytoin was analyzed by HPLC.

The results revealed that pharmacokinetic parameters from an innovator brand(Dilantin®),i.e., Vd/F, first-order absorption rate constant (K01), first-order elimination rate constant (K10), first-order absorption half-life (K01-HL), first-order elimination half-life (K10-HL), the maximum concentration (Cmax) and time to peak plasma concentration (Tmax) were 175.18 L, 0.26 h^{-1}, 0.2 h^{-1}, 5 hours, 19 hours, 1.98 μg/ml and 9.6 hours, respectively. Comparative bioavailability study indicated that two local brands of phenytoin (brand A, B) capsules were inequivalent to the innovator, Dilantin®, in the extent of drug absorption (AUC_{0-24}). Brand C was excluded from *in vivo* study because it had different dissolution pattern.

Since phenytoin has a narrow therapeutic window (10-20 μg/ml) and zero-order kinetics, if seizures can be controlled by one phenytoin brand, changing to other brand should be avoided without any necessity.