Preliminary Report

Effect of Doses on the Bioavailability of Phenytoin from a Prompt-Release and an Extended-Release Preparation: Single Dose Study

Noppamas Rojanasthien MD*, Nuchanart Chaichana PhD*,
Supanimit Teekachunhatean MD*, Boonyium Kumsorn MS*,
Chaichan Sangdee PhD*, Siwaporn Chankrachang MD**

** Department of Pharmacology, Faculty of Medicine, Chiang Mai University, Chiang Mai*
*** Department of Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai*

Objective: *To determine the effect of doses on the bioavailability of a prompt-release and an extended-release phenytoin capsule after given as single doses.*
Material and Method: *Eight healthy male volunteers were given single oral doses of 100, 200, and 300 mg of a prompt-release preparation (Ditoin®) and an extended-release phenytoin (Dilantin Kapseals®) preparation in a crossover design with a two weeks washout period after an overnight fast. Serial blood samples were collected over 72 h post-dose. Plasma phenytoin concentrations were determined by HPLC and pharmacokinetic parameters were analyzed by non-compartmental model.*
Results: *Rate of phenytoin absorption from the prompt-release preparation was more prolonged after the 300-mg dose (T_{max} 4.5 h) than those of the 100- and 200-mg doses (T_{max} 3.5 and 3 h, respectively). Similarly, the T_{max} of the 200- and the 300-mg extended-release preparation (5.5 and 4 h) were more prolonged than the 100-mg dose (3 h). Bioequivalence analysis showed that the C_{max} of all doses of the prompt-release preparation were higher than those values of the extended-release preparation with the mean C_{max} ratio (90% CI) of 1.32 (1.24-1.40), 1.26 (1.14-1.40), and 1.29 (1.10-1.51) for the 100-, 200- and 300-mg doses, respectively. The extent of absorption ($AUC_{0-\infty}$) of 100-mg phenytoin was bioequivalent between the two preparations [mean AUC ratio (90% CI) of 1.15 (1.11-1.18)], however, for higher doses, the prompt-release products produced higher bioavailability than the extended-release products [mean AUC ratio (90% CI) of 1.19 (1.07-1.33) and 1.17 (0.98-1.38), respectively for the 200- and 300-mg doses]. The difference in the bioavailability did not affect the elimination of phenytoin and their half-lives were comparable (11-13 h).*
Conclusion: *The bioavailability of phenytoin from both preparations increased proportionally over the dose range of 100-300 mg, however, the bioavailability of the prompt-release preparation was higher than the corresponding doses of the extended-release product.*

Keywords: *Phenytoin, Bioavailability, Single-dose*

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Phenytoin is a commonly used anti-epileptic drug. It is a weak organic acid with a high p*K*a and is poorly soluble in water[1]. Oral phenytoin preparations are available as free acid in suspension and chewable tablet, whereas phenytoin capsule contains the sodium salt form. Although the salt form is readily soluble in water, little absorption occurs in the stomach where the pH is acidic and phenytoin is precipitated. The absorption of phenytoin begins as the drug enters the duodenum where the pH is more alkaline and then slows down as the drug enters the jejunum and ileum[1]. Due to its limited solubility, the absorption rate of pheny-

Correspondence to : Rojanasthien N, Department of Pharmacology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. Phone: 053-945-359, Fax: 053-217-144, E-mail: nrojanas@mail.med.cmu.ac.th

toin is prolonged and secondary peak may be seen. In addition, its bioavailability could be less than 100% for patients with rapid gastrointestinal transit times[2]. The rate and the amount of phenytoin absorbed are dose dependent and its absorption may be saturated[1,3]. Jung et al[4] investigated the dose-proportionality of phenytoin after single high doses of 400, 800, and 1600 mg in healthy volunteers. Results showed that the time to reach the peak concentrations (T_{max}) increases from 8.4 hours for the 400-mg dose to 13.2 hours and 31.5 hours for the 800- and 1,600-mg dose, respectively. Furthermore, the maximal plasma concentrations (C_{max}) after single oral doses of 400-, 800- and 1,600-mg phenytoin are 3.9, 5.7 and 10.7 mg/ml, respectively, while a 1,600-mg dose administered in divided doses achieves the C_{max} at a higher level of 15.3 μg/ml[4].

In addition to the characteristic limitation in solubility of phenytoin, factor that affects bioavailability and rate of phenytoin absorption is the difference in pharmaceutical factors of oral formulations. Both prompt-release and extended-release oral formulations of phenytoin sodium are commercially available. Formulation-related differences in phenytoin dissolution rates may result in significantly altered absorption rate such as T_{max} for extended-release preparations that can range from 4-12 hours as contrast to prompt-release formulation with a more rapid rate of absorption of 1.5-3 hours[5]. However, at higher doses or when loading doses are employed, the absorption rate of phenytoin is slow and results in delayed peak concentrations of 3-12 hours[2,6]. The steady-state levels of phenytoin in plasma for fast-release dosage forms are 2-3 μg/mL higher than that of the slow-release formulations[7] and the bioavailability of a slow-release preparation is only 80% compared with a fast-release product[8].

To achieve therapeutic concentrations in adults, phenytoin is generally maintained as a single or divided daily dose of 100-300 mg. Since the extent and the rate of absorption from prompt-release and extended-release formulations are different, switching between the two products will alter their pharmacokinetics and may cause either toxicity or lack of therapeutic effects. Theoretically, the two preparations may not be used interchangeably, but in practice, their characteristic absorption profiles at therapeutic dose range have never been compared. Therefore, the present study aimed to investigate the effect of doses (therapeutic doses) on the bioavailability of two preparations, a prompt-release and an extended-release phenytoin after single oral dose administration in healthy male volunteers

Material and Method

Drug formulations

1. Prompt-release product; Ditoin® 100 mg (Atlantic Laboratories Corp., Ltd., Bangkok, Thailand, Lot. PD 021044 lox).

2. Extended-release product; Dilantin Kapseals® 100 mg (Warner-Lambert, Inc., Fajardo, Puerto Rico under the authorization of Parke Davis, NJ, USA, imported by Warner Lambert Ltd. (Thailand), Lot. 03752 F).

Study design and method

Eight healthy male volunteers with an average age of 31.4 ± 7.9 years old and body mass index ranged from 19.3-25 kg/m^2 were enrolled. All were non-smokers and were in good health as determined by medical history, physical examination, and routine laboratory tests. No other drugs were allowed 1 month before and during the study period to avoid the effects of drug interactions. After giving written informed consent, volunteers were enrolled to the present study, which consisted of six single-dose drug administrations with a 2-week washout period. Dosage of the study drug started from 1 capsule x 100 mg (100 mg) to 2 capsules x 100 mg (200 mg), then 3 capsules x 100 mg (300 mg). On the study day, a single dose of 1, 2 or 3 of 100-mg phenytoin capsules (either the prompt-release or the extended-release product then cross over to another brand after washout period) was administered with 240-mL water. Thereafter, volunteers remained in the upright position and fasted for 2 h. Water, lunch, and dinner were served at 2, 4, and 10 h after dosing, respectively. Blood samples (5 mL each) were collected before the dose and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 15, 24, 36, 48, and 72 h thereafter. Plasma samples were immediately frozen at -20□C until assay. Volunteers refrained from drinking caffeine-containing beverages and the vital signs were routinely monitored. The same study procedures were repeated as well as identical meals and fluid were served at each study period.

HPLC analysis of plasma samples

Phenytoin plasma concentrations were determined by HPLC method modified from two publications[9,10]. Briefly, the HPLC system consisted of an isocratical pump (LC-10AS), degasser (DUG-3A), UV detector (SPD-10A), integrator communication bus module (CMB-10A), column oven (CTO-10A) and auto-injector (SIL-10Ai). After solid phase extraction (Strata® 50 μm C18-E 100 mg/mL, Phenomenex, USA), the separation was performed at 55°C on an analytical column

(Inersil® C8, 5 μm 4.6 x 150 mm, GL Sciences, Japan) coupled with a guard column (Inersil® C8, 5 μm 4.6 x 10 mm, GL Sciences, Japan). The mobile phase was a mixture of 10 mM potassium dihydrogen phosphate (pH 5.9): methanol (50: 42 v/v). Carbamazepine was used as an internal standard (IS). The retention time for phenytoin and IS were approximately 10.0 and 11.7 min, respectively. The linear regression analysis between phenytoin concentrations and the peak height ratios of the drug and the IS over the determination range of 0.1-20 μg/ml gave the correlation coefficients of 0.999 or better. Within-run accuracy and precision were determined using five aliquots each of three levels of control sample and single calibration curve-run concurrently. The data of five different days in the same study manner were calculated for between-run assay validation. The precision (% CV) of within-run and between-run were 1.71% and 7.58%, respectively. The mean recovery of phenytoin and the IS were 95.74% and 89.33%, respectively.

Pharmacokinetic parameters measurement

Peak phenytoin plasma concentrations (C_{max}) and time to peak concentrations (T_{max}) were obtained directly from the observed data. The phenytoin pharmacokinetic parameters were calculated using non-compartmental analysis. The calculation was performed using TopFit, a pharmacokinetic data analysis program for PC[11]. The slope of the terminal log-linear portion of the concentration-time curve was determined by least-squares regression analysis and used as the elimination rate constant (K_e). The plasma half-life ($t_{1/2}$) was calculated as $0.693/K_e$. The area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable point (Ct) (AUC_{0-t}) was calculated using the trapezoidal rule. Extrapolated AUC from Ct to infinity ($AUC_{t-\infty}$) was determined from Ct/K_e. Total $AUC_{0-\infty}$ was the sum of $AUC_{0-t} + AUC_{t-\infty}$.

Statistical analysis

Bioavailability of the prompt-release Ditoin® (Test) and the extended-release Dilantin Kapseals® (Reference) was assessed by means of analysis of variance (ANOVA) and calculated the standard 90% confidence interval (90% CI) and coefficient of variation (%CV) for the ratio Test/Reference of $AUC_{0-\infty}$ as well as C_{max} values after logarithmically (ln) transformed data[12]. The 90% CI of 0.80-1.25 for the ratios Test/Reference of the average C_{max} and $AUC_{0-\infty}$ were accepted as bioequi- valence interval. Dose-proportionality with respect to $AUC0_{-\infty}$ and Cmax were analyzed in the same manner after dose-normalized and ln-transformed data from the three doses. Dose-linearity was determined using linear regression analysis and coefficient of determination (R^2) for the C_{max} and $AUC_{0-\infty}$. A p-value of less than 0.05 was considered significant.

Results

Individual plasma-concentration time curves of phenytoin after single oral administrations of 100-, 200-, and 300-mg doses of the prompt-release and the extended-release phenytoin as well as their mean values are depicted in Fig. 1-3, respectively. Fig. 4A and B depicted dose-linearity of Ditoin® and Dilantin Kapseals® with regard to the AUC and C_{max}, respectively. Phenytoin pharmacokinetic parameters (mean $\pm$ SD) of the two preparations are shown in Table 1A-C for 100-, 200-, and 300-mg doses, respectively. Table 2 demonstrates the mean (90%CI) of the ration of the C_{max} and AUC between the two preparations.

Absorption of phenytoin after oral administration was slow and the T_{max} after different doses were variable. The median values of T_{max} were 3.5 h (range 2-6 h) and 3.0 h (range 2-4 h) for 100 mg of the prompt-release and the extended-release phenytoin, respectively. The T_{max} of 200-mg the prompt-release was 3.0 h (range 1.5-6 h), however, was prolonged to 5.5 h (range 2-15 h) for 200-mg the extended-release phenytoin. The T_{max} of 300-mg the prompt-release and the extended-release phenytoin were not much different (4.5 h, range 3-12 h and 4.0 h, range 1.5-15 h, respectively). The average $t_{1/2}$ of phenytoin were comparable at each dose of the two preparations, being 12.65 vs. 12.88 h, 12.53 vs. 11.03 h and 13.04 vs. 13.17 h for 100-, 200-, and 300-mg the prompt-release and the extended-release phenytoin, respectively. The elimination profiles (Fig. 3) were comparable for each of the matched doses of the two preparations as indicated by the almost-parallel decline in the elimination phase and comparable $t_{1/2}$ values.

The mean C_{max} of phenytoin after 100-, 200- and 300-mg oral doses of the prompt-release preparation were 2.12 ± 0.34, 3.88 ± 0.88, and 5.31 ± 1.11 mcg/mL, respectively, while the corresponding values were lower for the extended-release phenytoin being 1.62 ± 0.33, 3.05 ± 0.51, and 4.17 ± 1.18 mg/mL, respectively. The C_{max} ratio for the prompt-release/the extended-release phenytoin were 1.32, 1.27, and 1.31, corresponded to the bioequivalence assessment that showed the mean C_{max} ratio (90% CI) of 1.32 (1.24-1.40), 1.26 (1.14-1.40), and 1.29 (1.10-1.51) for 100-, 200-, and 300-mg doses, respectively. Since the upper limits of the 90% CI of

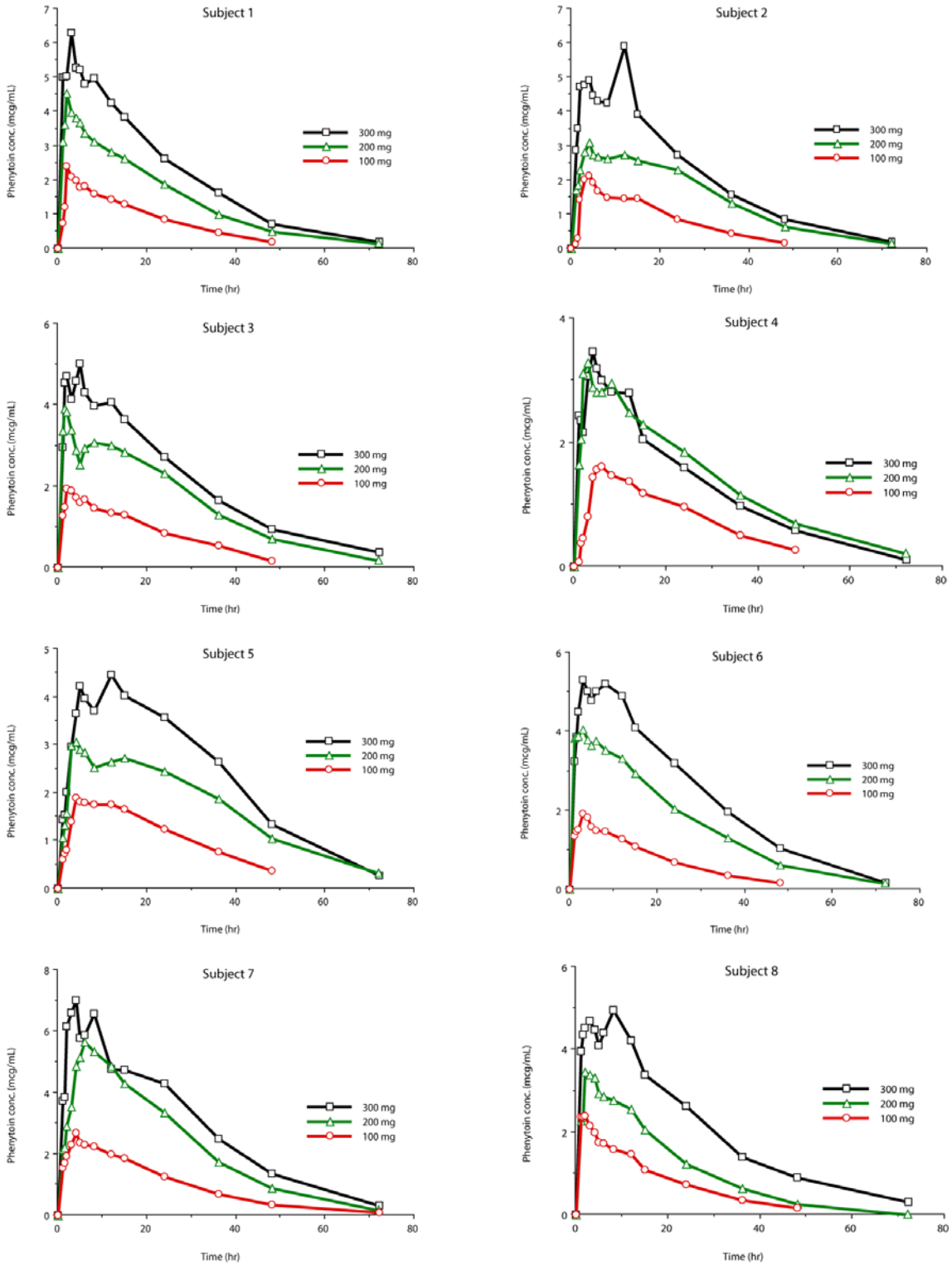

Fig. 1 Plasma concentration-time curves of individual subject after single oral administration of 100-, 200- and 300-mg of the prompt-release phenytoin, respectively

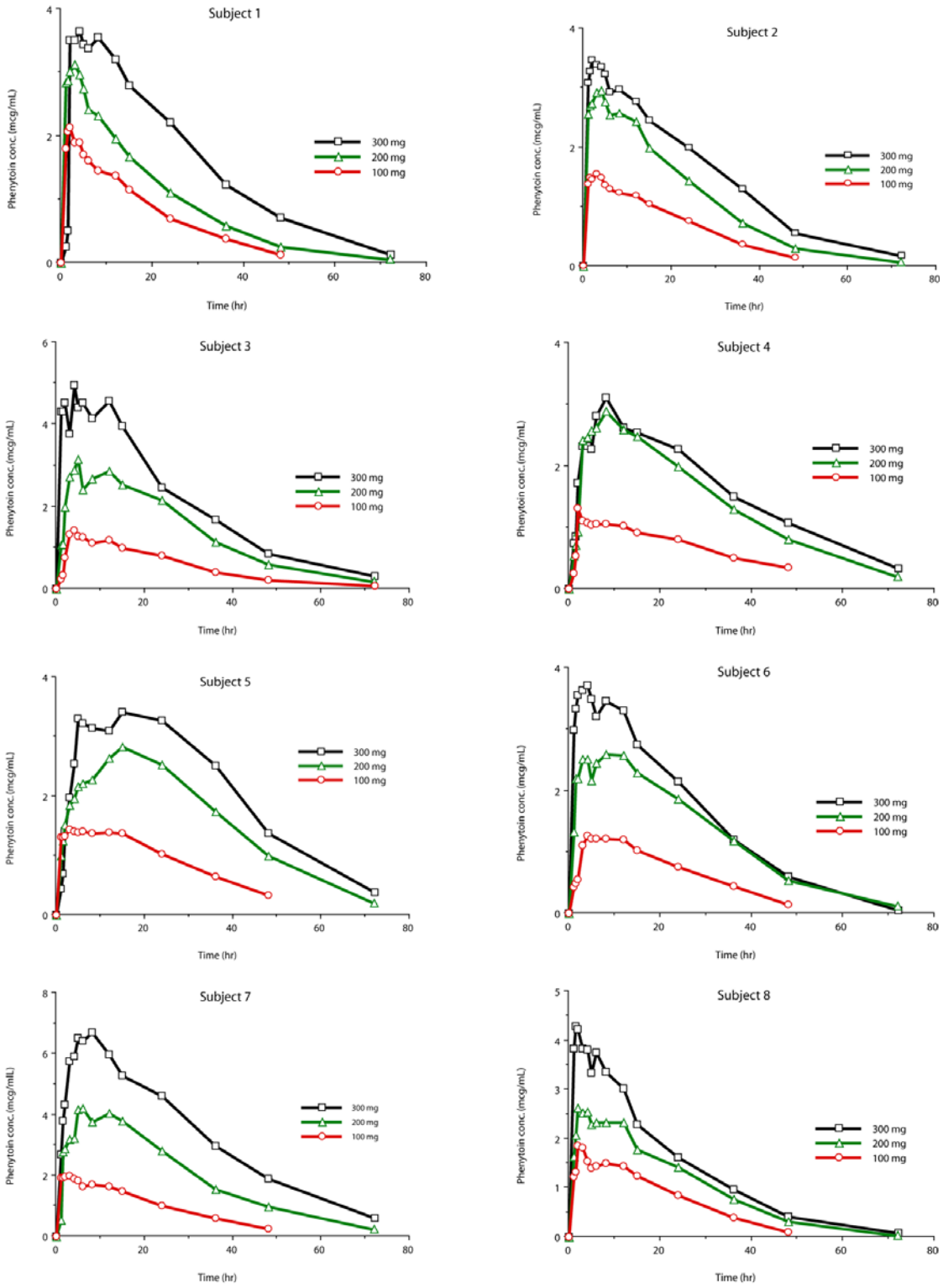

Fig. 2 Plasma concentration-time curves of individual subject after single oral administration of 100-, 200- and 300-mg of the extended-release phenytoin, respectively

Table 1A. Comparison of phenytoin pharmacokinetic parameters after oral administration of 100 mg Ditoin® (T) and Dilantin Kapseals® (R)

	C_{max} (mcg/mL)		F_{rel}	AUC (mcg.hr/mL)		F_{rel}	T_{max} (hr)		$T_{1/2\beta}$ (hr)	
	T	R		T	R		T	R	T	R
S1	2.40	2.13	1.13	48.30	42.78	1.13	2.00	2.00	12.00	10.90
S2	2.13	1.55	1.37	46.24	39.13	1.18	4.00	3.00	10.50	11.70
S3	1.95	1.42	1.37	47.18	39.93	1.18	2.00	4.00	11.60	14.60
S4	1.62	1.31	1.24	46.72	43.30	1.08	6.00	2.00	15.00	18.20
S5	1.89	1.44	1.31	63.40	54.51	1.16	4.00	3.00	15.30	16.10
S6	1.91	1.27	1.50	41.32	36.49	1.13	3.00	4.00	12.50	9.83
S7	2.68	1.98	1.35	68.91	55.77	1.24	4.00	3.00	12.50	12.90
S8	2.39	1.85	1.29	45.28	42.36	1.07	2.00	2.00	11.80	8.82
Mean	2.12	1.62	1.32	50.92	44.28	1.15	3.50*	3.00*	12.65	12.88
SD	0.34	0.33	0.11	9.74	7.07	0.06	1.41	0.83	1.67	3.22

* Median

Table 1B. Comparison of phenytoin pharmacokinetic parameters after oral administration of 200 mg Ditoin® (T) and Dilantin Kapseals® (R)

	C_{max} (mcg/mL)		F_{rel}	AUC (mcg.hr/mL)		F_{rel}	T_{max} (hr)		$T_{1/2\beta}$ (hr)	
	T	R		T	R		T	R	T	R
S1	4.55	3.13	1.45	104.12	66.53	1.57	2.00	3.00	12.80	10.60
S2	3.10	2.95	1.05	105.68	76.91	1.37	4.00	4.00	12.00	10.30
S3	3.92	3.15	1.24	115.62	100.42	1.15	1.50	5.00	12.70	12.80
S4	3.29	2.89	1.14	101.96	102.61	0.99	3.00	8.00	15.20	14.00
S5	3.07	2.83	1.08	126.45	115.60	1.09	4.00	15.00	14.10	11.10
S6	4.05	2.60	1.56	116.99	91.62	1.28	3.00	8.00	11.20	10.50
S7	5.66	4.22	1.34	162.13	142.03	1.14	6.00	6.00	10.90	13.30
S8	3.46	2.63	1.31	74.58	70.81	1.05	2.00	2.00	11.30	5.60
Mean	3.88	3.05	1.27	113.44	95.82	1.21	3.00*	5.50*	12.53	11.03
SD	0.88	0.51	0.18	24.92	25.22	0.19	1.46	4.10	1.51	2.61

* Median

Table 1C. Comparison of phenytoin pharmacokinetic parameters after oral administration of 300 mg Ditoin® (T) and Dilantin Kapseals® (R)

	C_{max} (mcg/mL)		F_{rel}	AUC (mcg.hr/mL)		F_{rel}	T_{max} (hr)		$T_{1/2\beta}$ (hr)	
	T	R		T	R		T	R	T	R
S1	6.30	3.65	1.73	152.49	111.69	1.37	3.00	4.00	12.10	11.40
S2	5.93	3.46	1.72	154.04	106.43	1.45	12.00	2.00	12.80	13.50
S3	5.03	4.96	1.01	155.50	153.69	1.01	5.00	4.00	17.00	15.90
S4	3.46	3.12	1.11	91.59	120.58	0.76	4.00	8.00	12.30	17.20
S5	4.46	3.41	1.31	172.56	156.13	1.11	12.00	15.00	11.00	13.20
S6	5.32	3.72	1.43	168.38	109.33	1.54	3.00	4.00	10.90	7.14
S7	7.02	6.71	1.05	211.82	247.61	0.86	4.00	8.00	12.70	16.20
S8	4.95	4.29	1.15	149.37	96.97	1.54	8.00	1.50	15.50	10.80
Mean	5.31	4.17	1.31	156.97	137.80	1.20	4.50*	4.00*	13.04	13.17
SD	1.11	1.18	0.29	33.26	49.41	0.31	3.81	4.42	2.14	3.34

* Median

Table 2. The mean (90%CI) of the ratio of the C_{max} and AUC of Ditoin (T) and Dilantin Kapseals® (R)

Dose mg	C_{max} mcg/mL		Mean (90% CI) of C_{max}	AUC mcg.h/mL		Mean (90% CI) of AUC
	T	R	BE range 0.80-1.25	T	R	BE range 0.80-1.25
100	2.12	1.62	1.32 (1.24-1.40)	50.92	44.28	1.15 (1.11-1.18)
200	3.88	3.05	1.26 (1.14-1.40)	113.44	95.82	1.19 (1.07-1.33)
300	5.31	4.17	1.29 (1.10-1.51)	156.97	137.80	1.17 (0.98-1.38)

Ditoin	Mean (90% CI) of C_{max}	Ditoin	Mean (90% CI) of AUC
$\frac{200}{100}$	0.91 (0.81-1.02)	$\frac{200}{100}$	1.11 (0.99-1.24)
$\frac{300}{100}$	0.83 (0.76-0.90)	$\frac{300}{100}$	1.02 (0.87-1.19)
Dilantin		Dilantin	
$\frac{200}{100}$	0.95 (0.84-1.08)	$\frac{200}{100}$	1.06 (0.92-1.23)
$\frac{300}{100}$	0.85 (0.71-1.01)	$\frac{300}{100}$	1.00 (0.88-1.14)

C_{max} ratios were above the limit of 1.25, it is suggested that the rate of the prompt-release absorption is higher than that of the extended-release phenytoin. The intra-subject C_{max} coefficient of variations (% CV) estimated from S^2 of the ANOVA was 6%, 11%, and 16% with respect to 100-, 200-, and 300-mg doses.

The extent of phenytoin absorption represented by the $AUC_{0-\infty}$ of 100-, 200-, and 300-mg the prompt-release (50.92 ± 9.74, 113.44 ± 24.92, and 156.97 ± 33.26 mcg.h/ml, respectively) were higher than the corresponding values of the extended-release phenytoin (44.28 ± 7.07, 95.82 ± 25.22, and 137.80 ± 49.41 µg.h/mL, respectively). The bioequivalence test revealed that the mean $AUC_{0-\infty}$ ratio (90% CI) of 1.15 (1.11-1.18), 1.19 (1.07-1.33), and 1.17 (0.98-1.38) for 100-, 200-, and 300-mg doses, respectively. Stated differently, the relative bioavailability of 100-, 200-, and 300-mg Dilantin Kapseals were 88%, 85%, and 89% of Ditoin, respectively. The intra-subject%CV of the $AUC_{0-\infty}$ estimated from S^2 obtained from the ANOVA were 3%, 11%, and 18% for the 100-, 200-, and 300-mg doses, respectively. These low%CV of $AUC_{0-\infty}$ were similar to those values of C_{max}.

The values of $AUC_{0-\infty}$ and C_{max} were dose normalized to the 100-mg dose, and analysis of variance was then preformed on a ln-transformed data. The mean (90% CI) ratio $\frac{200}{100}$ of mg and $\frac{300}{100}$ mg Ditoin for $AUC_{0-\infty}$ were 1.11 (0.99-1.24) and 1.02 (0.87-1.19) and for C_{max} were 0.91 (0.81-1.02) and 0.83 (0.76-0.90), respectively. The corresponding values for the extended-release phenytoin were 1.06 (0.92-1.23), 1.00 (0.88-1.14) and 0.95 (0.84-1.08), 0.85 (0.71-1.01), respectively (Table 2). The results showed no statistically significant dose effect for the dose-normalized $AUC_{0-\infty}$ and C_{max} indicating dose-proportionality for these parameters. Furthermore, intra-individual linear regression analysis also demonstrated dose-linearity for $AUC_{0-\infty}$ and C_{max} (R^2 ranged from 0.914 to 0.999), except volunteers No. 4 whose R^2 for $AUC_{0-\infty}$ of Ditoin was 0.833. The average R^2 were 0.9958 vs. 0.9986 and 0.9924 vs. 0.9934 for the $AUC_{0-\infty}$ and C_{max} of Ditoin vs. Dilantin Kapseals (Fig. 4A, B). The T_{max} values were variable among doses and the prolonged in T_{max} at higher doses were not dose-related (R^2 average 0.751, ranged 0.216 to 0.853 for Ditoin and average 0.644, range 0.280 to 0.996 for Dilantin Kapseals (data not shown).

Discussion

Phenytoin were prepared as prompt-release

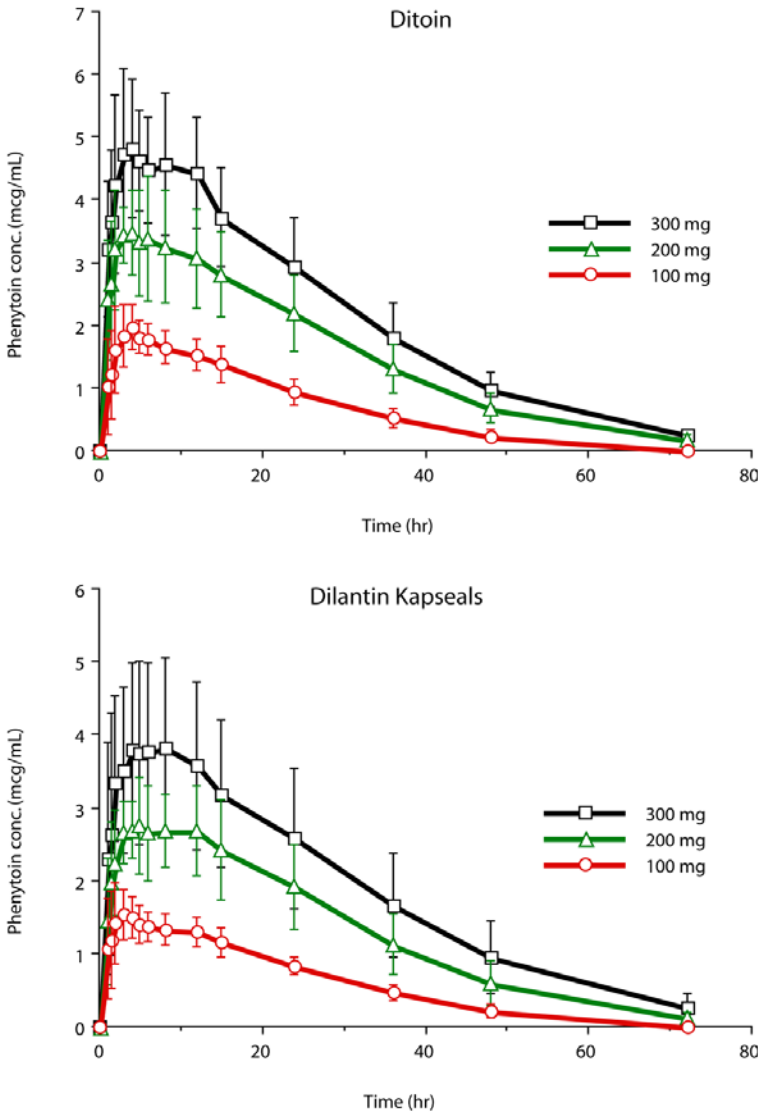

Fig. 3 Mean plasma concentration-time curves after single oral administrations of 100-, 200- and 300-mg Ditoin® and Dilantin Kapseals®, respectively

and modified-release preparations. The modified-release form may be suitable for once-a-day dosage in adults, if seizure control is established with divided doses[13]. Once-a-day dosage increases patient compliance and offers a convenience to the nursing personnel. The pharmacokinetic profiles of phenytoin prepared either as prompt-release or modified-release preparations, are different in many ways. As to be expected, various single doses of the prompt-release phenytoin in the present study (100, 200, and 300 mg) produced higher C_{max} and $AUC_{0-\infty}$ but shorter T_{max} than did the corresponding doses of the extended-release preparation. Their $T_{1/2}$ were comparable, which is not surprising since the present study was a crossover one and the elimination characteristic in general, is not affected by the drug preparation. The 100 mg of the prompt-release capsule was bioequivalent to the same strength of the extended-release phenytoin only in terms of the $AUC_{0-\infty}$ ratio but not of the C_{max} ratio or T_{max} difference. Since it was not feasible to collect plasma samples in shorter paces than what the authors did in the present study, C_{max} and T_{max}, which were

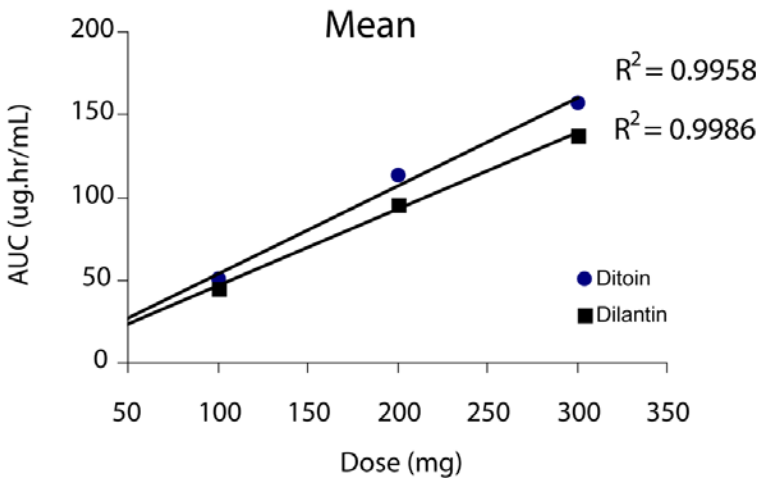

Fig. 4A Linear regression analysis of areas under the concentration time curves for dose-linearity of Ditoin® and Dilantin Kapseals®

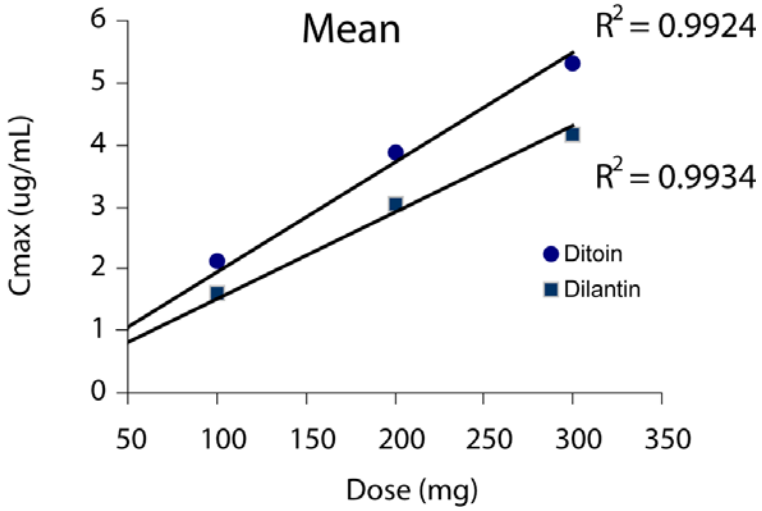

Fig. 4B Linear regression analysis of maximal plasma concentrations for dose-linearity of Ditoin® and Dilantin Kapseals®

monitored at specific time points, could, therefore, be more variable than AUC which was a parameter that covered the whole time cycle of its pharmacokinetics. However, phenytoin is intended for chronic use, C_{max} will be of significance only if it overshoots the therapeutic range and T_{max} will be much less important, since it will take 4-5 half-lives for phenytoin levels to reach steady-state no matter what the T_{max} is. It is, therefore, conceivable that the prompt-release may be used interchangeably with the extended-release preparation but plasma phenytoin levels should be monitored frequently in the early months of epileptic treatment.

From the results of the present study, the mean C_{max} and $AUC_{0-\infty}$ of 100, 200 and 300 mg phenytoin increased proportionally to the dose administrations. Nonetheless, the ranges of T_{max} were prolonged at higher doses (range 2-6, 1.5-15, and 1.5-15 h for 100, 200, and 300 mg single doses of phenytoin, respectively). Both preparations of phenytoin in the present study showed zero order absorption at higher doses since the drug was more slowly absorbed and consequently resulted in prolonged T_{max} which resemble the results reported previously[3-4]. Although zero-order elimination of phenytoin in the prompt-release and the

extended-release preparations was not encountered when given as single low doses (100-200 mg), it became apparent in certain subjects receiving 300-mg single dose. Therefore, caution should be exercised when high doses of phenytoin either as the prompt-release or the extended-release preparation are prescribed as single dose since plasma concentrations may be lower than expected. Moreover, because of non-linear elimination, additional multiple-doses studies may be required to demonstrate phenytoin bioavailability[14,15].

Although the prompt-release and the extended-release phenytoin preparations demonstrated the dose-proportionality of the bioavailability after oral administrations over the dose range of 100-300 mg, in the present study, the bioavailabilities of each dose of the prompt-release product were higher than the corresponding doses from the extended-release preparation. The reason that the prompt-release product had higher bioavailability in the present study may be due to better dissolution and higher release rate, thus resulting in a better absorption and higher bioavailability. There is also a potential for incomplete drug release from a slow-release phenytoin formulation throughout the gastrointestinal pH range and results in an incomplete absorption especially at higher doses[16]. Because a prompt-release product is potentially more bioavailable than an extended-release one, this preparation should be suitable for oral loading dose administration in patients who required rapid steady-state serum level and where intravenous administration is not desirable.

In conclusion, it is recommended that careful monitoring of phenytoin serum levels should be carried out, when a change in the dosage form or brand is prescribed to ensure that therapeutic concentrations are achieved and to avoid unexpected toxicity.

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ผลของขนาดยาต่อชีวปริมาณออกฤทธิ์ของยาเฟนิโทอินแคปซูลที่เตรียมแบบออกฤทธิ์เร็วและออกฤทธิ์เนิ่นเมื่อศึกษาโดยการให้ยาครั้งเดียว

นพมาศ โรจนเสถียร, นุชนารถ ชัยชนะ, ศุภนิมิต ทีฆชุณหเถียร, บุญเยี่ยม คำสอน, ชัยชาญ แสงดี, ศิวาพร จันทร์กระจ่าง

วัตถุประสงค์: *เพื่อศึกษาผลของขนาดยาต่อชีวปริมาณออกฤทธิ์ของยาเฟนิโทอินแคปซูลที่เตรียมแบบออกฤทธิ์เร็วและออกฤทธิ์เนิ่นหลังจากให้ยาครั้งเดียว*

วัสดุและวิธีการ: *อาสาสมัครชายสุขภาพดี 8 รายได้รับยาเตรียมเฟนิโทอินแบบออกฤทธิ์เร็ว (ไดโทอิน®) และออกฤทธิ์เนิ่น (ไดแลนตินแคพซิล®) ครั้งเดียวในขนาด 100, 200, และ 300 มก. แบบสลับไขว้ โดยเว้นระยะเวลาระหว่างช่วงการศึกษา 2 สัปดาห์ หลังจากงดน้ำและอาหาร ทำการเก็บตัวอย่างเลือดก่อนและหลังจากได้รับยา เป็นระยะเวลานาน 72 ชั่วโมง เพื่อนำไปวัดความเข้มข้นของเฟนิโทอินในพลาสมาด้วยวิธีการของโครมาโตกราฟีสมรรถนะสูง และวิเคราะห์ค่าตัววัดทางเภสัชจลนศาสตร์แบบ non-compartment*

ผลการศึกษา: *อัตราการดูดซึมของเฟนิโทอินจากยาเตรียมแบบออกฤทธิ์เร็วในขนาด 300 มก. (ระยะเวลาที่ความเข้มข้นในพลาสมาสูงสุด, T_{max} = 4.5 ชั่วโมง) จะนานกว่าขนาด 100 และ 200 มก. (T_{max} = 3.5 และ 3 ชั่วโมง ตามลำดับ) ในทำนองเดียวกัน T_{max} ของยาเตรียมแบบออกฤทธิ์เนิ่นขนาด 200 และ 300 มก. (5.5 และ 4 ชั่วโมง) จะนานกว่าขนาด 100 มก. (3 ชั่วโมง) การวิเคราะห์ชีวสมมูลพบว่าความเข้มข้นสูงสุดในพลาสมา (C_{max}) ที่เกิดจากทุกขนาดของยาเตรียมเฟนิโทอินแบบออกฤทธิ์เร็วมีค่าสูงกว่าค่า C_{max} ของยาเตรียมแบบออกฤทธิ์เนิ่น โดยมีค่าเฉลี่ย [ช่วงความเชื่อมั่น 90% (90% CI)] เท่ากับ 1.32 (1.24-1.40), 1.26 (1.14-1.40), และ 1.32 (1.10-1.51) สำหรับขนาด 100, 200, และ 300 มก. ตามลำดับ ปริมาณการดูดซึม ($AUC_{0-\infty}$) ของเฟนิโทอินในขนาด 100 มก. ของยาเตรียมทั้งสองแบบมีชีวสมมูลกัน (1.15, 90% CI 1.11-1.18) อย่างไรก็ตาม ยาเตรียมแบบออกฤทธิ์เร็วในขนาดสูงขึ้นจะให้ค่าชีวปริมาณออกฤทธิ์สูงกว่ายาเตรียมที่ออกฤทธิ์เนิ่น (1.19, 90% CI 1.07-1.33 และ 1.17, 90% CI 0.98-1.38 สำหรับขนาด 200 และ 300 มก ตามลำดับ) ความแตกต่างกันของชีวปริมาณออกฤทธิ์ไม่มีผลกระทบต่อการกำจัดเฟนิโทอินและค่าครึ่งชีวิตของเฟนิโทอินจากยาเตรียมทั้งสองแบบซึ่งมีค่าใกล้เคียงกัน (11-13 ชั่วโมง)*

สรุป: *ชีวปริมาณออกฤทธิ์ของเฟนิโทอินจากยาเตรียมทั้งสองแบบเพิ่มขึ้นเป็นสัดส่วนกับขนาดยา 100-300 มก. อย่างไรก็ตามชีวปริมาณออกฤทธิ์ของเฟนิโทอินจากยาเตรียมแบบออกฤทธิ์เร็วมีค่าสูงกว่ายาเตรียมแบบออกฤทธิ์เนิ่นในขนาดเดียวกันทุกขนาดที่ศึกษา*