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The bioequivalence study of oral gabapentin 300 mg capsule

Supeecha Wittayalertpanya* Sumana Chompootaweep*
Yavarat Hinsui* Pajaree Lilitkarntakul*

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Background : *Gabapentin is an antiepileptic drug with the structure similarity to GABA. Gabapentin provides notable benefit, reducing seizure frequency in patients with partial seizures. A new product of gabapentin 300 mg has been developed. The bioequivalent data compared with the innovator's product is required in order to assure the quality and performance of the new generic product.*

Objective : *To compare the bioavailability of new generic product of oral gabapentin capsule manufactured by Unison Laboratories Co.,Ltd. with the innovator's product. The pharmacokinetic parameters of gabapentin in Thai subjects have been studied.*

Design : *Randomized, two-treatment, two-period, two-sequence, single dose crossover design.*

Setting : *Department of Pharmacology and Chula MRC Bioequivalence Center, Faculty of Medicine, Chulalongkorn University.*

* Department of Pharmacology, Faculty of Medicine, Chulalongkorn University

Materials and Methods : *The study was performed in 14 healthy Thai male volunteers. Each received a single oral dose of 300 mg gabapentin. Double blind randomized two-way crossover design was used with two weeks washout period between treatments. After drug administration, serial blood sample was collected over a period of 32 hours. Gabapentin plasma level was determined by the automated High Performance Liquid Chromatography (HPLC) with fluorescence detection after deproteinized with acetonitrile and derivatization with o-phthaldehyde (OPA) reagent containing 2-mercaptoethanol. The difference of phamacokinetic parameters, C_{max} and $AUC_{(0\text{-}inf)}$, were analyzed by Two Way Analysis of Variance (ANOVA) and 90 % confidence interval.*

Results : *The maximum concentration (C_{max}, μg/ml) of gabapentin was 3.04 ± 0.55 (range 2.16 - 4.04) and 3.26 ± 0.62 (range 2.48-4.52) μg/ml for generic and innovator' s product, respectively. The time to peak plasma gabapentin concentration (T_{max}, hr) of generic and innovator's product was 3.00 ± 0.68 (2.00 - 4.00) and 3.18 ± 0.80 (2.00 - 5.00), respectively. The area under the plasma concentration-time curve ($AUC_{(0\text{-}inf)}$, μg.hr/ml) was 28.48 ± 7.14 (15.03 - 42.98) and 29.81 ± 6.33 (20.88 - 44.15), respectively. The 90 % confidence interval of mean difference of C_{max} and $AUC_{(0\text{-}inf)}$ in term of log transformed data of generic to innovator's product were 82.80 - 104.61 % and 85.57-104.36 %, respectively. They were within the range of the acceptance criteria 80-125 %.*

Conclusions : *Gabapentin from the two formulations were bioequivalent.*

Keywords : *Gabapentin, Bioequivalence, HPLC.*

Reprint request : Wittayalertpanya S. Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

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เหตุผลของการทำวิจัย : *ยา gabapentin เป็นยาต้านชักที่มีลักษณะสูตรโครงสร้างคล้ายสารสื่อประสาท GABA ยามีประสิทธิภาพลดความถี่ของการเกิดอาการชักในผู้ป่วย partial seizure ชนิดต่าง ๆ ได้ ปัจจุบันบริษัทยาในประเทศได้ผลิตยาสามัญ gabapentin รูปแบบแคปซูลเหมือนยาต้นแบบ จึงต้องทำการศึกษาหาค่าชีวสมมูลของยาสามัญใหม่นี้เปรียบเทียบกับยาต้นแบบ เพื่อยืนยันถึงคุณภาพของยาอันจะเป็นประโยชน์ต่อผู้ใช้ยาต่อไป*

วัตถุประสงค์ : *เพื่อเปรียบเทียบชีวสมมูลของยาสามัญ gabapentin 300 มิลลิกรัม รูปแคปซูลให้โดยรับประทาน ที่ผลิตในประเทศ โดยบริษัท ยูนีซัน จำกัด เปรียบเทียบกับยาต้นแบบ และหาค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ ของยา gabapentin ในคนไทย*

รูปแบบการวิจัย : *การวิจัยแบบทดลองเชิงข้ามสองทางแบบสุ่ม*

สถานที่ทำการศึกษา : *ภาควิชาเภสัชวิทยา และศูนย์การศึกษาชีวสมมูล คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

ตัวอย่างและวิธีการศึกษา : *ทำการศึกษาในอาสาสมัครชายไทยสุขภาพดี 14 ราย ซึ่งแต่ละรายจะได้รับยา gabapentin 300 มิลลิกรัม รูปแคปซูลสำหรับรับประทานที่ผลิตในประเทศและที่เป็นยาต้นแบบ โดยใช้รูปแบบการศึกษาแบบสุ่มสลับข้างและ double-blind เว้นระยะห่างของการให้ยาเป็นเวลา 2 สัปดาห์ อาสาสมัครถูกเจาะเลือดที่เวลาก่อนและหลังรับประทานยาเป็นระยะ ๆ จนถึงเวลา 32 ชั่วโมง จากนั้นนำตัวอย่างพลาสม่ามาตกตะกอนโปรตีนด้วยอซีโทรไนไทล์ และทำการติดฉลากสารเรืองแสงด้วย OPA วัดระดับยา gabapentin ด้วยวิธี เอชพีแอลซี และใช้เครื่องฟลูออเรสเซนส์ตรวจวัด ทดสอบความแตกต่างของค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ ได้แก่ ค่าระดับยาในเลือดสูงสุด (C_{max}) พื้นที่ใต้กราฟความเข้มข้นของยากับเวลา (AUC_{0-inf}) ด้วย two way analysis of variance (ANOVA) และเปรียบเทียบบค่าเฉลี่ยที่ความเชื่อมั่นที่ 90 %*

ผลการทดลอง : ค่า C_{max} ของ gabapentin ของยาสามัญและยาต้นแบบมีค่าเท่ากับ 3.04 $\pm$ 0.55 (2.16 - 4.04) และ 3.26 $\pm$ 0.62 (2.48 - 4.52) ไมโครกรัม/มิลิลิตร ตามลำดับ ค่าเวลาที่ระดับยาในเลือดสูงสุด (T_{max}) ของยาสามัญและยาต้นแบบมีค่าเท่ากับ 3.00 $\pm$ 0.68 (2.00 - 4.00) และ 3.18 $\pm$ 0.80 (2.00-5.00) ชั่วโมง ตามลำดับ และค่า AUC_{0-inf} มีค่าเท่ากับ 28.48 $\pm$ 7.14 (15.03 - 42.98) และ 29.81 $\pm$ 6.33(20.88 - 44.15) ไมโครกรัม.ชั่วโมง/มิลลิลิตร ตามลำดับ เมื่อทดสอบความแตกต่างของค่าเฉลี่ยของค่า log C_{max} และ AUC_{0-inf} ที่ความเชื่อมั่น 90 % ระหว่างยาสามัญกับยาต้นแบบได้ค่าเท่ากับ 82.80 - 104.61 % และ 85.57 - 104.36 % ตามลำดับ ซึ่งค่าที่ได้อยู่ในช่วง 80 -125 % อันอยู่ในเกณฑ์ที่ยอมรับได้

สรุป : ยา gabapentin ที่ผลิตจาก 2 บริษัทมีชีวสมมูลเท่าเทียมกัน

คำสำคัญ : Gabapentin, ชีวสมมูล, เอชพีแอลซี

Gabapentin is an antiepileptic drug. Despite its structural similarity to g–aminobutyric acid (GABA), gabapentin apparently does not act via the mechanism related to this neurotransmitter, but most probably by events modulated through its interaction with a receptor thought to be associated with the L-system amino acid carrier protein.[1,2] The profile of its anticonvulsant activity in animal studies thus predicts its clinical efficacy in patients with partial seizures and secondarily generalized tonic-clonic seizures. Present clinical evaluation is largely restricted to proof of efficacy trials of gabapentin as add on therapy in patients with partial epilepsy resistant to conventional treatment. Gabapentin (usually 600 to 1800 mg/day) provides notable benefit, reducing seizure frequency by $\geq$ 50 % in 18 to 28 % of patients with refractory partial seizures. Overall, seizures frequency decreased by 18 to 32 % during 3-month treatment periods. Patients with complex partial seizures, and partial seizures secondarily generalized, are particularly likely to respond to gabapentin.[3]

Mean maximum plasma gabapentin concentrations are attained 2 to 3 hours after a single oral 300 mg dose, and measured 2.7 - 2.99 mg/L in healthy volunteers.[4] Absorption kinetics of gabapentin are dose-dependent, rather than dose-proportional, possibly due to a saturable transport system. Thus, bioavailability of a single 300 mg oral dose of gabapentin is 60 %, but decreases with increasing dose.[4,5] As demonstrated in rats, gabapentin is extensively distributed in body tissues, concentrating particularly in the pancrease and kidney. Unlike GABA, gabapentin has some lipophilicity and readiness to cross the blood-brain barrier, producing CSF: plasma concentration ratio of 0.09 to 0.14 as measured in 5 patients.[5-7] The volume of distribution is large, estimated as 50 to 60 L in healthy volunteers. The drug is not bound to human plasma protein.[5] Elimination of gabapentin is wholly accountable by renal clearance, in contrast to many antiepileptic drugs which are metabolized. The elimination half-life of gabapentin is about 5 to 7 hours after a single oral dose of 200 to 400 mg. As expected, renal impairment reduces drug clearance and augments plasma gabapentin concentrations in a linear fashion.[8]

The adverse events are mild. The most common are somnolence, fatigue, ataxia and dizziness, which have been reported in by about 75 % of gabapentin recipients. Other events such as tremor, diplopia, nausea and vomiting each of which is experienced by < 10 % of gabapentin recipients. The overall proportion of patients reporting adverse events during gabapentin administration has been calculated to be about 75 %, versus 55 % for placebo.[3]

Currently, only the innovator's product (Neurontin ®) containing gabapentin 300 mg is commercially available in Thailand. A new formulation of gabapentin 300 mg is developed at Unison Laboratories Co.,Ltd.,Thailand. The bioequivalent data of a new generic product compared with the innovator's product (reference product) is required in order to assure the quality and performance. Moreover, the pharmacokinetic parameters of gabapentin in Thai subjects have also been studied.

Materials and Methods

Materials

Test product:

Test drug-product of Gabapentin 300 mg capsule was used for *in vivo* the study of bioequivalency. One was the generic product of Unison Laboratories Co., Ltd. (Vultin ®) lot no. C01/2-027 and the other was innovator's product (Neurontin ®, Phizer)

lot no. 0054071.

Chemicals and Reagents

Gabapentin, 1-(amino-methyl) cyclohexane acetic acid, was supplied by Unison Laboratories Co., Ltd. Acetonitrile and methanol HPLC grade were obtained from MERK. o-Phthaldehyde (OPA), 2- mercaptoethanol and monobasic potassium phosphate HPLC grade were obtained from Sigma Chemical Co., Ltd. Boric acid and sodium hydroxide AR grade were purchased from MERCK.

Methods

Subjects:

The study has been approved by the Ethics Committee for Research of the Faculty of Medicine, Chulalongkorn University. Fourteen healthy Thai male volunteers aged between 18 - 45 years were recruited in the study. All subjects had normal body built with BMI between 18 -24, weighing within $\pm$ 10 % of ideal body weight. All of them were in good health as confirmed by physical and clinical laboratory examination including serology, hematology and biochemical test. Each subject had no history of allergy to gabapentin. They abstained from other drug intake and alcoholic consumption, two weeks prior to and throughout the study. Caffeine containing beverage was not allowed 3 days prior to and throughout the study. The method and condition of the study were clearly explained to all participants. Informed consent form was signed and obtained from each person prior to entering the experiment. At least eight weeks before the first treatment, they were not allowed to donate a unit of blood or to participated in any other clinical trial. Subjects with cigarette smoking, alcoholic and caffeine intake habit were excluded.

Study design:

The study was a randomized , two-treatment, two-period, two-sequence, single dose crossover design with two weeks of drug-free interval between the periods. The randomization result is shown in table 1. Each subject was told to fast for approximately eight hours prior to the study and randomly assigned to receive a single dose of 300 mg gabapentin with 200 ml of water. On the study day a standardized light lunch was given to each subject 4 hours after the blood sampling was taken. Blood samples were collected immediately before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 24 and 32 hours after drug intake. The plasma was separated by centrifugation and stored at – 70°C until analysis.

Table 1. The layout of study design.

SEQUENCE	No. of subject	PERIOD 1	PERIOD 2
1	5, 6, 7, 8, 11, 12, 13	Generic product	Innovator's product
2	1, 2, 3, 4, 9, 10, 14	Innovator's Product	Generic product

Analytical method

Sample preparation:

The 300 µl of plasma was mixed with 1,200 µl of acetonitrile on a vortex mixer for 30 second and centrifuged at 1,000 rpm for 5 minutes. The supernatant was transferred to an autosampler glass vial and derivatized with OPA by fully automation. 20 µl of derivatized sample was injected into HPLC system.

instruments and condition:

Chromatography was carried out at room temperature on a Shimadzu-HPLC system-10AD series. A reverse phase column 250 X 4.6 mm i.d., C18, 5 µm ODS guarded with an inersil ODS-3, 5 µm was used. The mobile phase consisted of 0.02 M phosphate buffer (pH 4.7) : acetonitrile (45:55; v/v) flowing through the system at the rate of 1.5 ml/min. The HPLC column temperature was 40°C. Eluent was monitored by fluorescence with excitation and emission wavelengths of 230 and 420 nm, respectively.

Data analysis:

The pharmacokinetic parameters were determined. C_{max} and T_{max} were taken directly from the individual concentration versus time data. The elimination rate constant (Kel) was estimated by log-linear least squared regression of the terminal part of the plasma concentration versus time curve. Half-life was calculated by the equation of 0.693/Kel. The area under the concentration versus time curve (AUC_{0-inf}) was calculated by linear trapezoidal rule. Clearance was determined based on the equation of Fดdose/ AUC_{0-inf}. F (% bioavailability) of a single dose of gabapentin 300 mg formulated as a capsule was estimated to be 60 % relative to an intravenous formulation.[8] Vd were determined by the equation of Cl/Kel.

The comparison of bioavailability of the generic product of 300 mg gabapentin to the innovators's product was assessed using the relevant pharmacokinetic parameters, C_{max} and $AUC_{0-inf,}$ both were transformed to logarithmic data for statistical analysis. The difference of the corresponding log C_{max} and log $AUC_{(0-inf)}$ between two products was tested by Two Way Analysis of Variance (ANOVA) for a crossover design followed by the test of 90 % confidence interval (Two-one sided test).

The two products are considered to be bioequivalent when each 90 % confidence interval is within 80 - 125 %.

Adverse events

The subjects were requested to report all events appearing at baseline (predose), during and after the drug intake to the medical staff. All adverse events encountered during the clinical study were reported on the Case Report Form. The severity of the adverse events was graded according to a three-point scale (mild, moderate, severe) and reported in detail as indicated on the Case Report Form.

Result

The demographic data:

All subjects were judged to be healthy based on physical examination, medical history, vital signs and clinical laboratory tests. All of them had negative HIV test and their urinary tests were normal. Table 2 provides the demographic data of the subjects

enrolled. BMI of each subject was within the range of 18 - 24.

Pharmacokinetic parameters:

The plasma gabapentin concentration at each sampling time up to 32 hours following a single oral dose of 300 mg generic and reference products was determined. The graphic profile curve of mean plasma gabapentin concentration vs time is illustrated comparing the two products as shown in Figure 1.

The pharmacokinetic parameters for bioequivalence study including peak plasma gabapentin concentration (C_{max}), time to peak plasma gabapentin concentration (T_{max}) and area under the plasma gabapentin concentration-time curve ($AUC_{0\text{-}inf}$) were determined. The mean values (mean ± SD) of C_{max} of generic product and innovator's product were 3.04 ± 0.55 and 3.26 ± 0.62 μg/ml, respectively. After oral single dose, mean (range) of T_{max} of generic product was 3.00 hrs (2 - 4 hrs) and that of reference product was 3.18 hrs (2 - 5 hrs) and the relative ratio was 0.94. The mean values (mean ± SD) of $AUC_{(0\text{-}inf)}$ of generic and reference product were 28.48 ± 7.14 and 29.81 ± 6.33 μg.hr/ml as shown in Table 3. According to ANOVA and 90 % confidence interval analysis, the mean difference of C_{max} and $AUC_{(0\text{-}inf)}$ (log transformed data) of generic product compared to reference product were 82.8-104.61 % and 85.57 - 104.36 %, respectively (Table 4).

Table 2. Mean clinical laboratory and demographic data of 14 subjects enrolled in the study.

Parameters	Normal values	Mean ± SD	Range
Hemoglobin (g/dl)	12-18	14.75 ± 0.77	13.4-16.3
Hematocrit (%)	37-52	44.77 ± 2.42	41.1-49.1
Glucose (mg/dl)	70-110	91.57 ± 6.51	79-101
BUN (mg/dl)	10-20	12.14 ± 2.88	9-18
Creatinine (mg/dl)	0.5-2	0.96 ± 0.16	0.7-1.3
Uric acid (mg/dl)	2-7	7.21 ± 0.85	5.4-8.5
SGOT (U/L)	0-38	19 ± 5.56	10-32
SGPT (U/L)	0-38	14.36 ± 7.22	7-33
Alkaline phosphatase (U/L)	39-117	81.71 ± 19.42	46-117
Anti HIV	-	Negative	-
Urinalysis	-	Normal	-
Age (year)	-	20.07 ± 1.27	18-22
Body weight (kg)	-	63.54 ± 7.66	51-77.5
Height (cm)	-	172 ± 0.05	163-108.5
BMI	-	21.43 ± 1.43	19.2-23.92
Pulse rate (/min)	-	70.43 ± 8.31	60-88
Sytolic blood pressure (mmHg)	90-140	113.57 ± 8.42	100-130
Diastolic blood pressure (mmHg)	60-90	71.43 ± 8.64	60-80

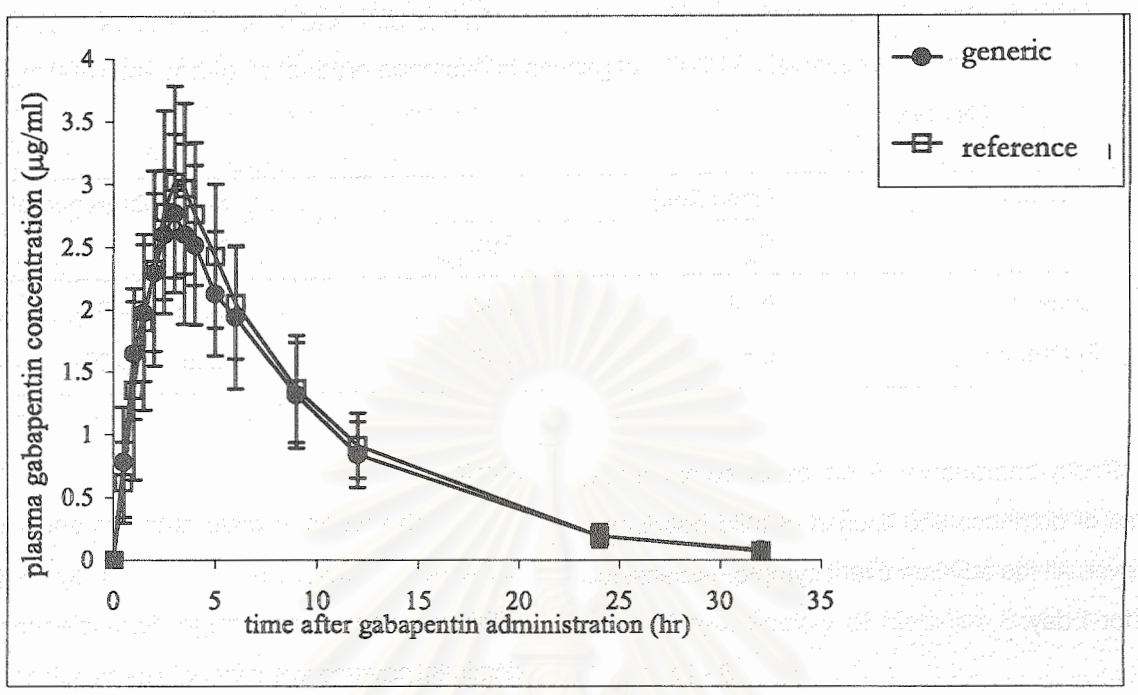

Figure 1. Mean plasma gabapentin concentration-time curve after single oral dose 300 mg of generic and reference product of gabapentin (n=14).

General pharmacokinetic parameters including $T_{1/2}$, clearance and Vd of gabapentin in subjects receiving generic product were 5.78 ± 1.07, 6.32 ± 1.98 and 51.22 ± 15.99, respectively. The same parameters of reference product were 5.34 ± 0.78, 6.04 ± 1.30 and 45.57 ± 10.46, respectively (Table 3).

Adverse events

Adverse events were monitored during and after the drug administration. Neither Vultin ® nor Neurontin ® showed serious adverse events. On the study day, some of the participants reported mild adverse events after taking both formulations.

Table 3. Mean pharmacokinetic parameters (mean ± SD) of gabapentin from 14 subjects following a single oral dose of 300 mg of generic and reference product.

Parameters	Mean ± SD	
	Generic product	Reference product
$AUC_{(0\text{-}inf)}$ (mg.hr/ml)	28.48 ± 7.14	29.81 ± 6.33
C_{max} (mg/ml)	3.04 ± 0.55	3.26 ± 0.62
T_{max} (hr)	3.00 ± 0.68	3.18 ± 0.8
Kel (hr^{-1})	0.12 ± 0.02	0.13 ± 0.02
Half life (hr)	5.78 ± 1.07	5.34 ± 0.78
Cl (l/hr)	6.32 ± 1.98	6.04 ± 1.30
Vd (l)	51.22 ± 16	45.57 ± 10.46

Table 4. Mean C_{max} and $AUC_{(0\text{-}inf)}$ in term of log transformed data and mean difference of 90 % confidence interval (90 % CI) of generic to reference product of gabapentin 300 mg (N=14).

Product	Mean (log)		Mean difference of 90 % CI
	C_{max}	$AUC_{0\text{-}Inf}$	
Generic	0.48	1.44	82.80-104.61
Reference	0.51	1.46	85.57-104.36

The effects comprised 6 cases of somnolence, 1 case of dizziness and 1 case of mild headache. However, all the adverse event symptoms persisted only for 1 day.

Discussion and Conclusion

The purpose of the study was to determine the bioequivalence of gabapentin following an administration of 300 mg capsule of generic and reference product. The analytical method was modified by the method of Tang PH *et al,*[9] Forrest G *et al,*[10] and Chollet DF *et al,* [11] using automated HPLC with fluorescence detection. The assay was practical and reliable approved by the method validation guidance of US FDA, CDER, CVM.[12]

Accuracy was presented in term of the percentage of recovery within the acceptance range 80 - 125 %, with % CV < 15. In term of precision, the percent of coefficient of variation in intra-day and inter-day assay were also within the acceptance range (% CV < 15 %). Thus, these data revealed validity in accuracy and precision. The standard curve covered the range of human plasma concentration of gabapentin dosage 300 mg followed good linearity with the correlation coefficient (R^2) closed to 1. Gabapentin in plasma was well stable within two months long term interval or even three cycles of freeze and thaw.

The fourteen male subjects enrolled in the study were healthy. Their BMI and body weight were within the acceptance range. Somnolence was the dominant adverse event for both formulations, 4 cases of generic product and 2 cases of reference product. Other adverse events were dizziness and headache. These manifestations are common side effect described in gabapentin preparation.[3]

The result of mean pharmacokinetic parameters (mean ± SD) of gabapentin from 14 subjects including $AUC_{(0\text{-}inf)}$, C_{max} and T_{max} were calculated using the data from plasma gabapentin concentration at each time of blood collection. $AUC_{(0\text{-}inf)}$ is the prominent parameter indicating whole drug existing in the body. C_{max} and T_{max} show the evidence involving drug absorption. In the study, we found that C_{max} and $AUC_{(0\text{-}inf)}$ (log transformed data) of generic product compared to reference product were not significantly different when analyzed by ANOVA for two-way crossover design and 90 % confidence interval. The mean differences of C_{max} and $AUC_{(0\text{-}inf)}$ (log transformed data) of test to reference are within the range of acceptance criteria of 80 - 125 %. The relative ratio of T_{max} of the test to reference products was 0.94. Hence, it could be concluded that the new generic product of gabapentin and the innovator' s

product were bioequivalent. The result of ANOVA test for log transformed data of $AUC_{(0\text{-inf})}$ reveals significantly different in effects including sequence, period and subject. These parameters represent the variability in each subject at different period and sequence which normally occurs in clinical study. However, drug or formulation effect did not show significant difference. Furthermore, there was no significant difference of the effects when log transformed of C_{max} was tested.

The elimination half-life of a single oral dose of gabapentin in Thai subjects was 5-6 hours, comparable to the previous report.[8] Virtually, gabapentin has widespread distribution into all body tissues. Its volume of distribution (Vd) is 50-60 L as reported by Vollmer *et al.*[5] In healthy Thai volunteers, Vd of gabapentin was also large, approximately to 50 L. The data from our study also show no difference in clearance comparing to the prior report[5]. Of the other pharmacokinetic parameters, $AUC_{(0\text{-inf})}$, C_{max} and T_{max}, there are no differences from those prior data of Vollmer *et al.*[8] as reported 24.6 mg/L·hr, 2.77-2.99 mg/L and 3.0-3.2 hr, respectively.

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References

1. Suman-Chauhan N, Webdale L, Hill DR, Woodruff GN. Characterisation of [3H] gabapentin binding to a novel site in rat brain: homogenate binding studies. Eur J Pharmacol 1993 Feb 15; 244(3): 293 - 301
2. Taylor CP. Mechanism of action of new antiepileptic drugs. In : Chadwick D,ed. New Trends in Epilepsy Management: the Role of Gabapentin.London: Royal Society of Medicine Services, 1993: 13 - 40
3. Goa KL, Sorkin EM. Gabapentin. A review of its pharmacological properties and clinical potential in epilepsy. Drugs 1993 Sep 46(3): 409 - 27
4. Richens A. Clinical pharmacokinetics of gabapentin. In : Chadwick D,ed. New Trends in Epilepsy Management: the Role of Gabapentin.London: Royal Society of Medicine Services, 1993: 41 - 6
5. Vollmer KO, von Hodenberg A, Kolle EU. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. Arzneimitteltorschung 1986 May; 36(5): 830 - 9
6. Vollmer KO, Turck D, Bockbrader HN, Busch JA, Chang T. Summary of Neurontin (gabapentin) clinical pharmacokinetics. Abstract. Epilepsia 1992; 33 (Suppl. 3); 77
7. Ben-Menachem E, Persson LI, Hedner T. Selected CSF biochemistry and gabapentin concentrations in the CSF and plasma in pateints with partial seizures after a single oral dose of gabapentin. Epilepsy Res 1992; 11: 45 - 9
8. Vollmer KO, Anhut H, Thomann P, Wagner F, Jahnchen D. Pharmacokinetic model and absolute bioavailability of the new anticonvulsant gabapentin. Adv Epileptology 1989; 17: 209 - 11
9. Tang PH, Miles MV, Glauser TA, DeGrauw T. Automated microanalysis of gabapentin in

human serum by high-performance liquid chromatography with fluorometric detection. J Chromatogr B Biomed Sci Appl 1999 Apr 30; 727(1-2): 125 - 9

10. Forrest G, Sills GJ, Leach JP, Brodie MJ. Determination of gabapentin in plasma by high-performance liquid chromatography. J Chromatogr B Biomed Appl 1996 Jun 7; 681(2): 421 - 5
11. Chollet DF, Goumaz L, Juliano C J, Anderegg G. Fast isocratic high–performance liquid chromatographic method for the simultaneous determination of gabapentin and vigabatrin in human serum. J Chromatogr B Biomed Appl 2000 Sep 15; 746(2): 311 - 4
12. U.S. Department of Health and Human Services FDA, CDER, CVM. Guidance for Industry: Bioanalytical Method Validation. May 2001, BP