การเปรียบเทียบระดับยาฟีนัยโตอินในซีรัมจากการให้ยาไดแลนตินอินฟาแทป และไดแลนตินแคปซีลผ่านทางสายยาง

นางสาว นปนันท์ คุ้มหมื่นไวย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
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Comparison of serum phenytoin levels after administration with Dilantin Infatabs® and Dilantin Kapseals® via nasogastric tube feeding

Miss Napanan Khummuenwai

A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science in Pharmacy in Clinical Pharmacy

Department of Pharmacy

Faculty of Pharmaceutical Sciences

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นปนันท์ คุ้มหมื่นไวย : การเปรียบเทียบระดับยาฟีนัยโตอินในซีรัมจากการให้ยาไดแลนตินอินฟาแทป และไดแลนตินแคปซีลผ่านทางสายยาง (COMPARISON OF SERUM PHENYTOIN LEVELS AFTER ADMINISTRATION WITH DILANTIN INFATABS® AND DILANTIN KAPSEALS® VIA NASOGASTRIC TUBE FEEDING) อาจารย์ที่ปรึกษา : รศ.ดร.ดวงจิต พนมวัน ณ อยุธยา อาจารย์ที่ปรึกษาร่วม:นพ. สมชาย โตวณะบุตร และ ภญ.เสริมสุข จันทร์ใต้. 85 หน้า. ISBN 974-53-2505-8.

การศึกษานี้เป็นแบบ open-labelled, crossover clinical trial โดยมีวัตถุประสงค์เพื่อเปรียบเทียบระดับยา ฟีนัยโตอินในซีรัม จากการให้ยาไดแลนตินอินฟาแทป (ยาฟีนัยโตอินรูปแบบยาเม็ด) และไดแลนตินแคปซีล (ยาฟีนัยโตอินรูปแบบแคปซูล) ผ่านทางสายยาง ผู้ป่วยที่เข้าร่วมการวิจัยจะเริ่มจากได้รับยาไดแลนตินอินฟาแทป 300 มิลลิกรัมต่อวันผ่านทางสายยางอย่างน้อย 5 วันแล้วเจาะเลือดเพื่อวัดระดับฟีนัยโตอินและระดับแอลบูมินในซีรัม หลังจากนั้นจึงเปลี่ยนยาเป็นไดแลนตินแคปซีล 300 มิลลิกรัมต่อวันผ่านทางสายยางอย่างน้อย 5 วันแล้วเจาะเลือดเพื่อวัดระดับฟีนัยโตอินและระดับแอลบูมินในซีรัมอีกครั้งหนึ่ง มีผู้ป่วยจำนวน 17 รายเข้าร่วมการวิจัยนี้ ระดับยาฟีนัยโตอินในซีรัมเฉลี่ยหลังจากได้รับยาไดแลนตินอินฟาแทปและไดแลนตินแคปซีล คือ 6.03±5.92 และ 3.80±2.71 ไมโครกรัมต่อมิลลิลิตร ตามลำดับ ระดับแอลบูมินในซีรัมเฉลี่ยที่วัดพร้อมกับระดับยาไดแลนตินอินฟาแทปและไดแลนตินแคปซีล คือ 2.51±0.49 และ 2.45±0.40 กรัมต่อเดซิลิตร ตามลำดับ ระดับยาฟีนัยอินที่ปรับค่าแอลบูมินต่ำแล้วเฉลี่ย หลังจากได้รับยาไดแลนตินอินฟาแทปและไดแลนตินแคปซีล คือ 10.33±11.60 และ 6.28±4.76 ไมโครกรัมต่อมิลลิลิตร ตามลำดับ ระดับยาฟีนัยโตอินในซีรัม และระดับยาฟีนัยอินที่ปรับค่าแอลบูมินต่ำแล้ว จากการให้ยาฟีนัยโตอินรูปแบบยาเม็ดและรูปแบบแคปซูลแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (P=0.019 และ P=0.035 ตามลำดับ) เหตุผลที่ทำให้ระดับยาจากการให้ยาฟีนัยโตอินรูปแบบยาเม็ด และรูปแบบแคปซูลแตกต่างกัน ส่วนหนึ่งน่าจะมีสาเหตุมาจากการที่ในรูปแบบแคปซูล ยาฟีนัยโตอินอยู่ในรูปเกลือโซเดียม ขณะที่ในรูปแบบยาเม็ด ยาฟีนัยโตอินอยู่ในรูปกรดอิสระ ระหว่างการศึกษาไม่มีผู้ป่วยรายใดเกิดการชัก และอาการไม่พึงประสงค์จากยาฟีนัยโตอิน ค่า Vmax/F เฉลี่ย (เมื่อกำหนด Km=4 มิลลิกรัมต่อลิตร) จากการให้ยาฟีนัยโตอินรูปแบบยาเม็ดและรูปแบบแคปซูล คือ 501.32±137.02 และ 612.90±346.18 มิลลิกรัมต่อวัน ตามลำดับ ซึ่งไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติที่ระดับความเชื่อมั่น 95 % แสดงว่าชีวอำนวยผล (F) ของยาทั้งสองรูปแบบไม่ต่างกันอย่างชัดเจน ถ้าต้องการปรับระดับยาในซีรัมให้อยู่ในระดับกึ่งกลางของช่วงที่ให้ผลในการรักษาคือ 15 ไมโครกรัมต่อมิลลิลิตร ผู้ป่วยจะต้องปรับขนาดยาฟีนัยโตอินในรูปแบบยาเม็ด และในรูปแบบแคปซูลเป็นประมาณวันละ 400 และ 500 มิลลิกรัม ตามลำดับ อย่างไรก็ตาม เนื่องจากค่าชีวอำนวยผลของยาทั้งสองรูปแบบมีค่าค่อนข้างต่ำ และมีความผันแปรค่อนข้างสูง เมื่อให้พร้อมอาหาร วิธีการให้ยาห่างจากมื้ออาหารประมาณ 2 น่าจะเป็นวิธีที่ปลอดภัยกว่า ซึ่งอาจจะช่วยเพิ่มระดับยาฟีนัยโตอินให้สูงขึ้นได้ อย่างไรก็ตาม ควรจะมีการศึกษาเพิ่มเติมก่อนทำการสรุปผลที่แน่นอนต่อไป

ภาควิชา.....เภสัชกรรม.....ลายมือชื่อนิสิต.....นปนันท์ คุ้มหมื่นไวย.....

สาขาวิชา....เภสัชกรรมคลินิก.....ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา.....2548.....ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

##4676569033 : MAJOR CLINICAL PHARMACY

KEY WORD : PHENYTOIN/NG TUBE FEEDING

NAPANAN KHUMMUENWAI : COMPARISON OF SERUM PHENYTOIN LEVELS AFTER ADMINISTRATION WITH DILANTIN INFATABS® AND DILANTIN KAPSEALS® VIA NASOGASTRIC TUBE FEEDING. THESIS ADVISOR : ASSOC.PROF. DUANGCHIT PANOMVANA NA AYUDHYA, Ph.D., THESIS CO-ADVISOR : SOMCHAI TOWANABUT, M.D., SERMSOOK JANTAI, M.Sc. 85 pp. ISBN 974-53-2505-8.

The purpose of this open-labelled, crossover clinical trial is to compare serum phenytoin levels after administration with Dilantin Infatabs® (phenytoin acid tablet) and Dilantin Kapseals® (phenytoin sodium capsule) through NG tube feeding. Patients enrolled were started with receiving Dilantin Infatabs® 300 mg daily through NG tube feeding for at least 5 days then serum phenytoin level was determined. The dosage formulation was changed to Dilantin Kapseals® 300mg daily which was again administered through NG tube feeding for at least 5 days and serum phenytoin level was again determined. Seventeen subjects completed the whole process of study. Mean serum phenytoin concentrations after administration of phenytoin tablet and capsule were 6.03±5.92 μg/mL and 3.80±2.71 μg/mL, respectively. Mean serum albumin concentration measured at the time of phenytoin tablet and capsule administration were 2.51±0.49 and 2.45±0.40 g/dl, respectively. Mean serum phenytoin concentrations adjusted for their low serum albumin concentrations after administration of phenytoin tablet and capsule were 10.33±11.60 and 6.28±4.76 μg/mL, respectively. Measured serum phenytoin concentrations and adjusted phenytoin concentrations after administration with phenytoin tablet and phenytoin capsule were significantly different (p=0.019 and p=0.035, respectively). The reasons which caused the serum phenytoin concentrations obtained from capsule to be significantly lower than that obtained from tablet was partly due to the sodium salt form of phenytoin in capsule while it is the free acid form in the tablet. During the study, all patients were seizure free and none of the patients showed serious adverse drug reaction. The mean Vmax/F (when assume Km=4 mg/L) after administration phenytoin tablet and phenytoin capsule were 501.32±137.02 and 612.90±346.18 mg/day, respectively. These values were not significantly different indicated that bioavailabilities of two dosage form were not significantly different. When the desired serum phenytoin concentration was set at 15 μg/mL, the appropriate dosage required for phenytoin tablet and capsule were around 400 and 500 mg/day. Since these predicted dosages were quite high and the bioavailability of either tablet or capsule was quite low and varied highly. Feeding standard dose of phenytoin (300 mg/day) 2 hours apart from feeding diet formula might be a safer method to increase serum phenytoin concentration. Further studies are strongly recommended before any definite conclusion could be made.

Department.....Pharmacy.....Student's signature.....Napanan Khummuenwai.....

Field of study...Clinical Pharmacy...Advisor's signature.....Duangchit Panomvana.....

Academic year.....2005.....Co-advisor's signatures.....Somchai Towanabut.....

.....Sermsook Jantai.....

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ABBREVIATIONS

AEDs	Antiepileptic drugs
Alb	Serum albumin concentration
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CI	Confidence interval
C_{NB}	Normal binding phenytoin serum concentration
CNS	Central nervous system
C_{Obs}	Observe serum phenytoin concentration
C_{ss}	Steady-state serum phenytoin concentration
CVA	Cerebrovascular accident
D/C	Discharge
F	Bioavailability of phenytoin
IBW	Ideal body weight
Km	Michaelis-Menten constant
R	Rate of phenytoin administration
NG tube	Nasogastric tube
S	Salt factor of phenytoin
SCr	Serum creatinine concentration
TBW	Total body weight
t_{pk}	Time to peak concentration
V	Volume of phenytoin distribution
v	Rate of drug elimination
Vmax	Maximum rate of metabolism
τ	Dosing interval

CHAPTER I

INTRODUCTION

Epilepsy is one of the most common serious disorder of the brain, affect 50 million people worldwide. It may cause persistence deformity to the patients, decrease the quality of life and lead to lots of expense for treatment. Incidence of epilepsy varies throughout the world. It's approximately 0.3 to 1 %. Prevalence of epilepsy has been estimated to be 5 to 10 person per 1000. Incidence of epilepsy is highest at the first 5 years of age and elderly. In Thailand, the incidence of epilepsy is approximately 1%, and the prevalence of epilepsy is 29.2 persons per 1000 and prevalence of active epilepsy is 5.9 persons per 1000.

More than half of epileptic patients in Thailand are unknown cause. For infants, epilepsy may result from the birth trauma, fever or infections. For adults, it's from cerebrovascular disease, stroke, CNS infection, head trauma or brain tumor. The treatment of epilepsy in adults and elderly are removed the cause of epilepsy and prevention of seizure. Antiepileptic drugs (AEDs) are commonly prescribed for these people, especially in patients who have brain lesion.

Although there is increasing interest in the use of new AEDs such as lamotrigine, gabapentin, topiramate and vigabatrin for the management of seizure disorder in adults and elderly, the majority of these patients are still treated with traditional AEDs such as phenobarbital, carbamazepine, valproic acid and phenytoin. Phenytoin is still widely used in these patients, accounting overall for more than 50% of AEDs prescriptions in US.

In Thailand, Phenytoin is common AEDs used for adults and elderly because of it's effective for most common seizure type in this people such as partial and generalized tonic-clonic seizure, prophylaxis post-traumatic seizure. There are many

other reasons for this: Phenytoin are low cost, less sedating drug, can be given once daily, it is available in formulations suitable for oral and parenteral use.

The last reason mention above is very important for patients who have post-traumatic seizure or post-stroke seizure since most of these patients can not take the oral dosage form, they usually receive all medications by parenteral route or enteral tube feeding.

Although phenytoin is available in many formulations, but in primary care hospitals of Thailand, it is available only in two formulations, phenytoin injection and phenytoin sustained-release capsule. Phenytoin sodium (phenytoin sustained-release capsule) is in the list of medications available in all hospitals, while phenytoin acid (phenytoin prompt-release tablet) is available in some hospitals only. Therefore some patients who receive enteral tube feeding usually receive phenytoin sustained-release capsule through enteral tube. There are several properties of phenytoin that require special attention:- 1) Phenytoin is weak acid, non soluble 2) Phenytoin has narrow therapeutic range 3) Phenytoin has non-linear pharmacokinetics 4) Problem from non-pharmaceutical equivalence or non-bioequivalence of different formulations or manufactures.

There were few studies on phenytoin suspension and prompt-release tablet administered through enteral tube feeding but none was observed about phenytoin sustained-release capsule. Although there is no indication of phenytoin sustained-release capsule for enteral tube feeding patients, it is common practice in primary care hospitals of Thailand where prompt-release tablet is not available. This study was therefore designed to compare steady-state serum phenytoin levels after phenytoin sustained-release capsule and phenytoin prompt-release tablet administered through enteral tube feeding.

Objective

To compare serum phenytoin levels after administration with Dilantin Infatabs® (phenytoin acid prompt-release tablet) and Dilantin Kapseals® (phenytoin sodium sustained-release capsule) through nasogastric tube feeding.

Significances of Study

1. Serum phenytoin levels after multiple doses administration through nasogastric tube feeding in Thai patients is known.

2. The serum phenytoin levels after administration with Dilantin Infatabs® (phenytoin acid prompt-release tablet) and Dilantin Kapseals® (phenytoin sodium sustained-release capsule) through nasogastric tube feeding are compared.

3. Informations about phenytoin administering through nasogastric tube feeding, i.e., the suitability of the present dosage regimen, seizure controlled, adverse drug reaction including any inconvenience that shall occur are evaluated.

CHAPTER II

REVIEW OF LITERATURES

Review of seizure

A seizure is a paroxysmal event due to abnormal, excessive hypersynchronous discharges from an aggregate of central nervous system (CNS) neurons. Approximately 5 to 10% of population will have at least one seizure during their lifetime, with the highest incidence occurring in early childhood and late adulthood. *(1)*

Epilepsy is a condition in which a person has recurrent seizure due to chronic, underlying process. Using the definition of epilepsy as two or more unprovoked seizure, the incidence of epilepsy is approximately 0.3 to 1% in different populations throughout the world, and the prevalence of epilepsy is 29.2 persons per 1000 of Thailand. *(2)*

The International League Against epilepsy (ILAE) had published the international classification of epileptic seizure as table1. *(3)* This system is based on the clinical features of seizures and associated electroencephalographic finding. The main characteristic that distinguishes the different categories of seizures is whether the seizure activity is partial or generalized. Partial seizures are those in which the seizure activity is restricted to discrete areas of cerebral cortex. Generalized seizures involve diffuse regions of the brain simultaneously in a bilaterally symmetric fashion. Partial seizures are often associated with structural abnormalities of the brain. In contrast, generalized seizures may result from cellular, biochemical, or structural abnormalities that have a more widespread distribution.

Table 1 The Commission on Classification and Terminology of the ILAE 1981: Criteria used for the classification of seizure. *(3)*

I. Partial (focal, local) seizures

A. Simple partial seizures

1. With motor sign: focal motor with or without march, versive, postural, phonatory
2. With somatosensory or special sensory symptom: somatosensory, visual, auditory,olfactory, gustatory,vertiginous simple hallucinations (e.g. tingling, light flashing, buzzing)
3. With autonomic symptoms or sign, including epigastric aura
4. With psychic symptoms (disturbances of higher mental function): dysphasic, dysmnestic, cognitive, affective; illusions, structured hallucinations

B. Complex partial seizures

1. Simple partial onset followed by impairment of consciousness
   a. With simple partial features A1 to A4) followed by impaired of consciousness
   b. With automatisms
2. With impairment of consciousness at onset
   a. With impairment of consciousness only
   b. With automatisms

C. Partial seizure evolving to secondarily generalized seizures (tonic-clonic ,tonic, or clonic)

1. Simple partial seizure evolving to generalized seizures
2. Complex partial seizures evolving to generalized seizures
3. Simple partial seizure evolving to complex partial seizures evolving to generalized seizures

II. Generalized seizure

A. Absence seizure

1. Absence with impairment of consciousness only, mild clonic componenta, atonic components, tonic components,automatism, autonomic components
2. Atypical absence seizures with changes in tone more pronounced than in A1 and with onset and/or cessation that is not abrupt

B. Myoclonic seizures

C. Clonic seizures

D. Tonic seizures

E. Tonic-clonic seizures

F. Atonic seizures

(Combinations May occur, such as B and F or B and D)

III Unclassified epileptic seizure.

The cause of seizures and epilepsy

Seizures are a result of a shift in the normal balance of excitation and inhibition within the CNS. Given the numerous properties that control neuronal excitability, there are many ways to perturb this normal balance, and therefore many different causes of both seizures and epilepsy.

The cause of epilepsy cannot be determined in 60% to 80% of children and adolescents and less than 50% of epilepsy cases in the elderly are attribute to a specific etiology. More than 30% of new-onset epilepsy cases in the elderly may be attributed to cerebrovascular disease, including ischemic and hemorrhagic strokes. *(4)* Other identifiable causes of seizure in adult and elderly include metabolic disturbance, brain tumor, central nervous system (CNS) infection, head injury or neurosurgery, brain abscess and alcohol withdrawal. In practical, it is useful to consider the etiologies of seizures base on the age of the patient, as age is one of the most important factors determining both the incidence and likely causes of seizures or epilepsy. Table 2 shows the causes of seizures according to age.

Table 2 The causes of seizures according to age. *(1)*

Neonates (<1month)	Perinatal hypoxia and ischemia Intracranial hemorrhage and trauma Acute CNS infection Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxime deficiency) Drug withdrawal Developmental disorders Genetic disorders
Infants and children (>1 month and <12 years)	Febrile seizures Genetic disorders (metabolic, degenerative, primary epilepsy syndromes) CNS infection Developmental disorders Trauma Idiopathic
Adolescents (12-18 years)	Trauma Genetic disorders Infection Brain tumor Illicit drug use Idiopathic
Young adults(18-35 years)	Trauma Alcohol withdrawal Illicit drug use Brain tumor Idiopathic
Older adults (>35 years)	Cerebrovascular disease Brain tumor Alcohol withdrawal Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia) Alzheimer's disease and other degenerative CNS diseases Idiopathic

Treatment of seizure

Therapy for a patient with seizure disorder in almost always multimodal and includes treatment of underlying conditions that cause or contribute to the seizure, avoidance of precipitating factor, suppression of recurrent seizures by prophylactic therapy with antiepileptic drugs (AEDs) or surgery.*(1,5)*

Seizure cause by a structural CNS lesion such as a brain tumor, vascular malformation, or brain abscess may not recur after appropriate treatment of underlying lesion. However, despite removal of the structural lesion, there is a risk that the seizure focus will remain in the surrounding tissue or develop de novo as a result of gliosis and other processes induced by surgery, radiation, or other therapies. Most patients are therefore maintained on the AEDs for at least 1 year, and an attempt is made to withdraw medications only if the patient has been completely seizure free. *(1)*

Antiepileptic drugs therapy is the mainstay of treatment for most patients with epilepsy. The overall goal is to completely prevent seizures without causing any untoward side effect, preferably with a single medication and a dosing schedule that easy for the patient to follow. Although, the new AEDs such as lamotrigine, topiramate, gabapentin, tiagabine, vigrabatin and oxcarbamazepine have available, drug therapy of epilepsy are generally used classical AEDs such as phenytoin, phenobarbital, carbamazepine and valproic acid. These classical AEDs are used as first-line therapy for most seizure disorder because they are effective and less expensive.

Antiepileptic drugs therapy should be started in any patient with recurrent seizure of unknown etiology or a known cause that cannot be reversed. Patients with a single seizure due to an identified lesion such as a CNS tumor, infection, or trauma, in strong evidence that the lesion is epileptogenic, should be treated. *(6-8)* Seizures occurring early after head trauma worsen both intracranial hypertension and associated hypoxia in injured tissue, therefore, administration of AEDs needs to be initiated as early as possible in patients with severe head trauma. Several studies show that pharmacological control of early seizure with phenytoin is effective. *(9-11)* The selection of AEDs for different seizure types are shown in table3.

Table 3 Antiepileptic drug of choice in Thailand *(2)*

	First-line	Alternative
Generalized tonic-clonic	Valproic acid, Phenytoin Carbamazepine, Phenobarbital	Clonazepam, Clobazam
Partial	Carbamazepine, Phenytoin Valproic acid, Phenobarbital	Clonazepam, Clobazam
Absence	Valproic acid	Clonazepam, Acetazolamide
Myoclonic, Atonic, Tonic	Valproic acid	Clonazepam, Nitrazepam
Infantile spasms	ACTH, Prednisolone, Vigabatrin, Valproic acid	Nitrazepam, Clonazepam, Clobazam

Review of Phenytoin

1. Chemistry

Phenytoin is a hydantoin derivative anticonvalsant. It is a generic name of 5,5-diphenyl-2,4-imidazolidinedione (acid form). Phenytoin acid form has a molecular weight of 252.26 and pKa of 8.06-8.33. It is practically insoluble in water; the solubility is 0.0014 g/mL. As the phenytoin sodium, it has molecular weight of 274.25 and freely soluble in water. The sodium salt contains phenytoin acid 91.98%. *(12-13)*

Oral formulation of phenytoin has three formulations, aqueous suspension (Dilantin-125 suspension®) and chewable tablet (Dilantin Infatabs®50 mg) contain of phenytoin acid. Gelatin capsule (Dilantin Kapseals®100 mg) contains of phenytoin sodium which equivalent to 92 mg of phenytoin acid.

2. Pharmacology

Phenytoin blocks post-tetanic potentiation (PTP) by influencing synaptic transmission in a variety of way, including: *(14)*

- Alterations in ion fluxes (sodium, potassium, chloride) associate with depolarization, repolarization, and membrane stability.
- Calcium uptake in presynaptic terminals and calcium energy metabolism.
- The sodium-potassium adenosine triphosphatase-dependent ionic membrane pump.
- Cyclic nucleotide build-up.
- Calcium-dependent synaptic protein phosphorylation and transmitter release.
- Cerebellar stimulation.

3. Indications

Indication of phenytoin is suppression and control of different types of seizures including primary or secondary generalized tonic-clonic seizure and simple or complex partial seizure. In addition, phenytoin is also effective for prevention and treatment of seizure during and following neurosurgery, *(12-13)* prophylaxis of post-traumatic epilepsy and poststroke epilepsy. *(15-19)* For un-labelled uses, phenytoin is useful as an antiarrthythmic agent, an alternative to magnesium sulfate in severe preecclamsia. Moreover, it has been used in the treatment of trigeminal neuralgia, recessive dystrophic epidermolysis bullosa and junctional epidermolysis bullosa. *(12)*

4. Pharmacokinetics

Absorption

Phenytoin is almost completely absorbed from the gastrointestinal tract (85% to 95%) when administered orally as the capsule, chewable tablet, or suspension. Because of phenytoin is a weak acid with pKa of 8.3, it is thus poorly soluble in water but well dissolved in an alkali medium. Although phenytoin sodium is much better soluble in water, but in acid medium of the stomach, phenytoin sodium is rapidly converted to free phenytoin acid with subsequent precipitation. On passage to the duodenum where pH is approximately 7.0-7.5, more of the drug is considerably soluble in the intestinal fluid. Therefore, phenytoin is rapidly absorbed in the duodenum where the maximum absorption occurs.

The absorption rate of phenytoin is greatly influenced by dosage formulation factors such as particle size and ingredient, and may also be affected by food intake. Moreover, the absorption rate of phenytoin may affected by dissolution rate in gastrointestinal tract and dose of administration.

Time to peak concentration (t_{pk}) of phenytoin occur within 3 to 12 hours after administration. A second peak may be observed within 8 to 15 hours. Continued administration of the drug, steady-state is usually reached in 5-14 days. *(20)*

Distribution

After absorption, phenytoin is rapidly and widely distributed throughout the body. The volume of distribution of phenytoin in patients with normal renal function and serum albumin concentration is approximately 0.6 to 0.8 L/kg.

Phenytoin is 69% to 93% bound (average 90% bound) to the albumin fraction of serum protein. The free form of phenytoin passes through the blood brain barrier to the brain and provides pharmacological actions.

Decreasing the serum albumin concentration such as patients with severe hepatic failure, nephrotic syndrome, critical illness or burns, the total phenytoin seems to be decrease or unchanged but the free fraction of phenytoin is increase, result to increase pharmacological action or toxicity.

Metabolism and Elimination

Phenytoin is metabolized by the hepatic microsomal mixed-function oxidase system (cytochrome P-450 system). The hydroxylation is the principle metabolic pathway of phenytoin in human, accounting for 70-90% of administered phenytoin. The cytochrome P450 isoforms of CYP2C9 are major responsible for phenytoin hydroxylation while CYP2C19 contributes in a minor extent. The elimination of phenytoin is mainly by hepatic metabolism to the several forms of inactive metabolites, while less than 5% of dose of phenytoin is excreted unchanged in urine.

The clearance of phenytoin from serum occurs primarily by metabolism, and the rate of this metabolism is capacity limited. This implies that as the maintenance does is increase, the serum concentration rises disproportionately. This disproportionate rise in the steady state serum level makes dosage adjustment difficult.

The half-life of phenytoin after oral administration ranges from 7 to 42 hours, averages 22 hours. The half-life of phenytoin after intravenous administration ranges from 10 to 15 hours. *(21)* The half-life of phenytoin varies among patient populations. Elderly patients may have lower body clearances than adult and may have longer phenytoin half-life.

5. Dosage Regimen and Clinical Applications

Loading dose

When a rapid therapeutic concentration is desired, a loading dose is recommended. The loading dose is 15-18 mg/kg, administer by intravenous infusion rate not exceed 50 mg per minute. This makes rapidly achievement of therapeutic

serum level. For neonates, children, and adolescent, the maximum intravenous infusion rate is 1-3 mg/kg/min. *(22)*

Oral phenytoin loading dose may be given in patients who do not require intravenous phenytoin infusion or have adverse reaction from intravenous infusion. For children adolescents and adults, the oral loading dose usually given in 5 mg/kg increments every 2 hours until the total dose has been administered. Table 4 shows the recommended loading dose.

Table 4 The loading dose of phenytoin *(22)*

Age	Loading dose (mg/kg)
Neonates and infants (<1 year)	15-20
Children (1-<12 years)	15-18
Adolescents (≥12 years), adults and geriatrics	15-20

Maintenance dose

The maintenance dose is follow after loading dose about 12-24 hours. The initiate maintenance dose is showed in table 5. The steady state serum phenytoin concentration may achieve in 5-14 days. *(20)* Adjustment of maintenance dose should be small increment (30-100 mg) base on clinical response.

The therapeutic serum phenytoin concentration should be 10-20 mg/L. However, many studies demonstrate that patients may achieve seizure control with serum concentration in range of 5-10 mg/L. *(23-24)* Some patients report to had seizure-free with phenytoin level around 3 mg/L.*(25)* The reasons for the achievement of seizure control with variation in serum phenytoin concentration are not clearly understood. Maybe some factors such as differences in severity of seizure process, nature of the seizure process, and variation in phenytoin pharmacokinetics.

Table 5 The maintenance dose of phenytoin *(20)*

Age	Maintenance dose (mg/kg)
Neonates (4 weeks)	3-5
Infants (4 weeks-<1 year)	4-8
Children (1-<12 years)	4-10
Adolescents (12-<18 years)	4-8
Adults and geriatrics (≥18 years)	4-7

6. Adverse Reactions

The most common dose-related adverse effect is central nervous system (CNS) effect such as headache, vertigo, insomnia and drowsiness. The phenytoin intoxication usually develops in patients who have phenytoin serum level exceed 20 mg/L. However, some adverse phenytoin effects can be seen at therapeutic concentration. The severity of phenytoin toxicity is increased with the increased serum phenytoin concentration (Table6). The paradoxical intoxication can occur in patients received overdose of phenytoin. *(26)* Moreover, chronic high concentration of phenytoin may result impaired mental function.

Table 6 Signs and symptoms of phenytoin intoxication related to phenytoin concentrations in normal serum albumin patients. *(12-13)*

Phenytoin concentration	Signs and symptoms
<10 mg/L	None
10-20 mg/L	Mild nystagmus may be present
20-30 mg/L	Nystagmus on lateral gaze, slight ataxia, drowsiness
30-40 mg/L	Nystagmus on vertical gaze, more intense ataxia and lurching gait, vomiting, slurred speech
40-50 mg/L	Lathargy, confusion, disorientation
>50 mg/L	Opisthothonic posturing

The non-dose-related adverse reaction of phenytoin such as gingival hyperplasia is the most common of non-dose-related phenytoin effect.*(27)* More than 50 percent of patients treated phenytoin longer than 3 months can be observed the gingival hyperplasia. Other non-dose-related adverse reaction of phenytoin such as nausea, vomiting, diarrhea, some dermatological effect and CNS effect are shown in table 7.

The cardiovascular adverse reaction had been report when rapidly administration of intravenous phenytoin (>50 mg/min). Some patients received rapidly intravenous phenytoin infusion observed hypotension, conduction abnormalities, arrhythmia and respiratory depression. Thus, used of intravenous phenytoin should be monitor cardiovascular function and should not infuse at rate exceed 50 mg/min. *(28)*

Table 7 Non-dose-related adverse effects of phenytoin. *(13,28-29)*

Hepatic system (1-10%)* Hepatitis Pancreatitis Hypersensitivity with hepatic involvement	Endrocrine&Metabolic system (1-10%)* Diabetis insipidus Hyperglycemia Osteomalacia
Hematologic system Magaloblastic anemia, Leucopenia (1-10%)* Granulocytosis, Pancytopenia rare*	
Dermatologic system Hypertrichosis, Coarsening of the facial features >10%* Scarlarliniform or mobilliform rash, Stevens-Johnson's syndrome, Toxic epidermal necrolysis <1%*	
Gastrointestinal system Gingival hyperplasia >50% Nausea/vomiting, Diarrhea, Constipation, Gastrointestinal discomfort >10%* Dysphagia, Loss of taste, Anorexia 1-10%*	
Central nerveous system (1-10%)* Peripheral neuropathy Cerebella degeneration Psychotic Impairment of cognitive function	

* Incidence of adverse reaction

7. Drug Interactions

Numerous drugs are reported to interact with phenytoin, but capacity-limited metabolism makes assessment of these interactions difficult. Table 8 is a partial list of drugs that influence phenytoin. Emphasis is given to those drugs most likely to alter phenytoin pharmacokinetics and/or to be encountered in the clinical.

Table 8 Drugs that alter phenytoin pharmacokinetics *(22,30)*

Drug	Effect on phenytoin concentration	Mechanism
Amiodarone	Increase	Inhibition of metabolism
Antacid	Decrease	Decrease absorption
Carbamazepine	Decrease	Induction of metabolism
Chloramphenicol	Increase	Inhibition of metabolism
Cimetidine	Increase	Inhibition of metabolism
Ciprofloxacin	Decrease	Induction of metabolism
Disulfiram	Increase	Inhibition of metabolism
Fluconazole	Increase	Inhibition of metabolism
Fluoxetine	Increase	Inhibition of metabolism
Folic acid	Decrease	Induction of metabolism
Isoniazid	Increase	Inhibition of metabolism
Phenobarbital	Increase or decrease	Inhibition or induction of metabolism
Phenylbutazone	Increase	Inhibition of metabolism, Plasma protein displacement
Rifampin	Decrease	Induction of metabolism
Salicylates	Decrease	Plasma protein displacement
Sulfonamides	Increase	Inhibition of metabolism, Plasma protein displacement
Theophylline	Decrease	Decrease absorption
Ticlopidine	Increase	Inhibition of metabolism
Trimethoprim	Increase	Inhibition of metabolism
Valproic acid	Decrease	Plasma protein displacement
Vigabatrin	Decrease	Induction of metabolism

Some disease states or conditions are known alter the pharmacokinetics of phenytoin. However, as drug interaction with phenytoin, the effects of interaction are difficult to quantify.

Hepatic disease or cirrhosis

Phenytoin is eliminated from the body primarily by hepatic metabolism. Therefore, patients with significant hepatic disease may require reduced maintenance dose. These patients frequently also have hypoalbuminemia, which alters the reported or measured phenytoin concentration. The reported phenytoin concentration can be "adjusted" by using Equation 1. *(20,31)* The altered albumin has little effect on the loading dose required to achieve therapeutic unbound plasma and tissue concentrations.

$$C_{NB} = \frac{C_{Obs}}{0.9(Alb/4.4) + 0.1} \qquad \text{Eq. 1}$$

Renal failure

Patients with end-stage renal failure have a decreased plasma phenytoin binding affinity for albumin. They also usually have low albumin. These factors, which greatly affect the reported concentration, have little influence on the unbound phenytoin concentration and the therapeutic effect. Therefore, patient with renal failure should initially receive normal loading and maintenance doses. However, these patients, sometime, have hypoalbuminemia. The reported phenytoin concentration of end stage renal function patients can be "adjusted" by using Equation 2 *(20,32)*

$$C_{NB} = \frac{C_{Obs}}{(0.9)\,(0.44)\,(Alb/4.4) + 0.1} \qquad \text{Eq. 2}$$

Obesity

Phenytoin has significant lipid solubility and increased volume of distribution in obese patients so the loading dose of phenytoin requires some adjustment. Equation 3 is calculation volume of distribution of phenytoin in obese patients. *(20,32)* Equation 4 and 5 is calculation of ideal body weight (IBW) for male and female.

V (L) = 0.65(L/kg) x [IBW+ 1.3(TBW-IBW)] Eq.3

Note V Volume of phenytoin distribution in litters

IBW Patient's ideal body weight in kilograms

TBW Patient's total body weight in kilograms

IBW for male = 50 + (2.3)(Height in inches >60) Eq. 4

IBW for female = 45 + (2.3)(Height in inches >60) Eq. 5

Malabsorption

There is little direct evidence that phenytoin is incompletely absorbed. However, patients with diarrhea or rapid GI transit probably have incomplete phenytoin absorption, especially if they take large single doses resulting in prolonged absorption.

Enteral tube feeding

The first report of the potential interaction between phenytoin and enteral tube feeding was published in 1982 by Bauer. *(34)* The low serum concentrations of phenytoin were found in 20 neurosurgery patients receiving phenytoin suspension through nasogastric (NG) tube feeding together with continuous nasogastric tube feedings. When the feedings were discontinued the average phenytoin concentration rose in seven days.

After that, several studies *(35-38)* supporting the interaction but ethical considerations limit the ability to conduct a prospective randomized controlled trial in patient.

However, some studies refused this interaction. *(39-41)* One of these studies conduct in ten healthy volunteers. The randomized controlled trial was study. The subjects received phenytoin by NG tube feeding concomitant with continuous enteral tube feedings for 14 days before and after the phenytoin dose. There was no significant interaction found in this study.

The exact mechanism of interaction is unknown. Many researchers have been study. Some studies *(42-44)* suggested that there is physical incompatibility between phenytoin and certain components such as protein hydrolysate in enteral feeding formulas, resulting in complexation of phenytoin particle and, therefore, decrease bioavailability. One *(45)* suggested that binding of phenytoin to the tube lumen as the mechanism; others proposed that the interaction is pH-related. *(44,46-47)*

8. Capacity-Limited Metabolism and Michaelis-Menten Parameters

For most drugs, the rate of metabolism is proportional to the plasma concentration. The relationships between metabolic rate of drugs that follow first-order kinetics to steady-state serum concentrations are normally linear. This linearity means that if the dose is increased, the serum concentration will be increased proportionally. *(20,48)*

By the saturation or capacity-limited function of the enzyme, the serum concentration of drug is not proportionally related to the dose of drug but depends on the amount of drug that interacts with enzyme. When all of the enzymes are saturated with the drug molecules, the maximum rate of metabolism is reached and cannot be further exceeded.

Phenytoin metabolism appears to have a capacity-limited metabolism even at the therapeutic concentrations. This results in clearance values that decrease with

increasing serum concentration. Therefore, when the maintenance dose is increased, the serum concentration rises disproportionately. This disproportionate rise in the steady-state serum level makes dosage adjustment difficult. Any small change in phenytoin dose may result in large increases in serum concentrations and toxic effects can occur even through the usual dose is prescribed.

The capacity-limited enzyme reaction is described by the Michaelis-Menten equation; whitch commonly assumes that the rate of drug elimination (v) is dependent upon the steady-state concentration of both enzyme and the drug concentration (Css) as follows: *(49-50)*

$$v = \frac{Vmax \times Css}{Css + Km} \qquad \text{Eq. 6}$$

Vmax is the maximum rate of metabolism (mg/day) and it is directly proportional to the total concentration of enzyme. Km, the Michaelis-Menten constant, is defined as the substrate concentration when the rate of reaction is equal to one-half maximum rate of reaction or 1/2Vmax and is inversely related to the affinity of the drug to enzyme. In chronic administration, phenytoin dosing rate (R) is thus assigned according to the rate of drug elimination (v). in other words, the Michaelis-Menten equation is used to calculate phenytoin maintenance dose and to predict its serum concentration at the steady-state.

In most patients, Km values are usually between 1-20 mg/L, average value is approximately 4 mg/L. Vmax values are usually between 5-15 mg/kg/day, average value is approximately 7 mg/kg/day. Calculation of Vmax and Km by the following equations: *(20)*

$$Vmax = \frac{(S)(F)(dose/\tau)(Km + Css)}{Css} \qquad \text{Eq. 7*}$$

* If Km is assumed to be 4 mg/L.

When two maintenance dose and two steady-state serum phenytoin concentration, we can calculate Km and Vmax of individual patients by following equations:

$$-Km = \frac{R_1 - R_2}{(R_1/Css_1) - (R_2/Css_2)} \quad \text{Eq. 8}$$

R_1 and R_2 are the rates of phenytoin administration of initial dose and new dose

Or $R = (S)(F)(dose/\tau)$ Eq. 9

Review of assay methods

Many analytical techniques are available for measurement of phenytoin serum concentration, such as spectrophotometry, immunoassay, and chromatography. Chromatographic methods are specific and sensitive enough to measure all currently used drugs and their metabolites over the full concentration range of clinical interest, but they take long time to assay. The immunoasaay techniques are now commonly used in clinical laboratory, such as immunochemical techniques, radioimmunoassay, and fluorescence polarization immunoassay (FIPA, TDX®). These techniques are rapid and sensitive. *(51-52)*

Synchron® CX7 system (Beckman coulter,Inc.)

The Synchron® CX7 system is fully automated analyzer for measure chemical and electrolyte concentration in serum, plasma, urine, or cerebrospinal fluid. The CX7 system include of CX4 for measure general chemistry and drug concentration, and CX3 for measure critical care chemistry. For phenytoin principle of assay is a particle enhanced turbidimetric inhibition immunoassay method. A particle-bound drug (PBD) binds to phenytoin-specific antibody (Ab) forming insoluble aggregates causing light scatter. Nonparticle-bound phenytoin in the patient sample competes with the PBD for

the antibody binding site, inhibiting the formation of insoluble particle phenytoin-antibody aggregates. The rate particle aggregation is inversely proportional to the concentration of phenytoin in the sample. *(53)*

Reaction Scheme

Phenytoin sample +PBD+A–› PBD-Ab Aggregates +Phenytoin sample -Ab

Specimen storage

Freshly drawn serum or plasma is the preferred specimens. If assays are not completed immediately, they should not remain at room temperature longer than 8 hours. If assays are not completed within 8 hours, serum or plasma should be stored at +2 to +8 °C. If assays are not completed within 48 hours, serum or plasma should be stored at -15 to -20 °C.

CHAPTER III

MATERIALS AND METHODS

Materials

1. Phenytoin

1.1 Phenytoin tablet (Dilantin Infatabs®) contains of 50 mg phenytoin acid

1.2 Phenytoin capsule (Dilantin Kapseals®) contains of 100 mg phenytoin sodium (equivalence to 92 mg phenytoin acid).

2. Patient Profile (Appendix A-D) used for record:

2.1 Patient's demographic data including name, gender, age, body weight, hospital number (HN), admission number (AN), smoking and drinking history.

2.2 Patient's clinical data including past medical history, chief complaint, present illness, drug allergy, medication data, nutrition and laboratory data.

3. Synchron® CX7 system (Beckman coulter,Inc.)

3.1 No.407370, phenytoin calibrator

Six levels of accurately measured amounts of phenytoin in human serum at the following concentrations:

Level	Phenytoin concentration (μg/mL)
1	0.0
2	2.5
3	5.0
4	10.0
5	20.0
6	40.0

3.2 No. 45511, phenytoin controls:

Three levels of phenytoin in human serum should read within the range.

3.3 No.469188, phenytoin reagent kit: reactive ingredient;

Phenytoin particle reagent	4.8	mL
Monoclonal anti-phenytoin antibodies (mouse)	7.0	mL
Phenytoin reaction buffer	80.0	mL

4. Curity® NG tube (Candoll-gammatron,Inc.)

NG tube Levin's type 125 cm.

Marked at 45, 55, 65, 75 cm. from distal end.

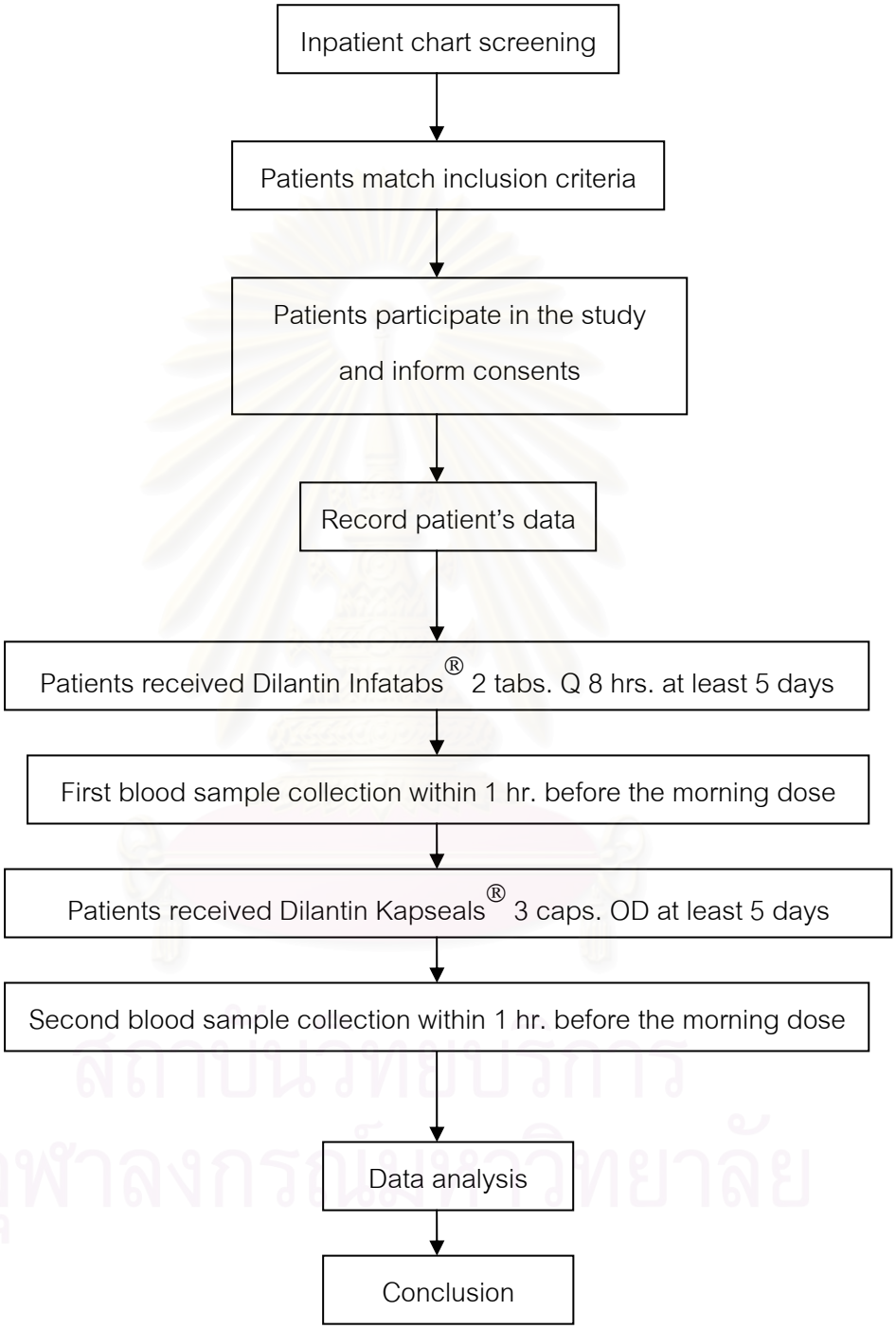
Methods

1. Study Design

This study was open-labelled, crossover clinical trial for comparison of serum phenytoin levels after administration with Dilantin Infatabs® (phenytoin acid prompt-release tablet) and Dilantin Kapseals® (phenytoin sodium sustained-release capsule) through nasogastric tube feeding. Efficacy of phenytoin in controlling seizure including any obvious side effect that might occur will be observed.

Patients enrolled were started with receiving Dilantin Infatabs® 2 tablets every 8 hours through nasogastric tube feeding for at least 5 days then serum phenytoin level was determined. Then, the dosage formulation was changed to Dilantin Kapseals® 3 capsules once daily which was again administered through nasogastric tube feeding for at least 5 days and serum phenytoin level was again determined.

Figure 1 Step of investigation



2. Ethical approval

The study design was approved by the human research committee of Prasat Neurological Institute before study.

3. Subjects

Sample size calculation from following equation:

$$n = \frac{S^2 (Z_\alpha + Z_\beta)^2}{D^2} \quad \text{Eq.10}$$

The previous study (33) conducted in 20 neurosurgery patients. Ten patients receiving phenytoin suspension 300 mg per day coadministered with continuous nasogastric feedings had a mean serum phenytoin concentration of 2.59±0.96 μg/mL. When the feedings were discontinued, the mean serum phenytoin concentration rose to 10.22±2.90 μg/mL. Ten other patients who was stabilized on phenytoin suspension 300 mg per day, the mean serum phenytoin concentration decreased from 9.80±3.27 μg/mL to 2.72±1.09 μg/mL when coadministered with continuous nasogastric feeding.

Using the mean serum phenytoin concentration coadministered with continuous nasogastric feedings:

$$\text{Mean} = \frac{2.59 + 2.72}{2}$$

$$= 2.66 \quad \mu g/mL$$

$$S^2 = \frac{S_1^2 + S_2^2}{2}$$

$$= \frac{(0.96^2) + (1.09^2)}{2}$$

$$= 1.05$$

$\alpha = 0.05$ (two-sided) ; $Z_{\alpha/2} = 1.96$

β = 0.2 ; Z_β = 0.84

D = 20 % of the averaged mean (calculated above)

= 2.66 x 20 %

= 0.53 μg/mL

$$n = \frac{(1.05) \times (1.96+0.84)^2}{0.53^2}$$

= 29.4 $\cong$ 30 patients

Assume drop out 10 %

n = 33 patients

Sample size: at least 33 patients

3.1 Inclusion criteria

Inpatients at Prasat Neurological Institute whom treated with phenytoin by nasogastric tube feeding. All patients were recruited to the study according to the following conditions.

3.1.1 Older than 18 years old.

3.1.2 Receive the nutrition by nasogastric tube feeding

3.1.3 Receive phenytoin as monotherapy to control seizure

3.1.4 Receive phenytoin by nasogastric tube feeding

3.1.5 Agreed to be included in the study after the objective and procedures of the study were explained and signed informed consent before commencing the study.

3.2 Exclusion criteria

Patients with the following conditions were excluded from the study:

3.2.1 Concurrently used other antiepileptic drugs

3.2.2 History of phenytoin allergy

3.2.3 Discharge from hospital

3.2.4 Off NG tube feeding

3.2.5 Physician did not agree to be recruited to the study according to any reason.

All of patients' available data to study were recorded including age, gender, weight, height, medical history, and smoking history, alcohol drinking history, diagnosis, and drugs administered, dosage regimen and clinical responses to phenytoin therapy, adverse drug reactions, drug interactions and laboratory data.

4. Dosage Regimen and Administration

4.1 Phenytoin preparations available at Prasat Neurological Institute are:

4.1.1 Injection preparation was Dilantin (50 mg/mL) Pfizer.

4.1.2 Oral preparations were Dilantin Kapseals 100 mg and Dilantin Infatabs 50 mg Pfizer

4.2 The usual dose regimen of phenytoin prescribed to patients at Neurosurgical ward of Prasat Neurological Institute are as follow:

4.2.1 Sodium phenytoin injection (50 mg/mL) composes of 92% phenytoin is used for treatment seizure or prophylaxis post-traumatic seizure. In adults, a loading dose is 10-15 mg/kg and a maintenance dose is 4-7 mg/kg/day, dilute in 0.9% normal saline injection, should be administered slowly via rate not exceeding 50 mg/min.

4.2.2 Phenytoin tablet 50 mg composes of 100% phenytoin administered to NG tube feeding patient. The recommended maintenance dose is

usually 300 mg per day divided every 8 hours or calculated according to the body weight of patients. The recommended maintenance dose is 4-7 mg/kg/day.

4.2.3 Sodium phenytoin capsule 100 mg composes of 92% phenytoin. The recommended maintenance dose is usually 300 mg once daily or calculated according to the body weight of patients. The recommended maintenance dose is 4-7 mg/kg/day.

5. Blood Sample Collection

After the patients received the fixed dose (300 mg/ day) of each phenytoin formulation through nasogastric tube feeding for five to seven days, the phenytoin serum concentration was considered to achieve steady state. Five milliliters blood sample was drawn from forearm of the patient for determination of serum total phenytoin concentration.

Through blood sample was drawn not over 1 hour before the administration of the next dose of phenytoin which was given with breakfast. Immediately assay was preferred. If assays were not completed within 8 hours, serum should be stored at +2 to +8 $^{\circ}$C.

6. Therapeutic Monitoring of Phenytoin

All patients treated with phenytoin were monitored for their clinical responses to phenytoin prophylaxis and phenytoin therapy. The clinical responses were determined for both beneficial effect and adverse drug reaction. The data record form and adverse drug reaction assessment form are shown in Appendix E.

The patient who had inappropriate phenytoin serum level would be informed to the physician. The patient who had uncontrolled seizure or had severe adverse drug reaction should be dropped out.

The pharmacokinetics theories applied for adjustment of individual appropriate phenytoin dosage regimen were based on serum level (determination from serum concentration) and clinical response of the patient.

For patients who have hypoalbuminemia, the reported phenytoin serum concentration can be adjusted by using the following equation.

$$C_{NB} = \frac{C_{Obs}}{0.9(Alb/4.4) + 0.1} \quad \text{Eq.1}$$

7. Michaelis-Menten Parameters

The pharmacokinetic parameter (Vmax) when assume Km=4 mg/L (population average value) and the individual Km and Vmax can be calculated by following equation.

$$Vmax = \frac{(S)(F)(dose/\tau)(Km + Css)}{Css} \quad \text{Eq.7}$$

$$-Km = \frac{R_1 - R_2}{(R_1/Css_1) - (R_2/Css_2)} \quad \text{Eq.8}$$

R_1 and R_2 are the rates of phenytoin administration of initial dose and new dose

Or $$R = (S)(F)(dose/\tau) \quad \text{Eq.9}$$

The above equation can be rearranged for calculation predicted serum phenytoin concentration and suitable dose for individual patients as follow:

$$Css = \frac{(Km)[(S)(F)(Dose/\tau)]}{Vmax - [(S)(F)(Dose/\tau)]} \quad \text{Eq.11}$$

$$\text{Dose} = \frac{(V_{max})(C_{ss})(\tau)}{(K_m + C_{ss})(S)(F)} \quad \text{Eq.12}$$

8. Analytical Method

The concentration of phenytoin in serum samples were determined by using turbidimetric inhibition immunoassay method. By using Automated Analyzer, Synchron CX® Systems Beckman Coulter,Inc. The process was shown in appendix F.

9. Data Analysis

9.1 Descriptive ststistic

9.1.1 Determine the patient's demographic data such as age, gender, weight, height, smoking history, drinking history, diagnosis and laboratory data.

9.1.2 Determine the mean±SD and median of serum phenytoin concentration after administration of phenytoin tablet and phenytoin capsule.

9.1.3 Determine the mean±SD and median of serum albumin concentrations measured at the time of phenytoin tablet and phenytoin capsule administration.

9.1.4 Determine the mean±SD and median of adjusted serum phenytoin concentration after administration of phenytoin tablet and phenytoin capsule.

9.1.5 Determine the percentage of patients with serum phenytoin concentrations within different concentration ranges.

9.1.6 Determine the mean±SD and median of pharmacokinetic parameters such as Vmax, predicted serum phenytoin concentration and dose required.

9.2 Paired t-test and Wilcoxon Signed Ranks Test

9.2.1 Compared the serum phenytoin concentration after administration of phenytoin tablet and phenytoin capsule.

9.2.2 Compared the serum albumin concentrations measured at the time of phenytoin tablet and phenytoin capsule administration.

9.2.3 Compared the adjusted serum phenytoin concentration after administration of phenytoin tablet and phenytoin capsule.

9.2.4 Compared the Vmax value after administration of phenytoin tablet and phenytoin capsule.

9.2.5 Compared the measured and predicted serum phenytoin concentration after administration of phenytoin tablet and phenytoin capsule.

CHAPTER IV

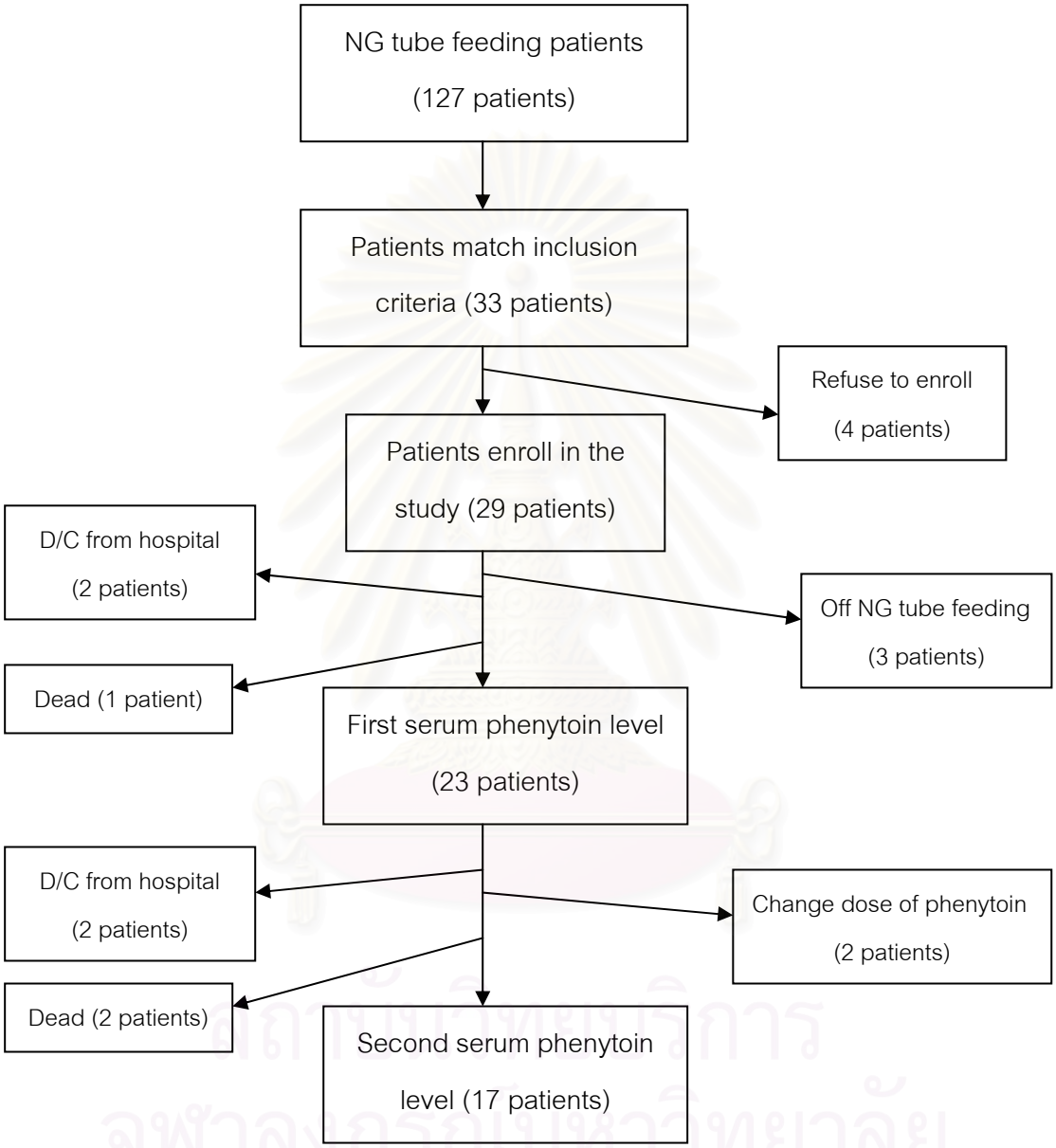
RESULT

Study Population

Inpatient charts of neurosurgical wards at Prasat neurological institute was performed during October 2004 to October 2005 were screened. There were 127 patients received enteral nutrition by NG tube feeding. However, only 33 patients matched the inclusion criteria. These 33 patients were asked to participate in the study. Four patients refused to enroll in the study, 29 patients had entered to the study. However, three patients were off NG tube feeding because they could take food by mouth, two patients discharge from the hospital because of clinical improvement, and 1 patient was dead from his disease status. Therefore, only 23 patients were participated until the first blood sample was drawn.

Finally, only 17 patients completed the whole process of study. After the first blood sample had been collected, 2 more patients were discharged from the hospital due to clinical improvement, physician order to change the dosage of 2 patients, and 2 patients was dead from his disease status. The numbers of patient participated in each step of investigation were concluded in Figure 2.

Figure 2 Number of patients participated in each step of investigation.



Patients' Characteristics

1. Demographic data

There were 17 patients finished the study. They were 10 females (58.8%) and 7 males (42.1%). Age range from 18 to 89 years, mean age was 62.94±15.94 years. Weight range from 45 to 85 kg., mean weight was 61.18±11.18 kg. Height range from 154 to 176 cm., mean height was 160.88±6.07 cm. Most of them jobless (70.6%) since majority were older than 60 years. Three patients (17.6%) had smoking history but all of them stop smoking before enrolled in the study. Five patients (29.4%) had drinking history. Table 9 showed the patient's characteristics, ie, age sex, body weight and occupation. Table 10,11 showed smoking and drinking history.

2. Patient's clinical data

Fourteen patients (82.4%) who finished the study had cerebrovascular disease, two patients (11.8%) had brain tumor, and one patient had head injury (Figure 3). Fourteen patients (82.4%) had craniotomy. Some patients had concomitant disease such as hypertension (9 patients, 52.9%), diabetes mellitus (1 patient, 5.9%), osteoarthritis (1 patient, 5.9%) and Parkinson disease (1 patient, 5.9%). None of the patient showed sign of seizure during the study period. Table 12 showed patient's present illness, craniotomy history and concomitant diseases.

The concurrent medicine used during the study were shown in table 13.The laboratory data such as liver function test (AST, ALT Alkaline phosphatase) and renal function test (BUN,Serum creatinine) were shown in table 14.

Table 9 Patient's characteristics

Case	Sex	Age(year)	BW(kg)	Occupation
1[a,b]	male	68	65	no
2[b]	male	68	65	no
3[b]	male	67	75	agriculturist
4[a,b]	male	74	68	no
5	male	39	70	gov.officer*
6[a,b]	male	66	70	gov.officer*
7	female	89	45	no
8	female	54	70	business
9	female	71	67	no
10	female	59	55	business
11	female	18	50	no
12	female	65	52	no
13	female	79	48	no
14	female	66	46	no
15	female	53	53	business
16	female	63	56	no
17	male	71	85	no

*gov.officer = government officer

[a] smoking

[b] drinking

Table 10 Smoking history

History	Number of patients	Percent
Smoking	3	17.6
Not smoking	14	82.4
total	17	100.0

Table 11 Drinking history

History	Number of patients	Percent
Drinking	5	29.4
Not drinking	12	70.6
total	17	100.0

Table 12 Patient's present illness, craniotomy history, concomitant disease, and dose of phenytoin recieved.

Case	Present illness	Craniotomy	Concomitant disease	Dose of phenytoin (mg/kg)
1	CVA	Yes	No	4.62
2	CVA	No	Hypertension	4.62
3	CVA	Yes	Hypertension	4.00
4	CVA	Yes	Hypertension	4.41
5	Brain tumor	Yes	Osteoartritis	4.29
6	Head injury	Yes	Hypertension	4.29
7	CVA	Yes	Hypertension, Parkinson dz.	6.67
8	CVA	No	No	4.29
9	CVA	Yes	Hypertension	4.48
10	CVA	No	Hypertension,DM	5.45
11	Brain tumor	Yes	No	6
12	CVA	Yes	No	5.77
13	CVA	Yes	No	6.25
14	CVA	Yes	No	6.52
15	CVA	Yes	Hypertension	5.66
16	CVA	Yes	No	5.36
17	CVA	Yes	Hypertension	3.53
Mean±SD	-	-	-	5.07±0.95

Table 13 Concurrent medicine

Case	Concurrent medicine
1	Cardura (2) 1x1 ,FBC 1x3, Ventolin NB prn q 6 hr.
2	Ranitidine (150) 1x2, Nimotop (30) 2 tab. prn q 6 hr., Rocephin iv 1 g q 12 hr. Paracetamol (500) 2 tab. prn
3	Nexium (20) 1x1, Bactrim 2x3, $CaCO_3$ 1x3, Theodur 1x2
4	Isordil (10) 1x2, Omeprazole (20) 1x1, NaCl 1x2, FBC 1x2, Folic acid 1x1 $B_{1\text{-}6\text{-}12}$ 1x2, Amikin 750 mg iv OD, Fortum 1 g iv q 8 hr.
5	Paracetamol (500) 2 tab. prn, $B_{1\text{-}6\text{-}12}$ 1x3, Ranitidine (150) 1x2, Sinemet (25/250) ½ x2, Ofloxacin (100) 2x2
6	$B_{1\text{-}6\text{-}12}$ 1x2, Nexium (20) 1x1, Paracetamol (500) 2 tab. prn, Amitriptyline (10) 1x2, Amikin 750 mg iv OD, Sulperazone 2 g iv q 12 hr.
7	Artane (2) ½ x 2, Seroquel (25) 1x2, Enaril (20) 1x2, Nimotop (30) 2 tab. prn q 6 hr., Sodamint 2x2, Madopar (250) ½ x2, FBC 1x3, Omeprazole (20) 1x1
8	Nimotop (30) 2 tab. prn q 6 hr., Enaril (5) 1x2, Paracetamol (500) 2 tab. prn, Omeprazole (20) 1x1, $B_{1\text{-}6\text{-}12}$ 1x3, Sulperazone 2 g iv q 12 hr.
9	Paracetamol (500) 2 tab. prn, $B_{1\text{-}6\text{-}12}$ 1x3, Ranitidine (150) 1x2, Ventolin NB prn q 6 hr., Humulin (70/30) sc 15 u morning and 5 u evening
10	Omeprazole (20) 1x1, Nimotop (30) 1x3, FBC 1x3, Vit C (500) 1x3, Paracetamol (500) 2 tab. prn, Senokot 3x1, Ventolin NB prn q 6 hr., Humulin (70/30) sc 15 u morning and 5 u evening
11	Nexium (20) 1x1, Vit C (500) 1x3, $B_{1\text{-}6\text{-}12}$ 1x3, Paracetamol (500) 2 tab. prn, Fortum 1 g iv q 8 hr., Cloxacillin 1 g q 6 hr.
12	Ranitidine (150) 1x2, Fortum 1 g iv q 8 hr., Amikin 750 mg iv OD, dexamethasone 4 mg iv q12 hr., Paracetamol (500) 2 tab. prn
13	Nexium (20) 1x1, Folic acid 1x1, $B_{1\text{-}6\text{-}12}$ 1x3
14	Omeprazole (20) 1x1, Diovan (160) 1x1, $B_{1\text{-}6\text{-}12}$ 1x3
15	Cardura (2) 1x1, Enaril (20) 1x2, Lipitor (10) 1x1
16	Ranitidine (150) 1x2, Paracetamol (500) 2 tab. prn
17	Omeprazole (20) 1x1, Ciprofloxacin 400mg iv q 12Hr.

Figure 3 Percent of patients were diagnosed (n=17)

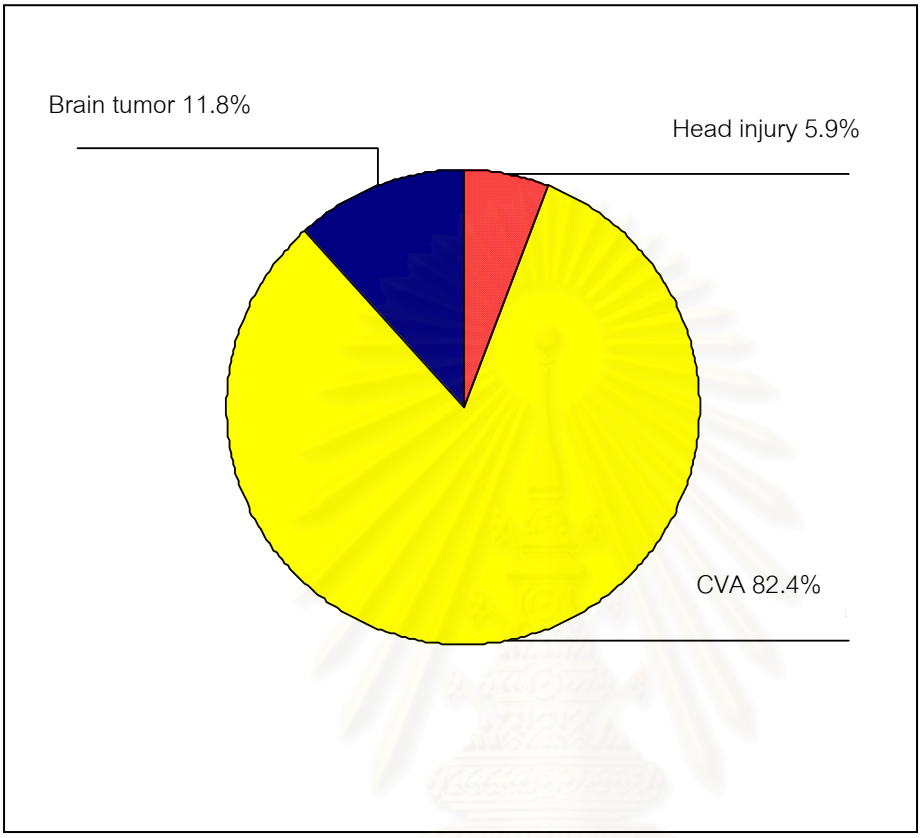


Table 14 Liver function test, BUN and serum creatinine of 17 patients

Case	AST (5-40mg/dL)*	ALT (5-40mg/dL)*	ALP (35-125mg/dL)*	BUN (8-25 mg/dL)*	SCr (0.6-1.6 mg/dL)*
1	23	16	81	17	1.1
2	58	74	322	27	1.1
3	39	48	86	12	0.8
4	36	43	82	15	1.0
5	29	32	111	10	0.9
6	77	71	122	23	0.9
7	22	16	95	20	1.1
8	178	198	505	13	0.5
9	17	23	100	28	1.2
10	133	179	463	12	0.6
11	66	57	102	6	0.7
12	52	166	136	18	1.1
13	75	59	261	12	0.8
14	37	38	84	7	0.6
15	28	28	111	18	0.8
16	40	41	94	6	0.6
17	97	217	148	15	0.9
Mean±SD	59.24±43.17	76.82±67.52	170.76±134.95	15.24±6.64	0.86±0.21

* Normal ranges

3. Serum phenytoin concentration

Serum phenytoin concentration and clinical response of all patients were determined at steady state. Seventeen patients completed two times of serum phenytoin concentration determination. Table 15 showed serum phenytoin concentrations and serum albumin concentrations of all 17 patients who completed the study.

Serum phenytoin concentrations after administration 300 mg of phenytoin tablet were ranged from 1.2 to 26.6 μg/mL, mean was 6.03±5.92 (4.60) μg/mL. Serum albumin concentrations measured at the time of phenytoin tablet administration were ranged from 1.8 to 3.7 g/dl, mean was 2.51±0.49 (2.40) g/dl. Serum phenytoin concentrations after administration of phenytoin tablet and adjusted for serum albumin concentrations were ranged from 2.10 to 52.25 μg/mL, mean was 10.33±11.60 (6.99) μg/mL.

Serum phenytoin concentrations after administration of 300 mg phenytoin capsule were ranged from 0.4 to 9.1 μg/mL, mean was 3.80±2.71 (3.00) μg/mL. Serum albumin concentrations measured at the time of phenytoin capsule administration were ranged from 1.8 to 3.2 g/dl, mean was 2.45±0.40 (2.60) g/dl. Serum phenytoin concentrations after administration phenytoin capsule and adjusted for serum albumin concentrations was range from 0.85 to 17.88 μg/mL, mean was 6.28±4.76 (4.75) μg/mL.

When the extreme concentration of patient number 3 was excluded, serum phenytoin concentrations after administration 300 mg of phenytoin tablet and capsule were ranged from 1.2 to 12.1 μg/mL and 0.4 to 8.9 μg/mL, respectively. Mean serum phenytoin concentrations after administration of phenytoin tablet and capsule were 4.74±2.72 μg/mL and 3.74±2.41 μg/mL, respectively. Adjusted serum phenytoin concentrations after administration of phenytoin tablet and capsule were ranged from 2.10 to 18.55 μg/mL and 0.85 to 14.09 μg/mL, respectively. Mean adjusted serum phenytoin concentrations after administration of phenytoin tablet and capsule were 7.71±4.35 μg/mL and 5.56±3.83 μg/mL, respectively.

Figure 4 showed the boxplot of serum phenytoin concentration after phenytoin tablet and phenytoin capsule administration along with the serum phenytoin concentration adjusted for their albumin concentrations. Patient number 3 showed extreme value which could be considered as outlier.

Steady-state serum phenytoin concentrations after administration with phenytoin tablet and phenytoin capsule were significantly different (p=0.054, paired t-test and p=0.019, Wilcoxon Signed Ranks Test). The serum phenytoin concentrations adjusted for low albumin concentrations were also significantly different (p=0.075, paired t-test and p=0.035, Wilcoxon Signed Ranks Test) between the two dosage forms. Serum albumin concentrations collected at two different times after administration with phenytoin tablet and with phenytoin capsule were not significantly different (p=0.602, paired t-test and p=0.582, Wilcoxon Signed Ranks Test). The details were shown in Table 16.

When the extreme concentration of patient number 3 was excluded, serum phenytoin concentrations along with their adjusted for low albumin concentrations after administration with phenytoin tablet and with phenytoin capsule still showed significant different at p=0.028 and p=0.051 (paired t-test), respectively.

Moreover, when calculated the logarithm of ratio of adjusted serum phenytoin concentration after administration phenytoin capsule and phenytoin tablet, as shown in table 18, the 90%confidence interval was range from 0.59 to 0.94.

4. Efficacy and adverse drug reaction

During the study, all patients were seizure free even through they had serum phenytoin concentration which were lower than therapeutic range. After phenytoin tablet administration, most of patients had adjusted serum phenytoin concentration (C_{NBtab}) within the range of 5.01-10.01 μg/mL (7patients, 41.18%). Two patients (11.76%) had adjusted serum phenytoin concentrations equal to or lower than 3 μg/mL. There were 3 patients (17.65%) and 4 patients (23.53%) with adjusted serum phenytoin concentrations within the range of 3-5 and 10.01-20 μg/mL, respectively.

There was 1 patient (5.88%) with adjusted serum phenytoin concentration which was higher than 20 μg/mL.

After phenytoin capsule administration, most patients had adjusted serum phenytoin concentration (C_{NBcap}) within the range of 3.01-5 μg/mL (6 patients, 58.82%). There were 4 patients (23.53%) with adjusted serum phenytoin concentration lower than 3 μg/mL. There were 4 patients (23.53%) and 3 patients (17.65%) with adjusted serum phenytoin concentration within the range of 5.01-10 and 10.01-20 μg/mL, respectively. None of the patient had adjusted serum phenytoin concentration higher than 20 μg/mL. The percentage of patients whose serum concentrations were within the 5 different classified ranges were shown in table 17. Figure 5 showed the bar plot of percentage of patients whose adjusted serum phenytoin concentrations were categorized in difference concentration ranges.

None of the patients showed serious adverse drug reaction (ADR) during the study. This may result from low serum phenytoin concentration in most patients and they received phenytoin for a short period. No minor adverse drug reaction had been record also. However, some adverse drug reaction such as ataxia could not be evaluated in these patients.

Table 15 Serum phenytoin concentration and serum albumin concentration of 17 patients.

Case	C_{sstab} (μg/mL)	Alb_1 (g/dL)	C_{NBtab} (μg/mL)	C_{sscap} (μg/mL)	Alb_2 (g/dL)	C_{NBcap} (μg/mL)
1	5.1	3.7	5.95	4.3	2.6	6.81
2	2.9	2.0	5.70	1.5	2.0	2.95
3	26.6	2.0	52.25	9.1	2.0	17.86
4	2.6	2.3	4.56	2.3	2.7	3.53
5	3.5	3.1	4.77	5.7	2.9	8.22
6	6.2	1.9	12.69	1.7	1.9	3.48
7	4.7	2.8	6.99	6.7	2.2	12.18
8	3.2	3.0	4.48	3.0	2.6	4.75
9	4.0	2.3	7.01	2.5	3.2	3.31
10	1.2	2.3	2.10	0.4	1.8	0.85
11	6.0	2.7	9.20	6.1	2.7	9.35
12	3.3	2.7	5.06	1.7	2.4	2.88
13	7.0	2.4	11.85	4.9	2.7	7.51
14	8.0	2.8	11.89	3.2	2.8	4.76
15	12.1	2.7	18.55	8.9	2.6	14.09
16	4.6	1.8	9.83	0.5	2.0	0.98
17	1.5	2.2	2.73	2.1	2.6	3.32
Mean±SD	6.03±5.92	2.51±0.49	10.33±11.60	3.80±2.70	2.45±0.40	6.28±4.76
*Mean±SD	4.74±2.72	2.54±0.49	7.71±4.35	3.47±2.41	2.48±0.40	5.56±3.83
Median	4.60	2.40	6.99	3.00	2.60	4.75

*Mean±SD excluded patient number 3

C_{sstab} serum phenytoin concentration after administration phenytoin tablet

Alb_1 serum albumin concentration after administration phenytoin tablet

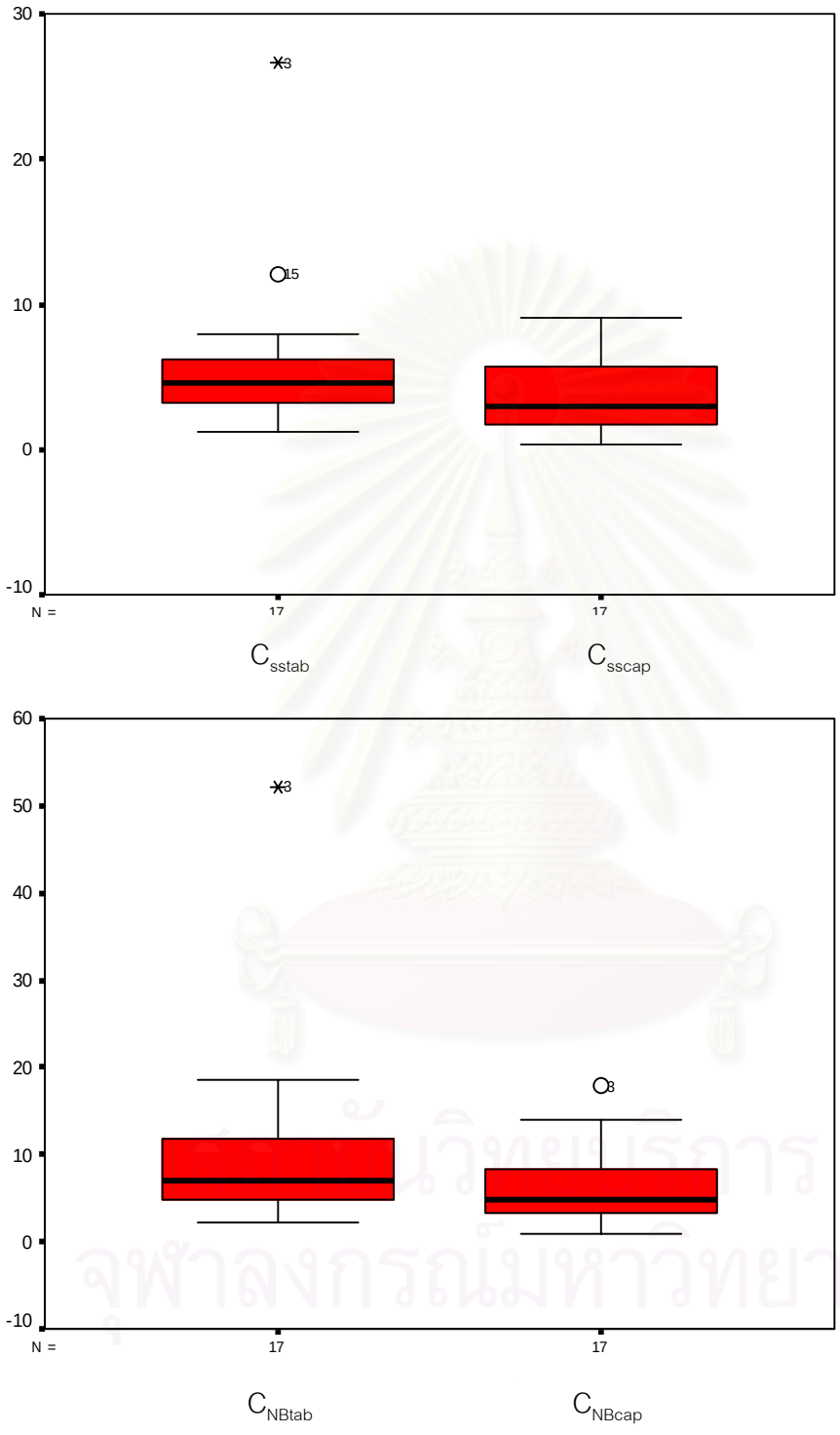
C_{NBtab} serum phenytoin concentration after administration phenytoin tablet and adjusted by serum albumin concentration

C_{sscap} serum phenytoin concentration after administration phenytoin capsule

Alb_2 serum albumin concentration after administration phenytoin capsule

C_{NBcap} serum phenytoin concentration after administration phenytoin capsule and adjusted by serum albumin concentration

Figure 4 Boxplot of serum phenytoin concentration



* Patient number 3 = outlier = Q_3 + 3IQR

IQR (Interquartile Range) = Q_3 –Q_1

Figure 5 Bar plot showed percentage of patients whose adjusted serum phenytoin concentrations fell in difference categorized concentration ranges.

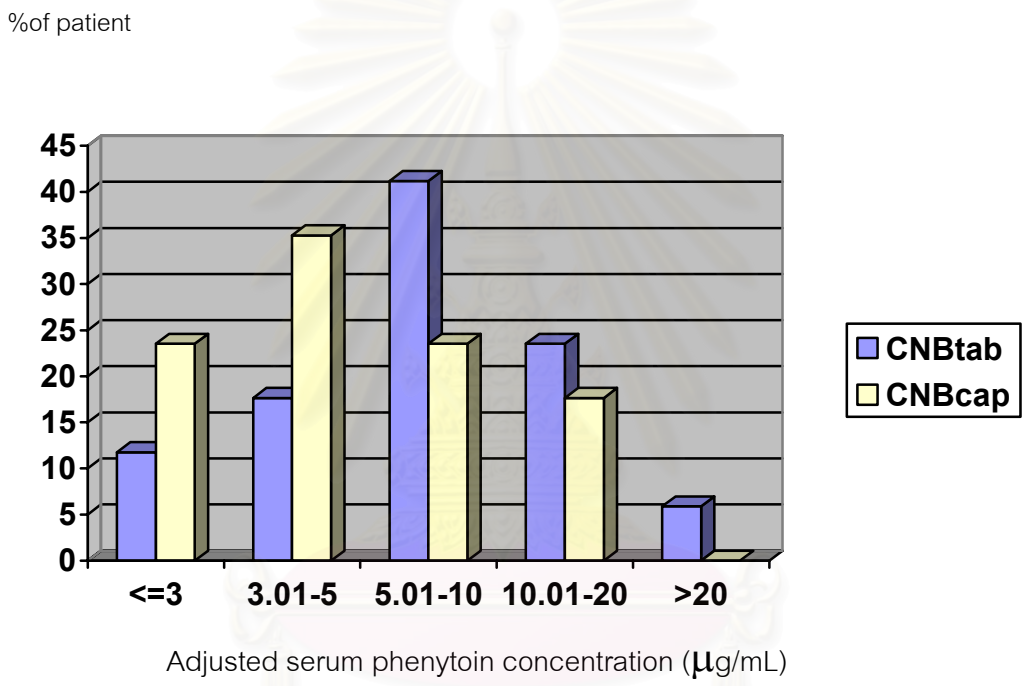


Table 16 Comparisons of the serum phenytoin concentrations and serum albumin concentrations between phenytoin tablet and phenytoin capsule

Paired t-test	n	P-value	n *	P-value
C_{sstab} and C_{sscap}	17	0.054	16	0.028
Alb_1 and Alb_2	17	0.602	16	0.603
C_{NBtab} and C_{NBcap}	17	0.075	16	0.051

* excluded patient number 3 due to outlier data

Comparisons of the serum phenytoin concentrations and serum albumin concentrations between phenytoin tablet and phenytoin capsule (nonparametric test)

Wilcoxon Signed Ranks Test	n	P-value
C_{sstab} and C_{sscap}	17	0.019
Alb_1 and Alb_2	17	0.582
C_{NBtab} and C_{NBcap}	17	0.035

Table 17 Percentage of patients with serum phenytoin concentrations within different concentration ranges

Serum phenytoin level (μg/mL)	C_{sstab}		C_{NBtab}		C_{sscap}		C_{NBcap}	
	case	%	case	%	case	%	case	%
≤ 3	4	23.53	2	11.76	9	52.94	4	23.53
3.01-5	6	35.29	3	17.65	3	17.65	6	35.29
5.01 - 10	5	29.41	7	41.18	5	29.41	4	23.53
10.01 - 20	1	5.88	4	23.53	0	0	3	17.65
>20	1	5.88	1	5.88	0	0	0	0
Total	17	100	17	100	17	100	17	100

Table 18 The logarithm of ratio of adjusted serum phenytoin concentration after administration phenytoin capsule and phenytoin tablet.

Case	Log C_{NBtab}	Log C_{NBcap}	Log C_{NBcap} / Log C_{NBtab}
1	0.77	0.83	1.08
2	0.76	0.47	0.62
3	1.72	1.25	0.73
4	0.66	0.55	0.83
5	0.68	0.92	1.35
6	1.10	0.54	0.49
7	0.84	1.09	1.29
8	0.65	0.68	1.04
9	0.85	0.52	0.62
10	0.32	-0.07	-0.21
11	0.96	0.97	1.01
12	0.70	0.46	0.65
13	1.07	0.88	0.82
14	1.08	0.68	0.63
15	1.27	1.15	0.91
16	0.99	-0.01	-0.01
17	0.44	0.52	1.20
Mean±SD	0.87±0.33	0.67±0.36	0.77±0.42
90%CI			0.59 - 0.94

5. Michaelis-Menten parameters

The pharmacokinetic parameter (Vmax/F) of 17 patients when assume Km=4 mg/L (population average value) can be calculated by using equation 7. Mean Vmax/F calculated from serum phenytoin concentration after administration of phenytoin tablet was 501.32±137.02 (471.76) mg/day while mean Vmax/F calculated from serum phenytoin concentration after administration of phenytoin capsule was 612.90±346.18 (508.51) mg/day. Vmax/F of each patients when assume Km=4 was shown in table 19. Table 20 was the comparison of Vmax/F after administration phenytoin tablet and capsule, the different was not statistically significant (p = 0.246).

Since two different dosage forms were administered and their corresponding serum concentrations were measured, if the dosages administered were assumed to be different, the pharmacokinetic parameters of individual patient could be calculated. Km was calculated from equation 7 and 8, then, individual Km obtained were used to calculate Vmax using equation 7. The Km and Vmax of individual patient were shown in table 21. The Km values ranged from -7.7395 to 7.0146 mg/L, and the mean±SD equal to 0.0554±2.9734 mg/L. The Vmax values ranged from 47.59 to 426.87 mg/day, and the mean±SD was 282.06±99.23 mg/day (0.95 to 7.80 mg/kg/day, mean±SD was 4.79±2.00 mg/kg/day).

Table 19 Vmax/F (assume Km=4mg/L)

Case	$Vmax_{tab}/F_{tab}$ (mg/day)	Vm_{tab}/F_{tab} (mg/kg/day)	$Vmax_{cap}/F_{cap}$ (mg/day)	Vm_{cap}/F_{cap} (mg/kg/day)
1	501.60	7.72	438.22	6.74
2	510.66	7.86	650.69	10.01
3	322.97	4.31	337.76	4.50
4	563.29	8.28	589.09	8.66
5	551.69	7.88	410.26	5.86
6	394.57	5.64	593.33	8.48
7	471.76	10.48	366.63	8.15
8	567.61	8.11	508.51	7.26
9	471.14	7.03	609.21	9.09
10	870.45	15.83	1568.18	28.51
11	430.45	8.61	394.05	7.88
12	537.19	10.33	659.74	12.69
13	401.30	8.36	422.96	8.81
14	400.91	8.72	508.09	11.05
15	364.69	6.88	354.37	6.69
16	422.13	7.54	1400.07	25.00
17	740	8.71	608.16	7.15
Mean±SD	501.32±137.02	8.37±2.42	612.90±346.18	10.38±6.48
Median	471.76	8.11	508.51	8.48

Km Substrate concentration at which rate of metabolism will be one-half of Vmax

$Vmax_{tab}$ Maximum rate of metabolism (mg/day) after administration phenytoin tablet 300 mg/day

$Vmax_{cap}$ Maximum rate of metabolism (mg/day) after administration phenytoin capsule 300 mg/day

F_{tab} Bioavailability after administration phenytoin tablet 300 mg/day

F_{cap} Bioavailability after administration phenytoin capsule 300 mg/day

Table 20 Comparisons of the maximum rate of metabolism (Vmax) obtained after administration of phenytoin tablet and phenytoin capsule (assume Km = 4 mg/L)

	n	P-value Paired t-test	P-value Non-parametric test*
$Vmax_{tab}/F_{tab}$ and $Vmax_{cap}/F_{cap}$	17	0.139	0.246
Vm_{tab}/F_{tab} and Vm_{cap}/F_{cap}	17	0.133	0.193

* Wilcoxon Signed Ranks Test

Table 21 Individual Km and Vmax calculated from C_{NBtab} and C_{NBcap}

Case	Km(mg/L)	Vmax(mg/day)	Vmax(mg/kg/day)
1	-2.4373	177.16	2.73
2	0.5852	330.82	5.09
3	2.4745	314.21	4.19
4	1.9275	426.87	6.28
5	-0.8175	248.56	3.55
6	0.4310	310.19	4.43
7	-1.1832	249.19	5.54
8	-2.7347	117.04	1.67
9	0.5923	325.34	4.86
10	0.1330	318.97	5.80
11	-7.7395	47.59	0.95
12	0.6551	338.84	6.52
13	2.1024	353.24	7.36
14	0.7318	318.46	6.92
15	7.0146	413.44	7.80
16	0.0958	302.93	5.41
17	-0.8902	202.08	2.38
Mean±SD	0.0554±2.9734	282.06±99.23	4.79±2.00

The values of Vmax/F obtained from administering of phenytoin tablet as shown in table 19 were used to predicted serum concentration that should be obtained after administration of phenytoin capsule showed in table 22. The predicted phenytoin serum concentrations from capsule were ranged from 1.86 to 23.51 μg/mL while the mean was 6.98±5.08 (5.64) μg/mL. On the other hand, the Vmax/F values obtained from phenytoin capsule were used to calculate the predicted phenytoin serum concentration from tablet as shown in table 23. The predicted phenytoin serum concentrations from tablet were ranged from 0.95 to 31.78 μg/mL and the mean was 8.84±8.29 (5.76) μg/mL. The measured serum phenytoin concentrations and the predicted serum phenytoin concentrations after administration of phenytoin tablet and capsule were not significantly different at 95% confidence level as shown in table 24 (p=0.554 and p=0.435 respectively). This may imply that the difference of bioavailabilities between phenytoin tablet and capsule were not strong enough for definite conclusion. From table 22, the mean percentage difference between predicted and measured serum phenytoin capsule concentration was -62.24±168 (-17.29). From table 23, the mean percentage difference between predicted and measured serum phenytoin tablet concentration was -0.78±67.45 (17.62).

Since the concentrations of phenytoin obtained were mostly lower than the therapeutic range (10-20 μg/mL) the desired serum phenytoin concentration was set at 15 μg/mL, the appropriate dosage required for phenytoin tablet and capsule could be calculated using Km equaled to 4 mg/L and Vmax/F equaled to the values shown in table 19, the result were shown in table 25. From table 25, the mean dosage required for phenytoin tablet was 394.12±114.40 mg/day or round up to be 400 mg/day and the mean dosage required for phenytoin capsule was 523.53±296.92 mg/day or round up to be 500 mg/day. These dosages were higher than the usual dose of phenytoin, so, the individual serum phenytoin concentration should be monitored when using in clinical practice.

Table 22 The predicted phenytoin capsule serum concentrations calculated from Vmax/F value from phenytoin tablet.

Case	Measured C_{NBcap} (μg/mL)	Predicted C_{NBcap} (μg/mL)	Difference (μg/mL)	Percent difference (%)
1	6.81	4.89	1.91	28.10
2	2.95	4.70	-1.76	-59.68
3	17.88	23.51	-5.63	-31.50
4	3.53	3.84	-0.32	-8.98
5	8.22	4.00	4.22	51.30
6	3.48	9.31	-5.83	-167.62
7	12.18	5.64	6.54	53.71
8	4.75	3.79	0.96	20.27
9	3.31	5.66	-2.34	-70.76
10	0.85	1.86	-1.00	-117.37
11	9.35	7.15	2.20	23.57
12	2.88	4.23	-1.35	-46.92
13	7.51	8.81	-1.30	-17.29
14	4.76	8.84	-4.08	-85.81
15	14.09	12.45	1.64	11.63
16	0.98	7.55	-6.57	-669.20
17	3.32	2.38	0.94	28.41
Mean±SD	6.28±4.76	6.98±5.08	-0.69±3.57	-62.24±168
Median	4.75	5.64	-1.00	-17.29

Table 23 The predicted phenytoin tablet serum concentrations calculated from Vmax/F value from phenytoin capsule.

Case	Measured C_{NBtab} (μg/mL)	Predicted C_{NBtab} (μg/mL)	Difference (μg/mL)	Percent difference (%)
1	5.95	8.68	-2.73	-45.86
2	5.70	3.42	2.27	39.93
3	52.25	31.78	20.47	39.18
4	4.56	4.15	0.41	8.93
5	4.77	10.88	-6.12	-128.27
6	12.69	4.09	8.60	67.76
7	6.99	18.01	-11.02	-157.79
8	4.48	5.76	-1.27	-28.35
9	7.01	3.88	3.13	44.65
10	2.10	0.95	1.16	55.02
11	9.20	12.76	-3.56	-38.71
12	5.06	3.34	1.72	34.07
13	11.85	9.76	2.09	17.62
14	11.89	5.77	6.13	51.51
15	18.55	22.07	-3.52	-18.97
16	9.83	1.09	8.73	88.90
17	2.73	3.89	-1.17	-42.78
Mean±SD	10.33±11.60	8.84±8.29	1.49±7.01	-0.78±67.45
Median	6.99	5.76	1.16	17.62

Table 24 The significant test of measured serum phenytoin concentration and predicted serum phenytoin concentration

	n	P-value	P-value*
Measured C_{NBtab} and Predicted C_{NBtab}	17	0.394	0.554
Measured C_{NBcap} and Predicted C_{NBcap}	17	0.436	0.435

* non-parametric test (Wilcoxon Signed Ranks Test)

Figure 6 Bar plot showed number of patients who had measured phenytoin concentration more than predicted phenytoin concentration

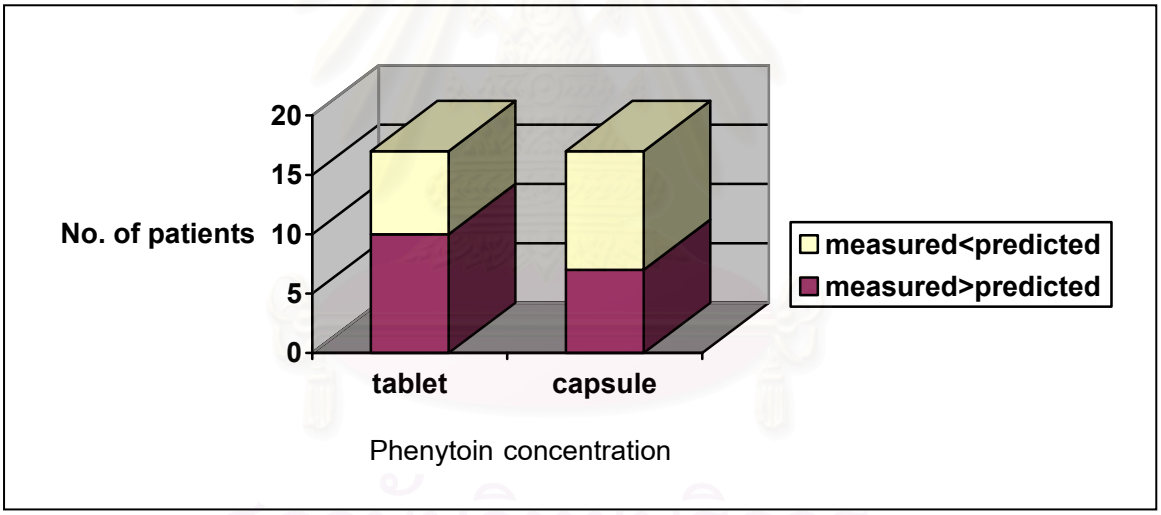


Table 25 The dosage of phenytoin tablet and capsule calculated from one steady steady-state serum phenytoin concentration after administration phenytoin tablet and capsule (assume desired serum phenytoin concentration was 15 μg/mL).

Case	Required *$dose_{tab}$ (mg/day)	Round up $dose_{tab}$ (mg/day)	Required **$dose_{cap}$ (mg/day)	Round up $dose_{cap}$ (mg/day)
1	396.00	400	376.04	400
2	403.15	400	558.37	550
3	254.97	250	289.84	300
4	444.70	450	505.51	500
5	435.54	450	352.05	350
6	311.51	300	509.15	500
7	372.44	350	314.61	300
8	448.12	450	436.36	450
9	371.95	350	522.78	500
10	687.20	700	1345.69	1350
11	339.83	350	338.14	350
12	424.10	400	566.14	550
13	316.81	300	362.95	350
14	316.51	300	436.00	450
15	287.91	300	304.10	300
16	333.26	350	1201.44	1200
17	584.21	600	521.87	500
Mean±SD	395.78±108.18	394.12±114.40	525.94±297.06	523.53±296.92

*$dose_{tab}$ Dose of phenytoin tablet

**$dose_{cap}$ Dose of phenytoin capsule

CHAPTER V

DISCUSSION

Serum phenytoin concentrations highly varied among patients after consuming either phenytoin tablet or phenytoin capsule. Other studies on enteral tube feeding patients usually received phenytoin suspension. However, in Thailand the phenytoin suspension was not available, therefore, tablet or capsule dosage forms of phenytoin were used instead.

Phenytoin tablet and phenytoin capsule required different administration process. Phenytoin tablet needed to crush and suspended in water before administration. Size of the granules resulted from crushing the tablet were varied depended on different person (nurse) who crushed it, this may result in variation of phenytoin bioavailability. Phenytoin capsule is more convenience to use since it did not required crushing before administration. However, the granules were smaller and more bulky, some were sticked to the feeding tube and required more water to flush them down. This might cause variation in bioavailability also.

More than half of patients who receiving 300 mg daily of phenytoin tablet (11 patients, 64.71%) had serum phenytoin concentration within the range of 5-20 μg/mL. However, only 7 patients (41.18%) had serum phenytoin concentration within the range of 5-20 μg/mL after administration 300 mg daily of phenytoin capsule. If the therapeutic range was proposed to be 10-20 μg/mL as in general, then, only 23.53% of serum phenytoin concentrations from tablet and 17.65% of serum phenytoin concentrations from capsule were within the therapeutic range.

All patients enrolled could not take oral diet. They received the blenderized diet (Prasat Neurological formula) through nasogastric tube. This was different from other studies which using commercial enteral feeding formula such as Isocal, Ensure and Osmolite, etc. Some studies*(42,45)* indicated that the hydrolyzed protein or isolated

protein in commercial enteral feeding formula cause decreasing in serum phenytoin concentration. Moreover, other studies*(34-35)* revealed that continuous feeding make serum phenytoin concentration lower than interrupted feeding (separated from phenytoin administration for 2 hours). In this study, the enteral feeding formula which contain intact protein was feeding bolusly together with phenytoin administration might result in serum phenytoin concentration which was lower than the therapeutic range.

Doak et al *(41)* study the bioavailability of phenytoin acid suspension and phenytoin sodium solution administered through nasogastric tube feeding in 10 healthy volunteers, the mean bioavailability of phenytoin acid suspension and phenytoin sodium solution were 0.88±0.15 and 0.91±0.70, respectively. This indicated that the bioavailability of phenytoin tablet and phenytoin capsule administered through nasogastric tube feeding might also be lower than 1.

The serum phenytoin concentration after administration phenytoin tablet and capsule were significantly different when compared the means serum phenytoin concentrations of 16 patients.

When calculated the logarithm of ratio of adjusted serum phenytoin concentration after administration phenytoin capsule and phenytoin tablet, the 90%confidence interval was range from 0.59 - 0.94. It showed that both phenytoin formulations were not bioequivalence (90%CI should be within 0.8 – 1.25).

One reason which caused the serum phenytoin concentrations obtained from capsule to be significantly lower than that obtained from tablet should be caused by the difference in salt form between phenytoin tablet and capsule. Phenytoin tablet contained phenytoin in free acid form while phenytoin capsule contained phenytoin in sodium salt form. The dosages consumed were 300 mg daily of either free acid form or sodium salt form of phenytoin, the salt form contain less phenytoin than the free acid.

Majority of patients had the measured concentrations after consumed phenytoin tablet dosage form higher than their correspondent predicted concentrations (from pharmacokinetic parameters obtained from capsule). In contrary, the predicted

concentrations (from pharmacokinetic parameters obtained from tablet) were higher than the correspondent measured concentrations after administering phenytoin capsule in most patients. (Figure 6) These results might imply that bioavailability of phenytoin tablet could be higher than phenytoin capsule.

Accordingly, since the bioavailabilities of phenytoin tablet and capsule were not similar, individual Km and their corresponding Vmax as report in table 21 might not be valid. The pharmacokinetic parameters reported in table 21 were based on the assumption that bioavailabilities (F) of both tablet and capsule were the same. Since only one dosage of each formulation was given to the patient and neither formulation showed complete absorption when administered at the same time with diet feeding as done in this study. The population Km (Km=4mg/L) was used for calculation of Vmax for individual patient.

From table 17, most patients had subtherapeutic serum phenytoin concentrations (therapeutic range is 10-20 μg/mL). However, none of the patients had seizure during the study. This result was in agree with some literatures which reported that serum phenytoin concentrations which lower than the proposed therapeutic range could control seizure in some patients. However, the main reason for seizure free in this study might due to the indication of using phenytoin in this study was mainly for prophylaxis seizure after neurosurgery which has already had low incidence of seizure.

However, since high percentage of patients had their measured phenytoin concentrations lower than 5 μg/mL even after adjusted for low albumin, especially when administering with phenytoin capsule, the percentage of patients whose serum phenytoin concentrations lower than 5 μg/mL was higher than 58.81%, this might indicated that food interfered with phenytoin absorption. The dosage of phenytoin might require to be increased for a better clinical assurance. The predicted averaged appropriate dosage for phenytoin tablet was approximately 400 mg/day while for phenytoin capsule the dose was approximately 500 mg/day. These predicted dosages were quite high and the bioavailabilities of both tablet and capsule were varied, therefore, instead of increasing dose, a safer method to increase bioavailability or serum

phenytoin concentration might be obtained by feeding standard dose of phenytoin (300 mg/day) 2 hours apart from feeding diet formula as reported by Bauer (34). However, closely monitoring of serum phenytoin concentration is strongly recommended in either case.

.

CHAPTER VI

CONCLUSION

This study conducted in inpatients at Prasat Neurological Institute who admitted during October 2004 to October 2005. All patients included receive phenytoin as monotherapy for control seizure and received enteral tube feeding by nasogastric (NG) tube.

The 17 patients who had participated throughout the study were 10 females (58.8%) and 7 males (42.1%). Their ages ranged from 18 to 89 years, mean age was 62.94±15.94 years. Their body weights ranged from 45 to 85 kg., mean weight was 61.18±11.18 kg. Phenytoin was prescribed for prophylaxis after neurosurgery at fixed dose of 300 mg per day.

Patients enrolled were started with receiving phenytoin tablet (Dilantin Infatabs®) 300 mg/day through nasogastric tube feeding together with diet feeding for at least 5 days then serum phenytoin level was determined. Then, the dosage formulation was changed to phenytoin capsule (Dilantin Kapseals®) 300 mg/day which was again administered through nasogastric tube feeding together with diet feeding for at least 5 days and serum phenytoin level was again determined.

Serum phenytoin concentrations after administration 300 mg of phenytoin tablet were ranged from 1.20 to 26.60 μg/mL, mean was 6.03±5.92 μg/mL. Serum albumin concentrations measured at the time of phenytoin tablet administration were ranged from 1.8 to 3.7 g/dl, mean was 2.51±0.49 g/dl. Serum phenytoin concentrations after administration of phenytoin tablet and adjusted for serum albumin concentrations were ranged from 2.10 to 52.25 μg/mL, mean was 10.33±11.60 μg/mL.

Serum phenytoin concentrations after administration of 300 mg phenytoin capsule were ranged from 0.40 to 9.10 μg/mL, mean was 3.80±2.71 μg/mL. Serum

albumin concentrations measured at the time of phenytoin capsule administration were ranged from 1.8 to 3.2 g/dl, mean was 2.45±0.40 g/dl. Serum phenytoin concentrations after administration phenytoin capsule and adjusted for serum albumin concentrations was range from 0.85 to 17.88 μg/mL, mean was 6.28±4.76 μg/mL.

Steady-state serum phenytoin concentrations after administration with phenytoin tablet and phenytoin capsule were significantly different (p=0.019, Wilcoxon Signed Ranks Test). The serum phenytoin concentrations adjusted for low albumin concentrations were also significantly different (p=0.035, Wilcoxon Signed Ranks Test) between the two dosage forms.

When the extreme concentration of patient number 3 was excluded, mean serum phenytoin concentrations after administration of phenytoin tablet and capsule were 4.74±2.72 μg/mL and 3.74±2.41 μg/mL, respectively. Mean adjusted serum phenytoin concentrations after administration of phenytoin tablet and capsule were 7.71±4.35 μg/mL and 5.56±3.83 μg/mL, respectively. Serum phenytoin concentrations along with their adjusted for low albumin concentrations after administration with phenytoin tablet and with phenytoin capsule still showed significant different at p=0.028 and p=0.051, respectively.

When calculated the logarithm of ratio of adjusted serum phenytoin concentration after administration phenytoin capsule and phenytoin tablet, the 90%confidence interval was range from 0.59 - 0.94. It showed that both phenytoin formulations were not bioequivalence (90%CI should be within 0.8 – 1.25).

There were differences administration processes between phenytoin tablet and phenytoin capsule. Phenytoin capsule was more convenience to administered when compared to phenytoin tablet. The two dosage formulations showed variation in bioavailability which might cause by administration process.

The bioavailability of phenytoin tablet might be higher than phenytoin capsule. This conclusion implied from the results which showed that majority of patients had the measured concentrations after consumed phenytoin tablet dosage form higher than

their correspondent predicted concentrations, from pharmacokinetic parameters obtained from capsule. In contrary, the predicted concentrations from pharmacokinetic parameters obtained from tablet were higher than the correspondent measured concentrations after consuming phenytoin capsule in most patients.

The mean Vmax/F (when assume Km=4 mg/L) after administration phenytoin tablet and phenytoin capsule were 501.32±137.02 and 612.90±346.18 mg/day, respectively. These values were not significant different at 95% confidence level (p=0.139) is indicated that the difference in bioavailabilities between two dosage forms were still not strong enough for definite conclusion which might due to small number of subjects participated in this study while high variations among subjects even within the same dosage formulation were observed.

In conclusion, the reasons which caused the serum phenytoin concentrations obtained from capsule to be significantly lower than that obtained from tablet should be caused by:

1. The difference in salt form between phenytoin tablet and capsule. The dosages given to the patients were 300 mg daily of either phenytoin tablet or phenytoin capsule. Phenytoin tablet contained 300 mg of free phenytoin acid which was higher than the free drug in phenytoin capsule (300mg of phenytoin sodium) which contained 276 mg of free phenytoin acid.

2. The difference in bioavailability between phenytoin tablet and capsule as mentioned above.

After phenytoin tablet and capsule administration, most patients had their adjusted serum phenytoin concentration within the range of 5.01-10.01 μg/mL (7patients, 41.18%) and 3.01-5 μg/mL (6 patients, 58.82%), respectively (Figure 5). If the therapeutic range was proposed to be 10-20 μg/mL as in general, then, only 4 patients (23.53%) consuming tablet and 3 patients (17.65%) consuming capsule had their serum phenytoin concentration within the therapeutic range.

If the therapeutic range was proposed to be 5-20 μg/mL, more than half of patients who receiving 300 mg daily of phenytoin tablet (11 patients, 64.71%) had serum phenytoin concentration within the range of 5-20 μg/mL. However, only 7 patients (41.18%) had serum phenytoin concentration within the range of 5-20 μg/mL after administration 300 mg daily of phenytoin capsule. However, only 1 patient (5.88%) with adjusted serum phenytoin concentration higher than 20 μg/mL after phenytoin tablet administration and none of the patients had adjusted serum phenytoin concentration higher than 20 μg/mL after phenytoin capsule administration.

In this study, the enteral feeding formula was feeding bolusly together with phenytoin administration might bioavailability of phenytoin resulted in serum phenytoin concentration which was lower than the therapeutic range. However, during the study, all patients were seizure free even through they had serum phenytoin concentration lower than therapeutic range. None of the patients had adverse drug reaction (ADR) during the study.

The dosage of phenytoin might require to be increased for a better clinical assurance. The predicted averaged appropriate dosage for phenytoin tablet was approximately 400 mg/day while for phenytoin capsule the dose was approximately 500 mg/day. These predicted dosages were quite high and the bioavailabilities of both tablet and capsule were varied, therefore, instead of increasing dose, a safer method to increase bioavailability or serum phenytoin concentration might be obtained by feeding standard dose of phenytoin (300 mg/day) 2 hours apart from feeding diet formula as reported by Bauer (34). However, closely monitoring of serum phenytoin concentration and further studies are strongly recommended in either case.

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APPENDICES

APPENDIX A

Case no……..

Name……Sex…….Age……years

Occupation…… Weight…..kg. Height.....cm

Ward…….Bed……..HN……..AN……

Admit date…….Discharge date……...……..Admitted……...days

Physician……

Past illness and seizure history……...

Family history…….

Drug used……..

CC……

Present illness……

Dx. ……..

APPENDIX B

Case no. .....

Medication data

Drug and Dosage regimen	Date														

APPENDIX C

CASE NO…..

Phenytoin Administration Data

Date	Time	Dose and dosage form		Mix water (ml)	Water for flush NG tube (ml)
		Tablet	Capsule		

Phenytoin Serum Level

	Date	Sampling time	Analysis time	Phenytoin serum level (μg/ml)	Albumin serum level (g/dL)
1					
2					

APPENDIX D

Case no. .....

Nutrition Data

Type of NG tube.....

Date	Time	Nutrition formula	Administration		Volume
			Bolus	Continuous	

Laboratory Data

	Date										
Scr											
BUN											
AST											
ALT											
Alk. Phos.											
Albumin											
PHT level											

APPENDIX E

Case no. .....

ADR and Seizure Record

Date	Time	Seizure	ADR

Appendix F

Analytical Method

The concentration of phenytoin in serum samples were determined by using turbidimetric inhibition immunoassay method. By using Automated Analyzer, Synchron CX® Systems Beckman Coulter,Inc. The process of analyze was as follow:

Calibration

1. From the MASTER Screen, press **F3 CAL**.

2. Review the status to determine which chemistries need calibration.

3. Move cursor to the chemistries or drugs to be calibrated and press **SELECT**.

4. Press **F1 CALCUP ASSIGNMENT**. Based on the requested calibrations, the system determines the minimum number of sectors required for calibrator cup assignment. Using the list of available sectors, type the required sector numbers and press **ENTER**.

5. A list of cups assigned to the appropriate calibrators may be viewed by pressing **F2 CAL LOAD LIST**. If desired, a printout of the Cal Load List may be generated by pressing **F1 PRINT** Calibration selections will be automatically matched with active calibration programs if they exist.

6. Place fresh calibrator(s) in the appropriate cup positions and sector(s).

7. Load the sectors onto the system

8. Press **PREV SCREEN** or **MASTER SCREEN** to exit.

9. Press **START** to start the system when ready.

Assay sequence

1. From the MASTER Screen, press **F2 REAGENT LOAD**.

2. Move cursor to an unoccupied position or a position occupied by a reagent to be removed and press **SELECT** to highlight position.

3. Press **F1 AUTO LOAD**.

4. The operator will be allowed to load cartridges when the instrument status changes to “Loading Reagents” Press **PREV SCREEN** to Continue

5. Remove all caps from the reagent cartridge; prepare reagent if required. Check each cartridge for bubbles at the top and mouth of each compartment; remove bubbles if present.

6. The reagent carousel will rotate to the first position selected in ascending numeric order.

    a. To load a reagent cartridge: When prompted on the screen, open the reagent door and load the desired reagent cartridge.

    b. To remove or replace a reagent cartridge: When prompted on the screen, open the reagent door and remove the existing cartridge.

Close the reagent door. The reagent carousel will rotate to the next selected position. Repeat Steps 5 through 6 until all selected positions have been accessed.

Appendix G

Blenderized diet Prasat Neurological formula

Liver	100	g.
Pumpkin	100	g.
Banana or Papaya	100	g.
Egg	200	g.
Sugar	100	g.
Vegetable oil	10	g.
Water to	1000	mL.

VITAE

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