อัตราการควบคุมโรคลมชักได้และความสัมพันธ์ระหว่างขนาดยาฟีไนโทอิน กับความเข้มข้นของยาในซีรัมของผู้ป่วยเด็กโรคลมชักชาวไทย
Seizure Control Rate and the Association between Phenytoin Dose and Its Serum Concentration in Thai Pediatric Patients with Epilepsy

นิพนธ์ต้นฉบับ

Original Article

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วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ2563;15(2):124-129.

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษา 1) อัตราการควบคุมอาการชัก และ 2) ความสัมพันธ์ระหว่างขนาดยาฟีไนโทอินกับระดับความเข้มข้นในซีรัมของผู้ป่วยเด็กโรคลมชักชาวไทย **วิธีการศึกษา:** การวิจัยแบบย้อนหลังได้คัดข้อมูลจากเวชระเบียนของคนไข้เด็กโรคลมชักที่รักษาที่โรงพยาบาลราชบุรี ในช่วง 1 ตุลาคม 2557 ถึง 30 สิงหาคม 2560 สำหรับวัตถุประสงค์ที่ 1 ผู้ป่วยต้องใช้ยาฟีไนโทอินอย่างเดียวในขนาดใดก็ได้ ส่วนวัตถุประสงค์ที่ 2 ผู้ป่วยต้องใช้ยาขนาดที่แนะนำคือ 5 – 8 มก./กก./วัน การควบคุมอาการชักได้หมายถึง การปราศจากอาการชักอย่างน้อย 6 เดือนต่อเนื่อง ความเข้มข้นในซีรัมที่อยู่ในช่วงรักษา คือ 10 – 20 ไมโครกรัม/มิลลิลิตร ทดสอบความสัมพันธ์ระหว่างขนาดยาต่อวันกับความเข้มข้นของยาในซีรัมโดยสหสัมพันธ์ของเพียร์สัน **ผลการศึกษา:** ในผู้ป่วย 84 ราย พบอัตราการควบคุมอาการชักได้ร้อยละ 86.90 ในผู้ป่วย 57 รายที่ควบคุมได้และใช้ยาในขนาดที่แนะนำ พบว่าขนาดยาต่อวันสัมพันธ์ทางบวกกับความเข้มข้นในซีรัมอย่างมีนัยสำคัญทางสถิติ (r = 0.411; *P*-value = 0.002) **สรุป:** พบอัตราการควบคุมอาการชักได้ในระดับสูงในผู้ป่วยเด็กโรคลมชักชาวไทย และขนาดยาต่อวันสัมพันธ์ทางบวกกับความเข้มข้นในซีรัมอย่างมีนัยสำคัญทางสถิติ

คำสำคัญ: ยาฟีไนโทอิน, การควบคุมอาการชัก, ขนาดยาต่อวัน, ระดับยาในซีรัม

Abstract

Objective: To examine 1) seizure control rate and 2) the association between daily dose of phenytoin and its serum concentration in Thai pediatric patients who took phenytoin monotherapy. **Method:** In this retrospective study, medical records of pediatric epileptic patients of Ratchaburi Hospital, Thailand, from October 1, 2014 to August 30, 2017 were examined. To estimate seizure control rate, the patients had to use phenytoin monotherapy regardless of daily dose. For the 2nd study objective, the patients also had to use the recommended dose of 5 – 8 mg/kg/day. Seizure control was defined as having no seizures for a continuous period of 6 months or longer. Serum phenytoin concentration of 10 – 20 mcg/ml was defined as within therapeutic level. Association of phenytoin daily dose with its serum concentration was tested for correlation using Pearson's product moment correlation analysis. **Results:** Of 84 participants with phenytoin monotherapy, seizure control rate was 86.90%. Among 57 participants with seizure control and the recommended daily dose, daily doses of phenytoin were significantly, positively correlated with serum concentrations (r = 0.411; *P*-value = 0.002). **Conclusion:** Seizure control rate among Thai pediatric epileptic patients using phenytoin monotherapy was relatively high. Daily dose was significantly positively correlated with serum concentration.

Keywords: phenytoin, seizure control, daily dose, serum concentration

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Introduction

Phenytoin is a widely used antiepileptic drug (AEDs) in Thailand since it is relatively less costly compared with new AEDs. Phenytoin is expected for a long future use since it has been included in the National List of Essential Medicine of Thailand.[1-3] However, problems of phenytoin use have been existing and not fully understood or solved. The dose of phenytoin in pediatric patients according to the Clinical Practice Guidelines for Epilepsy is 5 - 8 mg/kg/day. [1,2]

According to our clinical practice experience at Ratchaburi Hospital, despite the appropriate dose of phenytoin prescribed by the physician, serum phenytoin concentrations of phenytoin in some patients were still below the desirable therapeutic range of 10 - 20 mcg/ml.[4-7] Whether efficacy and safety of phenytoin is related with its serum concentration has not been definitely concluded.

In daily practice, predicting phenytoin serum concentration after dose adjustment had not been optimal. Therefore, the correlation between phenytoin daily dose and its serum concentration could offer certain confidence for practitioners, especially among pediatric patients. In addition, phenytoin efficacy as the seizure control rate in pediatric patients has not been well known. In a report of the World Health Organization in 2006, phenytoin use was associated with a response rate up to 70% of epileptic patients in all age groups.[8] In Thai healthcare context, little has been known about its efficacy and safety in Thai pediatric patients; the care for these pateints could thus be suboptimal.

Based on the scarcity of information regarding the serum phenytoin concentration with respect to its daily dose among Thai pediatric epileptic patients, there has been a need to investgate such relationship to help improve epilepsy care. In addtition, the rate of seizure control among these Thai pediatric patients has not been reported. Such information was needed as the basis of effectiveness and for the improvement of epilepsy care for these patients. Specifically, this present study aimed to examine 1) seizure control rate among pediatric epileptic patients using phenytoin monotherapy and 2) the association between daily dose of phenytoin and its serum concentration in pediatric patients who took phenytoin monotherapy with the recommended and widely used dose of 5 – 8 mg/kg/day and had epilepsy under control in real-life practice.

Methods

In this retrospective study, the seizure control rate (study objective 1) and the association between daily dose of phenytoin and its serum concentration (study objective 2) in pediatric epileptic patients were examined. The **study population** for determining the rate of seizure control among phenytoin monotherapy was pediatric epilepsy patients taking only phenytoin for their seizure. For the evaluation of the association between phenytoin daily dose and its serum concentration (2nd objective), the study population was pediatric epilepsy patients taking only phenytoin with the dose of 5 – 8 mg/kg/day according to Thai clinical practice guidelines for epilepsy[1,2] and had their epilepsy under control. The reason for including only those with seizure control was that those with poor seizure would need the change of AED regimen change.

The **study sample** for determining the rate of seizure control among phenytoin monotherapy was pediatric epilepsy patients who received only phenytoin for epilepsy treatment (monotherapy) from the pediatric neurological clinic of Ratchaburi Hospital from October 1, 2014 to August 30, 2017. These patients were diagnosed with epilepsy by a pediatric neurologist in accordance with the diagnostic criteria of the International League Against Epilepsy (ILAE) 2010.[1,2] To be eligible, the patients had to take phenytoin either Dilantin Infatabs® or any extended release capsule. The study sample for evaluating of the association between phenytoin daily dose and its serum concentration was similar to that for determining seizure control rate and took the dose of 5 – 8 mg/kg/day phenytoin with their epilepsy under control.

In terms of exclusion, the researcher excluded patients taking any drugs with potential interaction with phenytoin which could affect serum phenytoin concentration. Drugs which could increase phenytoin effects and/or serum concentrations included benzodiazepines, valproic acid[9] and methylphenidate[10]; while drugs which could decrease phenytoin effects and/or serum concentrations were barbiturates, and carbamazepine.[9] The researcher also excluded patients who stopped or skipped at least one day of phenytoin dosing, had allergic reaction to phenytoin, had their AED dosage regimen changed, had other AED concomitantly with phenytoin, missed at least one follow-up visit, were transferred for epileptic care at other healthcare setting, or stopped receiving epilepsy care at Ratchaburi Hospital during study period. In addition, patients with abnormalities in their liver and/or kidney functions as diagnosed by the physician and/or indicated by laboratory tests were also excluded.

A serum phenytoin concentration for statistical analysis was chosen from the visit that seizure control was found after phenytoin dose adjustment. All serum phenytoin concentrations were at steady state. This was because the measure of phenytoin serum concentration was done at least 14 – 20 days after the start or adjustment of the dose which allowed the drug to reach its steady state.[1,2] The phenytoin serum concentration examination at Ratchaburi Hospital was analyzed by an automatic immunological analysis tool called ARCHITECT i2000SR.[11] Based on literature review and actual practice, therapeutic level of phenytoin serum concentration ranges from 10 to 20 mcg/ml. [4-7]

Seizure control was defined as “well controlled” or “not well controlled” as stated by the pediatric neurologist in medical records. In epilepsy clinic of Ratchaburi Hospital, seizure control was guided by the frequency, duration and severity of seizures.[1,2] Practically, having no seizures for a continuous period of 6 months or longer was considered “well controlled.” With multidisciplinary team approach of Ratchaburi Hospital, the evaluation on seizure control was usually carried out based on the diagnosis and assessment of the pediatric neurologist, together with the monitoring and evaluation by a pharmacist. The information about seizure control in the pediatric neurology clinic at Ratchaburi Hospital was highly adequate since two specialists spent a thorough examination with at least 10 to 15 minutes for each case and

multidisciplinary approach especially by pharmacist intervention could facilitate such comprehensive care and documentation.

In terms of adverse events, data of adverse drug reactions (ADRs) in the medical records among the patients with 5 – 8 mg/kg/day of phenytoin dose were extracted. ADRs associating with phenytoin verified by Naranjo's algorithm Thai version[12] as stated in medical records were eligible for study analysis.

Ethical protection

This retrospective study was approved by the Ethics Committee of Ratchaburi Hospital (approval number: COA-RBHEC 013/2018). Data of the sampled patients were kept confidential. Only assigned patient numbers, instead of their actual name and hospital identification number, were used.

Data analysis

Demographic and clinical status data were presented as frequency with percentage. Phenytoin serum concentration was presented as mean with standard deviation. Phenytoin dose in relation to serum phenytoin concentration categories (sub-, within, and supra-therapeutic levels) were presented. The use of Pearson's product moment correlation analysis to examine the association between daily phenytoin dose and its serum concentration was appropriate since the related assumptions for such analysis ADRs in relation to serum phenytoin concentration categories (sub-, within, and supra-therapeutic levels) werer also detailed. Significance level for this statistical analysis was set at a 5% type I error (or *P*-value < 0.05).

Results

Of the total of 185 epileptic pediatric patients with phenytoin monotherapy, 84 of them were eligible for the first objective of the study (rate of seizure control). For 101 patients excluded, the reasons for their exclusion were: mild skin allergy (17 or 16.83%), incomplete follow-up (24 or 27.72%), receiving drugs with potential interaction with phenytoin (8 or 7.92%), referral for healthcare settings close to their residence (18 or 17.82%), poor compliance with phenytoin regimen (14 or 13.86%), and poor compliance of their parents with phenytoin dosing (16 or 15.85%).

Of the 84 participants eligible for the first objective of the study (rate of seizure control), there were slightly more male than female patients (57.14% and 42.86%, respectively) (Table 1). The majoprity was in their 7 – 12 years of age (48.81%), followed by those in their 3 – 6 years (35.71%), and 13 – 15 years (15.48%). Being located in the Ratchaburi province, the majority of the participants at the clinic of Ratchaburi Hospital was the residents of Ratchaburi (51.19%) rather than those from other provinces under the supervision of regional health service 5. In terms of insurance payment scheme, most of them were covered by the Universal Coverage scheme (85.70%). Almost all of them had no other illness or comorbid disease (94.05%) and no drug allergy (94.05%). All of them had no family history of epilepsy and three-quarters (75.00%) had partial seizure treated with phenytoin while the rest 25.00% had generalized tonic-clonic seizure (Table 1).

Table 1 Demographic and clinical characteristics of the participants (N = 84).

Characteristics	N	%
Gender		
Male	48	57.14
Female	36	42.86
Age (year)		
3 - 6	30	35.71
7 - 12	41	48.81
13 - 15	13	15.48
Residential province		
Ratchaburi	43	51.19
Kanchanaburi	11	13.10
Nakhon Pathom	8	9.50
Phetchaburi	10	11.91
Prachuap Khiri Khan	4	4.76
Suphan Buri	5	5.95
Samut Songkhram	2	2.38
Samut Sakhon	1	1.19
Payment scheme		
Universal Coverage	72	85.70
Disability card	5	5.95
Out-of-pocket	2	2.38
Civil Servant Medical Benefit Scheme and other related schemes	5	5.95
Other illnesses or comorbid diseases		
No	79	94.05
Yes	5	5.95
Allergy	2	40.00
G6PD deficiency	2	40.00
Thalassemia	1	20.00
Drug allergy history		
No	79	94.05
Yes		
Amoxicillin	2	40.00
Phenobarbital	2	40.00
Ceftriaxone	1	20.00
Family history of epilepsy		
No history	84	100
Types of seizure treated with phenytoin		
Partial seizure	63	75.00
Generalized tonic-clonic seizure	21	25.00

Rate of seizure control

Of these 84 participants who took phenytoin monotherapy regardless of the daily dose, 73 patients (86.90%) were able to control the seizure while 11 (13.10%) were not. Among 11

participants with no seizure control, 7 of them (63.64%) had their phenytoin changed to other AED(s) and 4 (36.36%) used phenytoin concomitantly with other AED(s).

Regarding of type of seizure, among those 73 patients with seizure control, 53 of them (72.60%) had partial seizure while the rest (20 or 27.40%) had generalized tonic-clonic seizure. Among 11 with no seizure control, most of them (10 or 90.91%) had partial seizure while only 1 (9.09%) had generalized tonic-clonic seizure.

Association between phenytoin daily dose and its serum concentration among patienst with seizure control

Among 73 participants with seizure control, 69 of them (94.52%) were monitored for phenytoin serum concentration; while 4 patients (5.48%) were not. Among 69 participants with phenytoin serum concentration measured, the majority (57 or 82.61%) used phenytoin at the recommended dose of 5 – 8 mg/kg/day with an average dose of 6.63 ± 0.83 mg/kg/day (range: 5.00 – 8.00) and an average serum phenytoin concentration of 9.41 ± 3.98 mcg/ml (range: 4.23 – 19.05). Most of serum phenytoin concentrations were in sub-therapeutic range (64.91%), followed by those within therapeutic range (35.09%) (Table 2).

Table 2 Phenytoin dose and serum drug concentration measured in 69 patients.

Dosage (mg/kg/day)	N (%)	Average dose* (range)	Average serum conc.# (range)	N (%) by therapeutic range†	
				Sub-therapeutic range	Within therapeutic range
< 5	7 (10.14)	4.49 ± 0.36 (4.00 - 4.93)	10.83 ± 3.90 (3.60 - 15.12)	2 (28.57)	5 (71.43)
5 - 8	57 (82.61)	6.63 ± 0.83 (5.00 - 8.00)	9.41 ± 3.98 (4.23 - 19.05)	37 (64.91)	20 (35.09)
> 8	5 (7.25)	8.45 ± 0.25 (8.11 - 8.70)	8.21 ± 2.95 (4.82 - 11.33)	3 (60.00)	2 (40.00)
Total	69 (100)			42 (60.87)	27 (39.13)

* mg/kg/day presented as mean ± standard deviation.

concentration (mcg/ml) presented as mean ± standard deviation.

† Target therapeutic range: 10 - 20 mcg/ml.

It was found that there was a significant relationship between the daily dose of phenytoin and its serum concentration. Among 57 participants receiving the recommended phenytoin dose of 5 – 8 mg/kg/day, their actual daily doses of phenytoin were positively correlated with their serum phenytoin concentrations (r = 0.411) with a statistical significance (P-value = 0.002).

In addition, among these 57 participants with seizure control and the daily dose of 5 – 8 mg/kg/day, there were 39 patients (68.42%) with partial seizure and 18 (31.58%) with generalized tonic-clonic seizure. Among 39 patients with partial seizure, there were 27 (69.23%) with sub-therapeutic level and 12 (30.77%) within therapeutic level; while 10 (55.56%) with sub-therapeutic level and 8 (44.44%) with within therapeutic level were found in 18 patients with generalized tonic-clonic seizure.

Adverse drug reactions

Among 57 participants receiving 5 – 8 mg/kg/day phenytoin dose, 9 of them experienced adverse drug reactions (ADRs) (Table 3). The most frequently found ADR was gingival hypertrophy (5 participants or 55.56%), followed by dizziness (3 or 33.33%) and nausea (1 or 11.11%). Among these 9 participants experiencing ADRs, 5 (or 55.56%) had their phenytoin serum concentrations within therapeutic range of 10 – 20 mcg/ml; while the rest 4 participants were sub-therapeutic.

Table 3 Adverse drug reactions, daily dose, serum phenytoin concentrations, and therapeutic levels among 9 of 57 patients with 5 – 8 mg/kg/day of phenytoin dose.

Adverse drug reactions	Dosage (mg/kg/day)	Serum phenytoin conc. (mcg/ml)	Therapeutic level	N	%
Gingival	6.25	9.61	Sub-therapeutic	1	
hypertrophy	7.61	14.53	Within therapeutic	1	
	7.50	18.03	Within therapeutic	1	
	5.76	5.26	Sub-therapeutic	1	
	6.10	10.37	Within therapeutic	1	
Total				5	55.56
Nausea	6.51	16.32	Within therapeutic	1	
Total				1	11.11
Dizziness	6.67	8.81	Sub-therapeutic	1	
	5.36	11.97	Within therapeutic	1	
	5.55	7.65	Sub-therapeutic	1	
Total				3	33.33
Total				**9**	**100**

Discussions and Conclusion

In this retrospective study examing seizure control rate among 84 pediatric epileptic patients taking phenytoin monotherapy regardless of the daily dose, the seizure control rate of 86.90% was found. Since there has been no studies reporting seizure control rate among pediatric patients, it would be difficult to conclude how successful of phenytoin monotherapy in Thai pediatric patients was. However, based on the report of the World Health Organization in 2006 stating that phenytoin use was associated with a response rate up to 70% of epileptic patients in all age groups[8], the 86.90% control rate in our study suggested a somewhat successful care. This

could be attributable to the fact that epilepsy care at the pediatric neurology clinic at Ratchaburi Hospital used a multidisciplinary care approach where physicians and pharmacists took part in comprehensive evaluations of efficacy and safety of the therapy and the dosage regimen adjustment using all available tools including serum drug concentration.

Among 57 participants with phenytoin monotherapy with the recommended dose of 5 – 8 mg/kg/day, almost two-thirds had their serum phenytoin concentrations in subtherapeutic range (64.91%) while the rest (35.09%) were within therapeutic range (10 – 20 mcg/ml). This was surprising since a relative large number of the participants had their seizure under control. Their average daily dose (6.63 ± 0.83 mg/kg/day) was in the middle of the recommended dose of 5 – 8 mg/kg/day. This suggested that their dose of phenytoin could be increased relatively safely close to the upper limit (8 mg/kg/day) to reach the therapeutic level.

The finding that there was a significant, positive correlation between daily dose of phenytoin and its serum concentration (r = 0.411, P-value = 0.002) could help practitioners relatively more convinced to adjust the dose. However, this moderate correlation has certain level of limitation in practical use. A beta coefficient from regression could be more useful in deciding the increased dose for specific target serum concentration. More future studies with a larger sampel size should be conducted to determine the extent of the association.

Additional analysis showed that among 84 participants with phenytoin monotherapy, 10 of 11 participants (90.91%) who had no seizure control and 53 of 73 participants (72.60%) who had seizure control were patients with partial seizure. This finding suggested a lower seizure control rate among patients with partial seizure. This discrepancy could be of interest for future research to examine for its significance. If significant, it should alarm ways to improve the care for patients with partial seizure.

Another additional analysis on 57 participants with seizure control and the daily dose of 5 – 8 mg/kg/day showed almost no discrepancy regarding chance of having sub-therapeutic level between patiens with partial seizure and with generalized tonic-clonic seizure. Among 39 patients with partial seizure, there were 27 patients (69.23%) with sub-therapeutic level and 12 (30.77%) within therapeutic level. However, patients with generalized tonic-clonic seizure seemed to have a lower proportion of having sub-therapeutic level (10 of 18, or 55.56%). It has been inclonclusive about the relationship of type of seizure with either serum phenytoin concentration or clinical response as shown in a study with small sample size.[13] This relationship of type of seizure with either serum phenytoin concentration or clinical response, if any, could help improve the care and prompt future research.

In terms of adverse drug reactions, gingival hypertrophy, nausea and dizziness were found in 5, 1 and 3 patients with seizure and the recommended dose of 5 – 8 mg/kg/day, respectively. The incidence of gingival hypertrophy deemed somewhat alarming and should prompt a more comprehensive investigation. Our findings were consistent with the fact that these three adverse drug reactions were independent of daiy dose and serum concentration of phenytoin since patients with sub-therapeutic level also experienced the reactions.

This present study has certain limitations. With a relatively small sample, our findings could have a lower power of analysis. Future studies with a larger sample size are needed. To achiebe a better generalization to all Thai pediatric epileptic patients, studies with multi-centers are encouraged.

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