Effect of Pharmacist Participation in the Health Care Team on Therapeutic Drug Monitoring Utilization for Antiepileptic Drugs

Chaveewan Ratanajamit BPharm, PhD*, Peerasak Kaewpibal BPharm**,
Suwanna Setthawacharavanich MD***, Damrongsak Faroongsarng BPharm, PhD****

** Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand*
*** Graduate student in Master degree of Clinical Pharmacy, Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand*
**** Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand*
***** Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand*

Objective: *To compare the proportions of appropriate TDM utilization regarding the indication, sampling time, and application of the measured drug levels of antiepileptic drugs (AEDs) between the pre-intervention period and pharmacist intervention period.*
Material and Method: *The baseline evaluation and pharmacist intervention study of TDM use for phenytoin, carbamazepine, or valproic acid were conducted at a medical teaching hospital in Southern Thailand. TDM requests, interpretation and dosage adjustment recommendations were mainly responsible by residents. In the intervention period, each of the three-step TDM process was assessed by the pharmacist for appropriateness and a suggestion provided if necessary prior to a final recommendation made by the resident. The criteria for appropriateness of TDM for AEDs were developed and validated by two neurologists. The present study included 44 TDM tests (22 patients) during the baseline period and 43 tests (27 patients) during the intervention period. The proportions of appropriate TDM utilization between the two periods were compared using Chi-square test.*
Results: *In the baseline period, proportions of appropriately performed TDM were: indication (63.6%), sampling time (47.7%), and application of drug levels (63.6%). Pharmacist intervention significantly increased the proportions of appropriate indication (97.7%, p = 0.001), sampling time (79.1, p = 0.0023), and applications (83.7%, p = 0.0293). There were 12 tests (27.3%) and 29 tests (67.4%) (p = 0.0001) during the baseline and the intervention period, respectively, that met all 3 criteria of appropriate TDM use. Sixteen requests without indication found in the baseline period was reduced to one in the intervention period, and thus reduced the unnecessary cost by 90%. Of 59 steady-state drug levels, 34 (57.6%, p = 0.0005) significantly correlated with clinical responses.*
Conclusion: *Pharmacist intervention significantly improved appropriateness of TDM use, and substantially reduced unnecessary costs. Using a screening checklist including the indication, sampling time and data needed for proper interpretation of the results can help improve the appropriateness of TDM utilization.*

Keywords: *Therapeutic drug monitoring, TDM, Pharmacist, Antiepileptic drugs, Phenytoin, Carbamazepine, Valproic acid*

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Correspondence to: Ratanajamit C, Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla 90112, Thailand. Phone & Fax: 074-428-222, E-mail: chaveewan.r@psu.ac.th

Epileptic seizures are among the most prevalent neurologic disorders that require long-term antiepileptic drugs (AEDs) therapy[1]. Treatment with some AEDs, such as phenytoin, carbamazepine, valproic acid, and phenobarbital, require therapeutic drug monitoring (TDM) as they display significant pharmacokinetic inter-individual variability; narrow therapeutic range; potential to multiple/complicated drug-drug interactions; pharmacokinetic alterations related to disease states or organ impairment; or non-compliance in long-term use[2]. AED levels account for a substantial cost of all drug level measurements, thus the rational and appropriate use of drug levels and impact on the patients' outcomes have been addressed and determined[3-8]. The present study aimed at assessment of the effect of pharmacist participation in the TDM team on the appropriateness of TDM utilization for AEDs, namely, phenytoin, carbamazepine, and valproic acid regarding indication for drug level measurement, sampling time, and clinical application of the drug levels.

Material and Method

Study design and setting

This baseline evaluation and intervention study was carried out at Songklanagarind Hospital in Southern Thailand. Baseline study period was between April and June 2007, and the intervention period was between July and November 2007. In the study hospital, the health care team composed of general staff and specialists were assigned to be responsible for the patients in each ward and rotated monthly. TDM requests, interpretation and post-TDM dosage adjustment recommendations were mainly responsible by residents in the team, whose TDM use was assumed to be improved by the pharmacist intervention. Due to the rotated health care team the randomized controlled design, the gold standard for evaluation of the intervention effect, could not be properly used, and thus the pre- and post-intervention design was selected so as to avoid the contamination of the pharmacist intervention that could reduce the magnitude of the intervention effect. In the intervention period, the TDM process was assessed for appropriateness by the pharmacist and a suggestion was provided if necessary prior to a final recommendation made by the requesting resident. Blood level of the drug were determined by the toxicology laboratory located in the hospital. The present study was approved by the Ethics Committee of Faculty of Medicine, Prince of Songkla University (reference SUB.EC 50/400-002).

Study patients

Inclusion criteria

Adult patients were eligible if they were (1) admitted to the selected wards [*i.e.* medical ward, neurosurgery ward, or intensive care unit (ICU)] during the study period; (2) aged $\geq$ 18 years old; (3) diagnosed with epilepsy or seizures secondary to other causes; (4) prescribed with phenytoin, carbamazepine or valproic acid, with/without concomitant drugs for treatment or prophylaxis of seizures; and (5) not allergic to the prescribed drugs.

Exclusion criteria

The patients were ineligible if they had any of the following: (1) acute uncontrolled complication; (2) multi-organ failures; (3) pregnancy or breast-feeding condition; or (4) impaired communication.

Appropriateness criteria

The criteria for appropriateness of TDM use for AEDs were modified from the existing criteria developed by Affolter N, et al (2003)[3] and Schoenenberger RA, et al (1995)[8] and validated by two neurologist experts. The criteria composed of three aspects: (1) appropriateness of indication for TDM request; (2) appropriateness of sampling time; and (3) appropriateness of application of the drug levels. The indications classified as appropriate were: toxicity suspected; lack of response; assessment of compliance; change in clinical states of the patient; potential drug interaction due to change in comedications; and change in dosage regimens or drugs. Inappropriate requests were those done as routine level monitoring without clear indication. The time appropriate for the sample collection was based on the indication, for example, if the requested indication required a steady-state concentration, the sample should be collected at least 5 half-lives of the current dosage regimen. In addition, steady-state trough concentration (C_{trough}) measurement should be collected immediately prior to the administration of the next dose. In the case of drug toxicity, immediate blood sampling was considered appropriate. Clinical application of the patient's drug level was primarily based on clinical response.

Intervention

The pharmacist assessed whether the indication and sampling time of a TDM request were appropriate, otherwise some suggestions were given. The measured drug levels were interpreted

in conjunction with the clinical response, the demographics (age, weight, and height), the clinical status of the individual patient, the medication dose administered, the indication, and the pharmacokinetics of the drug. As noted above the application of the drug level was primarily based on clinical response, only if the therapeutic response was not achieved with the observed blood level, the recommendation was then made, such as dosage adjustment, and was provided to the requesting physician as rapidly as possible.

Data collection

The data collection form recorded the patient's demographics (age, weight, and height), and all related variables required for interpretation of the measured drug level (such as, serum albumin, serum creatinine), medication dosage regimen, date and time of the last dose, indication, sampling time, measured AED levels, interpretation of the level in relation to the last dose administered and the dosing history, calculated pharmacokinetic parameters (volume of distribution, elimination rate constant, elimination half-life, etc), clinical response (insufficient, good, or toxic response), and clinical application of the level (decreased dose, no dosage alteration, increased dose, changed to other AEDs, changed the dosage form, discontinued the AEDs, etc). The targeted therapeutic range of the study AEDs were: phenytoin 10-20 mg/L, carbamazepine 4-12 mg/L, and valproic acid 50-100 mg/L[9]. The phenytoin levels were corrected in patients with low serum albumin.

Outcomes

Primary outcome measures

The primary outcome was the proportion of antiepileptic drug levels prescribed with appropriate indication, the proportion of sample collected at the appropriate time, and the proportion of drug levels applied appropriately.

Secondary outcome measures

The secondary outcomes were clinical response and cost of performing inappropriate tests. Clinical response of each patient was determined when the drug level reached steady-state. In addition, it was assessed again at a follow-up visit approximately one month after discharge, without drug level measurement. The clinical responses were classified, based on the changes of seizure frequencies from baseline, into 3 categories, *i.e.*, good clinical response (free of seizure or seizure frequency reduced > 50%), insufficient response (seizure reduced < 50% or increased), or toxic response (patients presented signs/symptoms and/or drug level exceeding therapeutic range, and/or disappearance of toxic symptoms after reducing the dose)[10].

Sample size

The sample sizes required to test the main hypotheses were determined based on assumptions that the intervention increased at least 20% the appropriateness proportion for each task, with significant level at 5% (two-tailed test) and power of 80%. It was found that approximately 43 tests need to be enrolled in each period.

Statistical analyses

The proportion of appropriate use of TDM, regarding indication, sampling time, and application of drug levels, between baseline and intervention periods was compared by using Chi-square test or Fisher's exact test. The relationship between the drug levels and clinical responses was determine using Chi-square test where the drug levels were categorized as below, within or above therapeutic steady-state concentration, and clinical responses were categorized as insufficient, good, or toxic response. All of the analyses were done on commercial software (STATA program, version 8.0, Stata Corporation, Texas, USA).

Results

The study patients are summarized in Table 1. The authors included 44 TDM tests (22 patients) during the baseline study and 43 tests (27 patients) during the intervention study. Some patients were ordered for drug levels measurement more than once. Most patients were treated with monotherapy, while 6 in the baseline period and 12 patients in the intervention period were treated with polytherapy. Frequencies of individual AED prescribed for TDM and blood levels, classified by the study period, are summarized in Table 2. Phenytoin was the most commonly prescribed for level monitoring. Trough blood levels were measured in 21 samples (47.8%) during the baseline period and 34 samples (79.1%) during the intervention period.

The proportions of appropriate indication, sampling time and clinical application of drug levels are presented in Table 3. The most commonly requested indication was insufficient clinical response (16 (36.4%) in the baseline period and 14 (32.6%) in the intervention period). Eight tests were collected due to

Table 1. Summary of study patients

Variable	Baseline survey (n = 22)	Intervention period (n = 27)
Male, n (%)	11 (50.0)	14 (51.9)
Age, mean ± SD (range), years	52.4 ± 20.0 (22-83)	45.8 ± 21.7 (18-85)
IBW, mean ± SD (range), kg	53.1 ± 8.2 (35.0-68.4)	53.4 ± 8.3 (34.0-67.4)
Number of TDM requested per patient, n (%)		
Once	13 (59.1)	21 (77.8)
Twice	5 (22.7)	5 (18.5)
Three times	3 (13.6)	0 (0.0)
Six times	1 (4.5)	0 (0.0)
Seven times	0 (0.0)	1 (3.7)
Serum albumin, mean ± SD (range), (g%)	3.5 ± 0.7 (2.2-4.4)	3.4 ± 0.9 (1.8-5.2)

Table 2. Summary of TDM samples

Variable	Baseline survey (n = 44)	Intervention period (n = 43)
Drug requested for level measurement, n (%)		
Phenytoin	31 (70.5)	24 (55.8)
Carbamazepine	3 (6.8)	0 (0.0)
Valproic acid	10 (22.7)	19 (44.2)
Blood level, Mean ± SD (range), mg/L		
Phenytoin	16.5 ± 11.8 (0.7-118.9)	16.8 ± 15.6 (2.5-66.4)
Carbamazepine	11.5 ± 8.1 (3.1-19.3)	-
Valproic acid	54.2 ± 44.8 (5.2-137.8)	40.0 ± 22.8 (2.5-90.7)

suspected drug toxicities, 5 of which (phenytoin 2, valproic acid 1, and carbamazepine 2) had levels above the therapeutic ranges. The toxic symptoms found were dizziness (n = 2), lethargy (n = 1), drowsiness (n = 2), and phenytoin-induced nystagmus (n = 3). In the baseline study, the proportions of appropriate indication (63.6%), sampling time (47.7), and that of application of drug levels (63.6%) were moderate. Pharmacist intervention significantly increased the proportions of appropriately performed TDM services, *i.e.*, appropriate indication (97.7%, p = 0.001), sampling time (79.1%, p = 0.0023), and clinical applications of the measured drug levels (83.7%, p = 0.0293). Number (%) of tests that met all appropriateness criteria were 12 (27.3%) in the baseline period and 29 tests (67.4%) in the intervention period (p = 0.0001).

In the baseline period, 16 tests (36.4%) were inappropriately requested for routine level measurements in patients with satisfactory therapeutic effect and no changes in dosage or clinical states, 13 of which were phenytoin. These inappropriate tests accounted for 35% of total TDM costs. Only 1 (2.3%) unnecessary test was performed in the pharmacist intervention period, thus reducing the unnecessary cost by 90%. Proportions of patients responded to therapy were not different in both periods (77.3% in the baseline period and 81.5% in the intervention period).

The two most common appropriate clinical applications of the test results, in the baseline period versus in the intervention period, respectively, were no change of the dosage regimen (13 cases versus 20 cases) and increase the maintenance dose (8 cases versus 11 cases). In the baseline period, 5 well responded patients whose drug levels were slightly high without signs/symptoms of toxicity, were inappropriately reduced the dose. This might put the patient at risk to seizure. In contrary, 4 patients who had the levels above therapeutic range were given a loading dose instead of adding a new AED, which might put the patients prone to adverse effects. These inappropriate events were not observed during the intervention period.

Table 4 shows the relationship between the observed drug levels and clinical responses. Of 59

Table 3. Comparisons of proportions of appropriate indication, sampling time, and clinical application of test results between baseline and intervention period

Variable	Baseline period (n = 44)	Intervention period (n = 43)	% difference (95% CI) [p-value]
Appropriateness of indication, n (%)			
Appropriate	28 (63.6)	42 (97.7)	34 .1 (17.3-50.8%) [0.001]
Therapy initiation	4 (9.1)	6 (14.0)	
Dose alteration	0 (0)	9 (20.9)	
Compliance assessment	1 (2.3)	5 (11.6)	
Insufficient response	16 (36.4)	14 (32.6)	
Toxic sign/symptom presentation	4 (9.1)	4 (9.3)	
Others (*e.g.*, assessment of drug interaction, changing clinical states)	3 (6.8)	4 (9.3)	
Inappropriate	16 (36.4)	1 (2.3)	
No indication (*e.g.*, routine level monitoring without indication)	16 (36.4)	1 (2.3)	
Appropriateness of sampling time, n (%)			
Appropriate	21 (47.7)	34 (79.1)	31.3 (11.0-51.7) [0.0023]
Inappropriate	23 (52.3)	9 (20.9)	
Application of drug levels, n (%)			
Appropriate	28 (63.6)	36 (83.7)	20.1 (1.4-38.7) [0.0293]
Inappropriate	16 (36.4)	7 (16.3)	

Table 4. Cross-tabulation between steady-state drug levels and clinical responses during hospital admission and 1-month after discharge

Drug level	Clinical responses (n = 59)			p-value (Fisher's exact test)
	Insufficient response	Good response	Toxic response	
Below therapeutic range	17	10	1	0.0001
Within therapeutic range	11	11	1	
Above therapeutic range	0	2	6	

steady-state drug levels, 34 (57.6%, p = 0.0001) correlated well with clinical responses. 20/30 tests (66.7%) of phenytoin levels were highly correlated with clinical responses, while only 11/25 tests (44.0%) of valproic acid did (data not shown). Of 21 patients whose blood levels did not correlate with clinical responses, 12 (57.1%) received valproic acid. Although 3/3 tests (100%) of carbamazepine levels correlated well with clinical responses, the sample size was too small to draw any conclusion. However, 8 of 10 patients whose drug levels below therapeutic ranges and previously well responded, were not sufficiently controlled of seizure at follow-up a month later. It was found that most of them (6 of 8) received concomitant enzyme inducers, such as phenytoin or phenobarbital that might lower the drug levels to that below the therapeutic level. The proposed mechanism was, however, not confirmed since the level determination had not been done at that time. At the follow-up visit, none of those previously experienced drug toxicities were found.

Discussion

It was found that pharmacist intervention significantly improved indication, sampling time, and clinical application of drug levels. Pharmacist participation in the TDM service substantially reduced the unnecessary cost due to inappropriate requests. Steady-state phenytoin concentrations better correlated with clinical responses than that of valproic acid.

Pharmacist intervention significantly increased the proportion of appropriate requests. Many guidelines were developed to help improve TDM utilization appropriate and efficient[2,3,8,11]. In the present study, the authors modified the current request form in order to improve appropriateness of a request by providing a common indication checklist for level monitoring and to capture all important data needed for interpretation. It was evidenced that routine level monitoring of AEDs provided no clinical benefits[12], it was, thus, considered inappropriate indication in the present study. Using the screening checklist significantly reduced the unnecessary cost.

The proportion of appropriate sampling time during the baseline study was moderately low, but significantly increased by pharmacist intervention. Sample collection is an important part of the TDM processes that was performed inappropriately[13-15]. Blood samples obtained at the improper time could lead to misinterpretation and mismanage the dosage regimen. For instance, a blood sample taken before the distribution completed might overestimate the level and apply improperly. Several studies indicated that TDM was significantly inappropriately used by physicians, especially, the timing of blood sample collection[2,3,5,8]. In addition, most request forms were not designed to allow entry of data essential to the interpretation of drug level measurements[16]. The present study demonstrated that using a screening checklist including the indications, sampling time and all data essential for proper interpretation of the results can help improve the appropriateness of TDM utilization.

Interpretation of drug levels is a most important part of TDM service to achieve optimal use of the value. It requires knowledge of clinical data, precise sampling time, dosage regimen, steady state versus non-steady state concentration, and pharmacokinetic characteristics of the drug[17,18]. Interpretation of the drug levels might be more complicated in some clinical situations, for instance, patients receiving some other drugs that have a potential to drug interaction, or in hypoalbuminemia. It was reported that displacement of phenytoin from albumin binding site by valproic acid, or hypo-albuminemia could result in increased free levels. In such clinical situations, the free level is more reliable than the total level, especially, highly protein-bound drugs[19]. In the case that free level determination is unavailable, a measure for improvement of accurate interpretation should be done. In the present study, the total phenytoin level was corrected for low plasma albumin that might improve the clinical application of the level.

As TDM requires that the drug levels should relate well with the clinical responses, the results support this requirement. However, in the case of patients who responded well even at the very low levels, it may be safer to bring the drug level near/ within therapeutic ranges by increasing the dose, as failure of seizure control in long-term therapy were found in most patients.

The present study did not evaluate the time and cost of having pharmacists participate in the health care team. It was observed that the pharmacist intervention minimizing time the team spent on TDM utilization as well as improving both appropriateness of TDM utilization and unnecessary cost of the drug level measurement, that might balance the cost paid for an extra full-time clinical pharmacist.

Conclusion

Pharmacist participation in the TDM team potentially improves appropriateness of TDM use and resource implications. Using a screening checklist including the indication, sampling time and data needed for proper interpretation of the results can help improve the appropriateness of TDM utilization.

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ผลกระทบของการมีเภสัชกรร่วมทีมรักษาต่อการใช้บริการตรวจติดตามระดับยาในเลือดของยาต้านการชัก

ฉวีวรรณ รัตนจามิตร, พีรศักดิ์ แก้วภิบาล, สุวรรณา เศรษฐวัชราวนิช, ดำรงศักดิ์ ฟ้ารุ่งสาง

วัตถุประสงค์: *เปรียบเทียบสัดส่วนความเหมาะสมด้านข้อบ่งชี้, เวลาเก็บตัวอย่างเลือด และการประยุกต์ผลระดับยาในเลือดของยาต้านการชักระหว่างก่อน-หลังการแทรกแซงโดยเภสัชกร*

วัสดุและวิธีการ: *ศึกษาการใช้บริการตรวจติดตามระดับยาในเลือดของยา phenytoin, carbamazepine และ valproic acid ในผู้ป่วยในของโรงพยาบาลสงขลานครินทร์ ในช่วงเดือนเมษายนถึงเดือนพฤศจิกายน พ.ศ. 2551 โดยปกติแพทย์ประจำบ้านเป็นผู้รับผิดชอบสั่งเจาะวัดระดับยาในเลือด แปลผล และประยุกต์ผลระดับยาในเลือด แต่ในช่วงแทรกแซงนั้น เภสัชกรประเมินความเหมาะสมเกี่ยวกับการสั่งวัดระดับยาในเลือด โดยพิจารณาด้านข้อบ่งชี้ในการสั่งเจาะเลือด เวลาเก็บตัวอย่างเลือด แปลผลระดับยาในเลือด และให้คำแนะนำแพทย์ในการปรับขนาดยา กำหนดเกณฑ์ความเหมาะสมในด้านต่าง ๆ โดยปรับจากเกณฑ์ที่ได้จากการศึกษาต่าง ๆ และผ่านการตรวจสอบโดยแพทย์ผู้เชี่ยวชาญด้านประสาทอายุรกรรม จำนวนตัวอย่างการตรวจติดตามระดับยาในเลือดช่วงก่อนและหลังการแทรกแซงคือ 44 และ 43 ตัวอย่าง ตามลำดับ เปรียบเทียบสัดส่วนการตรวจติดตามระดับยาในเลือดของยาต้านการชักที่เหมาะสม ระหว่างช่วงก่อน-หลังการแทรกแซงโดยใช้สถิติ Chi-square ที่ระดับความเชื่อมั่น 95%*

ผลการศึกษา: *สัดส่วนตัวอย่างเลือดที่มีความเหมาะสม ช่วงก่อนและช่วงการแทรกแซง ตามลำดับ มีดังนี้ ด้านข้อบ่งชี้ 63.6% และ 97.7% (p = 0.0001) ด้านเวลาเก็บตัวอย่างเลือด 47.7% และ 79.1% (p = 0.0024) และด้านการประยุกต์ผลระดับยาในเลือดในการรักษาผู้ป่วย 72.7% และ 81.4% (p = 0.3370) ผู้ป่วยที่ตอบสนองต่อการรักษาด้วยยาต้านการชัก 77.3% และ 81.5% (p = 0.7370) ตัวอย่างที่มีความเหมาะสมครบทั้ง 3 ด้าน คือ ช่วงก่อนการแทรกแซง 12 ตัวอย่าง (27.3%) และช่วงแทรกแซง 29 ตัวอย่าง (67.4%) การแทรกแซงสามารถลดค่าใช้จ่ายที่ไม่จำเป็นเนื่องจากการสั่งวัดระดับยาที่ไม่มีข้อบ่งชี้ที่เหมาะสมลงได้ประมาณ 90% พบว่า จาก 59 ตัวอย่างเลือดที่วัดระดับยาที่สภาวะคงที่มี 34 ตัวอย่าง (54.5%) ที่ระดับยามีความสัมพันธ์กับผลการตอบสนองทางคลินิก (p = 0.0001)*

สรุป: *การศึกษาแสดงให้เห็นว่าการมีเภสัชกรอยู่ในทีมสุขภาพ ช่วยให้การใช้บริการตรวจติดตามระดับยาในเลือดของยาต้านการชักมีความเหมาะสมมากขึ้นและสามารถลดค่าใช้จ่ายที่ไม่จำเป็นลง*